Advances in the Treatment of Noninfectious Uveitis with Biologics: Anti-TNF and Beyond

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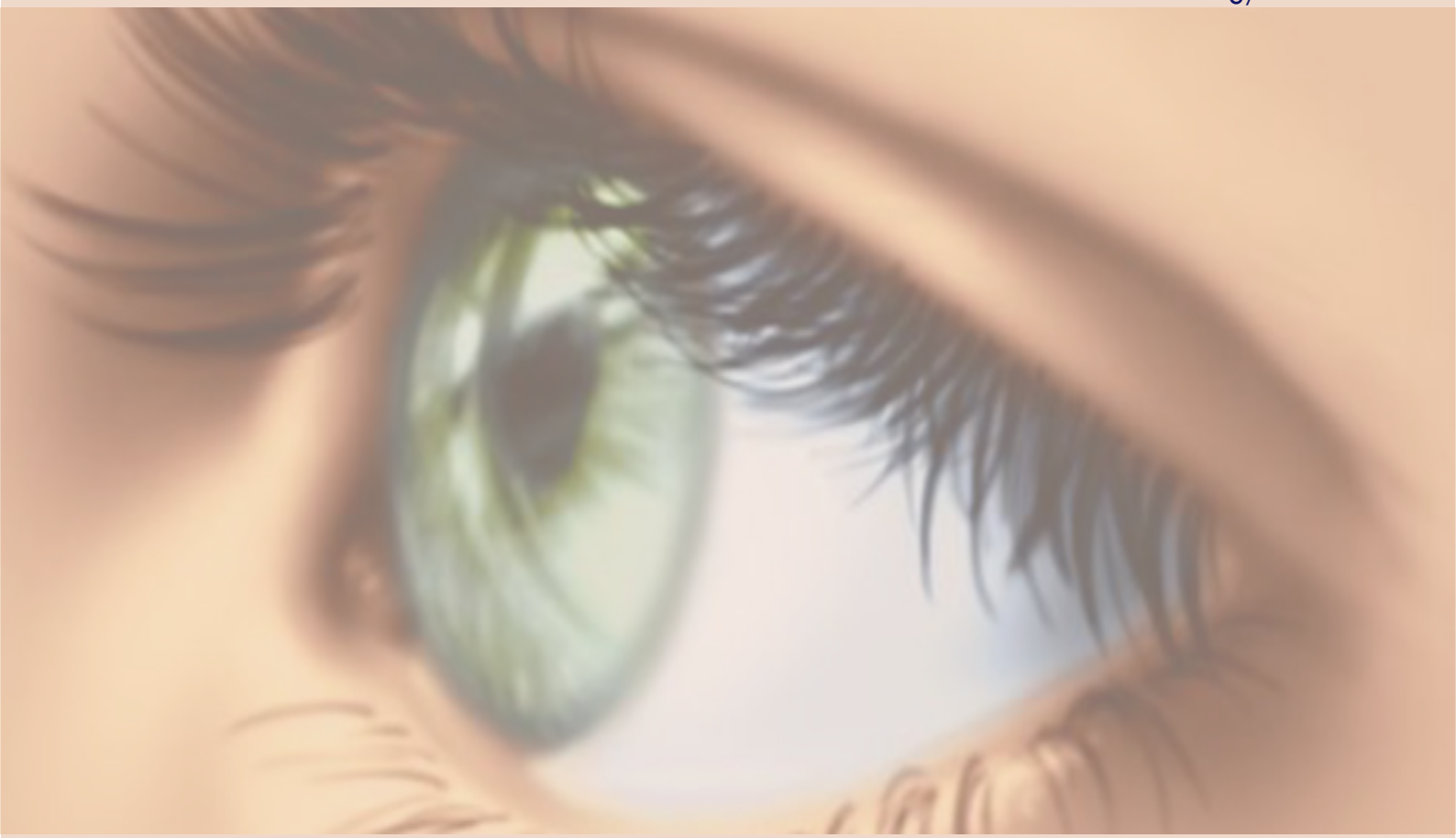

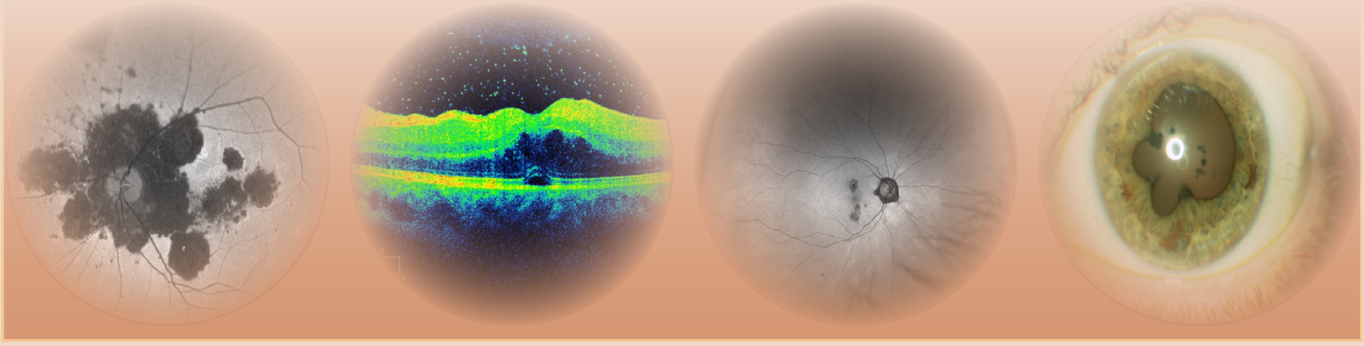

Edited by
Marina Mesquida

Advances in the Treatment of Noninfectious Uveitis with Biologics: Anti-TNF and Beyond

Chapter: Immunopathology of Non-Infectious Uveitis: General Concepts of Immunity and Autoinflammatory Response

Edited by: Dr. Marina Mesquida

Published by **OMICS Group eBooks**

731 Gull Ave, Foster City. CA 94404, USA

Cover OMICS Group Design team

First published June, 2014

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Immunopathology of Non-Infectious Uveitis: General Concepts of Immunity and Autoinflammatory Response

Blanca Molins [1]*, Núria Mendieta[2] and Marina Mesquida[3]

[1]Chief of Laboratory of Ocular Immunology and Inflammation, IDIBAPS, Hospital Clinic of Barcelona, Barcelona, Spain

[2]Ophthalmology Department, Hospital de Burgos, Burgos, Spain

[3]Clinical Institute of Ophthalmology, Hospital Clinic of Barcelona, Barcelona, Spain

***Corresponding author:** Blanca Molins, Chief of Laboratory of Ocular Immunology and Inflammation, IDIBAPS, Hospital Clinic of Barcelona, Barcelona, Spain, Tel: 932275667; E-mail: bmolins@clinic.ub.es

List of Abbreviations

α-MSH: α-melanocyte-stimulating hormone
BAB: blood-aqueous barrier
BRB: blood-retinal barrier
CGRP: calcitonin gene-related peptide
DAF: decay-acceleration factor
DCs: dendritic cells
DCIR: dentritic cell immunoreceptors
HLA: human leucocyte antigen
IFNγ: interferon gamma
IRBP: interphotoreceptor retinoid–binding protein
MHC: major histocompatibility complex
MIF: macrophage migration inhibitory factor
NO: nitric oxide
PDL-1: programmed death-ligand 1
PGE2: prostaglandin E 2
RA retinoid acid
RPE: retinal pigment epithelium
TCR: T cell receptor
TGFβ: transforming growth factor beta
Tregs: T regulatory cells
S-Ag: soluble antigen
VIP: vasoactive intestinal peptide
VKH: Vogt-Koyanagi-Harada syndrome

Summary

Non-infectious uveitis comprehends a heterogeneous group of intraocular inflammatory diseases that arise without a known infectious trigger. This complex group of disorders is often associated with immunological responses to retinal proteins, as experimental models of autoimmune uveoretinitis have shown. Herein we are going to discuss the biology of ocular immune privilege and the immunologic mechanisms that sustain non-infectious uveitis pathophysiology.

Introduction

The eye is a highly organized and complex organ with immunological properties that make it unique. The anatomy of the eye is structured in an outer layer, composed by cornea and sclera, a middle layer, predominantly vascular, called uvea (comprising iris, ciliary body, and choroid), and an inner layer called retina. From another point of view, the eye is separated in several compartments: the anterior chamber (localised between the iris and the cornea), the posterior chamber (between the lens and the iris), and the vitreous cavity, which contains the vitreous gel (a type II/XI collagenous avascular extracellular matrix). These ocular internal compartments ensure a sterile environment separated from the immune system by the blood-ocular barriers, which prevent free trafficking of cells and large molecules into and from the eye. Moreover, the eye has the ability to actively regulate immune responses through several mechanisms that conform what is known as ocular immune privilege [1]. The concept of ocular immune privilege is based on the presence of blood-ocular barriers, intraocular immune modulators, induction of T Regulatory Cells (Tregs), and lack of lymphatics [2]. Herein we are going to discuss the biology of ocular immune privilege and the immunologic mechanisms that hold non-infectious uveitis pathophysiology.

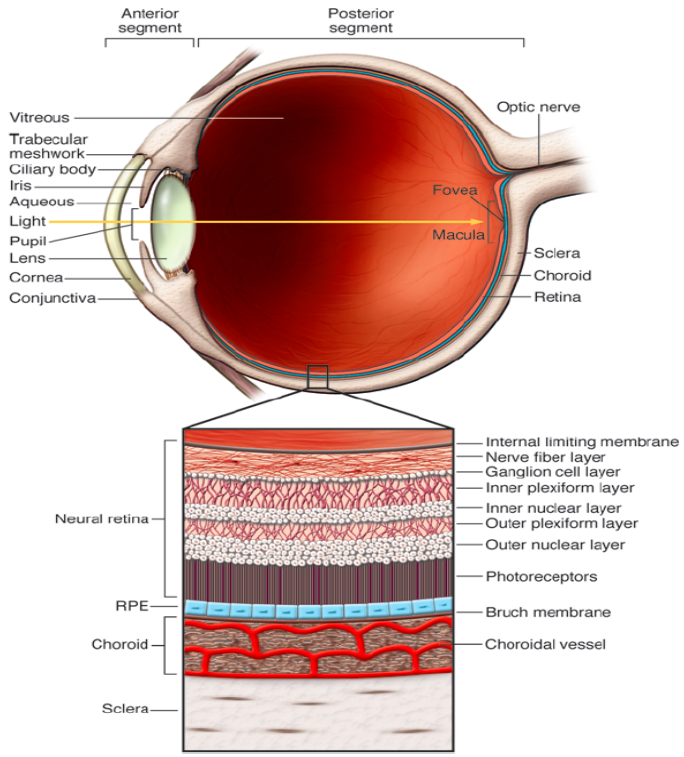

Figure 1: Anatomy of the eye.

Adapted from Caspi RR (2010) A look at autoimmunity and inflammation in the eye. J Clin Invest 120: 3073-3083.

Immunological Properties of the Eye

Resident immune cells

The uvea (comprising the iris, ciliary body, and choroid), the cornea, the conjunctiva, and the periocular fascia contain rich networks of innate immune cells such as bone-marrow derived resident macrophages and Dendritic Cells (DCs), which secrete a wide range of mediators that underpin ocular immune privilege. In addition, the retina contains specialized myeloid cells (microglia) and a small population of Dentritic Cell Immunoreceptors (DCIR) + Major Histocompatibility Complex (MHC) Class ^{II}hi DCs, which are located in the central retina around the optic nerve as well as in the pars plana [3]. The cornea contains a population of passenger leukocytes mostly in its peripheral rim. DCIR+MHC Class ^{II}hi DCs can also be found in the corneal periphery together with epithelial Langerhans cells and stromal Langerin cells [4]. Peripheral cornea has as well some lymphatics connecting with lymphatics in the conjunctiva. In contrast, the central cornea is avascular and has few DCs but contains MHC Class II^{+} macrophages [5]. These resident innate immune cells can also be found in the choroid, where they maintain homeostasis of the outer retina, alongside with fibroblasts and melanocytes [6]. Lymphocytes (whether B or T) are lacking in the non-inflamed eye outside the vascular structures.

Macrophages are essential cells of the innate immune system that play an important role in tissue repair, scavenging breakdown products. When a dysregulation of this process occurs, an inappropriate activation of the complement system takes place and “healing” macrophages may polarize to two pathogenic phenotypes: type 1 (inflammatory) or type 2 (neovascularisation promoting) [7,8]. Innate immune cells, in response to determinate stimuli, are largely responsible for establishing the milieu that instructs adaptive immunity, resulting in protective or pathogenic self-reactivity in the eye [8].

Blood-ocular barriers

The intraocular compartments are separated from the blood and lymphatic circulations by the Blood-Aqueous Barrier (BAB) and the Blood-Retinal Barrier (BRB). The BAB has two components: the endothelial cells of the ciliary body blood vessels and the non-pigmented epithelial cells of the ciliary body and posterior iridial epithelium [9]. These layers have tight junctions of the "leaky" type. Aqueous humour is secreted into the posterior chamber by the ciliary epithelium and flows through the pupil into the anterior

chamber, exiting the eye through the trabecular meshwork into the Schlemm's canal and finally it is collected by espiscleral veins and the subconjuntival lymphatics through the interstitial fluid flow [10]. The central cornea and the sclera are completely avascular.

The BRB is composed by two main structures: the inner barrier, formed by tight junctions between endothelial cells of the retinal vessels, and the outer barrier, which is supported by tight junctions between Retinal Pigment Epithelium (RPE) cells that separate the choroidal fluid from the retinal layers [11]. The RPE filters blood from the fenestrated, leaky choroidal vessels and closely interacts with photoreceptors providing nutrients from the choroidal bloodstream. It also removes waste products in the opposite direction. Breakdown of the BRB can thus occur either at the level of retinal vessels or at the RPE layer [12].

Ocular connections to secondary lymphoid tissues

The intraocular compartment of the eye lacks traditional lymphatic vessels. Instead, they can only be found in periocular tissues such as conjunctiva and episclera [12]. As noted above, aqueous humour from the anterior chamber drains via episcleral blood vessels (aqueous veins), and then through the venous circulation to the thymus, liver, and spleen. There is also a site-specific eye-draining lymph node that receives soluble and cell-associated antigenic material from the eye [13,14]. Fluid also tracks by transscleral flow from the vitreous cavity across the retina driven by a RPE Na^+K^+ ATPase pump which, when damaged, causes subretinal fluid accumulation [15].

Circulation of immune cells to and from the eye

Myeloid cells (macrophages and DCs) travel through the bloodstream from the bone marrow to populate certain ocular tissues, mostly the uvea (iris, ciliary body and choroid). Only few innate immune cells populate the retina and the peripheral cornea [16]. When ocular tissues are injured, bone marrow-derived myeloid cells, carrying antigen from the eye, travel to the eye-draining lymph node [16]. Experimentally, when cell-associated and/or soluble antigen are injected into the eye or applied to the abraded cornea, they can be detected in the spleen after several hours [17]. Resting T and B cells circulate normally through the uveal blood vessels but are unable to cross the blood-ocular barriers. It has been hypothesised that these T and B cells interact with eye-derived antigen presenting cells in the secondary lymphoid tissues such as spleen and lymph node, and respond appropriately to promote tolerance or an active immune response [18,19].

Ocular immune privilege

Immune privilege refers to a concept formulated in 1961 by the Nobel Prize in Immunology P.B. Medawar to define a property of certain organs (particularly those highly specialized, with limited capacity for renewal such as the eye and the brain) in which foreign antigens placed in those tissues failed to evoke a conventional immune response [20]. Such tissues apparently afforded a remarkable level of protection from immunological damage – termed immune privilege. Thenceforth the concept of immune privilege has been extended and is currently viewed as a property of several tissues (not only the eye or the brain) functioning as an immunoregulatory, tolerance-inducing mechanism in which immune responses to foreign antigens, particularly alloantigens, are suppressed, preserving normal tissue homeostasis [21]. In other words, immune privilege indicates that certain tissues or cells have an advantage over others, allowing them to modulate immune responses to foreign antigens or to be regarded themselves as non-immunogenic when transplanted (e.g., stem cells) [22]. At its core, immune privilege is a form of tolerance expressed through tissue-specific properties, is shown to be inducible toward foreign and alloantigens, and is assumed to be responsible for tolerance to ocular self-antigens.

Ocular immune privilege is believed to serve the purpose of limiting the extent to which innate and adaptive immune responses lead to intraocular inflammation [21]. By limiting intraocular inflammation, immune privilege preserves the integrity of the visual axis and thereby prevents blindness. Importantly, ocular immune privilege may develop *de novo* in accepted vascularized grafts [23,24] and constitutes part of the immune response to tumours [25]. As noted above, ocular immune privilege has been proved to be inducible and transferable through adoptive transfer of $CD8^+$ Tregs [26]. However, it is relatively easily bypassed when facing a sufficiently strong immunological response and the privileged tissues may be at greater risk of collateral damage because its natural defences are more easily breached than in a fully immunocompetent tissue, which rapidly rejects foreign antigens and restores immune integrity [27]. Indeed, immune privilege may be seen as a double-edged sword because the blood-ocular-barrier limits access of the immune system to the healthy eye, thereby impeding the establishment of peripheral tolerance to tissue-specific antigens localized within the eye, and also permits foreign antigens/organisms to "hide" in the immune-privileged sites [28]. This results in the persistence of non-tolerant T cells that can respond to ocular antigens. A microbial (through molecular mimicry) or endogenous stimulus may activate these auto-reactive T cells and lead to an autoimmune attack on the eye [29].

Biologic mechanisms of ocular immune privilege

In order to explain the concept of ocular immune privilege several mechanisms have been proposed, including lack of lymphatics, absence of MHC Class II+ professional antigen presenting cells (negates CD4 T cells) [27,30] lack of expression of MHC Class I on tissue cells (negates CD8 T cells), expression of Qa-1 and human leukocyte antigen (HLA)-G/E (negates Natural Killer cells), presence of immune modulators such as TGFβ, CD200, CD55, and CD46, Decay-acceleration Factor (DAF; modifies antigen presenting cells), sequestration of antigen from the developing immune system behind blood-ocular barriers (immunological ignorance), and lack of thymic expression of tissue antigens (no autoreactive T cells to escape to the periphery) [16,27,31]. Another important element contributing to ocular immune privilege is the capacity of the eye parenchymal cells to exert T cell suppressive activity [32,33] as well as generate Tregs [34,35]. In addition, expression of molecules such as FasL, PDL1 (Programmed cell Death 1 Ligand 1), CTLA4 (Cytotoxic T-Lymphocyte Antigen 4) and CTLA2 by ocular cells of the iris, ciliary body and RPE generate an immunosuppressive microenvironment [36,37]. The PD-1 pathway appears to have the capacity to promote T effector cell death similar to the Fas/FasL pathway [38], but also has the potential to promote Tregs. Recently retinoids (particularly retinoid acid, RA) have been implicated in the induction of Tregs by the RPE *in vitro* [39,40]. RA produced by lamina propria DCs has been identified as a major inducer of intestinal Tregs, and this property of DCs has been extended to non-intestinal DCs [41]. In these conditions, the Treg-inducing effects of RA required the presence of TGF-β [39]. Zhou and coworkers showed that vitamin A-deficient mice were incapable to convert naïve T cells to Tregs in the uninflamed eye *in vivo*, which was hypothesised as being due to an absence of locally produced RA, presumably by intraocular DCs [42]. They also showed that in active Experimental Autoimmune Uveoretinitis (EAU), committed T effector cells could not be converted to Tregs suggesting that this component of immune privilege was lost during inflammation [42]. The source of retinoids for Treg induction may be the population of ocular tissue-resident DC. [43]. Multiple potential routes for induction of Tregs have been proposed, highlighting the link between immune privilege and Treg induction [44]. However, how Tregs might mediate privilege is still unclear. It has been proved that

mice with defects in central tolerance such as those deficient in the autoimmune regulator gene *Aire*, required for negative selection of certain tissue-specific antigens, develop ocular inflammation as part of a multiple autoimmune diathesis [45,46]. *Aire* gene has also been implicated in induction of natural Tregs in the thymus [47]. Several studies have shown that patients with uveitis have decreased levels of circulating Tregs, which suggests that peripheral tolerance is necessary to maintain immunological homeostasis [48,49]. Tregs are important for peripheral tolerance, modulating activation of lymphocytes and thus controlling inflammation. Their suppressive activity is mediated by their production of antiinflammatory cytokines like IL-10 and TGF-β and by cell-contact inhibition of proliferation. In Behcet's disease Tregs levels seem to correlate with clinical remission [48,49]. In addition, Tregs occur as part of the infiltrating inflammatory cell population in the retina in EAU, indicating that they certainly play a role [50].

Another important aspect of immune privilege is the immunomodulatory nature of the intraocular microenvironment. Cells of the iris, ciliary body and RPE are able to produce mediators such as Nitric Oxide (NO), Prostaglandin E 2 (PGE2), and retinoids [51]. The aqueous humour has the capacity to suppress immune effector responses and inflammation and it is believed to be an important component of the ocular immune privilege. Normal aqueous humour has been shown to inhibit T cell activation, probably because it contains several immunosuppressive and modulatory factors such as α-Melanocyte-Stimulating Hormone (α-MSH), Vasoactive Intestinal Peptide (VIP), Calcitonin Gene-Related Peptide (CGRP), macrophage Migration Inhibitory Factor (MIF), and TGF-β2 [10,12]. Aqueous humour TGF-β2 is produced locally within the eye (iris-ciliary body) and it is thought to be the most important agent responsible for inhibiting T-cell responses *in vitro*.

However, this microenvironment is altered when there is a disruption in the blood-retinal barrier. Cytokines such as IFN-γ (generated systemically during viral infections) can activate RPE cells to up-regulate immunosuppressive activity via Programmed Death-Ligand 1 (PDL-1) [52] or to produce pro-inflammatory chemokines and cytokines locally, as well as induce MHC Class II expression on normally negative RPE [53] and endothelial cells. Secretion of IL-6 by RPE cells in an environment rich in TGF-β may be sufficient to convert CD4 Tregs to Th17 cells and completely alter the immunosuppressive microenvironment to a pro-inflammatory one [54,55]. In summary, the immunosuppressive properties of the eye associated with immune privilege are thought to be shaped by several mechanisms, each of them contributing to the overall ocular immune homeostasis.

The breakdown of immune privilege:

Non-infectious intraocular inflammation: Uveitis, or the inflammation of the uvea, is categorized on an anatomical basis as anterior, intermediate, or posterior, or as panuveitis if it involves both the anterior and posterior parts of the eye. Non-infectious uveitis comprehends a heterogeneous group of intraocular inflammatory diseases that are produced without a known infectious trigger [56]. This complex group of disorders is often associated with immunological responses to retinal proteins, as experimental models of autoimmune uveoretinitis have shown. Non-infectious uveitis is one of the leading causes of blindness in the developed world and is believed to be either autoimmune (driven by aberrant immune recognition of self) or immune-mediated (primarily an innate inflammatory reaction triggered by environmental/microbial or autologous/tissue damage "danger" signals) [57].

Non-infectious uveitis may be a manifestation of a systemic autoimmune syndrome such as Behçet's disease, sarcoidosis or Vogt-Koyanagi-Harada (VKH) disease. However, non-infectious uveitis may also be an eye-isolated disease, as it happens in Birdshot chorioretinopathy and sympathetic ophthalmia. Despite this categorization, many cases of non-infectious uveitis do not fulfil a defined classification and are referred to as "idiopathic."

With regards to pathophysiology, non-infectious uveitis are believed to have an autoimmune aetiology suggested by the lack of a known infectious trigger and by the frequent presence of immunological responses to retinal proteins such as uveal melanin (and related proteins involved in its metabolism), retinal arrestin (formerly known as retinal Soluble Antigen [S-Ag]), Interphotoreceptor Retinoid-Binding Protein (IRBP), and recoverin [57-59]. In addition, several uveitic conditions exhibit strong associations with particular HLA haplotypes [59] further supporting autoimmunity as cause of the disease. Indeed, despite their low expression on ocular cells, certain forms of uveitis have strong links with MHC Class I antigens (HLA B27: acute anterior uveitis; HLA B51: Behçet's disease; HLA A 29: Birdshot retinochoroiditis) [60-62]. Particularly striking are the associations of sympathetic ophthalmia and VKH disease with HLA DR4 (although VKH is also strongly associated with HLA DQ4) and of Birdshot chorioretinopathy with HLA A29 (relative risk of 49-224, depending on the study) [61,63-65]. Because HLA molecules are involved in antigen presentation, HLA associations are thought to reflect recognition of particular antigens and epitopes.

Ocular tissues contain many potential autoantigenic targets -especially the retina- apparently sequestered from the immune system [66]. It has been demonstrated that elimination in the thymus of self-reactive T cells (central tolerance) applies to retinal antigens [67]. The mechanisms underlying central tolerance rely on an immature T cell interacting with its cognate tissue antigen through its specific T Cell Receptor (TCR). Normal thymic expression of IRBP in mice detectably eliminates many T cells expressing TCRs that recognise IRBP, thereby reducing the autoreactive uveitogenic T cell repertoire [67]. Nevertheless, thymic expression of retinal antigens among individuals is variable, and levels of expression insufficiently high to induce the elimination of T cells bearing cognate TCRs may permit the escape of retinal antigen-specific T cells into the periphery [67]. In normal conditions, T cells reactive to tissue antigens that escape control in the thymus are subject to regulation by peripheral tolerance mechanisms, which induce T cells to become nonresponsive (tolerant) to their specific antigen when they encounter that antigen in healthy tissues. However, retinal antigens residing in the eye are relatively inaccessible. Therefore, circulating retinal antigen-specific T cells are likely to be "ignorant" of their cognate antigen rather than tolerant, and can be activated by a chance encounter with antigen (during tissue injury such as trauma or infection), possibly in the form of a microbial component that structurally mimics their cognate tissue antigen [31], therefore activating rare autoreactive T cells in the periphery. A good example would be sympathetic ophthalmia or "Horror autotoxicus" described by Mackenzie in 1830, referring to an intraocular inflammatory disease that develops in the fellow eye months or years after penetrating trauma to the first eye [68,69]. During ocular injury the damaged tissue exposes retinal autoantigens (in this case melanin-related antigens) that trigger an autoreactive inflammatory response in the fellow eye (Table 1).

In conclusion, immune privilege is one of the most important components of the eye for tissue homeostasis, keeping healthy tissues free of random migrants that may provoke inflammation. However, when faced with a serious challenge, immune privilege may fail to prevent severe destruction. As we have seen in this chapter, the process of immune privilege is not failsafe and when it fails, it fails gloriously, with irreparable damage to ocular structures and loss of sight.

Type of uveitis (race)	HLA genes
Birdshot chorioretinopathy (European descendent, Nordics)	A29
Behçet's disease (Asian, Mediterranean, European descendent)	B51
Ankilosing spondylitis-associated uveitis (European descendent)	B27 DR8
VKH (Asians, Latin Americans)	DR4 DRB1*0405
Sympathethic ophthalmia (various)	DR4 DRB1*0404 DRB1*0405 DQA1*03
Juvenile idiopathic arthritis (European descendent)	DR4, Dw2
Uveitis associated to multiple sclerosis (European descendent)	B7, DR2
Sarcoidosis (various)	B8, B13
Retinal vasculitis (various)	B44

Table 1: HLA alleles associated to non-infectious uveitis.

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Treatment Strategies in Non-Infectious Uveitis: General Concepts

David Díaz-Valle[1]* and Rosalía Méndez-Fernández[2]

[1]Head of Ocular Inflammation Unit, Hospital Clinico San Carlos, Madrid, Spain

[2]Ophthalmologist, Ocular Inflammation Unit Hospital Clinico San Carlos, Madrid, Spain

***Corresponding author:** David Díaz-Valle, Head of Ocular Inflammation Unit, Hospital Clinico San Carlos, Madrid, Spain, Tel: +34 646855547; E-mail:diazvalle@gmail.com

Abstract

The term uveitis refers to a group of inflammatory disorders affecting the uvea, the middle layer of the eye. Endogenous or associated with a systemic disease, noninfectious uveitis accounts for approximately 75% of total cases comprising of a heterogeneous group of inflammatory conditions. There is a wide spectrum of clinical forms of uveitis that are mainly classified according to criteria of anatomical location (anterior, intermediate, posterior orpanuveítis), laterality and clinical course (acute, recurrent or chronic). Chronic uveitis is associated with a greater degree of structural damage and is responsible for a greater percentage of visual loss than acute forms. Acute Anterior Uveitis (AAU) is the most prevalent form and usually requires only topical treatment with steroids and mydriatics. However, it is a cause of disability when flares are frequent or when tends to chronicity. Sulphasalazine and methotrexate have demonstrated a reduction in the number of flares and better control of inflammatory activity in cases of chronicity. Other patterns of uveitis with involvement of intermediate and posterior segments have a worse prognosis. Locally injected or systemic corticosteroids and/or immunosuppressive drugs are usually required in sight-threatening immune-mediated uveitis with involvement of posterior segment to halt the course of the disease. Treatment consists in a phase of induction of remission using high-dose of systemic corticosteroids administered orally or by means of intravenous infusion. The second phase is the maintenance of the long-term control of inflammatory activity. At this stage, the dose of corticosteroids is gradually reduced until withdrawal, and if necessary immunosuppressant's are added. Biological therapies, that are widely described in this book, are promising therapeutic options in refractory patients as a rescue therapy. However, there is clinical evidence of the use of these powerful drugs as first line therapy in selected cases (top-down approach).

Introduction

The incidence of uveitis in the general population is between 17 and 52 cases per 100,000 habitants per year with a prevalence of 0.1% [1]. People aged 20-50 years are most commonly affected. Uveitis are responsiblefor about 10% of legal blindness in developed nations and more than 35% of patients with uveitis present significant visual loss in at least one eye [2-4]. These data reveal the magnitude of the epidemiologic, diagnostic, and therapeutic problem posed - by the uveitis, as well as healthcare costs generated. So, both for diagnosis and, especially, for the proper treatment, close cooperation between ophthalmologists, rheumatologists and general practitioners are required in order to correctly classify the pattern of uveitis and associated comorbidities to establish the most appropriate therapeutic scheme.

General Principles and Treatment Strategies

Before starting the treatment, a number of considerations should be taken into account (Table 1).

General aspects related to uveitis treatment
■ The majority of patients with uveitis can modify significantly the course of their illness if they receive proper early treatment [10].
■ It is recommended to work in Multi-disciplinary Units to facilitate handling of the drugs used and early detection of side effects.
■ Infectious causes and masquerade syndromes should always be excluded before considering an immune-mediated mechanism.
■ Macular edema is the main cause of vision loss in uveitis patients.
■ Always analyze what is the cause of poor vision in a specific case. Is it reversible? Are there other causes of poor vision, such as cataract, glaucoma or macular edema that could require specific treatment?
■ Zero tolerance to inflammation
■ Limited tolerance to the use of corticosteroids.

Table 1: General aspects related to uveitis treatment.

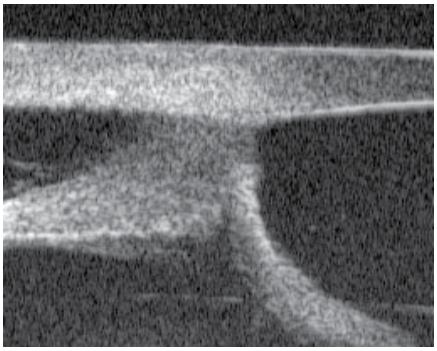
Infectious causes and masquerade syndromes should always be excluded before considering an immune-mediated mechanism, since therapeutic scheme is completely different. Some infectious causes, such as toxoplasmosis, herpes, syphilis and tuberculosis could produce uveitis and, frequently, clinical signs are indistinguishable from those produced by the immune-mediated uveitis. Some malignancies, especially CNS lymphoma, can also simulate a uveitis. Also traumatic, postoperative and drug-induced uveitis must be discarded [5-7].

Find out what factors, as well as inflammation, may be influencing the visual loss of the patient and their reversibility. There can be comorbidities such as glaucoma, cataract, persistent vitreous opacities or macular ischemia that have their particular management. It also

kept in mind that some lesions are irreversible (macular or optic atrophy, advanced glaucoma …) before starting an immunosuppressive treatment with iatrogenic potential risks in eyes without the possibility of visual recovery.

The most frequent cause of loss of visual acuity in patients with uveitis is macular edema (ME). When ME is chronic produces lesions in the retinal photoreceptors, which can potentially be irreversible [8,9]. For this reason, early and appropriate treatment is essential.

A fourth point that we must always consider is a general attitude of zero tolerance to inflammation. Sustained inflammation, even in low grade, can cause severe structural damage (Figure 1 A-D).



(A) Ultrasound biomicroscopy (UBM) in a patient with juvenile chronic arthritis (JIA) and chronic anterior uveitis. UBM shows a cyclitic membrane that causes a detachment of ciliary body and chronic hypotony.

Figure 1: A-D.Structural damage in patients with chronic long–standing uveitis.

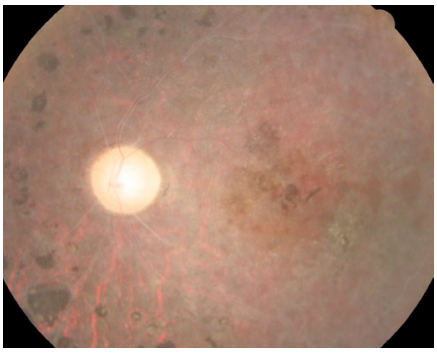


Figure 1: (B) Posterior pole of a patient with long-standing Behçet disease. There is optic atrophy with macular ischemia and diffuse occlusive vasculopathy.

Treatment is usually performed in two phases: induction of remission and maintenance. Due to its high and immediate efficacy, corticosteroids administered by different routes, are the drugs of choice in the induction of remission. However, in many cases, corticosteroids are not enough to sustained control of the inflammation in the long term. In other situations, the control of the inflammatory activity is not maintained when trying to reduce the dose of corticosteroids, or side effects of the treatment are not tolerable. In these cases, an immunosuppressive treatment for the maintenance of remission is necessary (Table 2). It is necessary to maintain immunosuppressant's for long time, in order to achieve a stabilization of inflammatory parameters and avoid relapses and new flares. Multidisciplinary units (ophthalmologists with internists or rheumatologists) have been developed to achieve a close follow-up both at the level of efficacy and for early detection of side effects, allowing a better management and control of these therapies.

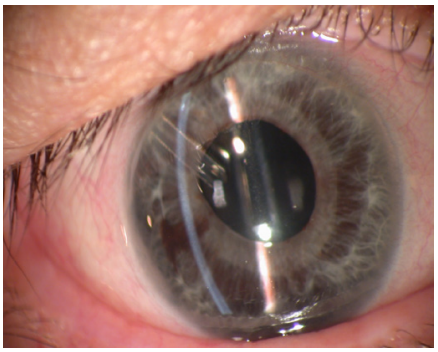


Figure 1: (C) Chronic refractory inflammatory glaucoma associated with uveitis. A tube shunt was required to control the intraocular pressure.

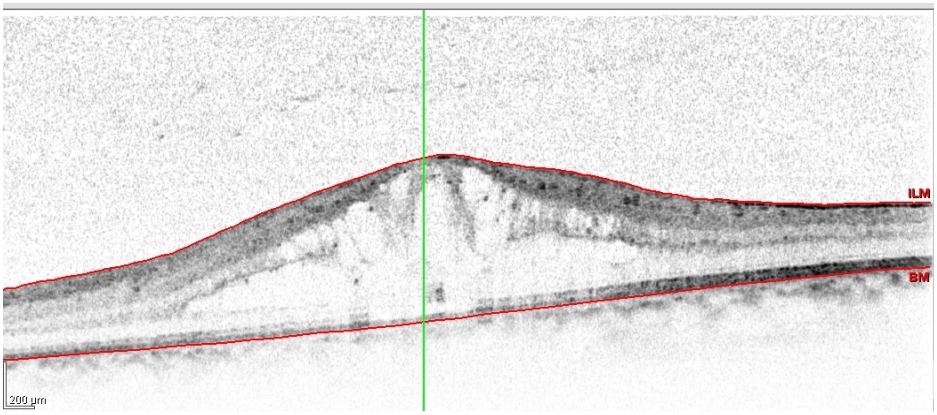


Figure 1: (D)Chronic uveitic macular edema with severe disruption of photoreceptor layer and coalescence of large cystic spaces.

General recommendations of steroid-sparing immunosuppressant's in uveitis
Sight-threatening immune-mediated intraocular inflammation and
■ Inflammation is not controlled with corticosteroids used in an appropriate schedule.
■ Unacceptable adverse effects or contraindications of corticosteroids
■ Chronic treatment with corticosteroids for more than 3 months in doses higher than 5 - 10 mg/day.
■ Specific entities with poor response to steroid immunotherapy (Behçet disease, Birdshot chorioretinopathy, serpiginouschoroidopathy…).

Table 2: General recommendations of immunosuppressant's in uveitis.

A different therapeutic algorithm should be used depending on the type of uveitis and anatomical location.

Therapeutic Algorithm for Anterior Uveitis (AU)

The AU is the most frequent form of uveitis, accounting for approximately 90% of uveitis in primary care and 50-60% in referral centers [11-13]. The most common form is AAU HLA B27+, associated or not with seronegative arthropathy: Ankylosing Spondylitis (AS), reactive arthritis, psoriatic arthritis and arthritis associated with Inflammatory Bowel Disease (IBD) [14]. Other etiologies associated are Fuchs disease, Juvenile Idiopathic Arthritis (JIA), sarcoidosis, Behçet's disease and Multiple Sclerosis (MS) or TINU syndrome.

Most cases respond well to topical treatment and have an excellent prognosis if treatment is early and adequate. Exceptions to this rule are chronic AU associated with JIA or Behçet's disease, which often requires systemic immunosuppressant associated with topical treatment [15].

Treatment of AU is a medical emergency because delayed treatment may result in complications, sometimes irreversible, including anterior and posterior synechiae, secondary glaucoma, cataract orCME, that make the disease difficult to treat, and sometimes, with a very poor final visual function.

Control of Inflammation

Treatment always starts with topical corticosteroids, usually eye drops during the daytime and ointment at bedtime.The steroid must have high anti-inflammatory activityand easy intraocular penetration. The most widely used topical steroids are dexamethasone, betamethasone and prednisolone.The frequency of instillation varies with the intensity of the inflammatory reaction, but in general, the initial treatment should be aggressive for controlling the process as soon as possible. The initial dose may be a drop every 1-3 hours, but there are cases where the inflammation is so severe that requires more frequent instillation (one drop every 15 to 30 minutes) or so slight that it can be controlled with more spaced doses. It is very important to use the right dose, since the use of a less aggressive regimen may lead to the erroneous conclusion that is a refractory uveitis [15].

When the inflammatory process begins to subside, the dosage must be gradually lowered. Steroid withdrawal should not be very fast (not less than 4-6 weeks of treatment) that may predispose a rebound of inflammation [16]. The most recurrent cases need a slower decrease in dose. Some patients require a minimum dose of topical corticosteroids for a long time to keep the eye without inflammation. During the active phase, the patient should be reviewed weekly or biweekly [15] to monitor changes of inflammation and possible side effects of treatment (ocular hypertension, cataract, increased susceptibility to infections...).

Sometimes is necessary the use of periocular corticosteroid infiltration. The most common situation is CME associated with AU, but also in cases of therapeutic noncompliance or very severe flares with slow response to intensive topical treatment.

Exceptionally, systemic corticosteroids may be indicated to control inflammation. We have already mentioned that AU associated with JIA or Behçet's disease often requires systemic immunosuppression associated with topical treatment [15].

Treatment of AU also requires cycloplegic-mydriaticeye drops for control of pain caused by the ciliary muscle spasm and to prevent synechiae or break already present [16,17]. The most widely used cycloplegic-mydriatic drops, from highest to lowest potency and duration of action, are atropine, homatropine, cyclopentolate and tropicamide. Atropine is used in severe inflammation, with intense pain, because it is the one that best controls the pain. Tropicamide, however, is used in milder uveitis or when inflammation has decreased to not interfere daytime vision. The dose should be adjusted to the severity of inflammation and withdrawing completely by the end of steroid treatment. To break synechiae already present, we can associate phenylephrine eye drops in the office, but not as an outpatient basis due to the risks related to its use.

Although AU has usually good prognosis, there are cases with multiple flares annually, with great impact in quality of live due to pain,

decreased vision and discomfort associated with pharmacological mydriasis. Furthermore, recurrent inflammation and treatment with topical steroids can produce structural damage to the eye such as cataract, synechiae or glaucoma. For these reasons, a treatment to reduce relapses should be very useful in this clinical setting [16,17].

• In AU B27-related, there is evidence that chronic administration of Sulfasalazine (SSZ) reduces the frequency and severity of recurrent episodes of uveitis [18-22]. Although medication is generally well tolerated, it is necessary to take into account the risk of adverse events like skin reactions, blood dyscrasias or Stevens-Johnson syndrome. Isolated episodes of uveitis not justify its use, it may be reasonable when there are three or more flares of AAU in the last year. The dose of SSZ is between 1.5 and 3 g/day divided into three doses.

• The incidence of AU in patients with AS treated with anti-TNF agents is less than in untreated patients, being lower in the group receiving infliximab or adalimumab than in the etanercept-treated group [23,24].

• Methotrexate may also prevent recurrences of AAU in cases with a high number of relapses [25].

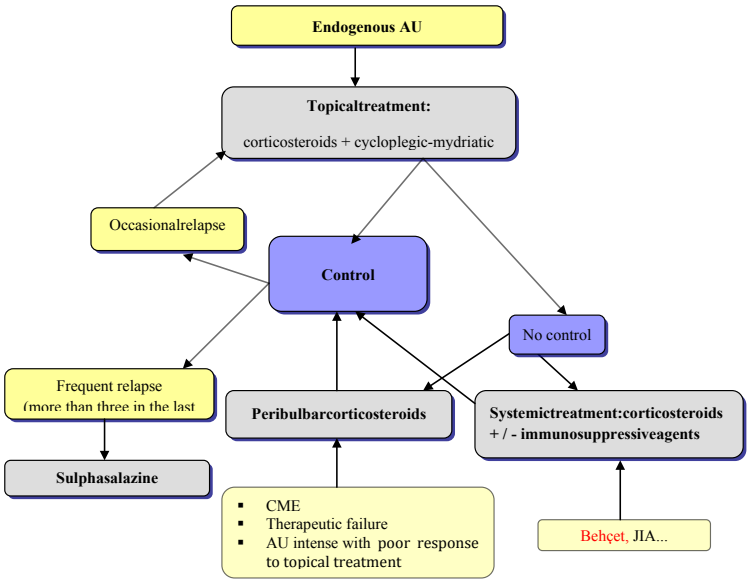


Figure 2: Therapeutic algorithm in endogenous Anterior Uveitis (AU).

Therapeutic Algorithm in Endogenous Intermediate Uveitis (IU)

When inflammation affects the intermediate or posterior uvea, topical corticosteroids are not going to significantly change the course of the disease, so it will be necessary other forms of treatment to control uveitis.

The classic treatment of IU is based on the four-step algorithm proposed by Kaplan [26], in which visual acuity is fundamental when starting treatment. Currently, many authors prefer early and aggressive treatment to preserve better visual acuity [27].

Periocular injection of corticosteroids is the first-line of treatment in most patients with IU; especially in unilateral or very asymmetric cases.We used different techniques for periocular administration, including subtenon, orbital floor or retrobulbarinjections [28]. A small amount (1ml) of a depot preparation of a corticosteroid is placed in the orbit, usually through the eyelid skin, either upper or lower or through the conjunctiva. The most popular choice is triamcinolone acetonide, but it is possible to use other corticosteroids such as betamethasone acetate and betamethasone sodium phosphate solution.Thus, using a fast-actingcombined with a depot formulation, it is assumed that the onset of effect is earlier than with triamcinolone.The injections can be repeated every 4-6 weeks according to clinical response.After 3 injections without clinical response, it is considered that this treatment is not effective and must be changed to another form of treatment.

Periocular injections are generally well tolerated and have few adverse effects, but there may be potential complications of injections (ocular perforation, hemorrhage, fat herniation, ptosis or orbital fat atrophy), and especially intraocular hypertension and cataract. Steroid-induced ocular hypertension occurs in up to 27% of patients treated.Uveitis patients have more risk than those treated by other causes. The risk is greater in patients with a history of hypertensive response to topical corticosteroids. Another side effect is cataract progression in up to 31% of patients [29,30].

Periocular treatment with corticosteroids is also used in other forms of uveitis, especially if there is associated CME.In certain forms of posterior uveitis or panuveitis with unilateral or highly asymmetric relapses, it is possible to use periocular corticosteroids, usually associated with systemic treatment.Clinical response to treatment depends on the inflammatory phenomena. Positive responses have been published in 96% of treated vitritis, 82% of the CME and only 33% in the case ofvasculitis [30].

If periocular administration is ineffective or insufficient, other forms of administration should be considered, such as intraocular or systemic treatment. The intravitreal route is a very attractive form of administration because it provides a maximum concentration of corticosteroid at the posterior segment with minimal systemic absorption. Treatment of uveitis and/or uveitic CME may be performed with intravitreal triamcinolone acetonide [31,32]. The effectiveness of treatment is rapid but is limited in time, so it is necessary to repeat injections. In order to avoid this inconvenience, it has been developed slow-release devices that maintain effective levels of intravitreal steroids for extended periods of time, reducing the complications of multiple injections. Fluocinoloneacetonide [33,34] has been used in the past, but currently the most widely used implant in clinical practice is the dexamethasone implant (Ozurdex®), with a better benefit/risk profile [35-37]. So, intravitreal administration of steroids is a very effective treatment in managing endogenous uveitis, which allows significant decrease in systemic medication necessary for control of these patients and, therefore, their side effects. We must always

take into account the risks associated with the procedure (endophthalmitis, retinal detachment, hemovitreous, ocular hypertension and cataracts) [38].

Systemic treatment is generally used, as first choice, in most cases of bilateral IU and, as a second option, in IU unresponsive or intolerant to local treatment. Systemic treatment is described in the next section of this chapter in the therapeutic algorithm for posterior uveitis and panuveitis.

Cryotherapy has proved to be an effective treatment for IU. Ablation of the peripheral retina eliminates the source of inflammatory mediators and the stimulus for neovascularization [26,27]. Currently, it tends to be replaced by photocoagulation usually associated with vitrectomy [39]. Vitrectomy acts eliminating the hazy vitreous and, therefore, improves the patient's vision and also reduces the burden of inflammatory mediators in the vitreous [40] improving the control of the inflammatory process and macular edema. Figure 3 shows our therapeutic algorithm for intermediate uveitis.

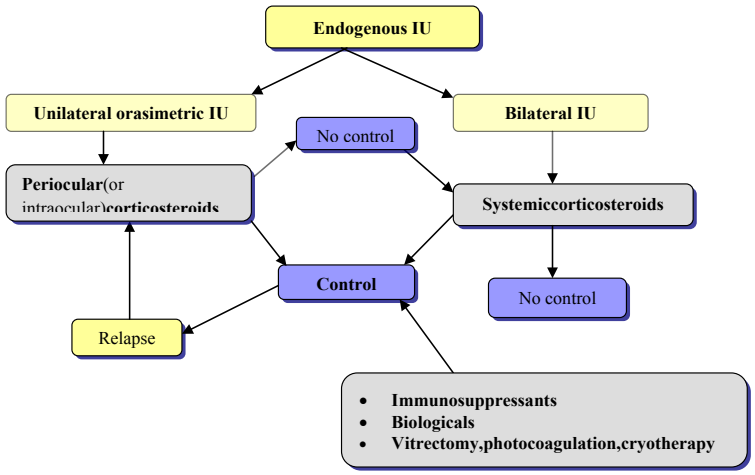


Figure 3: Therapeutic algorithm in endogenous Intermediate Uveitis (IU).

Therapeutic Algorithm in Posterior Uveitis and Panuveitis

In posterior uveitis, retina and/or choroid are the principal site of inflammation, having either multiple spots or single large lesions. In panuveitis or diffuse uveitis, inflammatory cells are spread roughly between the anterior chamber and vitreous cavity, and also there areinflammatory foci at the level of the retina, choroid or inflammation of the central retinal vessels.

Systemic corticosteroid treatment is usually used as first choice in the majority of the posterior uveitis, panuveitis and bilateral intermediate uveitis. Oral prednisone is the most commonly used steroid. The initial dose of oral prednisone is 1 mg/kg/day which is maintained until a satisfactory anti-inflammatory response is achieved, usually in 2-4 weeks. Thereafter, a gradual dose tapering process can begin. It can be performed following the recommendations of an expert panel (Table 3) [41]. Initially this can be quite rapid, but the lower the current dose, the slower the necessary reduction. During the process of dose reduction, the patient should be carefully monitored to ensure that inflammatory parameters are under control and there is a sustained suppression of the inflammation. If there is a relapse during dose reduction, a substantial increase of the dose is required to regain control (at least a doubling of current dose). Then, a gentler taper should be prescribed. A majority of cases of chronic uveitis may be controlled with dosage levels below 10 mg/day, but sometimes, higher doses are required. The maintenance of systemic steroid treatment, even at low dose, are associated with important side-effects, such as dyspepsia, osteoporosis and risk of low-trauma fractures, weight gain, steroid myopathy, avascular bone necrosis, skin changes (acne, subepidermal atrophy, capillary fragility), inter-current infections, growth suppression in children, adrenocortical suppression and ocular side effects (cataract, ocular hypertension) [42]. Due to its multiple adverse effects, the dose of corticosteroids as maintenance therapy in uveitis should be the lowest possible and its withdrawal should always be attempted.

Corticosteroid dosage	Suggested guideline
Initial dose	1 mg/kg/dia
Maintenance dose (adult)	< 10 mg/dia
Tapering Schedule	Over 40 mg/day, decrease by 10 mg/day every 1-2 weeks 40-20 mg/day, decrease by 5 mg/day every 1-2 weeks 20-10 mg/day, decrease by 2.5 mg/day every 1-2 weeks 10-0 mg/day, decrease by 1 to 2.5 mg/day every 1-4 weeks
Monitor	Blood pressure, weight, glucose levels every 3-6 months. Lipids (cholesterol and triglycerides) annually. Bone density within first 3 months and annually thereafter.
Supplemental treatment	Calcium 1500 mg daily and vitamin D 800 IU daily Omeprazol 20 mg/day if dose of prednisone 40 mg/day or more, history of peptic ulceration or also taking NSAID Estrogens and anti resortive agents as needed.

Table 3: It shows the general indications of steroid-sparing immunosuppressants.

Inpatients with particularly severe acute uveitis, for instance, Behçet disease, sympathetic uveitis or severe Vogt-Koyanagi-Harada syndrome, intravenous methylprednisolone should be considered. Methylprednisolone is administered in pulses of three daysby slow intravenous infusion over 1-2 h from 500 to 1000 mg/ day. The effect of this mode of treatment can be very rapid and uveitis usually responds in 48-72 h, then oral steroids with or without immunosuppressant can maintain inflammatory control.

Other route of administration is periocular or especially intravitreal steroid injection. This treatment can be used in patients with unilateral

or asymmetrical macular edemaevenin spite of long-term immunosuppression, unilateral flare-up of inflammation especially in Behçet's disease, repeatedly where immunosuppressant is intolerable and as an adjunct to cataract, glaucoma or vitrectomy surgery in uveitis patients. It is possible to use direct intravitreal injection of triamcinolone acetonide (IVTA) at a dose of 2-4 mg in 0.05-0.1 ml.This treatment is effective enough to permit reduction in steroids or oral immunosuppressant's in about 50% [43]. However, ocular side effects have limited their usage. At present, there are injectable sustained-release dexamethasone implant (Ozurdex®) that can be inserted by the pars plana and have a better benefit-risk profile compared with other implants such as fluocinoloneacetonide (Retisert®) [44].

In patients with severe uveitis in whom the dose of corticosteroids required to control the inflammation leads to unacceptable side effects or any other issues in Table 2, an immunosuppressant agent should be added. The aim is to maintain quiescence at a lower steroid dosage.This combination has been used with success in various forms of uveitis. There are few qualities randomized clinical trials on the topic, and most are retrospective reviews or case series without comparison.Recently, working groups of uveitis of the Spanish society of Rheumatology have carried out a work of evidence-based systematic review of the literature on treatment with immunosuppressant and biological agents in uveitis [45]. In chapter 3, there is a detailed description of the different immunosuppressant that can be used as a second-line therapy in the management of chronic severe uveitis.Regular assessment, usually each 6-8 weeks, of safety parameters is essential when monitoring immunosuppressive treatment.

There is a subgroup of patients with severe sight-threatening uveitis that are refractory or intolerant to conventional immunosuppressive treatments. In these cases, biological agents can be used. These are drugs specifically targeting pro-inflammatory cytokines involved in the immune response (TNF-α, IL-1, IL-2, etc). Biologicalcompounds potentially offer a safer profile and faster response than traditional immunosuppressive agents [46]. Among the biologics drugs, tumor necrosis factor-α (TNF-α) blockers (especially infliximab and adalimumab) have demonstrated promising results for the treatment of ocular inflammatory conditions in case series or retrospective reviews [47]. At present, there is a lack of evidence-based recommendations regarding the use of these agents for managing uveitis. In addition, there is no approval for use in uveitis in technical sheet and, in clinical practice; these drugs are used as compassionate use. Throughout this book, available drugs, dosages, safety issuesand experience of use in uveitis have been described in detail. Figure 4 shows our therapeutic algorithm for immune-mediated posterior uveitis or panuveitis.

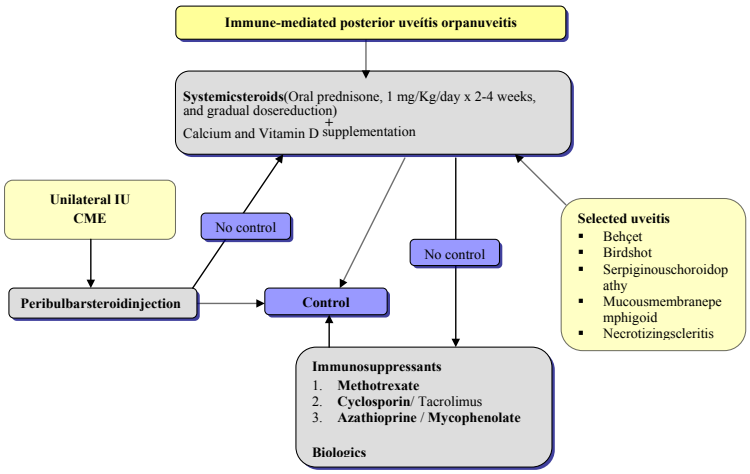


Figure 4: Therapeuticalgorithm in immune-mediated posterior uveítisorpanuveitis.

In current uveitis practice, biologics are usually used as third-line agents as rescue therapy for refractory cases in a step-up approach. However, there is ongoing arguments between uveitis specialists as to whether biologics should be considered as first-line therapy in certain cases (for instance, panuveitis in Behçet disease with macular involvement) following a top-down approach [48] (Figure 5).

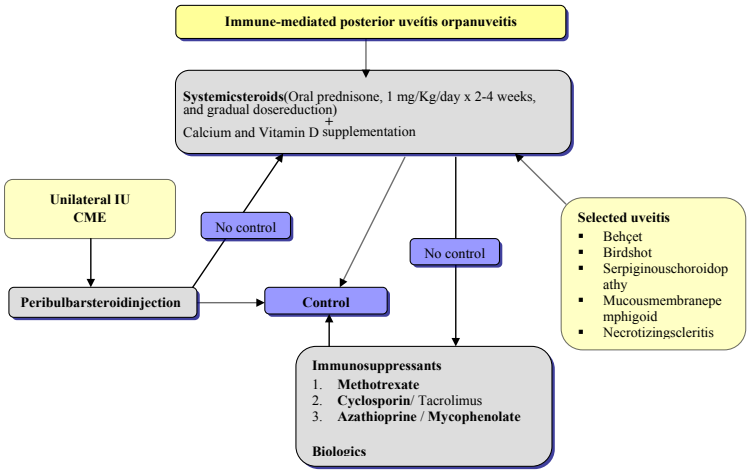


Figure 5: Global treatment strategy in severe immune uveitis.

The most usual approach is a step-up strategy, starting with corticosteroids and associating classical immunosuppressants and eventually biological in refractory cases. Fourth level (alkilating agents)is used sparingly nowadays. In selected patients with fulminant uveitis (for instance, Behçet disease with macular involvement) a top-down approach starting with biological therapy as first-line therapy could be used.

Another important issue regarding the use of anti-TNF- α is if this therapy could be discontinued in patients achieving sustained

control of their uveitis. Some studies show that this option may be possible, although most patients were on other immunomodulatory treatment at this time [49,50].

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Classical Immunosuppressive Therapies for Non-Infectious Uveitis

Alex Fonollosa* **and Joseba Artaraz**

Uveitis Unit, Ophthalmology Department, BioCruces Health Research Institute, Hospital Universitario Cruces (Bilbao), Spain

***Corresponding author:** Alex Fonollosa, Uveitis Unit, Ophthalmology Department, BioCruces Health Research Institute, Hospital Universitario Cruces (Bilbao), Spain, Tel: 0034646844328; E-mail: afonollosacalduch@gmail.com

Introduction

The first therapeutical option in uveitis is corticosteroids. Addition of immunosuppressive or immunomodulatory agents is indicated when costicosteroid treatment fails to control inflammation, when corticosteroid-sparing therapy is needed to minimize side effects of systemic corticosteroids and/or for certain entities that have shown better outcomes if immunosuppressive drugs are introduced early (i.e., Behçet's disease with retinal involvement or serpiginous choroiditis).

The conventional immunosuppressant's that will be discussed herein include three main groups of drugs:

a) Antimetabolites: methotrexate, azathioprine, mycophenolate mofetil, leflunomide.

b) Antibiotics: cyclosporine, tacrolimus.

c) Alkylating agents: cyclophosphamide, chlorambucil.

Some general issues to remark about immunosuppressive treatment are:

a) The most widely used immunosuppressive drugs are: cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil.

b) Except for cyclosporine, the use of all of them in uveitis is off-label.

c) Clinical trials comparing efficacy among treatments head to head for specific uveitic conditions are scarce; personal experience with particular drugs or learning from the rheumatologists' experience is taken into account to choose particular treatments.

d) Duration of treatment is not known but 18-24 months is considered a standard period. It is common to taper the dose after 6 months of therapy.

e) Reported efficacy from the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) multicenter retrospective study, which evaluated methotrexate, azathioprine, cyclosporine, cyclophosphamide and mycophenolate mofetil in a large number of patients from 4 centers in the USA, was approximately 60-70% [1-5].

Antimetabolites

Methotrexate

Mechanism of action: Methotrexate is an inhibitor of dihydrofolate reductase and other folate-dependent enzymes. This agent inhibits DNA synthesis and thus, diminishes the replication of rapidly-dividing cells such as lymphocytes. Methotrexate has been shown in randomized, controlled clinical trials to be effective for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis [6].

Use in uveitis: Several uncontrolled case series have shown that methotrexate is effective as a corticosteroid-sparing agent in various types of chronic non-infectious uveitis [7-9]. The SITE multicenter retrospective cohort study reported the outcomes on 384 patients treated with methotrexate [1]. It was found to be effective in completely controlling ocular inflammation in 66% of patients and allowed tapering of corticosteroids to 10 mg or less in 58% of them. Although it was used to treat a variety of ocular inflammatory conditions, it was most effective in patients with anterior uveitis and scleritis. Because of the wide experience in pediatric rheumatology, methotrexate is often the first choice in children with uveitis, especially in anterior uveitis associated to juvenile idiopathic arthritis.

In our unit, methotrexate is one of the most commonly used immunosuppressants. It is the first option for sarcoid related uveitis, scleritis and predominantly anterior uveitis. We would typically start with oral administration up to 15 mg/week, and switch to subcutaneous administration for higher doses (up to 25 mg) or if gastrointestinal adverse effects ensue.

Dosage, monitoring and side effects: Methotrexate is given weekly as a single dose. Usually starting with 7.5 mg/week and increasing at 2.5-5 mg increments every 2-4 weeks until there is a therapeutic effect or we reach the maximum dose of 25 mg/week. Bioavailability of oral methotrexate is generally high (mean 70%) but there is considerable individual variability. Most physicians would recommend subcutaneous administration for doses above 15 mg before discontinuing for lack of efficacy. Typically, folate is used concomitantly to reduce side effects. Before starting treatment, the following laboratory tests should be done: full blood count, electrolytes and creatinine, liver function tests and Hepatitis B and C serologies. Monitoring therapy requires full blood count and liver function tests every 2-4 weeks at the beginning and every 2-3 months afterwards.

The most common side effects are gastrointestinal (nausea, vomiting, diarrhea, anorexia) but improve with dose reduction or switching to subcutaneous administration. Cytopenias (especially leukopenia) may occur but the incidence is reduced by daily folate therapy. Hepatotoxicity is a more serious side effect, so patients should abstain from alcohol consumption. It usually manifests as elevated liver transaminase levels and is normally reversible with dose reduction or stopping treatment; but it can progress to cirrhosis. Methotrexate may cause interstitial infiltrates on chest X-ray, usually during first year of treatment. Common complaints are cough, dyspnea, fever and malaise. More rare adverse effects are alopecia, oligospermia, cutaneous vasculitis and infections (including localized and disseminated varicella-zoster virus infection). Methotrexate is teratogenic. Adequate contraception (for female as well as for male patients) is necessary. Regarding the risk of malignancy, recent retrospective studies have concluded that methotrexate has virtually no long-term carcinogenic effects [10].

Azathioprine

Mechanism of action: Azathioprine is a purine analog and interferes with DNA replication and RNA transcription. It inhibits the proliferation of B and T lymphocytes and reduces interleukin-2 synthesis. It selectively inhibits T-lymphocytes more than B-lymphocytes.

This drug has been used in transplantation and various rheumatic conditions like lupus nephritis, inflammatory myopathy and ANCA-associated vasculitis and also in bowel inflammatory disease.

Use in uveitis: In a randomized, controlled trial of azathioprine in Behçet disease, it was shown to be effective in decreasing relapses of ocular inflammation and in the prevention of eye disease in patients without ocular involvement [11]. It has also been used in scleritis secondary to relapsing polychondritis [12]. The SITE retrospective cohort study included 145 patients with a variety of inflammatory entities, treated with azathioprine. Overall, the inflammation was controlled in 62% of patients. It was most effective in controlling inflammation in patients with intermediate uveitis (90% achieved control) [2]. In our unit, we consider this drug as first option in intermediate uveitis. It is also used frequently in cases where methotrexate has not worked or there are unacceptable adverse effects. Azathioprine can be a good option in women of child-bearing age.

Dosage, monitoring and side effects: Administered orally at a dose of 2 mg/kg/day (typically 100-200 mg/day). We usually begin with a low dose of 50 mg/day for a week to monitor for gastrointestinal intolerance and then increase to the therapeutic dose. Prior to beginning treatment, a full blood count and liver function tests should be obtained. To monitor treatment, these tests are repeated every 4-8 weeks.

Azathioprine is inactivated in the liver, gastrointestinal tract and red blood cells by various enzymes, including Thiopurin Methyltransferace (TPMT). About 11% of the general population is deficient for the activity of TPMT, and 1 in 300 have absent enzyme activity. They have an increased risk of toxicity and probably should not be treated with azathioprine. The activity of TPMT can be measured prior to beginning treatment.

The most common side effects are gastrointestinal (anorexia, nausea and vomiting) occurring in more than 10% of patients. Bone marrow suppression (mainly leukopenia) is dose-dependent and normally responds to dose reduction. Azathioprine can also cause Hepatitis and Pancreatitis, which are usually reversible after stopping the drug.

A subject for debate in the literature is the risk of malignancies (such as lymphomas and skin cancer) in patients treated with this drug long-term. A recent publication concluded that azathioprine does not increase total cancer risk [13]. Azathioprine is not teratogenic and can be used in pregnant women if necessary [13].

Mycophenolate Mofetil

Mechanism of action: Mycophenolate Mofetil (MMF) inhibits the enzyme inosin monophosphate dehydrogenase, which disrupts the de novo synthesis of purine. Because this pathway is required by B- and T-lymphocytes for DNA synthesis, it will inhibit their proliferation.

MMF also decreases antibody production and interferes with lymphocytic chemotaxis.

This drug was first used in the 1990s as an immunosuppressant after kidney transplantation. Since then it has been shown to be effective in a variety of inflammatory conditions like lupus nephritis [14], systemic lupus erythematosus [15], inflammatory myopathy, and to maintain remission in Wegener's granulomatosis [16].

Use in uveitis: There are several retrospective studies showing efficacy of MMF in various ocular inflammatory conditions, alone [17] or in combination with cyclosporine [18]. In pediatric uveitis, MMF was useful as a steroid-sparing agent [19].

In the SITE study, MMF was effective in controlling inflammation in 73% of 236 patients within a year [5].

Dosage, monitoring and side effects: Maintenance dose is 1.5-3 g/day in 2 divided doses; we would generally start with a lower dose for several days and then increase to the therapeutic dose if it is well tolerated. The most common dose is 1 g twice a day. For monitoring, full blood count should be performed every 4-8 weeks.

The most common adverse effects are gastrointestinal (anorexia, nausea, vomiting and diarrhea) and are often the reason for discontinuation of treatment or reducing the dose. Leukopenia is not frequent and normally reverses with dose reduction. MMF may be teratogenic so appropriate contraception should be used. In transplant patients, there is a reported risk of opportunistic infections (especially *cytomegalovirus*).

In our unit, MMF is not used as a first line treatment but rather as an option when other immunosuppressants have failed.

Antibiotics

Cyclosporine

Mechanism of action: Cyclosporine inhibits T-cells immune responses. Evidence indicates that it inhibits calcineurin preventing the nuclear translocation of Nuclear Factor of Activated T-Cells (NFAT). This results in inhibition of the signaling cascade from T-cell receptor to genes encoding several lymphokines such as IL-2 and enzymes necessary to activate T-cells.

Unlike other immunosuppressive drugs, the effects of cyclosporine are observed much sooner: around 7-15 days after the onset of treatment.

Use in uveitis: Cyclosporine is one of the most widely used immunosuppressive drugs for treating patients with uveitis. It is the only one that has an indication for treating uveitis in the data sheet of the product. Several publications (mostly retrospective case series, but also some clinical trials) have shown its efficacy, both as monotherapy in steroid-resistant cases or in combination with other immunosuppressive drugs in the treatment of several types of uveitis including Behçet's disease [20,21], Vogt-Koyanagi-Harada syndrome [22], Birdshot chorioretinopathy [23], serpiginous choroiditis [24] and multifocal choroiditis and panuveitis [25]. Cyclosporine is our first choice immunosuppressive treatment in Vogt-Koyanagi-Harada syndrome, in moderate to severe Behçet's disease and in Birdshot chorioretinopathy.

Dosage monitoring and side effects: Dose: usually 1.5-2.5 mg/Kg twice a day orally. Though not mandatory, doses may be adjusted depending on blood levels of the drug, which can be measured (therapeutic levels: 150-300 ng/mL).

Adverse effects: the most frequent are hypertension (30%) and nephrotoxicity (25%). Other less frequent effects are: tremors, hirsutism, hypercholesterolemia, gum hyperplasia and abdominal discomfort.

Monitoring: blood pressure measurement, urinalysis and blood analysis (including complete hemogram with differential, BUN, serum creatinine, creatinine clearance, ions, liver function test, and lipid profile) performed baseline and every 1-2 months.

Tacrolimus (FK506)

Mechanism of action: Like cyclosporine, tacrolimus inhibits T-cell activation by inhibiting calcineurin. The drug binds to FK506 binding protein-12, which forms a complex with calcium, calmodulin and calcineurin.

Use in uveitis: As a T-cell inhibitor, tacrolimus is an effective drug for the treatment of several immune-mediated conditions. However, use in ocular inflammation has been limited because early studies showed significant side effects, but target serum levels were double than dose used today [26,27]. Using proper doses, a randomized controlled trial comparing cyclosporine and tacrolimus for the treatment of uveitis showed equal efficacy and superior short-term cardiovascular profile [28]. Hogan et al [29] showed an 85% probability of achieving ≤10 mg prednisone after 1 year and 2 months of treatment in their retrospective case series of 62 patients, with an excellent cardiovascular profile. More recently, the same group showed in a randomized controlled trial that tacrolimus alone was equivalent to tacrolimus plus 10 mg of prednisone in terms of control of inflammation [30].

Dosage, monitoring and adverse effects: Therapeutic dose: 0.03-0.08 mg/Kg/day. Adverse effects: nephrotoxicity and hypertension are the major dose-limiting side effects of tacrolimus but trials have shown it to be less likely to induce systemic hypertension and lipid abnormalities than cyclosporine [31].

Monitoring: baseline tests and subsequent monitoring are similar to those described for cyclosporine. Oral absorption of the drug is variable; hence, levels of tacrolimus should be monitored during therapy.

Alkylating Agents

Cyclophosphamide

Mechanism of action: Cyclophosphamide exerts a cytotoxic effect on rapidly proliferating cells by alkylating nucleophilic groups on DNA bases, particularly on the 7-nitrogen position of guanine. This leads to cross-linking of DNA bases; abnormal base pairing and DNA strand breakage. Immunosuppression is thought to be mediated by a direct cytotoxic effect on lymphocytes.

Use in uveitis: Cyclophosphamide is an effective immunosuppressant, especially for treating scleritis and intraocular inflammation associated with systemic vasculitis. However, it is associated with a variety of potential severe side effects including malignancy (see below), being its use limited to very severe cases refractory to first line immunosuppressive drugs like cyclosporine or methotrexate. Moreover, the advent of biological therapies, with a safer profile and great efficacy, has made this use even less frequent. Most specialists prefer intravenous pulse administration of cyclophosphamide since a rapid induction is achieved in patients with severe ocular inflammation and because associated side effects are less frequent. Recently, the results of the so-called Foster protocol for intravenous cyclophosphamide therapy have been reported. Sustained remission of inflammation occurred in 91.7 % of 65 patients within 9 months [32].

Dosage monitoring and side effects: Doses (intravenous administration): 1 g/m^2 body surface area. Our approach consists of 1 pulse per month for 3 months followed by standard first line immunosuppressive therapy. Foster's group [32] uses weekly or every 2 weeks infusions for 6 to 12 months. Adverse effects: potential toxic effects include leucopenia, hemorrhagic cystitis, secondary malignancy and sterility. As mentioned above, intravenous pulse administration avoids prolonged bladder exposure to its bladder-toxic metabolite acrolein and induces only transient neutropenia. In the SITE study, cyclophosphamide was discontinued by 33.5% of patients due to side effects within 1 year [4].

Monitoring: Complete hemogram, liver function tests and urinalysis prior to starting therapy. In Foster protocol dosages of cyclophosphamide are based on leukocyte count and neutrophil count, hence frequent hemograms are needed.

Other Immunosuppressive Drugs Used Less Frequently for the Treatment of Uveitis: Chlorambucil, Leflunomide and Dapsone

Chlorambucil: Cases of recalcitrant uveitis, including Behçet disease, sympathetic ophthalmia, juvenile idiopathic arthritis, serpiginous choroiditis, Crohn disease, and HLA-B27 associated uveitis treated with chlorambucil have been reported suggesting that is an effective treatment. A major side effect is bone marrow suppression. Other side effects include secondary hematologic malignancy, opportunistic infections and reactivation of *Herpes zoster*, sterility and amenorrhea. This profile of secondary effects has limited its use among uveitis specialists

Dapsone: This is a synthetic sulfone with anti-inflammatory properties. It has been shown to be effective in halting the progression of fibrosis in ocular cicatricial pemphigoid.

Leflunomide: It is used as a disease-modifying drug in patients with rheumatoid arthritis. Animal studies have shown leflunomide to be more effective than cyclosporine in inhibiting experimental autoimmune uveitis. Experience in human uveitic disease is limited [33].

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Tumor Necrosis Factor Alpha (TNF-α) Antagonists

Marina Mesquida*

MD, Uveitis Unit, Ophthalmology Department, Hospital Clínic de Barcelona, Barcelona, Spain

***Corresponding author:** Marina Mesquida, MD, Uveitis Unit, Ophthalmology Department, Hospital Clínic de Barcelona, Sabino Arana, 108028, Barcelona, Spain, Tel: +34932275667; Fax: +34932275662; E-mail: mesquida@clinic.ub.es

Introduction

Tumor necrosis factor alpha (TNF-α) is a pleiotropic cytokine expressed in a wide variety of inflammatory conditions contributing to the pathogenesis and perpetuation of autoimmune diseases. It is produced by different cell types and mediates its effects through two receptors, p55 (TNFR1) and p75 (TNFR2) [1]. During inflammation TNF-α activates T cells and macrophages and up regulates other proinflammatory cytokines. Experimental models of uveitis have provided substantial evidence of TNF-α's pivotal role in mediating intraocular inflammation [2,3]. Several studies showed that the serum and/or aqueous humor concentrations of TNF-α and soluble TNF-α receptors are increased in non-infectious uveitis, especially during periods of higher disease activity [4-7]. In late 1990s Dick et al. demonstrated the benefits of TNF-α inhibition in minimising the severity of experimental autoimmune uveoretinitis [8]. Neutralizing TNF-α activity results in skewed T-cell polarization with reduced IFNγ generation, suppressed levels of T-cell apoptosis, and reduced levels of classical myeloid cell activation, resulting in suppressing target organ damage [2,8]. There are currently 5 TNF antagonists approved in rheumatic diseases as shown in Table 1. Two broad strategies are used in targeting TNF: soluble receptors (i.e., etanercept) vs targeting antibodies (infliximab, adalimumab, golimumab, certolizumab). Amongst the targeting antibodies, a distinction can be made based on the route of administration (intravenous vs subcutaneous injection) and the level of humanization of the antibody structure (chimeric, humanized, or fully human). TNF inhibitors are the form of biologic therapy most commonly employed to treat uveitis. Although there is increasing evidence of their beneficial effects in the treatment of autoimmune uveitis, TNF inhibitors are not approved for such an indication, and therefore its use is off-label worldwide excepting infliximab for Behçet's uveoretinitis in Japan.

Etanercept

Etanercept (Enbrel®, Amgen Inc, CA, USA and Wyeth, NJ, USA) is a dimeric protein composed of soluble TNFR and a human IgGFc fragment. It competitively inhibits the binding of TNF-α and TNF-β, thereby resulting in decreased expression of adhesion molecules responsible for leukocyte migration and reduced synthesis of proinflammatory cytokines [9]. It is administered subcutaneously at a dose of 25 mg twice a week or 50 mg once a week. Etanercept has been effective in the treatment of several rheumatic diseases [10,11] although its effect in uveitis is debatable [11-16]. Foster et al. showed that etanercept has no significant efficacy over placebo in preventing relapses of uveitis [11]. Moreover, etanercept can worsen uveitis course or even induce ocular inflammation in a paradoxical effect [13-16].

Infliximab

Infliximab (Remicade®, Centocor, PA, USA) is a chimeric monoclonal antibody whose mechanism of action consists of neutralizing membrane-bound TNF-α and soluble TNF-α and suppressing TNF-α production by macrophages and lymphocytes [17]. An alternative inhibition mechanism of infliximab is the promotion of regulatory T (Treg) cells that acquire suppressive functions in the periphery [18]. Infliximab is the only chimeric TNF-α antagonist, composed of a mouse antigen binding (Fab) domain and a human Fc domain. This is the only TNF inhibitor that is given intravenously. The most frequent dosage regimen is an induction dose of 5 mg/kg at 0, 2, 6, and every 8 weeks thereafter depending on the clinical response. It is approved for use in rheumatoid arthritis, ankylosing spondilitis, psoriasic arthritis and plaque psoriasis and commonly used in Crohn´s disease.

Infliximab has the largest amount of data amongst the different TNF antagonists with respect to treating ocular inflammatory disease. Infliximab has been effective for a variety of forms of uveitis (Juvenile Idiopathic Arthritis (JIA)-associated uveitis, sarcoidosis, Birdshot, diffuse subretinal fibrosis, sympathethic ophthalmia) [19-24], but most of the evidence of the effectiveness of infliximab in ocular inflammatory disease comes from studies on its use in Behcet´s disease [25-31]. Two prospective studies of infliximab for refractory Behçet's uveitis showed a significant decrease in the mean number of ocular attacks compared with conventional immunosuppressive therapy [25,26]. Recently, Japanese investigators have conducted a multicenter prospective study [28] that shows the efficacy of infliximab in 63 patients with refractory Behçet's uveitis during the first year of treatment. At 12 months follow-up, uveitis improved in 92% of patients, unchanged in 8%, and worsened in none. An important advantage of infliximab therapy is the rapid onset of action compared with other medications, causing a rapid induction of remission. Control of ocular inflammation is frequently observed within 1 or 2 infusions, and its efficacy seems superior to intravenous methylprednisolone [31]. Rapid and successful management of acute fundus inflammation in ocular Behçet's disease is imperative to avoid vision loss due to permanent lesions in the retina and optic nerve. The long-term effects of repetitive infliximab infusions in preventing ocular relapses have been evaluated in several open prospective studies. Long-term remission can be sustained after cessation of therapy [29,32,33]. Infliximab is also efficacious in extraocular manifestations of Behçet's disease such as oral and genital ulcers and /or arthritis in the majority of patients (Figure 1). Recent reports have suggested the possibility of intravitreal use of infliximab [34,35]. Markomichelakis et al. conducted a pilot study in which a single intravitreal injection of infliximab (1 mg/0.05 mL) was given to 15 patients with Behçet's

uveitis at the onset of a unilateral attack. A statistically significant improvement in visual acuity was observed as well as resolution of intraocular inflammation signs. The authors suggest that intravitreal infliximab may be considered when systemic administration is not feasible or contraindicated. Further studies to assess the efficacy of intravitreal infliximab are required.

Regarding to safety issues, infliximab is considered to be a drug with low toxicity, although allergic reactions are frequent during infusion and usually treated without consequences with antihistamines and analgesics. Its combination with methotrexate is convenient in order to reduce the production of anti-infliximab antibodies associated to multiple infusions. On the other hand, it has to be taken into account that infliximab, like all other TNF antagonists, can reactivate latent tuberculosis (TB) and other opportunistic infections, and thus patients should have their risk of TB assessed with a prior history of exposure, chest X-ray and QuantiFERON assays, given that tuberculin skin test can be altered by the use of steroids and immunosuppressive medications. In addition, the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) cohort study showed that patients on anti-TNF therapies have a greater risk of cancer and overall mortality [36]. However, it has been proposed that TNF antagonists do not actually initiate cancer, but exacerbate pre-existing cases of undetected cancer. This statement must be considered when initiating therapy with these agents [37].

The remaining targeting antibodies are all given through subcutaneous injections.

Adalimumab

Adalimumab (Humira®, Abbott, Chicago, IL, USA) is a fully humanized monoclonal antibody that inhibits TNF-α. It is administered in subcutaneous injections 40 mg every 2 weeks. When uveitis relapses still occur despite this dose, adalimumab may be administered weekly until achieving control of inflammation [38]. Several reports have showed the efficacy of adalimumab in treating a variety of uveitis conditions, including JIA-associated uveitis, sarcoidosis, Behçet's and ankylosing spondilitis-associated uveitis [39-42]. Recently, Diaz-Llopis et al. conducted a prospective study of 131 patients with refractory uveitis treated with adalimumab [43]. This study showed statistically significant results regarding adalimumab efficacy in reducing anterior and vitreous inflammation, macular edema, immunosuppression and steroid loads, as well as improving visual acuity. Since adalimumab is a fully humanized antibody, it may offer superior side effect profile. Its most frequent side effect is the development of a self-limited cutaneous reaction at the injection site. Theoretically it has a lower risk of developing allergic reactions and anti-drug antibodies when comparing to infliximab. However, its effect is not as fast as infliximab, probably because of the subcutaneous route of administration. For this reason, we prefer using infliximab to induce rapid remission in the most sight-threatening and recalcitrant cases such as active Behçet's uveitis. Once inflammation is controlled, then you can maintain remission with either infliximab or switching to another TNF antagonist with a subcutaneous administration, more comfortable both for the patient and for the physician (totally ambulatory, avoiding hospitalization).

Pediatric uveitis differs from uveitis seen in adulthood not only because of the uveitis presentation and severity of disease but also by a worse prognosis and age-specific problems that may occur under therapy. Adalimumab has advantages over infliximab in pediatric uveitis due to less infusion reactions and intolerance and better treatment compliance (Figure 2).

There are currently many clinical trials studying the efficacy and safety of adalimumab in non-infectious uveitis such as the ADUR trial (NCT00348153), VISUAL I, II and III (NCT01148225), and ADJUVITE (NCT01385826).

Golimumab

Golimumab (Simponi®, Abbott, Chicago, IL, USA) is a fully human monoclonal antibody that inhibits both free and transmembrane TNF-α. It is injected subcutaneously, 50mg every four weeks. Golimumab is a recent development in TNF antagonism and has been recently approved for the treatment of various rheumatic conditions [44]. Due to its molecular structure -a fully human monoclonal antibody- has a lower probability of developing neutralizing antibodies compared to other anti-TNF, thus decreasing the risk of an allergic infusion reaction and any loss of efficacy. Although fully human, resistance to golimumab may potentially develop as well [44]. Other advantages of golimumab over other TNF antagonists include the reduced dosing schedule, being a monthly subcutaneous self-administration. Recently, three papers have been published regarding golimumab use in uveitis [45-47] showing its efficacy in retinal vasculitis, JIA-associated uveitis, and Behçet's disease. Further studies with longer follow-up to evaluate the long-term efficacy and safety of golimumab in a larger number of uveitis patients are warranted.

Certolizumab

Certolizumab (Cimzia®) consists only in the pegylated humanized Fab portion of a monoclonal antibody directed against TNF-α. Because its antibody structure lacks a constant region or Fc portion, there are limitations in certolizumab's ability to fix complement or recruit antibody-dependent cell-mediated cytotoxicity [48]. Certolizumab has been approved for Crohn's disease and rheumatoid arthritis in people who did not respond to standard therapy [49]. Certolizumab is dosed 400 mg subcutaneously 4 weeks after 3 dose-loading spaced every 2 weeks. Currently there are no studies demonstrating the efficacy of this drug in non-infectious uveitis.

Switching TNF Inhibitors

Acquired resistance to TNF antagonists may occur in the long term. In cases of refractory uveitis with loss of initial clinical response to one biological agent (secondary failure), switching to another agent can restore control of intraocular inflammation. In addition, switching helps controlling systemic symptoms and allows ease of administration. Why patients should respond to one biologic agent and not another, despite similar mechanisms of action, remains unexplained. Various possible hypotheses include differential bioavailability of these drugs and the development of anti-drug antibodies [50-52].

We consider infliximab and adalimumab as similar treatment options. They share a similar action profile but different routes of administration, immunogenic potential and therefore reason for using one or another should be related to nonclinical issues associated with the patient. Adalimumab appears to be effective and safe for treatment of refractory JIA-related uveitis, with a better performance in the medium-term period and it is more efficacious than infliximab in maintaining remission of chronic childhood uveitis.

Generic name (trade name; sponsoring companies)	Format	Targets	Approved indications	Status in ophthalmology	Proposed mechanisms of action	Dosage and administration
Infliximab (Remicade; Janssen/ Biotech)	Chimeric IgG1	TNF-α	CD, UC, RA, PsA, AS and PPs	Approved for refractory Behçet's uveitis in Japan since 2007	Neutralizes TNF activity by binding soluble and transmembrane TNF and inhibiting binding to TNFRs; induction of activated T cell and macrophage apoptosis	3-5 mg/kg iv infusion at 0, 2, and 6 weeks, followed by maitenance every 8 weeks thereafter; may increase to 10 mg/kg
Adalimumab (Humira; Trudexa/ Abbott)	Human (phage-produced) IgG1	TNF-α	RA, JIA, PsA, CD, AS and PPs	Off-label. Phase III clinical trials ongoing for noninfectious uveitis	Neutralizes TNF activity by binding soluble and transmembrane TNF and inhibiting binding to TNFRs; lyses TNF-expressing cells by CDC; induction of activated T cell and macrophage apoptosis	40 mg every other week as sc injection; may increase to 40 mg weekly if no good control of ocular inflammation
Certolizumab pegol (Cimzia; UCB)	Humanized Fab, PEG conjugate	TNF-α	CD, RA	Off-label	Neutralizes TNF activity by binding soluble and transmembrane and inhibiting binding to TNFRs	400 mg sc injection initially and at weeks 2 and 4, and then every 4 weeks
Golimumab (Simponi; Janssen/ Biotech)	Human (mouse-produced) IgG1	TNF-α	RA, PsA and AS	Off-label	Neutralizes TNF activity by binding soluble and transmembrane TNF and inhibiting binding to TNFRs	50 mg sc injection once a month
Etanercept (Enbrel; Amgen/Pfizer)	TNFR2 ECD–Fc (IgG1) fusion protein	TNF-α and TNF-β	RA, JIA, PsA, AS and PPs	Off-label	Neutralizes TNF activity by binding soluble and transmembrane TNF and inhibiting binding to TNFRs	50 mg once weekly as sc injection

Abbreviations: CD: Crohn's Disease; UC: Ulcerative Cholitis; RA: Rheumatoid Arthritis; JIA: Juvenile Idiopathic Arthritis; PsA: Psoriatic Arthritis; PPs: Plaque Psoriasis; AS: Ankylosing Spondilitis; CCL: Chronic Lymphatic Leukemia; SC: Subcutaneous

Table 1: TNF antagonists.

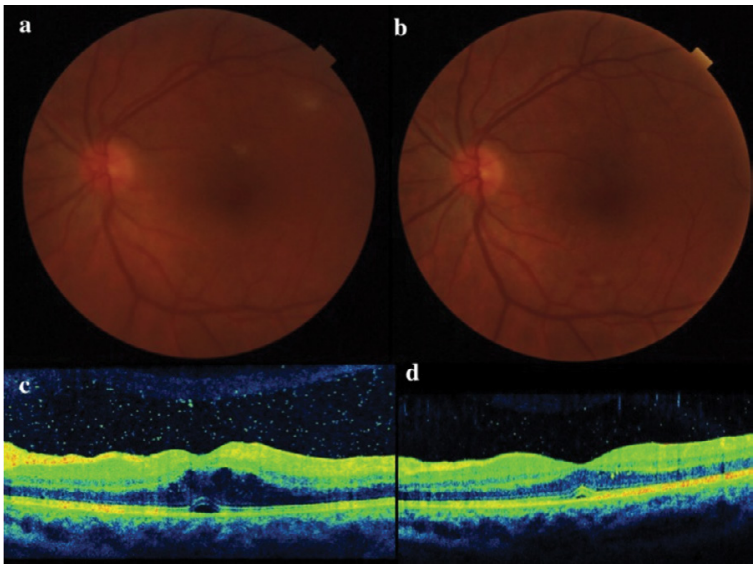

Figure 1: Figure 1A shows a fundus photograph of case of Behçet's disease with active posterior uveitis. There is vitreous haze and two retinal infiltrates in the posterior pole. Figure 1C shows an Optical Coherence Tomography demonstrating macular edema and abundant vitreous cells. These inflammatory signs rapidly resolved after initiating infliximab infusions (Figure 1 B, D).

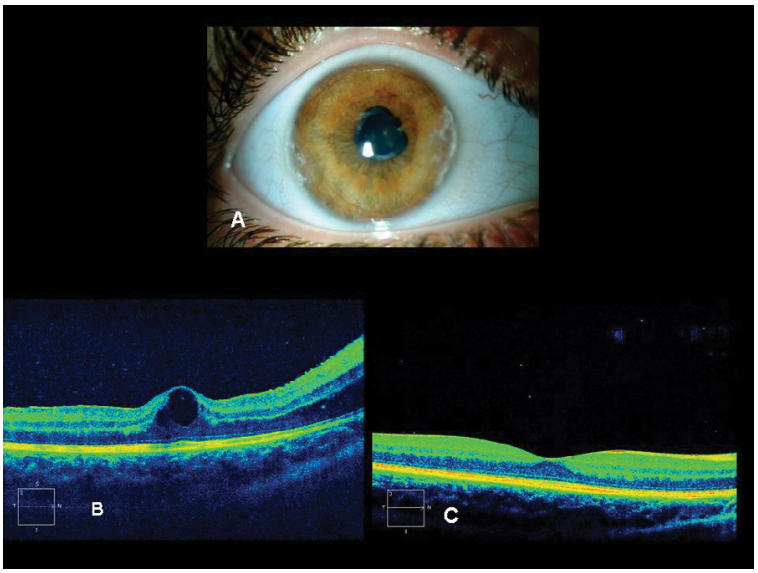

Figure 2: A case of Juvenile Idiopathic Arthritis-associated uveitis with band queratopathy, aphakia and 1+ cells in anterior chamber (A) and cystoid macular edema as shown in the Optical Coherence Tomography (B). After 2 months of adalimumab therapy macular edema has completely resolved (C).

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Miguel Cordero Coma[1]* and Raquel Salazar[2]

[1]Uveitis Unit, Ophthalmology Department, Hospital de León, León, Spain

[2]Ophthalmology Department, Hospital de Jarrio. Asturias, Spain

***Corresponding author:** Miguel Cordero Coma, Uveitis Unit, Ophthalmology Department, Hospital de León, León, Spain, E-mail: miguelcorderocoma@gmail.com

Interferon (IFN) was first described in 1957 by Isaacs and Lindenmann [1]. Its name refers to their ability for interfering in viral replication. In addition, interferons (IFNs) may exert many other antiviral, antiproliferative, and/or immunomodulatory effects which explain the widespread use of these drugs for treatment of many diseases including uveitis [2].

The Molecule

There are three recognized types of IFN in vertebrates: I, II and III [2,3]. Type II IFN corresponds to the immune-IFN or IFN-γ, whereas type III IFN encompasses the three described molecules of IFN-λ [3]. In humans, the type I IFN include the IFN-α and -β as well as other three subtypes of IFN with less clinical relevance (-ε, -κ y -ω). Only the subtypes IFN-ε, -κ are tissue-specific and expressed in the placenta the first and in queratinocytes the latter [4]. On the other hand, IFN-α and –β may be potentially synthesized by any cell of the human body, although the main sources of these molecules are monocytes, macrophages and dendritic cells (DCs) for IFN-α, and fibroblasts for IFN–β [2,4]. The production of type I IFN by DCs is really fast considering that it can reach about 200 to 1000 times the basal production of any other human cell. In this setting, DCs are considered the natural producers of IFN-α/β [3,4].

IFN-α is codified by 13 genes located in the chromosome 9 whereas the structure and integrity of IFN-β are determined by the integrity of only one gene located in the same chromosome [2-4]. Both molecules are secreted in an autocrine and paracrine fashion and share the same heterodimeric receptor (JAK-STAT) linked to an intracellular cascade which explains their multiple biologic effects [2-4].

The signal that initiates the synthesis of these molecules has its origin on the activation of one or more of the 13 *toll-like receptors* (TLRs) described in mammals [2,4]. Although some of their ligands are still unidentified, it is clear that those TLRs located at the cell membranes respond to proteic or lipidic components of bacteria, fungi and protozoa, whereas those located at the endosomal membranes respond to nucleic material of viruses and bacteria [4].

Mechanism of Action: Hypotheses

IFNs induce the expression of hundreds of genes associated with the defense response to viruses and bacteria, apoptosis, the cell cycle, inflammation and immunity; this comprises cytokines codifying genes, adhesion molecules, growing factors and pro-apoptotic factors among others [3]. In any case, their most important actions are related to their ability for integrating both the innate and the adaptive immune responses [3,4].

These immunomodulatory mechanisms include:

- Activation of immature DCs
- Increase expression of antigens from the major histocompatibility complex (MHC) class I
- Induction of cytotoxicity towards natural killer (NK) cells
- Maturation and activation of macrophages
- Stimulation of B-lymphocytes (B-cells), increasing their survival and promoting antibody (Ab) production and switching of immunoglobulins.
- Activation of T-lymphocytes (T-cells) CD4+ CD8+, reduction of circulating γδ T-cells and in vitro reduction of T-cells adhesion to the vascular endothelium [5-7].

These biologic effects would explain not only their therapeutic efficacy but also some of their side-effects. In this setting, stimulation of B-cells would justify their potential for inducing autoimmunity reactions in predisposing individuals, [4] whereas the induction of maturation and activation of macrophages would be the reason of the commonly associated flu-like syndrome [8].

In any case there is a substantial ignorance regarding the possible mechanism of action of IFN-α when used for treatment of ophthalmic conditions. Experimental models have shown its ability for promoting the integrity of the retinal microvascular endothelium by increasing its electric resistance and decreasing its permeability [9]. This might explain the encouraging outcomes when used for treatment of long-lasting uveitic cystoid macular edema [10,11]. Moreover, IFN-α might exert a beneficial effect on the secretion profile of several molecules in patients with Behçet disease-associated uveitis such as certain soluble cytokine receptors as well as some cytokine-antagonists and adhesion molecules [8]. Recently, serum analysis of patients with ocular Behçet's disease under IFN-α treatment has revealed a significant increase in levels of certain soluble adhesion molecules such as sICAM-1 and sVCAM-1[8]. Several investigators have proposed that increased sVCAM might block leukocyte adhesion to endothelium by binding competitively with the integrin very late antigen-4 (VLA-4) receptor [12]. By this mechanism, type I IFN may prevent T-cell binding with the vascular endothelial basement membrane and may reduce the trafficking of immune cells [12]. On the other hand, IFN-α has been found to be a potent inhibitor of platelet aggregation and a thrombolytic agent due to the activation of nitric oxide synthase [13] and the decrease of platelet counts [14].

Current Indications for Treatment of Uveitis

There are several commercially available IFN-α (α-2a, α-2b and pegylated forms of both) and IFN-β (β-1a and β-1b). FDA-approved indications of both IFNs are shown in (Table 1). However, off-label reported indications of IFNs are even higher and shown in (Table 2). There are also several reported routes of administration. Regarding this issue it should be emphasized that oral administration is not recommended based on the proteolitic effect of digestive enzymes. Following subcutaneous injection, IFN-α reaches its peak four hours later.

IFN-α	IFN-β
Hairy cell leukemia	Relapsing multiple sclerosis
Kaposi sarcoma (AIDS)	Relapsing-remitting multiple sclerosis
Melanoma	
Chronic hepatitis B and C	
Chronic myeloid leukemia Ph+	
Folicular lymphoma	
Condyloma acuminatum	

Table 1: FDA-approved therapeutic indications for IFN-α and –β [15].

IFN-α	IFN-β
-Actinic keratosis[16] - Atopic dermatitis[17] - Basocelular carcinoma[18] - Behçet disease[6] - Cryoglobulinemia[19] - Discoid lupus[20] - Hemangioma[21] - Keratoacanthoma[22] - Carcinoid tumor[23] - Malignant pleural effusion[24] - Mesothelioma[25]	- Multidrug-resistant tuberculosis[26] - Multiple mieloma[27] - Mycosis fungoides[28] - Myelofibrosis[29] - Psoriasis[30] - Pulmonary fibrosis[31] - Lung carcinoma[32] - Renal carcinoma[33] - Systemic sclerosis[34] - Recalcitrant uveítis[35]

Table 2: Reported off-label uses of IFNs.

Since the first reported use of IFN-α for treatment of Behçet-associated uveitis in 1986, [36] the number of studies focused on the use of IFN-α for treatment of ophthalmic diseases have gradually increased (Table 3). On the other hand, there is less reported experience with IFN, which has been basically employed for treatment of multiple sclerosis [12,37].

Research Group and Type Of Study	results
Kötter[38,39] Prospective study (1995-2000), Germany • 50 patients with recalcitrant ocular Behçet • Sex: 36M/14F • Age: 32 y.o (mean); 21-52 y.o (range) • Dose: IFN-α2a 6 MU/day SC • Other treatments: Tapering of systemic steroids to ≤10 mg/day and discontinuation of previous IMT	• Duration of treatment: 16.4 m (mean); 3-58 m (range) • Follow-up: 36.4 m (12-72 m) • Responders (%): 92% • Remission off therapy (%): 40% • Improvement or stabilization VA: 97.3%
Tugal-Tutkun[40] Retrospective study (2001-2005), Turkey • 44 patients with recalcitrant ocular Behçet • Sex: 30M/14F • Age: 30.3 y.o (mean); 14-67 y.o (range) • Dose: IFN-α2a 3-6 MU/day (depending on weight) SC • Other treatments: Tapering of systemic steroids to ≤10 mg/day and discontinuation of previous IMT	• Duration of treatment: 22.2±13.4 m (mean) • Follow-up: 7.8 m (mean); 3-16 m (range) • Responders (%): 91% • Remission off therapy (%): 20% • Reduction of relapses: 1.6±1.2 to 0.8±0.9
Bodaghi[35] Retrospective study (1995-2001), France • 45 patients with severe uveitis of various etiologies (23 Behçet-associated uveitis) • Sex: 27M/18F • Age: 32.3 y.o (median); 8-58 y.o (range) • Dose: IFN-α2a 3 MU 3 times/week SC • Other treatments: IV steroids (pulse) followed by oral steroids (1 mg/Kg/day) and discontinuation of previous IMT	• Duration of treatment: 30.6 m in Behçet (mean), 14-50 m (range); NA for other uveitides • Follow-up: 33.9 m in Behçet (mean), 18-59 m (range); 22 m for others (mean), 12-39 m (range) • Responders (%): 82.6% in Behçet group and 59% in other uveitides • Remission off therapy (%): 32% in Behçet and 23% in other uveitides • Improvement or stabilization VA: 76.3% in Behçet group and 65.4% in other uveitides
Sobaci[41] Prospective case-series (1993-2001), Turkey • 5 patients with serpiginous choroiditis • Sex: 4M/1F • Age: 42.8 y.o (mean); 23-68 y.o (range) • Dose: IFN-α2a 4.5 MU 3 times/week SC • Other treatments: Tapering of systemic steroids to ≤10 mg/day and discontinuation of previous IMT	• Duration of treatment: 7.2 m (mean); 6-12 m (range) • Follow-up: 31.6 m (mean); 16-48 m (range) • Responders (%): 100% • Improvement or stabilization VA (%): 87.5%

Deuter[42] Retrospective study (1994-2007), Germany • 53 patients with recalcitrant ocular Behçet • Sex: 41M/12F • Age: 31.1 y.o (median); 21-58.8 y.o (range) • Others: 45% turkish ethnicity • Dose: IFN-α2a 6 MU/day SC • Other treatments: Tapering of systemic steroids to ≤10 mg/day and discontinuation of previous IMT	• Duration of treatment: 22.4 m (mean); 9.2-79.9 m (range) • Follow-up: 58.5 m (mean); 1-153 m (range) • Responders (%): 98.1% • Remission off therapy (%): 88.7% • Improvement or stabilization VA: 90.6%
Gueudry[43] Retrospective study (1995-2004), France • 32 patients with recalcitrant ocular Behçet. • Sex: 19M/13F • Age: 30.3 y.o (mean); 11-58 y.o (range) • Dose: IFN-α2a 3 MU 3 times/week SC • Other treatments: Tapering of systemic steroids to ≤10 mg/day and discontinuation of previous IMT	• Duration of treatment: 32 m (mean); 16-50 m (range) • Follow-up: 43 m (mean); 11-84 m (range) • Responders (%): 87.5% • Remission off therapy (%): 40.6% • Reduction of relapses: 16.8±1.2 to 0.11±0.2 • Improvement or stabilization VA: 87.5%
Plskova[44] Prospective study (2002-2004), United Kingdom • 12 patients with severe and recalcitrant non-infectious uveitis (2 Behçet, 10 other etiologies) • Sex: 5M/7F • Age: 40.4 y.o (mean); 18-60 y.o (range) • Dose: IFN-α2b 6 MU/day SC • Other treatments: Tapering of systemic steroids to ≤15 mg/day and discontinuation of previous IMT	• Duration of treatment: 13.3 m (mean); 1-29 m (range) • Follow-up: 11 m (mean); 1-29 m (range) • Responders (%): 83% (after first month); 70% (three months after treatment); NA (six months after treatment)
Krause[45] Retrospective study (1988-2007), Germany • 45 patients with ocular Behçet • Sex: 28M/17F • Age: 31 y.o (mean) 15-50 y.o (range). • Others: 60% turkish ethnicity. • Dose: IFN-α2a 6-9 MU 3 times/week SC • Other treatments: Tapering of systemic steroids to ≤10 mg/day and discontinuation of previous IMT	• Duration of treatment: 30 m (mean); 1-101 m (range) • Follow-up: 6.67 years (mean); 0.3-22.3 years (range) • Responders (%): 78% • Remission off therapy (%): 20% • Improvement or stabilization VA: 92%
Sobaci[46] Prospective study (1996-2007), Turkey • 53 patients with recalcitrant ocular Behçet • Sex: 41M/12F • Age: 30 y.o (mean); 20-58 y.o (range) • Dose: IFN-α2a 4.5 MU 3 times/week SC • Other treatments: Tapering of systemic steroids to ≤10 mg/day and discontinuation of previous IMT	• Duration of treatment: at least 6 months (mean and range NA) • Follow-up: 65 m (median); 12-130 m (range) • Responders (%): 84.9% • Remission off therapy (%): 28.3% • Reduction of relapses: 3.61±1.1 to 0.56±0.75 patient/year • Improvement or stabilization VA: 88.7% • Regression of neovascularization
Onal[47] Prospective study (2005-2010), Turkey • 37 patients with recalcitrant ocular Behçet • Sex: 26M/11F • Age: 29 y.o (median) 18-52 y.o (range) • Dose: IFN-α2a 3 MU/day SC • Other treatments: Tapering of systemic steroids to ≤0.5 mg/Kg/day and discontinuation of previous IMT	• Duration of treatment: 21 m (median); 2-24 m (range) • Follow-up: 17 m (mean); 5-24 m (range) • Responders (%): 95% • Remission off therapy (%): 77% • Reduction of relapses: 3.52 to 0.75 patient/year

Table 3: Reported studies of the use of IFN-α for treatment of uveitis.

M: male; F: female; y.o.: years old; MU: millions of International Units; SC: subcutaneous; IMT: immunotherapy; m: months; VA: visual acuity; IV: intravenous; NA: data not available

Although there is a great heterogeneity in the treatment guidelines, the rate of responders (either partial or complete) in patients with recalcitrant ocular Behçet seems to be particularly high oscillating between 78-98% of included patients [35,38-40,42-47]. However it seems to be lower in patients with non-infectious uveitis of other etiologies [41,44]. Some authors have proposed racial and ethnic factors as a cause of these small differences found when comparing reported papers, [40] whereas other authors emphasize different employed dosages and treatment patterns as the main reason [6,48]. Another potential advantage of IFN-α when compared to traditional immunotherapy (IMT) seems to be the fast onset of action considering that the vast majority of patients show a positive response in the first 2 weeks of treatment achieving a complete control of inflammation during the first 4-6 weeks of treatment [6]. These reports also show good functional outcomes with a significant reduction of uveitis relapses [40,43,46,47] and therefore an improvement or stabilization of visual acuity (VA) in 76 to 97% of included patients [35,38,39,41-43,45,46]. Finally, we need to point out that remission off therapy (with absence of uveitis relapses during follow-up) is achieved in 20 to 88% of included patients [35,38-40,42,43,45-47]. Relapses seems to occur during the first year after discontinuation of IFN-therapy and respond favorably to a new cycle of treatment with IFN [43].

Adverse Reactions/Side-Effects

Almost all patients treated with IFN will complain of side-effects although these are usually dose-dependant and reversible after discontinuation of treatment (reported side-effects are shown in table 4). Serious side-effects such as convulsions or comma have been

reported when using high doses of IFN. Both IFN-α and IFN-β are included into FDA pregnancy category C which means that animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

IFN's Reported Side-Effects [35,38-48]	
- Flu-like syndrome: 95-100% - Leukopenia: 5-100% - Dermatologic reaction at injection site: 25-100% - Elevation of liver enzymes: 4-58% - Depression: 0-33% - Alopecia: 2.2-24% - Thyroiditis: 0-8% - Thrombocytopenia: 2-7% - Myalgia/arthralgia: 1.9-3%	- Weight loss: 0-33% - Pruritus: 0-25% (described at high doses) - Retinopathy: 0-25% - Worsening of previous psoriasis: 0-16% - Auto-antibodies: 0-16% - Fibromyalgia: 0-10% - Psychosis: 0-6.7% - Optic neuritis: 0-2% - Epilepsy: 0-2%

Table 4: Reported side-effects related to the use of IFN-α and IFN-β.

There is a strong theoretical and clinical evidence about the ability of IFNs for inducing and/or precipitating autoimmune diseases particularly in predisposing (genetically or environmentally) individuals [2]. Their effects over the expression of the MHC class I, the activation of DCs, the surveillance of T-cells and the induction of Ab production seem to clearly contribute to the development of their side-effects [2]. Some authors have mainly studied the role of TLRs on the appearance of these adverse reactions, [4] whereas other authors consider that the risk of developing these side-effects may be related to the underlying disease or the immune-status of the patient [2]. In this setting, the practitioner should watch out any autoimmune event occurring in the treated patient.

Another interesting issue of using IFN-α for anti-inflammation therapy is the relationship between therapy with IFN and the development of ocular adverse events. There have been reported panuveitis clinically indistinguishable from those associated to Vogt-Koyanagi-Harada syndrome in patients treated with IFN for chronic C-hepatitis [49]. A more common finding in these ocular patients is retinal hemorrhages and cotton-wool spots. The commonly transient and self-limited retinopathy might be related to disturbances in the retinal microvasculature caused by either anomalies in the leukocyte adhesion or increase thrombocyte aggregation, as have been explained above in the hypotheses of action [12-14,50]. The relatively high prevalence of this ocular side-effect explains the widespread retinal screening programs in patients with hepatitis treated with IFN, although these findings seem rare in patients receiving IFN therapy for recalcitrant uveitis [6,44].

A common concern that a physician has when prescribing type I IFN is the potential risk for inducing psychiatric disorders or even suicidal tendences. In this setting it is important to emphasize that the use of IFN is contraindicated if the patient has a history of certain several psychiatric conditions such as depression in the context of other alternative therapeutic approaches. Any psychiatric symptom after starting therapy with IFN requires an urgent evaluation by the specialist [6,48].

Unresolved Issues

The therapeutic approach of Behçet disease requires a multidisciplinary perspective with no available standardized treatment protocols. Therefore, treatment regimens are usually based on personal experience or retrospective studies [48]. There have been substantial advances in the immunotherapy field and treatment with biologic agents have considerably improved the visual prognosis of these patients. But even in this context, a great percentage of these patients will eventually have vision loss along their lives [48]. Since mid-1980s, IFN-α have demonstrated its efficacy in severe and recalcitrant forms of Behçet's uveitis [36]. However, the mechanism of action of this agent is still in discussion. Its immunomodulatory effects might be responsible for antigen removal although it seems to be more related with down-regulation of self-reactive T-cells and/or anti-exudative effects as recently demonstrated with uveitic cystoid macular edema [9-11].

Zierhut and colls. suggest that the efficacy of IFN-α is determined by several factors including the use of intermediate or high doses of this agent [38,39,42,48]. However, other authors propose lower doses considering a better tolerance [46,47]. In any case, discontinuation of other IMT the day before initiation of therapy with IFN together with tapering of systemic steroids up to 10 mg/day as soon as possible are mandatory, considering that these concomitant agents might antagonize the effects of IFN by a reduction on the transcription nuclear factor kappa-beta (NF-κB). It is also important to rule out the presence of other possible associated conditions that would contraindicate the use of IFN such as depression, psoriasis, epilepsia or sarcoidosis.

There is still a great controversy regarding the efficacy of IFN when compared to anti-tumor necrosis factor-alpha (anti-TNFα) agents. Both have shown encouraging results for treatment of non-infectious uveitis with a fast onset of action. Supporting a potential superiority of IFN-α (particularly in ocular Behçet patients) is the reported ability for inducing long-term remissions off-therapy in a high percentage of patients by substantially improving their visual prognosis [35,38-40.42,43,45-47]. However, only infliximab, from the anti-TNFα Group, has shown a similar effect in a low number of cases [51].

Regarding safety profile, side-effects are common when using IFN but usually transient and self-dependant [6,35,38-48]. Production of auto-antibodies have been described in less than 10% of treated patients, [6,38,39,48] whereas up to 70% in patients treated with infliximab in both rheumatological and ophthalmological trials [48].

Regarding economic costs of treatment in Germany, first year of treatment with infliximab would cost around 19,600 eur compared to 9,400 eur by IFN-α [48] in opinion of Zierhut and colls. IFN-α should be considered as second-line therapy for ocular Behçet excepting severe and recalcitrant uveitis in which it can be considered as first-line. On the other hand, anti-TNFα agents should be indicated only in cases refractory to or intolerant with IFN [43,48].

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IL-2 Receptor Antagonists: Daclizumab

Ariel Schlaen[1,2]* and Cristóbal Couto[1]

[1]Hospital de Clinicas "José de San Martín", Universidad de Buenos Aires, Buenos Aires, Argentina

[2]Hospital Universitario Austral, Universidad Austral, Buenos Aires, Argentina

***Corresponding author:** Ariel Schlaen, Universidad de Buenos Aires, Argentina, E-mail: ariel.schlaen@gmail.com

Introduction

Daclizumab is the humanized form of IgG1 monoclonal antibody directed against the 55 kDa alpha subunit of the IL-2 receptor, developed by Waldmann in 1981 [1]. Its molecular weight is 150 kDa and is approximately 90% human origin and 10% murine origin [2]. It was initially approved in 1997 by FDA for its use in the prophylaxis of renal graft rejection. Then its use was extended to other solid organ transplants, multiple sclerosis, and human T lymphocyte leukemia virus 1 (HTLV-1)-associated lymphoma/leukemia (Table1) [1,3]. The production of the drug was discontinued due to a reduced market demand as immunomodulator in the prevention of rejection following solid organ transplantation, the availability of alternative agents, but not to safety causes [3,4].

Prevention of solid organ rejection:
• Kidney
• Liver
• Heart
• Pancreatic islet
Adult T cell lymphoma/leukemia
HTLV-1 associated myelopathy/tropical spastic paraparesis
Multiple sclerosis

Table 1: Reported Non Ocular Clinical Uses of Daclizumab [1].

IL-2 Functions and Regulation

IL-2 is a pleiotropic type 1 cytokine of 15.5 kDa molecular weight, constituted by 4 alpha helical bundles. It is produced mostly by CD4+ T cells after their activation by antigen, but also in a lesser way by CD8+ T cells, natural killer (NK) cells, activated dendritic cells, and mast cells [5,6]. It induces T-cell growth and differentiation of regulatory T-cells (Treg), enhances NK cytolytic activity, promotes antibody production and B cell proliferation, and mediates the activation-induced cell death. The latter is important for the homeostasis and the elimination of autoreactive T-cells, at least in part by means of Fas - Fas L dependent mechanism [5,6].

IL-2 also promotes T helper (Th) 1 and Th2 differentiation, while inhibits the development of Th17. IL-2 is also necessary for IL-9 production [5,6].

IL-2 Receptors

There are three classes of IL-2 receptors. Those receptors are composed by the combination of three subunits, IL-2Rα, IL-2Rβ, and IL-2Rγ. IL-2Rα, also known as p55, Tac, and CD25, is absent or barely expressed on resting T and NK cells. Its expression is induced by T cell receptor (TCR), IL-2, and NK cells stimulated by IL-2. IL-2Rα constitutes the low affinity IL-2 receptor. On the other hand, IL-2Rβ, known as p75, binds poorly by itself with IL-2. This molecule is also part of the IL-15 complex. IL-2Rγ (p64) is also shared by IL-4, IL-7, IL-9, IL-15, and IL 21. When IL-2Rβ and IL-2Rγ combine, they form the intermediate affinity receptor. Both subunits, together with IL-2Rα, form the high receptor affinity. The heterodimerization of the IL-2Rβ and IL-2Rγ cytoplasmic domains is essential for signaling. Thus, only intermediate and high affinity receptors are functional. Intermediate affinity IL-2 receptor is present on resting immune cells. High affinity IL-2 receptor expression is present on activated lymphocytes [5-7].

Mechanisms of Action of Daclizumab

Given the pleiotropic effects of IL-2, the mechanism of action of daclizumab is not fully understood (Table 2). Apparently, daclizumab binds to IL-2Rα, which blocks the linkage between IL-2 and its high affinity receptor on activated lymphocytes [4]. In a study that demonstrates the presence of steroid refractory CD4 T cells in uveitis patients, it was also shown that *in vitro* IL-2 inhibition of peripheral blood mononuclear cells (PBMC) of normal patients, formerly stimulated with CD3-CD28 coated beads, leads to an inhibition of proliferation of CD4+ T cells. Furthermore, the exposure to a combination of IL-2 inhibition and dexamethasone resulted in a greater inhibition of CD4+ cells proliferation than either drug alone [8]. *In vivo*, it was shown that in uveitis patients treated with daclizumab, there is an expansion of 4 to 20 folds the number of CD56bright regulatory NK cells. Moreover, a significantly lower level of CD56bright regulatory NK cells was found in uveitis patients, compared with normal subjects. This kind of cells could secrete large amounts of IL-10, with a likely beneficial effect in individuals suffering from ocular inflammation [9].

However, IL-2 inhibition in mice can induce autoimmunity. It must be taken into account that CD25 stimulation also leads to Treg differentiation, and the relative contribution of IL-2 to CD25+ Treg versus CD25+ effector cells might explain this interspecies difference. Another fact that can account for the disparate effects of IL-2 inhibition between mice and humans is that daclizumab can block CD154 (CD40L) expression in humans, as it was shown by an *in vivo* study. Thus, inhibition of CD40L/CD40 signaling may lead to blockage of T and B cell activation and differentiation [10].

Another mechanism that may explain the efficacy of daclizumab against autoimmune disease is related with a possible activity against a subset of Th17 lymphocytes which can produce low levels of IL-2 (Th17-DP). Th17-DP cells may be responsible for perpetuating cycles of recurrent uveitis. The low level of IL-2 produced by this kind of cells is enough to promote their homeostatic expansion, while it is below the threshold to induce activation-induced cell death. IL-2 depletion leads these cells to become more susceptible to apoptosis. This makes Th17-DP a likely important target of daclizumab therapy [11].

Suppressor of cytokine signaling 5 (SOCS 5), a feedback regulator of Th1 cytokines by means of suppressing JAK/STAT signaling, was shown to be increased in PBMC of uveitis patients. Daclizumab decreased SOCS 5 mRNA levels in PBMC of uveitis patients, suggesting that Th1 response is suppressed by the drug, and also that measuring SOCS 5 mRNA levels may be useful to monitor therapeutic effects in uveitis patients [12]. Recently, it was shown that CD25, which is present in mature antigen presenting cells (m APC), polarizes to the immune synapse with naive antigen specific T cells. During this event, mAPC secrete IL-2 directed to the immune synapse, which binds with CD25. Then, IL-2/CD25 is presented in *trans* to the IL-2 intermediate affinity receptor of the T lymphocyte. This process is essential for activation of T lymphocytes. Daclizumab blocks this "third signal", which profoundly inhibits effective T lymphocytes activation by APC [13].

Blocks the linkage between IL-2 and its high affinity receptor
Inhibits the proliferation of CD4+ T cells
Expands the number of CD56bright regulatory NK cells
Blocks the expression of CD40L (CD154) in humans
Leads Th17-DP cells to become more susceptible to apoptosis
Decreases SOCS 5 expression in peripheral mononuclear blood cells
Blocks IL-2/CD25 *trans*-presentation in DC-mediated T cell activation

Table 2: Mechanisms of action of daclizumab.

Uses and Regimens of Administration Reported in Ocular Inflammatory Disease

Most of the information regarding daclizumab for ocular inflammation was originated in studies carried out by the National Eye Institute (NEI) along more than ten years of research [2,14-20]. Foster and other authors also contributed with several publications [21-24] (Table 3).

Daclizumab use in ocular inflammation was first reported in 1999 [2]. This was a phase I/II clinical trial which included 10 patients with severe intermediate or posterior uveitis. Daclizumab was administered intravenously at 1 mg/kg/dose in a slow drip over an hour. Infusion intervals were every 2 weeks, and they were gradually increased until week 24, when the medication was scheduled to be administered every 4 weeks. At baseline, all patients had been receiving prednisone at a minimum dose of 20 mg, cyclosporine, and/or antimetabolites for at least 3 months. All systemic immunosuppressive (IS) medication was tapered off in an 8 week period, while daclizumab was initiated at 2 weeks after the beginning of the tapering. During the study, 2 patients were discontinued. The first one had a 10 letter drop from baseline, and the other one had a uveitis flare up, therefore conventional IS treatment was reintroduced. There was an overall improvement of visual acuity, in particular in the worse eye. With the exception of one patient, none of the subjects experienced worsening of the vitreous haze. Given the withdrawal of previous IS medication, many patients improved their systemic parameters such as arterial hypertension, creatinine clearances, and cholesterol levels [2]. Between 11 and 15 months after enrollment, 7 patients were randomized to 4 or 6 week infusion schedules (3 and 4 patients, respectively) [14]. One patient was not randomized, and continued with 4 week interval drug administration. Recurrence of inflammation was noted in 3 of 4 patients in the 6 week interval group. Standard IS medication was used to treat these recurrences. When these relapses were controlled, daclizumab was reintroduced at 4 week interval schedule, with tapering of the IS therapy [14]. At 4 years of follow up, 6 patients were switched to subcutaneous daclizumab therapy. They received a dose of 2 mg/kg every 2 weeks for a month, and then 1 mg/kg every month. All these patients maintained a good visual acuity, and none of them had recurrences of the disease [14].

In parallel with this long term prospective study described above, a short term phase II clinical trial using subcutaneous daclizumab from the beginning in patients with intermediate or posterior uveitis, was reported in the same publication [14]. In this trial the drug was administrated every 2 weeks, with 2 induction doses of 2 mg/kg, followed by a maintenance dose of 1 mg/kg for 6 months. Five patients received this treatment regimen. Four of the 5 patients were able to reduce their concomitant IS medication by at least 50%. No patients had uveitis flares or loss of visual acuity during follow-up [14].

A similar prospective trial with the same subcutaneous regimen was carried out with the additional participation of two other centers [15]. Fifteen patients were included in this study, five of each center. All patients except one had controlled intraocular inflammation at baseline. Sixty seven percent of the patients achieved the primary efficacy end point of reducing the load of concomitant IS treatment by at least 50% together with no visual acuity loss greater than 5 letters from baseline at week 12 and 26. Best corrected visual acuity in worse eyes showed an average improvement of one Snellen line from baseline at 12 weeks and of 2 Snellen lines from baseline at week 26. None of the patients showed recurrence of inflammation at week 26 [15].

In a retrospective case series, Papaliodis and coworkers [21] reported 14 patients with ocular inflammatory diseases who underwent daclizumab infusions. Diagnoses were juvenile idiopathic arthritis associated uveitis (n=7), idiopathic panuveitis (n=3), scleritis (n=2), sclerouveitis (n=1), and ocular cicatrizal pemphigoid (n=1). In this study, visual acuity improved in 44% of the eyes (36% of the patients), did not change in 33% of the eyes (36% of the patients), and continued to impair in 22% of the eyes (27% of the patients). The degree of inflammation improved in 59% of the eyes, had no change in 11% of the eyes, and showed worsening in 30% of the eyes.

Efficacy and safety of daclizumab in the management of Behçet's disease associated uveitis were assessed in a small prospective,

placebo-controlled, randomized clinical trial [16]. The drug was administrated at a dose of 1 mg/kg every 2 weeks the first 6 weeks, and every 4 weeks until the end of the study. Results from this trial did not show any beneficial effect of daclizumab for the treatment of the ocular involvement of Behçet's disease [16].

Overall, the opinion of Nussenblatt et al. [14,15] is that intravenous and subcutaneous regimens described above are useful for well controlled ocular inflammatory disease, while poorly controlled ocular inflammation is less likely to have a favorable response to daclizumab. One of the proposed hypotheses is that lymph node lymphocytes had their CD25 not saturated at the former doses used, and maybe a higher initial dose of medication followed by standard daclizumab dose could achieve that even in more sequestered areas [17]. Then, it was proposed that higher doses of the drug would be effective to treat active intraocular inflammation.

In a pilot study, 5 patients with noninfectious intermediate, posterior, and panuveitis underwent treatment with a high dose regimen of daclizumab [17]. Patients received an infusion dose of 8 mg/kg at day 0, 4 mg/kg at day 14. At week 3, if participants showed improvement without serious adverse events (SAE) and did not show a visual acuity loss of 3 or more Snellen lines, they had the possibility to receive an extended treatment of 2 mg/kg subcutaneous daclizumab. At week 4, none of the patients had haze or trace haze in both eyes, and 8 of 9 eyes showed a decrease of the anterior chamber cells. At this time of assessment, vitreous cells showed a decrease in 5 of 10 eyes. Visual acuity experienced an average increase of 9 ETDRS letters (however, this change was not statistically significant). These data suggested that daclizumab at a high dose regimen is efficacious in patients with active uveitis.

High dose treatment with daclizumab efficacy was also assessed for the treatment of juvenile idiopathic arthritis associated active anterior uveitis [18]. Six patients were included in this study, and received infusions of daclizumab at a dose of 8 mg/kg at baseline, 4 mg/kg at week 2, and then 2 mg/kg every 4 weeks for a period of 52 weeks. Four of the 6 patients met the primary efficacy endpoint (two-step reduction in anterior chamber cells according to SUN Working Group [25]) at week 12. However, 3 patients failed to continue the treatment until week 52. One of them due to ocular treatment failure, and the other one two due to a rash possibly related to the study drug, as well as uncontrolled systemic manifestations of the disease [18].

In addition, daclizumab treatment in Birdshot retinochoroidopathy was assessed in a retrospective case series [22]. The dose of daclizumab used initially was of 1 mg/kg every 2 weeks. After suppression of inflammation was sustained over 3 infusions, intervals were increased by 1 week. This was repeated until the longest interval with effective control of inflammation was achieved [22]. When intervals were prolonged beyond 6 weeks, symptoms of floaters and blurred vision occurred in most patients. Seven of the 8 enrolled patients had their visual acuity stabilized or improved, with complete control of vitreous inflammation for an average period of follow up of 25.6 months. Retinal vasculitis showed angiographic resolution in 6 patients. In spite of the fact that electroretinogram (ERG) 30 Hz implicit times and bright scotopic amplitudes deteriorated in some patients, there was an improvement of both parameters in 3 eyes that were treated for more than 2 years. That observation was not reported with any of the traditional IS therapies. Two patients were discontinued from the study due to adverse events [22].

Another approach used to treat active ocular inflammatory diseases refractory to conventional IS therapy was described in a retrospective case series by Bhat et al. [23]. In this study, daclizumab infusions at a dose of 1 mg/kg were initially administrated at 2 weeks intervals. Based on the response, intervals were increased or decreased. If inflammation could not be controlled at certain dose and interval, then the dose was increased up to a maximum of 200 mg. Seventeen patients were included (3 patients were less than 16 years old), with an average of the duration of drug use of 23.6 ± 15.7 months. Time to control inflammation was 9.8 ± 11.3 weeks, and this was achieved in 88.2% of the patients. This study also pointed out that daclizumab can be used as a long term therapy, as also was shown in a previously described study [14].

The outcomes of one year daclizumab treatment for Stevens Johnson Syndrome were described in a prospective, non randomized, case series study. Five patients who failed conventional IS therapy were included in the study, receiving a drug regimen similar to another described above [2]. Control of ocular inflammation was achieved at a median of 8 weeks (range 6-10 weeks) in all the patients. Only 2 of them relapsed at 20-36 weeks, and they were controlled with topical corticosteroids [24].

The whole experience of the NEI during an 11-year period with the use of daclizumab in chronic, noninfectious intermediate and posterior uveitis was assessed in an interesting retrospective review [19]. This study included 39 patients with an average follow up of 40.3 months. Twenty-nine patients underwent intravenous administration with the standard regimen [2], 5 patients received subcutaneous administration [14], and 5 patients received a high dose intravenous regimen [17]. Ages ranged from 13 to 70 years old, and 41% were male. Visual acuity in the better eye improved by 2 lines or more in 7 patients (18.4%) and worsened by 2 lines or more in 6 patients (15.8%). There were no significant statistical associations between baseline vitreous cells, vitreous haze or anterior chamber cells with worsening or improvement in visual acuity, but the numbers were too small to make definitive conclusions. Vision loss of more than 2 lines was reported due to refractory inflammation in 2 cases. Other ocular complications that cause vision loss were macular edema, epiretinal membrane formation, glaucoma, and continued corneal decompensation in one case each. During treatment period, the mean number of IS medications per patient decreased from 1.89 medications/patient at baseline to 1.17 medications/patient at the end of the follow-up [19]. The mean number of flares was of 2.05 flares/patient with a rate of 0.62 flares/patient-year. Mean macular thickness in 19 patients with cystoid macular edema decreased from 259 μm at baseline to 235 μm at the end of the follow up. The amount of perifoveal leakage decreased in 32.5% of patients and 61.76% had no change in fluorescein angiogram during follow-up [19].

Another indication for the use of daclizumab was recently reported by Larson et al. [20]. In one patient with scleritis secondary to HTLV-1 associated adult T cell leukemia/lymphoma, daclizumab was administered intravenously at a dose of 8 mg/kg every 3 weeks, with a favorable response of the scleral inflammation [20]. T cell proliferation is stimulated during HTLV-1 replication, due to the expression of Trance activator X (Tax), a viral protein encoded in the provirus genome. Tax activates NF-κ/B, which up-regulates the expression of IL-2 and IL-2 receptors, then leading to growth promotion of infected cells [26]. This autocrine cytokine loop is inhibited by anti-Tax antibodies [1].

From the exposed data, daclizumab seems to be a promising additional therapeutic tool to treat ocular inflammation. However, further larger clinical trials are needed in order to evaluate accurately its efficacy, and also to assess its place in the IS therapy and the most suitable way to use it.

Publication	Study design	Number of patients	Diagnosis	Treatment Regimen
Nussenblatt et al. [2]	Phase I/II clinical trial	10 patients	IU/PU	IV 1 mg/kg Initially every 2 weeks, intervals increased until week 24, then every 4 weeks
Nussenblatt et al. [14]	Phase I/II clinical trial	8 patients	IU/PU	IV 1 mg/kg Randomized to every 4 or 6 weeks. At 4 years 6 patiens switched to SC administraion
	Nussenblatt et al. [14]	5 patients	IU/PU	SC every 2 weeks, initially 2 doses of 2 mg/kg, then 1 mg/kg
Nussenblatt et al. [15]	Open label interventional trial	15 patients	IU/PU	SC every 2 weeks, initially 2 doses of 2 mg/kg, then 1 mg/kg
Papaliodis et al. [21]	Retrospective case series	14 patients	JIA/IPS/SU/OCP	IV 1 mg/kg Initially every 2 weeks, intervals increased until week 24, then every 4 weeks
Buggage et al. [16]	Double-masked, placebo controlled clinical trial	17 patients	BD	IV 1 mg/kg Initially every 2 weeks for 6 weeks, then every 4 weeks
Yeh et al. [17]	Pilot study	5 patients	IU/PU	IV 8 mg/kg at day 0, 4 mg/kg at day 14, then 2 mg/kg every 4 weeks
Sen et al. [18]	Phase II pilot study	6 patients	JIA	IV 8 mg/kg at day 0, 4 mg/kg at day 14, then 2 mg/kg every 4 weeks
Sobrin et al. [22]	Retrospective case series	8 patients	BSC	IV 1 mg/kg every 2 weeks, then increased by 1 week until the longest effective interval was achieved
Bhat et al. [23]	Retrospective case series	17 patients	HLA-B27/ IAU/IU/MCP IP/IP&S/ SPU RV/IKU/AKC HSV-S	IV 1 mg/kg every 2 weeks, intervals increased or decreased according to response. Dose may be increased at a maximum of 200 mg
Fiorelli et al. [24]	Prospective case series	5 patients	SJS	IV 1 mg/kg Initially every 2 weeks, intervals increased until week 16, then every 4 weeks
Wroblewski et al. [19]	Retrospective chart review	39 patients	BD/IIU/SPU/ BSC/VKH/NS	IV (29 patients), high dose IV (5 patients), and SC (5 patients) described above in the table
Larson et al. [20]	Case series	1 patient	HTLV 1 L&S	8 mg/kg every 3 weeks

IU: Intermediate Uveitis; PU: Posterior Uveitis; JIA: Juvenile Idiopathic Artritis Associated Anterior Uveitis; IP: Idiopathic Panuveitis; S: Scleritis; SU: Sclero Uveitis; OCP: Ocular Cicatricial Pemphigoid; BD: Behçet's Disease; BSC: Birdshot Chorioretinopathy; HLA-B27: HLA-B27 Associated Anterior Uveitis; IAU: Idiopathic Anterior Uveitis; IU: Intermediate Uveitis; MCP: Multifocal Choroiditis And Panuveitis; IP&S: Idiopathic Panuveitis and Scleritis; SPU: Sarcoid Panuveitis; RV: Retinal Vasculitis; IKU: Idiopathic Keratouveitis; AKC: Atopic Keratoconjunctivitis; HSV-S: Herpes Simplex Virus Associated Scleritis; SJS: Stevens Johnson Syndrome; IIU: Idiopathic Intermediate Uveitis; VKH: Vogt Koyanagi Harada Disease; HTLV 1 L&S: Scleritis Secondary To HTLV-1 Associated Adult T Cell Leukemia/Lymphoma; NS: Non-Specified. IV: Intravenous; SC: Subcutaneous

Table 3: Reported clinical use of daclizumab in ocular inflammation.

Side Effects and Risk of Malignancy

Daclizumab is well tolerated in all its forms of administration. However, its use was associated most commonly with cutaneous side effects, which included drug eruption, eczema, fibrosis, psoriasis, and folliculitis [2,14,18,19]. Only one of 186 subcutaneous injections in a prospective study was associated with moderate pain that did not required any treatment. Another patient reported mild discomfort in 3 different injections, which needed the use of acetaminophen [15]. Other reported side effects are: elevated liver function tests, transient leukopenia, lower extremity edema, herpes zoster skin infection, fungal groin infection, upper extremity neuralgia, lymphadenopathy, palpitations, isolated chest pain with normal EKG, upper respiratory infections, gastrointestinal infections, and cramping [2,14-17,19,21-23]. One patient who received high dose regimen, complained about extreme lethargy and shortness of breath. Another patient on this regimen developed pneumonia requiring hospitalization and treatment with systemic antibiotics [19]. Importantly, one patient with Behçet´s disease developed cerebellar herniation after abrupt termination of daclizumab. Due to this experience, Wroblewsky et al. [19] recommended a slow increase of interval treatment before considering withdrawal of the medication.

One of the major overall concerns about IS therapy is the increased risk of malignancy. A metanalysis of clinical trials outcomes in patients undergoing kidney transplant showed no greater risk of malignancy with daclizumab [27]. However, 4 cases of malignancy in 39 patients were reported in the long-term retrospective review of Wroblewski et al. [19]. Two of the four cases occurred after only 3 doses, while the other two developed doses 50 and 51 of intravenous daclizumab. These patients also were using other IS therapy such as cyclosporine, sirolimus and mycophenolate mophetil. Thus, it is difficult to assess if malignancy occurrence in these cases is directly related to the anti-Tac antibody. Further larger and well-designed clinical trials are necessary for answering this question.

Final Considerations

Daclizumab seems to be a safe and promising drug in the treatment against ocular inflammation. It promotes tolerance in solid organ transplantation, noninfectious uveitis, and multiple sclerosis [13]. Although, as it was shown, at low doses the drug almost completely saturates CD25 in blood [14], therapeutic efficacy increases with higher doses of medication [17,18]. Thus, it was suggested that not only blood lymphocytes must have their CD25 saturated, but also those located in tissues and lymph nodes [13,17]. This is in agreement with the recently discovered pivotal role of CD25 and IL-2 in the interaction between mAPCs and T lymphocytes [13]. This is the rationale for the high dose regimen, which proved to be useful in controlling active intraocular inflammation [17,18]. Notwithstanding, the most

suitable dosing and regimen of the drug must be elucidated yet, considering also its safety aspects. Large, well-designed and controlled clinical trials are needed to solve these issues.

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IL-6 Receptor Antagonist: Tocilizumab

Anna Leszczynska* and Marina Mesquida*

Clinical Institute of Ophthalmology, Hospital Clinic of Barcelona, Barcelona, Spain

***Corresponding author:** Anna Leszczynska, Clinical Institute of Ophthalmology, Hospital Clinic of Barcelona, Barcelona, Spain, Tel: 932275667; E-mail: anna.m.leszczynska@gmail.com,

Marina Mesquida, Clinical Institute of Ophthalmology, Hospital Clinic of Barcelona, Barcelona, Spain, Tel: 932275667; E-mail: mesquida@clinic.ub.es

Biology of Interleukin-6

Interleukin-6 (IL-6) is a key cytokine featuring redundancy and pleiotropic activity [1]. It plays a central role in host defense against environmental stress such as infection and injury. Under physiological conditions IL-6 is barely detectable (1-5 pg/ml), although its levels can increase more than 100000 - fold during early phases of inflammation [1,2]. In infectious inflammation, IL-6 is produced by monocytes and macrophages immediately after the stimulation of Toll-Like Receptors (TLRs) with distinct Pathogen-Associated Molecular Patterns (PAMPs) [2]. In non-infectious inflammations such as burn or traumatic injury, Damage-Associated Molecular Patterns (DAMPs) from damaged or dying cells stimulate TLRs to produce IL-6 [3]. This acute IL-6 expression is key in host defense by stimulating various cell populations. When acting on hepatocytes IL-6 strongly induces a wide variety of acute-phase proteins such as C-Reactive Protein (CRP), serum amyloid A, fibrinogen, haptoglobin, among others [4]. CRP is a good biomarker of inflammation and is used as such in clinical laboratory tests. Importantly, its expression principally depends on IL-6 [5]. In lymphocytes, IL-6 induces B cell differentiation into immunoglobulin-producing cells [1]. IL-6 together with TGF-beta preferentially promotes differentiation of IL-17 producing T Helper cells (Th17) that play a crucial role in the induction of autoimmune tissue injury [6,7]. However, IL-6 inhibits TGF-beta-induced regulatory T cell (Treg) differentiation [8]. The resultant Th17 / Treg imbalance leads to breakage of immunological tolerance and is of pathological importance for the development of various autoimmune and chronic inflammatory diseases [9]. IL-6 also induces CD8-positive T cells to generate cytotoxic T cells [10].

Aside from its role in host defense, IL-6 has many other important biological functions. In hematopoiesis IL-6 induces maturation of megakaryocytes into platelets and activation of stem cells [11]. In bone marrow, IL-6 activates osteoclasts leading to bone resorption and osteoporosis [12]. Production of IL-6 in inflamed tissues induces excess of Vascular Endothelial Growth Factor (VEGF), which causes increased angiogenesis and vascular permeability [13]. The excess of IL-6 in dermal keratinocytes promotes their proliferations and dermal fibroblasts collagen production what may contribute to autoimmune diseases like psoriasis, systemic scleroderma, and thyroid eye disease [14-17]. Table 1 summarizes IL-6 principal biological functions.

Immune response and inflammation	Induction of final maturation of B cells into antibody producing cells
	Activation and proliferation of T cells
	Induction of cytotoxic T-cell differentiation
	IL-6 together with TGF-beta preferentially promotes differentiation of Th17 cells
	IL-6 inhibits TGF-beta-induced regulatory T cell (Treg) differentiation
	IL-6 induces excess of VEGF, which causes increased angiogenesis and vascular permeability
Bone homeostasis	In bone marrow, IL-6 activates osteoclasts leading to bone resorption and osteoporosis
Hematopoiesis	
	Induction of hematopoietic stem cells from G0 to G1
	Maturation of megakaryocytes into platelets
Stimulation of cell growth	Induction of the growth of myeloma/plasmocytoma cells
	Induction of mesangial cell growth
Inhibition of cell growth	Growth inhibition of myeloid leukemia cells and breast carcinoma cell lines
Neural system	Induction of neural cell (PC12) differentiation
Acute phase reaction proteins	IL-6 could induce a variety of acute phase proteins such as fibrinogen, alpha-1-antichymotrypsin, alpha-1-acid glycoprotein, and haptoglobin.
	IL-6 induces serum A amyloid, C-reactive protein, and alpha-1-antitrypsin in human hepatocytes.
	Serum levels of IL-6 correlate well with that of C-reactive protein and fever in patients with severe burns.

Table 1: Biological functions of IL-6 [1]

IL-6 Signalling

IL-6 triggers signal transduction after binding to the IL-6 receptor (IL-6R) [18]. There are 2 forms of the IL-6R, the transmembrane receptor protein and the soluble form (sIL6-R). It has been reported that soluble interleukin (IL)-6 receptor (sIL-6R) is detected in the serum of healthy individuals and its level is increased in patients with multiple myeloma and human immunodeficiency virus infection. After binding of IL-6 to transmembrane IL-6R, the resultant IL-6/IL-6R complex associates with gp130 protein [18]. The activated IL-6R complex forms a hexameric structure consisting of two molecules each of IL-6, IL-6R and gp130 (so-called classical signalling). The expression of transmembrane IL-6R is limited to few types of cells but the IL-6/sIL-6R complex can also transduce the IL-6 signal to

various cells that do not express transmembrane IL-6R but express gp130 (known as trans-signaling mechanism), so that IL-6 affects a wide variety of cells [1,2,18]. Tamura et al. suggested that increased circulating or locally produced sIL-6R induces osteoclast formation in the presence of IL-6 mediated by a mechanism involving gp130 [19].

Pathological Role of IL-6 in Development of Autoimmune Diseases

Dysregulated, persistent IL-6 production has been implicated in the development of various autoimmune, chronic inflammatory diseases, and even cancers [1,2,16,17]. The reason(s) why such dysregulated, continuous IL-6 production is induced remains to be clarified. Elucidation of mechanisms underlying persistent IL-6 synthesis in so many different diseases is of particular importance to tailor treatment. Such investigations are now in progress. Indeed, numerous animal models of diseases have disclosed the pathologic role of IL-6 in disease development, including mouse models of rheumatoid arthritis [20], systemic lupus erythematosus [21], scleroderma [22], Castleman's disease [23], Experimental Autoimmune Uveoretinitis (EAU) [24,25], and experimental autoimmune encephalomyelitis [26]. In those animal models, IL-6 blockade by means of gene-knockout mice or administration of anti-IL-6 or anti-IL-6R antibody can suppress such disease development either preventively or therapeutically [20-26].

Targeting IL-6

Tocilizumab (Actemra outside the EU, and RoActemra inside the EU) is a humanized monoclonal antibody, developed by grafting the complimentary-determining regions of mouse anti-human IL-6R antibody onto human IgG1.

Tocilizumab blocks IL-6 mediated signaling by binding to both soluble and Trans membrane IL-6 receptors [17]. This way it reduces IL-6 pleiotropic actions such as T cell activation, Th17 differentiation (and resultant Th17/Treg misbalance), antibody secretion, and hepatic acute phase proteins production (CRP) [27,28]. Indeed, CRP level is a hallmark for checking whether IL-6 activity is completely blocked *in vivo* [17].

Tocilizumab: Current and Future Indications

Tocilizumab has been approved by the Food and Drug Administration (FDA) for use in patients with rheumatoid arthritis who have active disease despite having been treated with one or more Disease Modifying Anti-Rheumatic Drugs (also called DMARDs), including other biologic response modifiers such as TNF inhibitors or methotrexate [29]. It is also approved for use in children over 2 years of age with the systemic form of Juvenile Idiopathic Arthritis (JIA) [30], and for Castleman disease in Japan and India [31]. Table 2 summarizes current and potential indications of tocilizumab. Recent pilot studies have suggested that tocilizumab may have broad application for other chronic, immune-mediated diseases such as systemic lupus erythematosus [32], systemic sclerosis [33], polymyositis [34], systemic vasculitis [35], Behçet's disease [36,37], Still's disease [38], Crohn's disease [39], relapsing polychondritis [40], polymyalgia rheumatica [41], and uveitis and its associated ocular complications [42-45]. It has been suggested that IL-6 blockade may be also useful as a treatment of organ specific immune diseases like acquired hemophilia A [46], autoimmune hemolytic anemia [47], amyloid A amyloidosis [48], graft-versus-host disease [49], as well as other non-organ specific autoimmune conditions [50,51]. Finally, it is expected that long-term treatment with tocilizumab may offer protection against the progression of atherosclerosis as it was observed that during tocilizumab treatment of patients with rheumatoid arthritis, HbA1c levels and insulin resistance indices improved [52].

Table 2 shows the approved and off-label uses of tocilizumab. Table 3 shows the concluded and ongoing clinical trials on efficacy of tocilizumab in diseases other than rheumatoid arthritis.

Approved indication	**Region where approved**
Rheumatoid arthritis	>90 countries worldwide
Castleman's disease	Japan, India
Systemic Juvenile Idiopathic Arthritis	Japan, India, USA, Europe
Off-label applications	**Type of scientific evidence**
Systemic Lupus Erythematosus	Case series
Systemic sclerosis	Case series
Polymiositis	Case series
Vasculitis syndrome	Case report and series
Crohn's disease	Case reports
Relapsing polychondritis	Case reports
Acquired hemophilia A	Case reports
Autoimmune hemolytic anemia	Case reports
Adult-onset Still's disease	Case reports and series
Amyloid A amyloidosis	Case reports
Polymialgia rheumatica	Case reports and series

Remitting seronegative, symmetrical synovitis with pitting edema	Case reports
Behçet's disease	Case reports and series
Uveitis	Case reports and series
Graft-versus-host disease	Case reports and series
Tumor necrosis factor associated periodic-syndrome	Case reports
Spondyloarthritis	Case reports
Pulmonary arterial hypertension	Case reports
Atopic dermatitis	Case reports
Sciatica	Case reports

Table 2: Approved and off-label uses of tocilizumab [17].

Targeted diseases	Trial identifier
ClinicalTrials.gov (USA)	
Adult onset Still's disease	NCT01002781
Relapsing polychondritis	NCT01041248
Type II diabetes, obesity	NCT01073826
Ankylosing spondylitis	NCT01209702
Grave's ophthalmopathy	NCT01297699
Cardiovascular disease in RA	NCT01331837
Polymialgia rheumatica	NCT01396317
Giant cell arteritis	NCT01450137
Acute graft versus host disease	NCT01475162
Non-ST elevation myocardial infarction	NCT01491074
Systemic sclerosis	NCT01532869
Transplant rates in highly sensitized patients awaiting kidney transplantation	NCT01594424
Schizophrenia	NCT01696929
Non infectious posterior, intermediate or panuveitis	NCT01717170
Castleman's disease	NCT01441063
Juvenile Idiopathic Arthritis	NCT01734382
Ovarian cancer	NCT01637532
Fibrous dysplasia of bone	NCT01791842
Primary Sjogren's Syndrome	NCT01782235
Horton's disease	NCT01910038
EU Clinical Trials Registry	
Ankylosing spondylitis	2009-017488-40, 2009-017443-34
Cardiovascular disease in RA	2010-020065-24
Grave's ophthalmopathy	2010-023841-31
Systemic sclerosis	2011-001460-22
Erdheim Chester disease	2012-003151-11
Polyarticular-course juvenile idiopathic arthritis	2011-001097-25
Giant cell arteritis	2011-006022-25
UMIN-CTR clinical trial (Japan)	
ANCA associated vasculitis	UMIN00002892
Systemic sclerosis	UMIN00005550
Neuromyelitis optica	UMIN00005889
Chronic glomerulonefritis	UMIN00006080
Colorectal cancer	UMIN00007493
Takayasu arteritis	UMIN00007845

Table 3: Concluded and going trials on efficacy of tocilizumab in diseases other than rheumatoid arthritis.

IL-6 Blockade in Ocular Inflammatory Diseases

Different studies have found significant elevation of IL-6 in ocular fluids derived from refractory/chronic uveitis patients and animal models [53,54]. Experimental Autoimmune Uveitis (EAU) is a rodent model of human uveoretinitis, and recent studies have revealed that highly proinflammatory IL-17-producing Th17 play a pivotal role in the development of EAU, human uveitis, and other experimental autoimmune diseases [55]. Several lines of evidence have shown that autoreactive Th1 and Th17 cells mediate EAU, and IL-6 was recognized as an essential factor in inducing early phase of Th17 differentiation from naïve T cells in combination with TGF-beta [56]. Th17 cells further produce IL-17, IL-6, and TNF-alpha, and these cytokines perpetuate inflammation by stimulating fibroblasts, endothelial cells, and macrophages to produce chemokines, with the subsequent recruitment of more neutrophils and macrophages to the retina, which results in tissue damage and chronic inflammation [56,57]. Several studies have demonstrated that the inactivation of the IL-6 gene or the blockage of the IL-6 molecule inhibited the development of uveitis by suppression of the Th17 response [58]. Yoshimura et al. [59] studied the role of Th17 cells on EAU by using IL-6- and IL-23- deficient mice, and confirmed that EAU development was reduced in these animals. They found that systemic administration of recombinant anti-IL-6-receptor antibody ameliorates EAU interfering with antigen-specific Th17 differentiation/expansion, and concluded that IL-6 blockade can suppress acute Th17 responses and ameliorate chronic/refractory intraocular inflammation.

On the other hand, TGF-beta alone promotes naive T cells to differentiate into Treg, which are considered immunosuppressive helper T cells [58]. Thus, Th17 and Treg cells are distinct subsets of helper T cells, and IL-6 signalling promotes Th17 cells and inhibits Treg cell differentiation. Haruta et al. [25] found that the IL-6 signalling blockade not only inhibited Th17 cell differentiation but also promoted antigen-specific Treg cells, which, in turn, suppressed the inflammatory effects of antigen-specific Th1 cells. Thus, the inhibitory effect

of the IL-6 blockade in the development of EAU is associated with suppression of the induction of both Th1 and Th17 cells and their dominant proinflammatory effects in this disease [25].

To date, reports on tocilizumab efficacy in clinical uveitis remain sparse. Adán et al. [60] reported the efficacy of tocilizumab in eight eyes of five uveitis patients with Cystoid Macular Edema (CME) refractory to conventional immunosuppressive drugs and anti-TNF therapy. After 6 months of tocilizumab infusions CME resolved in all eyes. These authors suggest that early use of tocilizumab in refractory uveitis patients could lead to better functional results than when indicated after long-term disease duration. Similarly, Muselier et al. [45] found that tocilizumab was effective in two uveitis patients diagnosed with Birdshot chorioretinopathy and idiopathic granulomatous panuveitis who were refractory to conventional immunosuppressive drugs. Tocilizumab induced uveitis control in both patients and also macular edema resolution in one case. Tappeiner et al. [44] reported that tocilizumab was effective for the treatment of ocular inflammation in 2 out of 3 patients suffering uveitis associated with juvenile idiopathic arthritis refractory to several disease modifying anti-rheumatic drugs and anti-TNF agents. Efficacy of tocilizumab in patients with uveitis accompanied with Behçet's and Castelman disease has also been reported [36,61,62].

To date there are two ongoing phase 1-2 clinical trials to study tocilizumab therapy for uveitis: the STOP-UVEITIS Study (NCT01717170), which is a study of the safety, tolerability, and bioactivity of tocilizumab on patients with non-infectious uveitis, and another study about tocilizumab in the management of juvenile idiopathic arthritis-associated uveitis (NCT01603355).

Another ocular inflammatory disease, whose etiology was shown to be associated with IL-6 action is thyroid eye disease [15,63]. Slowik et al. [64] proved that in patients with thyroid eye disease the IL-6 and soluble IL-6 receptor levels were significantly higher than in normal controls. They also showed that after efficient treatment soluble IL-6 receptor levels decreased in thyroid eye disease patients. Due to these findings tocilizumab was pointed as a potential treatment for thyroid eye disease resistant to endogenous corticosteroids treatment. To date there is one ongoing, phase three studies on tocilizumab efficacy in thyroid eye disease refractory to corticosteroids (NCT01297699). The purpose of this study is to investigate tocilizumab administration in patients with moderately to severely or sight-threatening Graves' ophthalmopathy without response to treatment with corticoid intravenous pulses. Currently these patients only have surgery as therapeutic alternative.

Dosing

Tocilizumab is given as intravenous infusions every 4 weeks. Although some patients may improve during the weeks after the first infusion, it may take as long as 6 -12 weeks to see results. For children with systemic juvenile idiopathic arthritis, dosing can be as frequent as every two weeks. Tocilizumab dose is adjusted according to the patient's weight. The dose in adults is 8 milligrams of tocilizumab per kilogram of body weight but not less than a total of 480 mg and not more than 800 mg every 4 weeks. The authors found no data in regard to a possible difference in dose recommendation in relation to patient's gender. In children, the dose is 8 milligrams per kilogram in those weighing over 30 kilograms (66 pounds) and 12 milligrams per kilogram in those under 30 kilograms. The drug should not be administered to children younger than 2 years old and should not combine with another biologic agent [65].

Safety

Il-6 is not only pro-inflammatory cytokine with activities in the innate and adaptive immune system but also governs the hepatic acute-phase control, stimulates regeneration of intestinal epithelial cells, and helps to control glucose homeostasis. Therefore a variety of side effects may occur as a result of the action of IL-6 receptor antagonist in human organism.

In clinical trials, adverse events associated with tocilizumab have included infections, infusions reactions and gastrointestinal perforation [66,67].

Laboratory abnormalities have included hyperlipidemia, transaminemia and neutropenia. Special attention should be also paid to possible increase in risk of neurological disorders and malignancies. Although up to date clinical trials have not shown statistically significant relation between tocilizumab and these diseases. There is no sufficient evidence on safety of tocilizumab in infants and pregnant women [68].

Infections

Reactions to tocilizumab infusions, including fever and chills, can occur, but these are rare. Perhaps the most concerning potential side effect with regular therapy is the risk of infection, as it is with most biologic therapies. The primary concern is for common bacterial infections. Unusual infections, such as Tuberculosis (TB), have not been seen frequently with tocilizumab, but they do remain a concern, and screening for prior exposure to TB is recommended before starting tocilizumab therapy. Screening and monitoring for TB and other important but unusual infections', including fungal infections, is important during treatment with tocilizumab. Overall, the rate of infection seen in clinical trials with tocilizumab was similar to that seen with other biologic drugs used in the treatment of rheumatoid arthritis [67]. In a recent meta-analysis of 6 randomized, controlled trials of tocilizumab 4mg/kg and 8mg/kg revised by Campbell et al. [68] the risk of infection was significantly higher than in placebo or control group (OR 1.30, 95% CI 1.07-1.58). Though opportunistic infections in patients treated with tocilizumab are rare, cases reported in literature include ophthalmic Herpes Zoster Virus infection, allergic bronochopulmonary aspergillosis and cytomegalovirus associated pneumonitis [68]. In patients treated with tocilizumab active infections should be discarded before the treatment is commenced. It is recommended to perform hepatitis B serology and tuberculin skin before starting the treatment. Patients diagnosed with latent tuberculosis should undergo prophylaxis treatment before starting tocilizumab infusions. In case of developing a severe active infection once treatment with tocilizumab has been initiated, therapy should be interrupted. No live or live attenuated vaccines shall be administered simultaneously with tocilizumab treatment, as its clinical safety has not been established yet [68].

Gastro-intestinal complications

Twenty-six cases of gastrointestinal perforation have been reported among clinical trials on tocilizumab with an incidence of 2.8 cases per 1000 patients per year (with no cases reported in control groups) [68]. Therefore tocilizumab shall be used with precautions in patients with history of intestinal ulceration or diverticulitis. In case of signs or symptoms of abdominal pain, gastrointestinal hemorrhage, fever or changes in bowel movements habits prompt evaluation shall be performed in order to discard gastrointestinal disease and a risk of concomitant perforation [68].

Active hepatic disease and insufficiency

Tocilizumab - especially when associated with methotrexate - may cause an increase in hepatic transaminases levels. Although no increased risk of clinical hepatitis was noted, the initiation of treatment with tocilizumab should be evaluated carefully in patients with hepatic transaminases level 1.5 fold higher than normal serum values and it is not recommended when the serum levels are 5 fold higher than normal range [68]. The values of transaminases shall be checked every 4-8 weeks in the first 6 months of treatment with tocilizumab and then every 12 weeks. If the transaminases levels are higher than 3 fold normal limits values the treatment should be interrupted. If the levels fall back below the mentioned limits the treatment may be reinitiated with a dose between 4-8 mg/kg [68].

Hematologic alterations

The initiation of treatment with tocilizumab should be evaluated carefully in patients with serum neutrophils and platelets counts. Treatment is not recommended when absolute neutrophils and platelets levels place below 500/ml and 50.000/uL, respectively. The neutrophils and platelets count should be performed every 4-8 weeks at the commencement of the treatment. The risk of neutropenia is higher in patients treated previously with anti-TNF agents [68].

Serum lipids alterations

The serum lipids levels should be evaluated 4-8 weeks after starting treatment with tocilizumab and if needed hyperlipidemia should be treated.

Neurological disorders

Currently the risk of central demyelinating process in patients treated with tocilizumab is not known. Therefore the clinicians shall pay a special attention to possible signs of a demyelinating disease in patients receiving tocilizumab [68].

Malignant tumors

There was no increased risk of malignancies noted in clinical trial. The risk and benefits ratio should be evaluated personally in patients with history of cancers though [68].

Use in pregnancy, children and elderly

Tocilizumab is not recommended in children under the age of 2 due to limited data on its safety and efficacy in this group of patients. There is no sufficient data on use of tocilizumab in pregnant women. Studies on animals have shown increase in miscarriage and embryo-fetal death with high dose. Women in fertile age group should be using effective contraceptive methods to prevent pregnancy during the treatment period and up to 6 months after its termination. There are no studies on tocilizumab excretion in human or animal milk and therefore the treatment is not recommended in breastfeeding women [69].

Use in renal and hepatic insufficiency

The dose adjustment is not needed in patients with mild renal insufficiency. Up to date there are no studies on use of tocilizumab in patients with moderate to severe renal failure or hepatic insufficiency [68].

Interactions with other drugs

In vitro studies have shown that expression of hepatic CYP450 enzymes is suppressed by IL-6. This inhibition may be reverted in patients treated with tocilizumab due to IL-6 actions suppression. This can affect the metabolism of drugs metabolized by CYP450, 3A4, 1A2, 2C9 or 2C19 enzymes like simvastatin, atorvastatin, calcium antagonists, theophylline, acenocoumarol, phenytoin, cyclosporine and benzodiazepines. It may be necessary to increase the dose of the aforementioned drugs to maintain their therapeutic effect [68].

Cost of Treatment with Tocilizumab

The price of 80 and 200 mg tocilizumab vial is 139.6 and 349 euros respectively. The habitual dosage of tocilizumab is 8 mg/kg every 4 weeks. The annual cost of treatment is of 12.159 euros for a single patient of an average weight of 67 kg. Additionally the costs of intravenous administration must be summed, which require 13 days of hospital ambulatory admission per patient.

Points to Remember

- Tocilizumab is a biologic response modifier for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis.
- It has been approved by the FDA for use in patients who have not responded to other DMARDs or other biologic response modifiers, and it may be given with or without methotrexate and/or other non-biologic drugs.
- Tocilizumab has shown efficacy in uveitis and its associated macular edema. Ongoing clinical trials are studying its efficacy in autoimmune uveitis and thyroid eye disease.
- It should not be taken with another biologic agent
- Infections, especially TB, should be ruled out. Blood tests will be used to monitor for increases in cholesterol or liver enzymes and for reductions in blood cell counts while taking tocilizumab.
- It should not be given to children under the age of 2, pregnant and breastfeeding women as sufficient safety data in these patient groups are lacking.

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IL-1β Antagonists: Anakinra, Rilonacept, Canakinumab, Gevokizumab

Maite Sainz de la Maza*

Uveitis Unit, Ophthalmology Department, Hospital Clinic of Barcelona, Barcelona, Spain

***Corresponding author:** MaiteSainz de la Maza, Uveitis Unit, Ophthalmology Department, Hospital Clinic of Barcelona, Barcelona, Spain, E-mail: msainz@clinic.ub.es

Introduction

Noninfectious uveitis has a complex and multifactorial etiology that involves the breakdown of the blood-eye and blood-retinal barriers as well as activation of both systemic and intraocular inflammatory components, mechanisms, and processes. Pro-inflammatory cytokines, such as Interleukin-1 Beta (IL-1β), Tumor Necrosis Factor Alpha (TNF-α), and Interleukin 6 (IL-6), play a central role within these ocular inflammatory events. The combined effects of IL-1β or IL-6 along with Transforming Growth Factor beta (TGF-β) induce T helper 17 cells which have demonstrated induction of a neutrophil-associated Experimental Autoimmune Uveitis/Uveoretinitis (EAU)[1-4]. It has also been reported that TNF-α, as well as vascular endothelial growth factor and IL-1β may contribute to the breakdown of the blood-retinal barrier in both, EAU and patients with uveitis. The possible mechanisms are related to opening of tight junctions and increased vesicular transport within the endothelial cells [5].

IL-1β and the Autoinflammatory Disorders

The IL-1 family comprises several members, including IL-1α, IL-1β, and IL-1 Receptor antagonist (IL-1Ra). These cytokines are produced by many cell types, including monocytes and macrophages.

IL-1β is a dominant mediator of inflammatory responses by inducing growth and differentiation of immune competent lymphocytes. IL-1β acts as a messenger to up regulate the innate immune system´s response to infection, injury, and stress [6]. IL-1β expression level and function are tightly regulated by a complex system of IL-1 family members and their receptors.

IL-1β exerts its effects through Interleukin-1 Receptor type I (IL-1RI) and Interleukin-1 Receptor Accessory Protein (IL-1RAcP), which together form the active signaling-competent complex. IL-1β also binds to a second receptor, Interleukin-1 Receptor type II (IL-1RII) which down-regulate the activity of IL-1β.

While IL-1β plays an important role in innate immunity, over expression can be deleterious [7]. Systemic effects from overexpression of IL-1β are the main cause of various autoinflammatory diseases.

IL-1β release is central to the pathogenesis of autoinflammatory diseases, as evidenced by elevation in serum levels of IL-1β, its correlation with disease development and severity, and the effectiveness of anti-IL1β antagonists in treating these disorders [8].

Autoinflammatory disorders are characterized by usually unprovoked recurrent episodes of features of inflammation caused by activation of the innate immune system. A new proposed classification of the immunological diseases with the differences between autoinflammation and autoimmunity is shown in Table 1 [8,9]. Many autoinflammatory disorders are associated with alterations of inflammasomes [10]. Inflammasomes are complex multimolecular structures, which respond to "danger" signals by activation of cytokines. Among these, IL-1 is the key player of the innate immune response and inflammation. Consequently, IL-1 blocking strategies are specific pathway targeting therapies in autoinflammatory diseases such as cryopyrin-associated periodic syndrome, Familial Mediterranean Fever (FMF), TNF-Receptor Associated Periodic Syndrome (TRAPS), HyperImmunoglobulinemia D Syndrome (HIDS), and Systemic Onset Juvenile Idiopathic Arthritis (SOJIA) [10-12]. This classification is relevant to the clinical situation because innate immune mediated disorders (autoinflammatory diseases) respond better to cytokine antagonism whereas autoimmune-mediated diseases may respond to anti-T and B cell therapies [9].

	Autoinflammation	Autoimmunity
Immunological disruption	Innate immunity	Adaptive immunity
Main cellular involvement	Neutrophils, macrophages	B and T cells
Antibody involvement	Few or no antibodies	Autoantibodies present
Clinical features	Recurrent, often unprovoked attacks	Continuous progression
Conceptual understanding	Tissue-specific factores/danger signals	Breaking of self-tolerance
Main genetic susceptibility	Cytokine and bacterial sensing pathways	MHC class II associations/adaptive response genes
Therapy	Anti-cytokine (IL-1, TNF, IL-6)	Anti-B and T cell
Examples	Ankylosing spondylitis Psoriatic arthritis Crohn's disease Systemic juvenile idiopathic arthritis Behçet´s disease	Rheumatoid arthritis Systemic lupus erythematosus Celiac disease

MHC: Major Histocompatibility Complex; IL: Interleukin; TNF: Tumor Necrosis Factor;[9]

Table 1: Comparison between autoinflammation and autoimmunity.

Behçet´s disease is a genetically complex disorder, which usually presents first in adulthood but is also observed in children. It is most common among young adults from Eastern Asia and Mediterranean countries, populations spread along the historical silk-road. The etiology is poorly known although there is a familial predisposition and an association with HLA-B51. The disease is characterized by genital and oral ulcerations, papulopustular skin lesions such as pseudofolliculitis, erythema nodosum and pyoderma gangraenosum, arthritis, vasculitis and uveitis. Severe vasculitis may worsen the prognosis by causing potentially life-threatening complications such as thrombophlebitis, arterial aneurysms and occlusion. Because Behçet´s disease shares clinical similarities with autoinflammatory disorders, such as the episodic nature and granulocyte activation in the pathogenesis, it may also be regarded as autoinflammatory disease. However, although IL-1β plays a role in Behçet´s disease and there is a biological response to IL-1 blockade, yet no information exists to suggest which inflammasome might generate the active cytokine[11].

Dysregulation in innate immunity has also been found in ankylosing spondylitis, psoriatic arthritis, and Crohn's disease, diseases often associated with uveitis. This has led to reclassifying these conditions as autoinflammatory conditions[11-13]. T-cell or B-cell targeted therapies such as Abatacept, Alefacept, Efalizumab, and Rituximab have shown only modest therapeutic effects in these diseases, whereas TNF-inhibitors have been found to be very effective[12].

IL-1β in Noninfectious Uveitis

Several animal models of uveitis have demonstrated a relationship between IL-1β and ocular inflammation. Elevated levels of IL-1 have been found in the eyes of mice [14] and rats [15] with experimental endotoxin-induced uveitis. IL-1 messenger RNA levels were markedly elevated in eyes of mice with EAU [16]. IL-1 levels were elevated in the aqueous humor of patients with intermediate uveitis [17-19]. Conversely, knockout mice deficient in IL-1 showed a profound reduction in the severity of immune complex-induced uveitis [20].

Human studies have shown IL-1 elevated levels in the aqueous humor of patients with birdshot chorioretinopathy [21]. In Behçet´s disease patients, IL-1β has been implicated as a mediator in its pathogenesis [22,23], has been found elevated in sera [24], and has been shown to be produced in large amounts by circulating monocytes [25]. Several studies have shown that gene polymorphism is involved in the mechanism of Behçet´s disease, which in turn leads to the increased expression of IL-1β [22].

IL-1β Antagonists

Advances in our understanding that the IL-1β is a key pro-inflammatory cytokine involved in the pathogenesis of uveitis, have increased interest in therapeutic agents targeting it. These therapeutic agents include the monoclonal antibodies Anakinra (Kineret®), Rilonacept (Arcalyst®), Canakinumab (Ilaris®), and Gevokizumab (XOMA 052). Inhibition of IL-1β may be achieved at different levels. Some agents target the IL-1β molecule directly (Rilonacept, Canakinumab, Gevokizumab) while others are antagonists to IL-1RI (Anakinra).

a. Anakinra (Kineret®)

Anakinra (Kineret® Swedish Orphan Biovitrum AB, Stockholm, Sweden) is a recombinant form of the naturally occurring human IL-1Ra, which blocks the activity of IL-1β by competitively binding to the IL-1RI. Anakinra has a short half-life of 4-6 hours and therefore needs to be administered daily; usually with an adult dose of 100 mg daily by subcutaneous injection or with a children dose of 1-2 mg/kg daily by subcutaneous injection. It has been used to treat a wide variety of autoinflammatory conditions, including Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA)-associated uveitis refractory to anti-TNF therapy, confirming the success in the preclinical experimental autoimmune uveitis model in mice [26]. It has also been effective in treating refractory Behçet´s disease [27]. Serious infections such as pneumonia and infectious cellulitis seem to be more frequent with Anakinra, although there is no increased risk of tuberculosis. Anakinra has reached USA Food and Drug Administration (FDA) approval for the treatment of CINCA and rheumatoid arthritis [28]. It has also been proven to be effective in a number of autoinflammatory disorders such as CAPS [29], SOJIA [30], FMF [31], HIDS [32] and TRAPS [33].

b. Rilonacept (Arcalyst®)

Rilonacept (Arcalyst®, Regeneron Pharmaceuticals, Tarrytown, New York, USA) (IL-1 Trap) is a fully human dimeric fusion protein, which incorporates the extracellular domain of both IL-1 receptor components: IL-1RI and IL-1RAcP. It has a half-life of 67 hours and it is administered once a week with 160 mg subcutaneously. Rilonacept has reached FDA approval for the treatment of familial cold autoinflammatory syndrome (FCAS) [34] and for Muckle-Wells Syndrome (MWS) [35]. Response has also been reported in patients with FMF [36], gout [37], SOJIA [38] and Schnitzler syndrome [39]. To date, no experience has been reported in uveitis.

c. Canakinumab (Ilaris®)

Canakinumab (Ilaris®, Novartis Pharmaceutical Corporation, East Hannover, New Yersey, USA) is a novel fully human IL-1β blocking IgG1 monoclonal antibody. It neutralizes IL-1β, by competing for binding to IL-1RI and therefore blocking signaling by the corresponding antigen-antibody complex. Intravenously or subcutaneously infused, it neutralizes the bioactivity of human IL-1β [40]. The agent has a half-life of 21-28 days and is administered with 150 mg subcutaneously in adults or 2 mg/kg subcutaneously in children once a month. That offers a considerable advantage over Anakinra, which must be injected daily and is often poorly tolerated by patients.

Canakinumab has promising clinical safety and pharmacokinetic properties, and demonstrated potential for the treatment of autoinflammatory disease conditions such as CAPS, MWS, SOJIA, FMF, gout, type II diabetes, TRAPS, and possibly for ocular inflammatory diseases [12,41,42]. Recent reports showed the efficacy of Canakinumab in Behçet's uveitis refractory to antimetabolites and TNF antagonists [41,42] and in Blau syndrome-related uveitis refractory to antimetabolites and several biologic response modifiers, including TNF antagonists and Abatacept [43].

d. Gevokizumab (XOMA052)

Gevokizumab (XOMA 052, XOMA Corporation, Berkeley, CA, USA) is a recombinant, humanized IgG2 monoclonal antibody that binds IL-1β, reduces affinity to IL-1RI, leaving intact the affinity for IL-RII. It is a modulating antibody that reduces the affinity for its IL-1RI: IL-1RAcP signaling-competent complex [44]. It down-regulates IL-1β activity in cytokine release assays. The monoclonal antibody was humanized using proprietary technology developed at XOMA with the goal of reducing the probability of eliciting anti-drug immunogenic responses. Under physiological conditions where increased levels of IL-1β cause pathology, Gevokizumab neutralizes

excess IL-1β while potentially allowing continued beneficial signaling in response to local inflammatory stimuli. Therefore, Gevokizumab may allow for better responsiveness of the innate immune system to infection as compared with a complete blockade of IL-1β activity.

Gevokizumab is produced in Chinese hamster ovary cells. Based on pharmacokinetic data from multiple studies, it has a circulating half-life of approximately 22 to 28 days, allowing convenient monthly subcutaneous dosing [45].

Based on its high potency, novel mechanism of action, long half-life and high affinity, Gevokizumab provides a new strategy for the treatment of a number of autoinflammatory diseases in which the role of IL-1β is central to pathogenesis [12].

Clinical Studies

To date, the clinical experience with Gevokizumab includes over 500 subjects who have been treated with the drug in a variety of clinical non ocular autoinflammatory disorders, primarily type 2 diabetes, but also type I diabetes, acne vulgaris, acute gout, cardiovascular disease, FACS, and MWS [7,46].

The emerging clinical safety profile of Gevokizumab supports doses of 30 mg and 60 mg once a month. The safety profile indicates that among over 315 subjects chronically treated with Gevokizumab for at least 6 months, there has been no evidence of increased infections, serious infections, opportunistic infections, chronic infections, hematologic toxicities such as neutropenia or leukopenia, malignancies, or auto-immune phenomena. The laboratory abnormalities with Gevokizumab were mild or moderate, and the majority reflected the disease under study.

An open-label pilot study was performed in patients with resistant Behçet´s disease uveitis [47]. Gevokizumab was administered to seven subjects with acute, vision-threatening posterior uveitis or panuveitis and/or retinal vasculitis resistant to Azathioprine and/or Ciclosporine in the presence of an acute exacerbation. All immunosupressive agents were discontinued other than baseline oral corticosteroids at 5 to 10 mg per day. Patients were given a single dose of 0.3 mg/kg intravenous (iv) Gevokizumab. Signs of intraocular inflammation began to resolve in all seven subjects from Day 1 to Day 4, with complete resolution of retinal findings achieved in 4 to 21 days (median 14 days). To those who responded to treatment prior to Day 28 and then had a second exacerbation between Day 28 and the end of the study at Day 98 were given a second dose of 0.3 mg/kg (iv) gevokizumab. All subjects had positive response to second infusion and were recurrence-free for a median of 115 days (ranging from 41 to 197 days). All seven subjects who participated in this study elected to receive further treatment in an open-label extension study. The authors reported no treatment-related adverse events. Limitations of this study include its open-label design, the small number of patients, the lack of assessments of the extraocular manifestations, and the short follow-up.

There are two ongoing randomized, placebo-controlled, double-masked study phase III clinical trials studying the safety and efficacy of Gevokizumab in noninfectious intermediate, posterior, or panuveitis. EyeguardTM-A is for patients currently active in spite of corticosteroids with or without immunosuppressive medications, and EyeguardTM-C is for patients whose disease is currently controlled with systemic oral corticosteroids (≥ 10 mg/day and < 25 mg/day prednisone equivalent) with or without immunosuppressive medications, but who have experienced active uveitic disease within the previous 12 months.

Concluding Remarks

Autoinflammatory disorders are characterized by usually unprovoked recurrent episodes of features of inflammation caused by activation of the innate immune system. Ankylosing spondylitis, psoriatic arthritis, Crohn's disease, and Behçet´s disease, disorders often associated with uveitis, have been classified as autoinflammatory disorders. Autoinflammatory disorders are associated with alterations of inflammasomes. Inflammasomes are complex multimolecular structures, which respond to "danger" signals by activation of cytokines. Among these, IL-1 is the key player of the innate immune response and inflammation. Consequently, IL-1 blocking strategies could be specific pathway targeting therapies in these diseases. Anakinra, Rilonacept, and Canakinumab have reached FDA and European agencies approval for several systemic diseases. Long-acting IL-1 inhibition using Canakinumab has been successful in several cases with Behçet´s disease resistant to conventional treatment. Gevokizumab has been shown to be effective and safe in Behçet´s disease. Currently there are two randomized, placebo-controlled, double-masked study phase III clinical trials studying the safety and efficacy of Gevokizumab in noninfectious intermediate, posterior, or panuveitis.

Undoubtedly, a lot remains to be learned about the complete network of signal cascades, ranging from signal recognition to the resulting inflammation in uveitis. Increasing knowledge about the specific cytokine production in uveitis will surely develop new opportunities to create molecules tan can intervene in this way.

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T-Cell Costimulation Modulator: Abatacept

Víctor Llorenç*

Section of Ocular Inflammation & Infection, Clinic Institute of Ophthalmology, Clinic Hospital of Barcelona, Barcelona, Spain

***Corresponding author:** Víctor Llorenç, Section of Ocular Inflammation & Infection, Clinic Institute of Ophthalmology, Clinic Hospital of Barcelona, Barcelona, Spain, Tel:+34657389263; E-mail: llorens.victor@gmail.com

The Molecule

Abatacept (Orencia®, Bristol-Myers Squibb Company, Princeton NJ, USA) is a fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of Cytotoxic T-Lymphocyte Antigen 4 (CTLA4). Abatacept is produced by recombinant DNA technology in a mammalian cell expression system (Chinese hamster ovaric cells). The apparent molecular weight of abatacept is 92 kilo Daltons. CTLA4, also known as CD152, is a protein receptor that down regulates the immune system. CTLA4 is found on the surface of T cells, which lead the cellular immune attack on antigens. Indeed, T cell attack can be turned "on" by stimulating the CD28 receptor on the T cell. In the other hand, the T cell attack can be turned "off" by stimulating the CTLA4 receptor, which acts as an "off" switch. Abatacept is a molecule capable of binding with more avidity to CD80 (B7-1) rather than to CD86 (B7-2). CD80/CD86 are a type of peripheral membrane proteins found on activated Antigen Presenting Cells (APC) that, when paired with either a CD28 or CD152 (CTLA4) surface proteins on a T cell, can produce a co-stimulatory signal to enhance or decrease the activity of the Major Histocompatibility Complex-T Cell Receptor (MHC-TCR) signal between the APC and the T cell, respectively. Besides, being present on activated APCs, CD80 is also found on T-cells themselves. Binding of the CD80 on T-cells to CTLA4 causes inhibition of the activity of T-cells. In summary, abatacept is a selective co-stimulation modulator as it inhibits the co-stimulation of T cells [1,2].

Costimulation

There are several steps to activate the immune system against a pathogen. The T Cell Receptor (TCR) must first interact with the MHC surface protein. CD4 or CD8 proteins on the T-cell surface form a complex with the CD3 protein, which can then recognize the MHC. This is also called "Signal 1" and its main purpose is the T cell activation. However, MHC binding is insufficient for producing a T cell response by itself. In fact, lack of further stimulatory signals conduces the T cell into anergy. The co-stimulatory signal (necessary to continue the immune response) may come from B7-CD28 and/or CD40-CD40L interactions. There are other important activation signals that play a role in immune responses. In the Tumour Necrosis Factor (TNF) molecules family, the protein 4-1BB (CD137) on the T cell may bind to 4-1BBL on the APC. The B7 (B7-1/B7-2) protein is present on the APC surface, and it interacts with the CD28 receptor on the T cell surface. This is one source of "Signal 2" (cytokines can also contribute to T-cell activation). This interaction produces a series of downstream signals which promote the target T cell's survival and activation [3,4].

Mechanism of Action

Abatacept prevents APCs from delivering the co-stimulatory signal to T cells to fully activate them. Note that binding of the activation signal without its complementary co-stimulatory signal also helps to enable down regulation of T cells by way of T cell anergy. Simple signalling without co-stimulation allows the cell to recognize the primary signal as "self" and not ramp-up responses for future responses as well.

Ordinarily, full T cell activation requires: 1) binding of the T Cell Receptor (TCR) to the antigen-MHC complex on the APC, and 2) a co-stimulatory signal provided by the binding of CD28, a T cell protein, to the B7 protein on the APC. Abatacept contains a high-affinity binding site for B7, works by binding to the B7 protein on APCs and preventing them from delivering the co-stimulatory signal to T cells, thus preventing the full activation of T cells [5]. Blockade of CD28 is effective in stopping T cell activation, a mechanism that the immune system uses to down regulate T cell activation. T cells can express the surface protein CTLA4 (CD152) as well, which can also bind B7, but with twenty times greater affinity for B7 proteins, and lacks the ability to activate T cells. As a result, the T cell is blocked from receiving the B7 protein signal and is not activated. CTLA4-knockout mice are unable to stop immune responses, and develop a fatal massive lymphocyte proliferation [6].

Abatacept is the basis for the second-generation belatacept, currently being tested in clinical trials. They differ by only 2 amino acids. In organ transplantation, belatacept is intended to provide extended graft survival while limiting the toxicity generated by standard immune-suppressing regimens such as calcineurin inhibitors (for example cyclosporine) [7] (Figure 1).

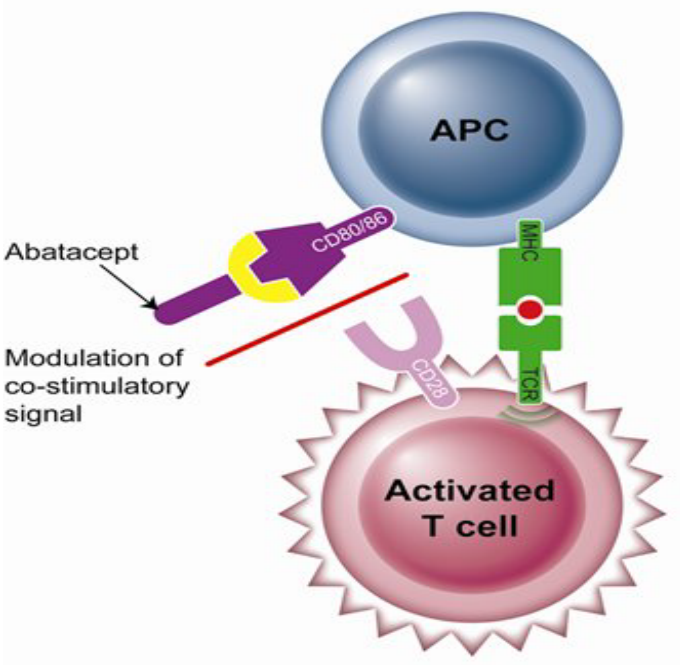

Figure 1: Abatacept mechanism of action.

Adapted from http://drugline.org, last free access August 28th, 2013.

Abbreviations: APC-Antigen Presenting Cells; MHC - Major Histocompatibility Complex; TCR - T-Cell Receptor; CD28 - Cluster of Differentiation 28; CD80/86 - Cluster of Differentiation 80 (B7-1) and 86 (B7-2).

Formulation and Dosage

Abatacept is currently presented in two forms: powder for intravenous infusion and prefilled syringe for subcutaneous injection (FDA approved for self-administration). Abatacept for intravenous infusion is supplied as a sterile, white, preservative-free, lyophilized powder for intravenous administration. Following reconstitution of the lyophilized powder with 10 mL of sterile water for injection, the solution of abatacept is clear, colorless to pale yellow, with a pH range of 7.2 to 7.8. Each single-use vial provides 250 mg abatacept, maltose (500 mg), monobasic sodium phosphate (17.2 mg), and sodium chloride (14.6 mg) for administration. Solution for subcutaneous administration is supplied as a sterile, preservative-free, clear, and colorless to pale yellow solution with a pH of 6.8 to 7.4. Each single dose of subcutaneous injection provides 125 mg abatacept, dibasic sodium phosphate anhydrous (0.838 mg), monobasic sodium phosphate monohydrate (0.286 mg), poloxamer 188 (8 mg), sucrose (170 mg), and quantity sufficient to 1 mL with water for injection. Unlike the intravenous formulation, solution for subcutaneous administration contains no maltose [8]. Intravenous abatacept is given by a 30-minute intravenous infusion. Doses are calculated on the basis of body weight as follows: <60 Kg, 500 mg (2 vials); 60 to 100 Kg, 750mg (3 vials); >100 Kg, 1000 mg (4 vials). After the first dose, a second one will be given around day 15 and a third dose around day 30. Continued therapy is one dose every 4 weeks thereafter. Subcutaneous schedule is possible after a single intravenous loading dose (as per body weight). Then, the first 125 mg subcutaneous injection should be given within a day, followed by 125 mg subcutaneous injections once weekly thereafter. Nevertheless, patients who are unable to receive an infusion may initiate weekly subcutaneous injections without an intravenous loading dose. Dose for children aged 6 to 17 with less than 75 Kg body weight is 10 mg/Kg body weight calculated before each administration. Pediatric doses should not exceed 1000 mg in any case.

Patients transitioning from intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Safety and efficacy in children less than 6 years old have not been tested in clinical trials. Therefore, abatacept is not recommended in these patients. Dose adjustment is not necessary in elderly patients and remains unknown whether it is necessary in liver or kidney dysfunction [8-10].

Current Indications and Clinical Trials

Placebo-controlled, double-blinded randomized clinical trials conducted in patients with rheumatoid arthritis and Juvenile Idiopathic Arthritis (JIA) have demonstrated therapeutic benefits of abatacept and allowed its FDA-approval. Abatacept is indicated in the treatment of moderate to severe active adult rheumatoid arthritis. For this indication, abatacept may be used as monotherapy or in combination with immunosuppressive agents other than TNF antagonists [11-13]. A second indication is moderate to severe active polyarticular JIA in pediatric patients aged 6 years and older. In this indication abatacept may be used as monotherapy or concomitantly with methotrexate [14].

A phase II placebo-controlled clinical trial with abatacept in psoriatic arthritis demonstrated efficacy in the main scores of the disease [15]. Nevertheless, a randomized trial on chronic inflammatory bowel disease was early terminated due to lack of efficacy [16]. Abatacept is also in trial for the treatment of type 1 diabetes. In diabetic patients in the "honeymoon phase" of the disease, abatacept may protect surviving beta cells from autoimmune attack [17]. In addition, abatacept is currently in a phase II trial for multiple sclerosis [18] and has been tested for non-life-threatening manifestations of Systemic Lupus Erythematosus (SLE) [19].

Abatacept in Uveitis

The interaction between CD80/CD86 and CD28 has been successfully inhibited by CTLA4 Ig in experimental models of autoimmune uveitis, resulting in inflammation severity reduction but did not induce long-term remission [20]. To date, limited clinical experience

has been published regarding abatacept efficacy in uveitis. Abatacept has been assayed off-label in long-lasting refractory cases of uveitis with important ocular sight-threatening complications, and therefore functional and clinical improvement sometimes can be difficult to appreciate. However, a tendency to sight improvement, steroid- and immunosuppressive-sparing effects and uveitic inflammatory control have been described in some isolated case reports and one short case series [21-24].

Angeles-Han reported the first uveitis case treated with abatacept. She was a 16 years old patient suffering from psoriatic arthritis associated uveitis since she was 5. Multiple successive combinations of classic immunosuppressive treatments including methotrexate, cyclosporine A, mycophenolate and cyclophosphamide along with etanercept, infliximab, daclizumab or rituximab were unsuccessful to control the inflammatory process in her left eye, which required penetrating kerathoplasty and pars plana vitrectomy for chronic sequelae. After starting abatacept infusions 10mg/Kg at 0, 2, 4 weeks and monthly thereafter, there was a clear improvement in uveitis control that was maintained for 18 months of follow up [21].

Zulian and coworkers reported a prospective trial in 7 patients with severe JIA-related uveitis refractory or intolerant to immunosuppressive agents and 2 or more TNF-α antagonist. All patients responded to abatacept 10 mg/Kg at 0, 2, 4 weeks and then every 4 weeks. Six of the 7 patients maintained a clinical remission after a mean of 9.2 months of treatment. One patient withdrew from the study with skin reactions, oral mycosis and arthritis flare. Even though there was an acceptable follow up for a therapeutic test (7-11 months, mean 9.2 months) it is noteworthy that only 1 patient achieved complete remission, whereas a sustained mild inflammatory background was observed at final follow up in all but one patient. Time to response after abatacept commencement was acceptable in 6 patients ranging between 2 weeks and 1 month but resulted very delayed in one patient (6 months). Probably, a delay of 6 months is not acceptable in order to achieve control of recalcitrant uveitis with potential irreversible sequelae [22].

Zulian & Zannin updated the follow up of their 6 patients in a posterior letter to the Editor. They reported that, at a mean follow up of 21 months (range 19-23), 5 patients maintained remission of both uveitis and arthritis and 2 of them could stop steroids and classic immunosuppressants. The sixth patient relapsed after 12 months of abatacept therapy with flares of arthritis and uveitis, needing prednisone and methotrexate dose increase to achieve disease control [23].

Elhai et al. also reported 2 cases of juvenile idiopathic arthritis-associated uveitis refractory to both classic immunosuppressants and two anti-TNF-α that achieved remission after abatacept commencement and during a follow up of 16 and 10 months respectively. One patient achieved inflammatory control within the first infusion and the other after 3 months (5 infusions). Interestingly, the authors reported sustained remission with spared abatacept infusions every 6-7 weeks instead of every 4 weeks. However the second case was not able to decrease concomitant immunosuppressive drugs [23].

Kenawy and coworkers also reported 2 patients with JIA-associated uveitis refractory to immunosuppresive and anti-TNF-α who started abatacept therapy and were followed for 12 months. Both patients achieved remission of their uveitis at 2 months (4 infusions), including resolution of cystoid macular edema in one case. However, joint disease continued to flare up in one of the patients [24]. This article agrees with other reports in suggesting a delay in joint disease response despite rapid ocular inflammatory control [22,24].

Our Experience with Abatacept

In our experience at the ophthalmology department of the Hospital Clinic de Barcelona, four abatacept-treated patients were found in the uveitis database. Diagnoses were 3 JIA and 1 ankylosing spondylitis-associated uveitis. All 4 cases were long-lasting uveitis refractory or intolerant to systemic steroids, classic immunosuppressive agents and anti-TNF-α.

In the JIA group, 3 adult women aged 31, 20, and 22 were treated with abatacept for 2, 15 and 21 months, respectively. In the first case, clinical response to abatacept was insufficient despite combined cyclosporine and unacceptable high dose of steroids, and therefore abatacept was withdrawn after 2 months of therapy and switched to rituximab. A severe herpetic oesophagitis obligated to withdraw rituximab and the patient was then switched to tocilizumab. Currently the patient has remained under control with tocilizumab plus cyclosporine 100 mg/12 hours and oral prednisone 7.5 mg/day at 11 months of follow up since tocilizumab commencement.

The second case was managed with abatacept plus leflunomide 10mg/d, prednisone 5 mg/d and an intravitreal implant of dexamethasone in the right eye, achieving fast and sustained remission until 15 months later when the right eye flared up with macular edema. Flare was managed with a second dexamethasone implant with good response for 7 months when another aggressive flare started in the right eye. After 2 flares in the right eye, systemic treatment was switched to golimumab plus leflunomide and prednisone, and a third dexamethasone implant injected. The patient has remained under remission since golimumab introduction 8 months ago.

The third JIA case was treated with abatacept and oral prednisone 5 mg/day. The patient achieved sustained remission for 21 months. However, she presented with 3 successive mild to moderate flares between January and June 2012, and systemic treatment was then switched to golimumab plus methotrexate 15 mg/week with complete response until the last visit in July 2013 (ICOF, unpublished data).

Finally, we assayed an off-label use of abatacept in a 38 years old man with HLA-B27+ AE and uveitis since he was 22 years of age. He was managed effectively with infliximab and methotrexate for 42 months but septic knee arthritis forced to stop infliximab. After resolution of the knee infection, etanercept plus cyclosporine 150 mg/12 h was started without uveitis control in the left eye and then switched to adalimumab plus methotrexate 20 mg/week with partial ocular and articular response. We tried to go back to infliximab plus methotrexate, but an aggressive anaphylaxis despite premedication obligated to withdraw the treatment. Finally, abatacept was started along with methotrexate, oral prednisone and dexamethasone implant in the left eye. Five months later, 2 successive uveitis flares involving also the right eye obligated to withdraw the treatment. The patient was then switched to golimumab with partial remission and good tolerance (ICOF, unpublished data).

In conclusion, our own short experience with abatacept is partially consistent with available literature since only 2 out of 3 patients with refractory JIA-associated uveitis achieved incomplete and transient remission. Moreover, the ankylosing spondylitis-associated uveitis patient failed to respond to abatacept. Published data regarding abatacept therapy for ankylosing spondylitis demonstrates poor response in anti-TNF-α naïve patients and no response in anti-TNF-α resistant cases as our patient [25,26] (Table 1).

Reference	n	Uveitis type	IS & anti-TNF-α ineffectiveness/intolerance	Uveitis Remission	Adverse events
Angeles-Han et al. [21]	1	PsA	1/1	1/1	no
Zulian et al. [22].	7	JIA	7/7	5/7[1]	1/7
Elhai et al. [23].	2	JIA	2/2	2/2	no
Kenawy et al. [24].	2	JIA	2/2	2/2[2]	no
ICOF (unpublished)	3	JIA	3/3	2/3[3]	no
ICOF (unpublished)	1	AS	1/1	no	no

Table 1: Reported studies on the use of abatacept for treatment of uveitis.

PsA - Psoriatic Arthritis-Associated Uveitis; JIA - Juvenile Idiopathic Arthritis; AS - Ankylosing Spondilytis; IS - Classic Immunosuppressives; ICOF - Clinical Institute of Ophthalmology, Hospital Clinic of Barcelona, Barcelona, Spain.

In all but 1 patient partial remission was observed. One patient responded only after 6 months of abatacept commencement. One patient relapsed after 12 months and another patient interrupted the treatment because of adverse events and joint flare up [1]. One patient reached uveitis but not joint disease remission. One patient failed to respond at only 2 months from abatacept commencement, the 2 patients who responded were in a partial and transient manner with frequent mild-moderate flare ups that required intravitreal dexamethasone implants or increasing doses of systemic prednisone [2,3].

Adverse Reactions/Side Effects

Acute infusion-related events

Acute infusion reactions (adverse reactions occurring within 1 hour of the start of the infusion) in clinical studies have been described in around 9% of the abatacept-treated groups (6% for placebo-treated groups) [27-29]. Acute infusion reactions included hypotension, increased blood pressure, and dyspnea. However 96% of the reactions were mild to moderate and less than 1% of abatacept-treated patients discontinued the treatment due to an acute infusion-related event. Anaphylaxis was observed in less than 0.1% of patients on abatacept administered intravenously in controlled and open-label clinical trials. Other reactions potentially associated with drug hypersensitivity such as hypotension, urticaria, and dyspnea occurring within 24 hours of abatacept infusion, were uncommon (<1%) [27-29].

Infections

Available data from clinical trials clearly showed an increased risk of infection in abatacept-treated patients. Upper respiratory tract infections, along with headache and nausea were the most commonly reported adverse events in rheumatoid arthritis clinical trials (≥ 10%). Moreover, infections were the most frequently related to treatment interruption or discontinuation adverse events. A part of respiratory tract infections, including bronchitis and pneumonia, herpes zoster reactivation, localized infections, urinary tract infections, influenza and herpes simplex have been also reported in clinical trials.

Infections were more frequent among abatacept-treated patients receiving concomitant anti-TNF-alpha therapy than in placebo-treated patients receiving anti-TNF-alpha therapy, thus combined abatacept and anti-TNF-alpha therapy increase the risk of infection and this combination has to be avoided [27-30].

Adverse reactions in patients with Chronic Obstructive Pulmonary Disease (COPD)

Clinical studies showed more adverse events in COPD patients treated with abatacept than in placebo-treated patients. There were more respiratory disorders including COPD exacerbation and pneumonia in abatacept dosed patients, some of them serious cases [27-29].

Tuberculosis

No increased risk of tuberculosis was observed in clinical trials, although patients enrolled in clinical trials were screened and appropriately treated for latent tuberculosis. Tuberculosis have been described in abatacept-treated patients and guidelines for latent tuberculosis screening before treatment have to be followed due to unknown reactivation potential of abatacept [27-29].

Malignancies

Although the overall frequency of malignancies is similar in abatacept-treated (1.3%) and placebo-treated (1.1%) patients in controlled clinical trials, lung cancer was more common in the abatacept-treated groups (0.2%). Taking into account controlled and open-label studies with abatacept (2688 patients), there were 0.21 cases of lung cancer per 100 patients-years and 0.10 cases of lymphoma per 100 patients-years. However patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk for the development of lymphoma. Other malignancies included skin, breast, bile duct, bladder, cervical, melanoma, etc. The potential role of abatacept in the development of malignancies in humans is unknown [27-30].

Autoimmune diseases

Abatacept-treated patients in placebo-controlled clinical trials did not increase autoantibody titters such as anti-nuclear antibodies or anti-DNAds during the follow up period [28]. Nevertheless, multiple sclerosis was reported after long term treatment with abatacept [30]. Systemic vasculitides, including cutaneous vasculitis and leukocytoclastic vasculitis, have been described during the post-approval use of abatacept in adult rheumatoid arthritis patients [30].

Conclusion

To date there is very limited experience regarding abatacept therapy for noninfectious uveitis. Reported cases are usually long-lasting uveitis refractory to multiple combinations of classic immunosuppressants and anti-TNF-α. There is still no experience in the management of naive uveitis cases with abatacept since clinical trials are lacking. Abatacept appears to be safe and effective in some cases of JIA-associated uveitis when resistant to anti-TNF-α plus DMARDs. However, mild ocular inflammatory background can persist, leading to the development of structural sequelae or delayed treatment failure.

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Laura Pelegrín[1]* and José Hernández-Rodríguez[2]

[1]Uveitis Unit, Department of Ophthalmology, Hospital Clinic, University of Barcelona, Barcelona, Spain

[2]Vasculitis Research Unit, Department of Autoimmune Diseases, Hospital Clínic, IDIBAPS; University of Barcelona, Barcelona, Spain

***Corresponding author:** Laura Pelegrín, Uveitis Unit, Department of Ophthalmology, Hospital Clinic, University of Barcelona, Barcelona, Spain, Tel: 932275611; E-mail: laurapelegrin79@hotmail.com

Introduction

Rituximab (RTX) is a chimeric human-mice monoclonal antibody directed against the surface marker CD20 of pre-B lymphocytes, those normal and neoplastically transformed. RTX contains the complementary determining regions of the murine anti-CD20 antibody 2B8 in conjunction with human kappa and IgG1 heavy-chain constant region sequences [1]. RTX is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids with a molecular weight of 145 Kd and has a binding affinity for the CD20 antigen of approximately 8.0 nM, which is similar to the parent murine antibody, 2B8.

Current Indications of Rituximab

RTX was firstly approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 1997 and 1998, respectively, to treat B-cell non-Hodgkin lymphomas resistant to other chemotherapy regimens [2,3]. It has also achieved other indications, which include CD-20 positive chronic lymphocytic leukemia, diffuse large B-cell lymphoma, low-grade or follicular lymphoma, all of them in combination with the standard chemotherapy [4]. In follicular lymphoma, RTX may be administered as a single agent for maintenance therapy.

RTX has been also approved by FDA and EMA to treat several autoimmune diseases. These include rheumatoid arthritis (RA), in combination with methotrexate, after an inadequate response or intolerance to other disease-modifying antirheumatic drugs including any tumor necrosis factor (TNF)-antagonist therapies [5] and anti-neutrophil cytoplasmic antibody-associated (ANCA) vasculitis, specifically granulomatosis with polyangiitis (GPA; formerly known as Wegener's granulomatosis) and microscopic polyangiitis (MPA), in addition to glucocorticoids, both at the disease onset and in relapsing disease [6].

RTX has evidenced some efficacy in other autoimmune diseases, such as essential cryoglobulinemic vasculitis (and also hepatitis C virus-associated cryoglobulinemia) [7], Systemic Lupus Erythematosus (SLE) [8], Juvenile Idiopathic Arthritis (JIA) [9,10], immune thrombocytopenic purpura [11], autoimmune hemolytic anemia, pure red cell aplasia, Evans syndrome [12], bullous skin disorders (pemphigus, pemphigoid) [13], and multiple sclerosis [14], among others. Although there is no FDA or EMA approved indication for RTX in these diseases, RTX is widely used off-label to treat difficult/refractory cases. For many of these inflammatory/autoimmune conditions, in which ocular involvement becomes evident and sometimes a medical emergency, RTX has been tested, usually with good results [15].

Mechanisms of Action, Dosage and Administration

CD20 antigen is a tetraspan membrane protein that acts as a calcium channel, and is expressed on the surface of only premature and mature B lymphocytes. This surface marker varies along the different B cell maturation process, appearing first in the late stages, while it is no longer expressed when B cells differentiate into plasma cells. Even as its naive ligand remains unknown, its activation is associated to B cell activation and proliferation [16]. In vitro studies using anti-CD20 antibodies have suggested that CD20 may activate intracellular signaling pathways, leading to cell cycle arrest apoptosis or lysosome-mediated cell death [17,18]. Because by targeting CD20, only mature B cells are affected, all precursor stem cells and plasma cells remain unaffected. Furthermore, long-living plasma cells residing in the bone marrow are also left unharmed, and consequently, the antibody production remains intact and the immune memory against previously fought infectious agents is also preserved [19].

Once bound to CD20, RTX may inhibit proliferation and differentiation of B cells and ultimately lead to the death of these cells. The exact pathway leading to cell death remains unclear. However, different and probably combined mechanisms seem to participate, including antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity (which seems to be mediated by the Fc portion of RTX) and CD20+ cells apoptosis [16,20,21]. This combined effect results in the elimination of B cells, although a new population of healthy B cells can be later develop from lymphoid stem cells.

While RTX dosage varies among diseases, two intravenous regimens are most extensively used according to the disease for which these schemes were initially delineated:- "lymphoma regimen," used in all lymphoproliferative disorders at 375 mg/m2 weekly for 4 weeks [22]; and -"RA regimen", used for RA: two doses of 1000 mg 2 weeks apart [23]. In ANCA-associated vasculitis and other autoimmune conditions, for which RTX is used off-label, both regimens have shown similar results [24]. Regimens using RTX doses of 50 mg/m^2 have resulted in the same degree and duration of peripheral B-cell depletion, and effect on antibody response as 375 mg/m^2 [25]. Indeed, in some diseases, such as immune thrombocytopenic purpura, lower RTX doses are being tested [26].

Elimination of circulating B cells (CD19+) has been equally proved with all therapeutic regimens. Circulating CD19+ B cells are usually depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in most patients [27-29]. B-cell recovery begins at approximately 6 months following completion of treatment, and tends to return to normal by 12

months, although some patients may have a sustained B cell depletion for more than 2 years [27,28]. However, when the total B-cell count returns to normal, there appears to be a change in B cell phenotype, with a relative deficiency in CD27 expression, a surface marker of memory B cells [30]. This suggests that the repopulated B cells are primarily naïve, at least during the 2 years after RTX administration. Despite the profound B-cell depletion, only mild reductions in IgM and IgG serum levels occur from 5 to 11 months following RTX administration can be observed, and only a small percentage of patients may have reduced values [27].

As a conclusion, peripheral B cell depletion induced by RTX is associated with remission of B cell monoclonal proliferation in lymphoproliferative disorders and with control of disease activity in autoimmune disorders. In addition, as B cells act as antigen-presenting cells, their removal has an impact on T cell activation, as it has been demonstrated in conditions mainly T-cell-mediated (e.g. Behçet's disease) [31,32].

Rituximab Side Effects

RTX infusion is safe and well tolerated in most patients and more than 500.000 patients have received RTX for different diseases worldwide to date [33]. However, side effects have been reported in more than 10% of patients. Major and minor side-effects are shown in Table 1. These side effects are mostly mild and transient and often occur during intravenous infusion. Infusion-related complications are caused by the non-humanized anti-CD20 antibodies and usually occur in the first infusion and do not tend to recur after that. The previous administration of paracetamol, steroids and antihistaminic drugs, as RTX premedication, are used to control or/and avoid these side effects.

Common (>10%)	Less common (<10%)
Angioedema (11%)	Edema
Hypotension (10%)	Flushing
Asthenia (26%)	Hypertension
Chills (33%)	Anxiety
Dizziness (10%)	Anemia
Fever (53%)	Elevated LDH
Headache (19%)	Hyperglycemia
Pruritus (14%)	Bronchospasm
Rash (15%)	Dyspnea
Abdominal pain (14%)	Sinusitis
Diarrhea (10%)	Throat irritation
Nausea (23%)	Urticaria
Vomiting (10%)	
Leukopenia (14%)	
Lymphopenia (48%)	
Neutropenia (14%)	
Thrombocytopenia (12%)	
Back pain (10%)	
Myalgia (10%)	
Cough (13%)	
Rhinitis (12%)	
Infection (31%)	
Night sweats (15%)	

Table 1: Side effects related to Rituximab.

Although sporadic viral acute infections or reactivation with severe or fatal outcomes in patients treated with RTX have been reported [34,35], overall there is no higher risk of infections when RTX is compared with classical immunosuppressive agents [6,28]. However, some authors have reported higher incidence of severe systemic infections with the use of biologic therapy combined with immunosuppressive therapy in patients with autoimmune diseases [36]. Progressive multifocal leukoencephalopathy was reported in two patients with SLE treated with RTX. However, this severe complication may not be attributed to RTX since it has also occurred in SLE patients receiving other immunosuppressive agents or even, not receiving any treatment [37]. Nevertheless, infections, malignancies and other possible long term consequences of RTX have still to be evaluated in future studies.

Treatment of Uveitis and Other Ocular Manifestations

There is currently limited data available regarding the use of RTX in diseases affecting the eye, without randomized controlled trials supporting RTX use in ocular inflammation. Although RTX has been successfully used to treat ocular disease related to systemic inflammatory conditions as well as others affecting the eyes alone, the data available are based on case reports or case series.

Intravenous RTX has been reported to be effective in cases of orbital inflammation associated with GPA, RA and GPA associated peripheral ulcerative keratitis [15,38-43], RA, GPA and Sjögren syndrome associated scleritis [44-49], idiopathic chronic anterior uveitis [50] and RA and JIA-associated uveitis [15,51-53], ocular cicatricial pemphigoid [54] and ocular BD [15,31,55-57]. RTX is also useful in patients with Sjögren's syndrome and keratoconjuctivitis sicca, with better response in patients with residual function of the exocrine glands [58,59].

According to the Standardization of Uveitis Nomenclature, the definition of disease remission is reserved for inactive disease for at least 3 months after discontinuing all treatments for eye disease [60]. All main cases reported of ocular involvement treated with RTX and their outcomes, divided into drug-free remission or quiescent disease on immunosuppressive therapy, are described in Table 2 [19].

Disease	Authors	Cases	Rituximab treatment regimen	Follow-up (months)	Outcome
Ophthalmic GPA (retro-orbital tumor)	Taylor et al. 2009 [46] Joshi et al. 2011 [40] Baslund et al. 2012 [39]	10 20 10	2 x 1,000 mg, 2-week interval 2 x 1,000 mg, 2-week interval 2 x 1,000 mg, 2-week interval	12 18 17	Quiescent disease on IS therapy Quiescent disease on IS therapy 40% clinical improvement
Anterior scleritis in Sjögren's **Scleritis associated with GPA** **Scleritis associated with RA**	Ahmadi-Simab et al. 2005 [49] Cheung et al. 2005 [48] Iaccheri et al. 2010 [44] Onal et al. 2008 [47] Chauhan et al. 2009 [45]	1 1 1 1 3	4 x 375 mg/m2, 4-week interval 2 x 1,000 mg, 2-week interval 2 x 1,000 mg, 2-week interval 2 x 1,000 mg, 2-week interval 2 x 1,000 mg, 2-week interval	6 7 9 12 6-24	Quiescent disease on IS therapy Quiescent disease on IS therapy Remission Remission Remission
Ocular cicatricial pemphigoid	Foster et al. 2010 [54]	12	2 x 1,000 mg, 2-week interval	57,5	Stabilization of BCVA and disease progression
Uveitis associated with JIA	Heiligenhaus et al. 2011 [51] Miserocchi et al. 2011 [53]	10 8	2 x 1,000 mg, 2-week interval 2 x 1,000 mg, 2-week interval + 3rd at 12 months as needed + 4th at 21 months as needed	11 14,8	70% remission 13% remission 75% quiescent disease on IS
Uveitis associated with BD	Sadreddini et al. 2008 [31] Davatchi et al. 2010 [57]	8 20	2 x 1,000 mg, 2-week interval 2 x 1,000 mg, 2-week interval	24 6	Quiescent disease on IS therapy Improvement in clinical indices

Table 2: Main cases reported and case series of patients with ocular inflammation treated with Rituximab.

Ocular involvement in GPA is present in more than a half of patients, being scleritis, keratitis, optic nerve damage or proptosis and pain due to orbital inflammatory masses the most frequently ocular manifestations. Orbital masses may be part of the presenting symptoms in 2% of GPA patients, but these lesions may be developed by 15% of them during their disease course [61]. Intraconal or more frequently, extraconal occupation of the orbit is usually manifested as ocular pain, proptosis, scleritis, or eyelid swelling, whereas ocular movement limitation, diplopia, and visual loss may be also present due to a compressive effect on the extra ocular muscles or optic nerve [61]. Although the combination of glucocorticoids and cyclophosphamide remains the first line therapy for treating orbital masses in patients with GPA, RTX has shown good results as alternative drug in patients refractory to previous therapies [39,40,46,62-64]. Of note, several reports of ophthalmic GPA did not obtain good response to RTX [65-67]. However, in these cases, RTX failure might be due to a lack or a lower dose of RTX, when used for retreatment [66,67]. Therefore, RTX retreatment (e.g. at 6-monthly intervals) with full doses after B-cell reconstitution (in absence of clinical manifestations of active disease) or after the occurrence of disease flare seem to be associated with a successful response in GPA orbital disease [40,46,62-64]. Other ocular manifestations of GPA, including episcleritis, conjunctivitis, blepharitis, keratitis (also peripheral ulcerative keratitis), have been reported to improve after RTX administration [43,46-48,62].

Scleritis associated to systemic diseases, other than GPA, including RA [44,45,47] and Sjögren's syndrome [49], have also shown good response to RTX. BD is a T-cell-driven systemic autoimmune disorder affecting multiple organs, and among them, the eye is frequently affected. While historically BD has been treated with high-dose glucocorticoids and additional immunosuppressive agents recently, RTX has emerged as a possible alternative therapy. Several patients with BD and retinal vasculitis have been reported to respond to RTX [31,57]. JIA-associated uveitis refractory to conventional immunosuppressant's and anti-TNF agents has been reported to respond to RTX in two small case-series [51,53].

RTX has been also administered intravitreal in primary vitreoretinal lymphomas [68-71]. This local lymphoma may involve the vitreous, retina, optic nerve and sub retinal structures, and is typically classified as a diffuse large B cell lymphoma, Animal models and preliminary clinical studies have suggested that an intravitreal injection of 1mg rituximab has no untoward ocular effects [72,73]. RTX penetrates the entire retina [74] with a half-life of approximately 5 days, and remains effective for up to 3-4 weeks [68]. Clinical trials have indicated its effectiveness in inducing disease remission, alone or in combination with other chemotherapeutic agents, and they suggest that it may be used for reinducing remission in patients with disease relapse, even in those previously treated with radiotherapy and conventional chemotherapy [69,75].

Unresolved Issues and Future Perspectives

The appropriate dose of RTX and the number of RTX cycles for remission induction of ocular inflammation remains unresolved. The intravenous RTX regimens most extensively used ("lymphoma regimen" [22] and "RA regimen" [23]) has been indistinctively used in patients with ocular inflammatory diseases (Table 2) with similar results. Intravitreal RTX has been also reported useful in few cases of vitreoretinal lymphoma [68-71], but there is no experience of this way of administration in other ocular diseases. As it happens in other diseases for which RTX is approved (i.e. RA, ANCA-associated vasculitis), in diseases presenting with ocular involvement, the appropriate frequency and length of RTX treatment during the maintenance period remains to be elucidated.

Whereas dosages, frequency and length of treatment with RTX needs to be reevaluated and adjusted to a better control of lymphoproliferative and inflammatory/autoimmune diseases, including those with ocular involvement, other anti-CD20 monoclonal agents are currently under active clinical trials with the aim of improve efficacy and minimize side effects, even in cases showing suboptimal response and/or resistance to RTX [76-78].

Some of these biologic drugs include second-generation monoclonal antibodies (humanized B cell-depleting agents): ofatumumab, ocrelizumab, veltuzumab; and third-generation monoclonal antibodies: ocaratuzumab and obinutumumab. Third-generation anti-CD20 agents have a glycolengineered Fc fragment with enhanced binding to Fc gamma receptors, which seems to increase antibody-dependent cellular cytotoxicity [76,79].

Another present and future approach to B cell-mediated diseases is to block the interaction of B cell survival or growth factors with their receptors on B cells. In this regard, biologic agents such as belimumab and atacicept have been used in clinical trials with different results [80].

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Safety Issues: What to do Before Initiating and during Biological Therapy

Gerard Espinosa*

Department of Autoimmune Diseases, Hospital Clinic of Barcelona, Catalonia, Spain

***Corresponding author:** Gerard Espinosa, Department of Autoimmune Diseases, Hospital Clinic of Barcelona, Catalonia, Spain, E-mail: gespino@clinic.ub.es

Introduction

The rate of biologic therapies use in patients with non-infectious uveitis is rising rapidly [1]. The largest clinical experience exists with infliximab but most recently, an increasing number of reports of the effectiveness of other anti-TNF-α agents such as adalimumab [2] or golimumab [3], Anti-Interleukin (IL)-1 agents such as anakinra or gevokizumab, IL-6 blockers such as tocilizumab [4], and anti-CD 20 antibodies such as rituximab have appeared in the literature.

However, specific recommendations in terms of safety for their use in patients with intraocular inflammation are lacking. A rational approach is to extrapolate the accepted recommendations for biologics in patients with rheumatoid arthritis [5,6].

Before initiating and during therapy with this type of treatments it is important to keep in mind the main adverse events associated with their use such as infections, some hematologic and cardiac effects and the relationship with the development of certain types of malignancies.

In this chapter, we review the key points that physicians should take into account before starting and during treatment with biologic therapies. The majority of them will be in common for all biologic treatments except as indicated.

Before Initiating Biologics

The patient who will be treated with biologics should know the main signs and symptoms ("red flags") of the adverse effects associated with their use. The recommended previous evaluations before initiating biologic treatment are described in the (Table 1).

	Anti-TNFα agents Infliximab Adalimumab Etanercept Golimumab Certolizumab	**Anti-interleukin 1 agents** Anakinra Gevokizumab	**Interleukin-6 blocker** Tocilizumab	**Anti-CD 20 antibody** Rituximab
Before biologic therapy				
To rule out active infection including tuberculosis, malignancy, cardiac disease, and demyelinating disorder	X	X	X	X
To rule out close tuberculosis contacts	X	X	X	X
Pregnancy discouraging	X	X	X	X
Blood analysis including complete blood count, liver transaminase, and serum creatinine levels	X	X	X	X
Hepatitis B and C serology	X	X	X	X
Chest radiograph	X	X	X	X
Tuberculin skin test or interferon-γ-release assays	X	X	X	X
Pneumococcal and influenza vaccinations	X	X	X	X

Table 1: Monitoring patients under biologic therapy.

a) Blood analysis: When starting therapy with a biologic treatment, obtaining a complete blood count, liver transaminase levels, and serum creatinine levels for all biologic therapies.

b) Clinical examination: Before starting biologics a careful clinical examination is important in order to know some important data such as previous cardiac diseases, oncologic history or neurologic disorders. In fact, moderate or severe heart failure (New York Heart Association class III–IV with reduced ejection fraction of 50% or less [7]) is considered a contraindication for anti-TNF-α agents.

Regarding malignancies, anti-TNF-α agents were contraindicated in patients with prior lymphoproliferative disease that had been diagnosed and/or treated within the last 5 years [8]. The relationship between biologic agents and solid malignancies is scarce and controversial. If the patients have been treated for solid malignancies more than 5 years ago or have been treated for nonmelanoma skin cancer more than 5 years ago, the biologic agent could be initiated.

Some evidences from randomized controlled trials and observational studies [9] have demonstrated that anti-TNF-α agents have been associated with development of demyelinating disorders [10]. In fact, the duration from the introduction of anti-TNF-α therapy to the onset of demyelinating disorders was 5 months on average (range 1 week to 15 months) [11] or 12 months (range 2.5 months to 2 years) [9]. Therefore, they are contraindicated in cases of demyelinating disorders such as multiple sclerosis, optic neuritis, tranverse myelitis, and Guillain-Barré syndrome [12].

c) Active or latent infections: Given the high rate of serious bacterial infections associated with the use of biologic agents, an important point in the preliminary evaluation is to ensure the presence of active infection. In fact, bacterial infection or a bacterial infection currently requiring antibiotic therapy, active Tuberculosis (TB) or latent TB infection prior to starting preventive therapy, active herpes zoster infection, or active life-threatening fungal infections are reasons that contraindicate the therapy with biologic agents. It is mandatory to assess the patient's medical history in order to identify risk factors for TB before initiating biologic therapy [13]. Some of these recognized risk factors are the close contacts of persons known or suspected to have active TB, foreign-born persons from areas that have a high incidence of active TB (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia), persons who visit areas with a high prevalence of active TB, and infants, children, and adolescents exposed to adults who are at an increased risk for latent or active TB infection. Independently of the presence of any of these risk factors, tuberculin skin test or Interferon-γ-Release Assays (IGRAs) are advisable as the initial test in all patients starting biologic agents [14]. If any of them are positive, chest radiograph should be performed and if there are signs of active TB, sputum culture is necessary in order to confirm the presence of active TB.

The majority of patients that will be candidate to initiate biologic treatment will be under conventional immunosuppressant therapy. In this context, they may have false-negative tuberculin skin test or IGRA results. If this immunosuppressed patient has risk factors for latent TB infection, the repetition of these tests 1-3 weeks after the initial negative screening is advisable. In cases where latent TB infection was confirmed, the recommendation is to start a 9-month course of daily isoniazid and delay the anti-TNF-α therapy at least one month later. In patients with active TB, biologic agents can be initiated only after completion of the treatment.

In the presence of acute hepatitis B or C, biologic agents were contraindicated. In those untreated chronic hepatitis B patients or with treated chronic hepatitis B with liver dysfunction (Child-Pugh class B and higher) biologic agents should not be initiated. There is some evidence that etanercept could be safe in patients with hepatitis C.

d) Vaccinations: Importantly, live vaccines (e.g., varicella-zoster vaccine, oral polio, rabies) are contraindicated during biologic therapy. Conversely, all killed (pneumococcal, influenza intramuscular, and hepatitis B), recombinant (human papillomavirus vaccine for cervical cancer), and live attenuated (herpes zoster) vaccinations should be undertaken before starting a biologic agent. In fact, periodic pneumococcal and annual influenza vaccinations are advisable for all patients receiving biologic treatment [14].

e) Pregnancy and breastfeeding: Pregnancy and breastfeeding should be discouraged in patients who will initiate biologic therapy.

During Biologic Therapy

Patients under biologic therapy should be monitored periodically. However, there is not a definitive recommendation of the frequency of testing and it will be performed according the biologic agent and the clinical situation. A rational approach could include a first control one month after start of treatment and thereafter each 1 to 4 months according the tolerance and response to the treatment [6].

Importantly, in each control a clinical examination and a blood analysis including complete blood count, liver transaminase, and serum creatinine levels are mandatory. The physician should rule out in every visit the presence of active infection, cardiac or pulmonary manifestations and neurological symptoms. In fact, it's proved that patients with continuation of anti-TNF-α therapy even after the first appearance of neurological symptoms had a worst outcome when comparing with the patients that discontinued treatment, which most cases showed the partial or complete recovery of their neurological disorders [11]. One of the main points to keep in mind during anti-TNF-α therapy is the management of surgical operation due to the theoretically increased risk of infectious complications and/or delayed healing. However, this potential risk has not been clearly evaluated in the literature. The general recommendation in case of surgery not associated to high infection risk such as cataract is to discontinue the anti-TNF-α therapy for a period corresponding to two half-lifes before the operation. Of note, if the surgery should be performed in a septic environment such as peritonitis the anti-TNF-α therapy should be discontinued for a time period close to the duration of bioavailability, which is five half-lifes. In both cases, anti-TNF-α therapy could be reinitiated as soon as healing is confirmed and in the absence of infection [15].

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Safety Issues: Principal Adverse Events Related to Biological Therapy

María Victoria Hernández MD[1]* and Raimon Sanmartí MD[1]

[1]Arthritis Unit, Rheumatology Department, Hospital Clínic, Barcelona

***Corresponding author:** María Victoria Hernández MD, Arthritis Unit, Rheumatology Department, Hospital Clínic, Villarroel 170, stairway 11, 2nd floor 08036 Barcelona, Tel: + 34 932275400; Ext: 2236; E-mail: mvhernan@clinic.ub.es

Abstract

In the last decade, the use of biological therapy, mainly tumor necrosis factor (TNF) antagonists, has dramatically improved the prognosis of patients suffering from non-infectious uveitis, especially those affected by posterior uveitis, in which the visual prognosis is usually worse.

In addition to its proven efficacy, biological therapy has also been associated with the development of different adverse events, which in the most severe cases may require the withdrawal of therapy. We review the principal adverse events related to the use of biological agents in non-infectious uveitis described until the present.

How Can we Identify Adverse Events?

One of the basic things before reviewing the safety of any drug is to determine how adverse events are notified and, as a consequence, what is the basis of the known safety profile. The approval of a biological agent by the drug-regulatory agencies, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), as treatment for a chronic inflammatory condition is usually based on the results of clinical trials, mainly randomized, double-blinded placebo controlled trials (phase III), which focus on the efficacy of a biological agent, but also included a report of all adverse events occurring during the trial. However, as clinical trials are patient- and time-limited, some adverse events may not be reported, especially those that are infrequent. Metanalyses, which combine the results of different clinical trials in order to analyse a higher number of patients exposed to the biological agent may increase the identification of adverse events, although they frequently combine clinical trials with different characteristics such as different drug dosages or lengths of follow-up, which may affect the reached conclusions. Adverse events may also be identified by spontaneous reports by physicians to the authorities or regulatory agencies. However, it may take some time to recruit sufficient patients to discriminate whether the adverse event is a consequence of the drug used or whether it is related to the underlying disease or to a comorbid condition. Likewise, clinical observational studies, which are often multicentre and include more patients, may also identify adverse events, although it is difficult to avoid differences in the reporting of adverse events and make a standardized assessment, as suggested by OMERACT [1]. In addition, these are generally phase IV, post-drug-approval studies, and ethics committees may hesitate to approve the studies due to concerns about inducing prescription of the agent.

Currently, registries are the most widely used method of determining the frequency and severity of adverse events related to biological agents. These registries use to be national databases that include all patients starting a biological treatment and all adverse events occurring during or after exposure to a specific agent. Comorbidities and control groups are normally included in the analysis to determine whether the adverse event is related to the agent or to the underlying or concomitant conditions. There are now various national registries [2] that mainly include patients with chronic inflammatory rheumatic conditions, especially rheumatoid arthritis (RA), and therefore most data are based on this type of patient. The Spanish BIOBADASER registry is, to date, the only registry that includes patients with other inflammatory conditions treated with biological agents, such as uveitis [3]. Given the proven efficacy of biological agents in patients with uveitis, it could be interesting to establish a specific registry to analyse whether the 'classical' adverse events associated with biological therapy may differ in this type of patients. Pharmacovigilance programs can also help in looking for the adverse events for specific drugs. The monitoring centre of the World Health Organization also collects data from the whole globe to raise a signal for a particular drug.

Main Adverse Events Related to Biological Therapy

The main adverse events related to the use of biological agents may be classified as follows:

2.1 Infections: bacterial, viral, tuberculosis, opportunistic

2.2 Malignancies

2.3 Demyelinating disease

2.4 Cardiovascular risk

2.5 Immunogenicity

2.6 Malformations and miscarriage in pregnancy

2.7 Others adverse events

Infections

Tumor necrosis factor (TNF) antagonist agents are one of the most-used biological drugs in patients with non-infectious uveitis. TNF is a cytokine that plays a key role in the normal immune response to infection [4] and in tumor immune surveillance [5]. For this reason, TNF blockade would theoretically increase the development of both infections and malignancies. However, to analyse the risk associated with a biological agent, it is also necessary to take into account the risk associated with the underlying inflammatory condition. In RA patients, for example, there is a baseline higher risk of developing infections, including serious infections, [6,7] compared to other conditions. In addition to the underlying condition, predictors of a higher risk of infection include: older age, glucocorticoid treatment and some comorbidities, such as diabetes mellitus, chronic pulmonary illness and renal failure. Patients with uveitis are frequently receiving higher doses of glucocorticoids and immunosuppressive therapy when they start biological therapy, meaning that the risk of infection is higher and special attention should be paid to signs of infection at this time, in order to establish an early diagnosis and correct treatment.

The most-frequent types of infection are bacterial infections affecting the upper and lower respiratory tract, the urinary tract, and the skin and soft tissues [8]. Pneumococcal and influenza vaccination is recommended in these patients before started biological therapy [9]. The risk of infection in patients receiving biological therapy is calculated at approximately twice that of the general population. An increased rate of viral infections, especially herpes virus, has been found in patients treated with biological therapy, although vaccination is not required as the infection usually affects only the skin and disseminated infection is exceptional [10].

Data from the registries show that the risk of infection varies over time: the risk is higher during the first year, especially the first six months, and decreases over time [11,12]. Apart from the possible bias due to treatment being maintained only in patients who do not develop serious infections, this may be associated with more-intensive concomitant treatment (glucocorticoids, immunosuppressive agents) in the first months of biological therapy, which is progressively adjusted and reduced over time as the inflammatory disease is controlled.

Tuberculosis (TB) deserves special mention. During the first years after the approval of biological agents, cases of TB infection were reported [13,14] that had not been observed in clinical trials [15], resulting in warnings by regulatory agencies. These patients usually developed TB infection within the first months after starting biological therapy and the infection was sometimes disseminated or extrapulmonary and life-threatening [16]. Reactivation of latent TB infection (LTBI) by the biological therapy was suggested, and LTBI screening before starting biological therapy was recommended (see Chapter 12), resulting in a dramatic reduction in the number of cases of TB infection in these patients [17,18].

Malignancy

Another important safety issue in patients taking biological agents is the development of malignancies due to immunosuppression. Data from biological registries show an incidence of solid malignancies in patients receiving biological agents similar to that of RA patients received non-biological DMARDs [19]. A possible increase in skin malignancies, especially non melanoma skin malignancies, has also been described [19-21], although other studies found no increase [22-24]. Several environmental and non-environmental factors may affect the rate of cutaneous malignancy, including ethnicity and solar ultraviolet exposure among others, that could suggest the existence of different pathogenic mechanisms [25,26], explaining, in part, the different rates in patients exposed to TNF antagonists.

Analysis of the risk of hematologic malignancies initially suggests a higher incidence of leukaemia and lymphoma, but after adjustment for the underlying condition (RA), no higher risk of lymphoma was found, with a relative risk of biological therapy of 1.1 [0.6-2.1] related to RA patients [27]. Therefore, the apparent increase in risk is the same as for RA, which has higher inflammatory activity. In the Spanish BIOBADASER registry, no increase in the risk of malignancy or mortality was observed in patients receiving biological therapy [20], although closer attention was recommended in patients who were older, those receiving glucocorticoids and those with previous malignancies. Finally, the risk of malignancy does not increase after six years of biological therapy [28].

Demyelinating disease

After the approval of biological therapies, especially TNF antagonists, some cases of both new-onset and recurrent demyelinating disease (multiple sclerosis, optical neuritis) were reported in patients with inflammatory arthritis [29]. Most cases were associated with demyelinating lesions in the central nervous system, with the most frequent symptoms being paresthesia and visual abnormalities. Unlike true autoimmune disease, the outcome of these cases was normally partial or complete resolution of symptoms after drug withdrawal. However, recently, a different outcome pattern has been described, in which the demyelinating disorder can persist despite treatment discontinuation, suggesting a further, independent evaluation [30]. A recent analysis of the Biobadaser registry, which includes 21425 patient-years, no increased incidence of demyelinating disease was found in patients treated with anti-TNF agents [31].

Cardiovascular risk

Another safety concern related to biological therapy is the associated cardiovascular risk, especially in RA patients, who already have an increased cardiovascular risk due to persistent inflammation [32,33]. No studies have analysed whether the risk is also increased in other conditions with persistent inflammation, such as uveitis. However, there are some data on biological therapy coronary risk and the risk of heart failure, the two most important conditions associated with cardiovascular morbidity and mortality.

Coronary risk: The British biological registry [34] found no differences in the rate of myocardial infarction in RA patients treated with biological therapy compared to those treated with non-biological DMARDs. However, a reduction in the risk of myocardial infarction was found at 6 months in responders compared to non-responders, with the control of inflammation the suggestion mechanism for this reduction. In the US registry (CORRONA), a reduced risk of cardiovascular events was found in patients treated with TNF antagonists, which persisted after adjustment by age, gender, cardiovascular risk factors, RA characteristics and glucocorticoid treatment [35]. A reduction was also observed for non-serious cardiovascular events.

Heart failure risk: A warning of a worse prognosis and risk of death in patients with heart failure treated with biological drugs

was issued after the results of two clinical trials [36,37] and was made obligatory in the package insert of TNF antagonists, stating that these drugs were contraindicated in patients with heart failure stages III and IV according to the New York Heart Association (NYHA) functional classification [38]. However, the main objective of these clinical trials was not to evaluate the safety of these drugs in this group of patient but to analyse the clinical efficacy of the addition of biological therapy on the prognosis. The ATTACH study [36] analysed the effect of infliximab treatment on patients with heart failure stages III and IV and an ejection fraction < 35. An increase in the rates of hospitalization and deaths was found, but only in the group that received a dose of infliximab of 10 mg/kg, above the standard dosage. In the group receiving the standard 5mg/kg infliximab dosage there were no differences and no increased risk compared to placebo. The RENEWAL study [37] included the results of two studies: the European RECOVER study and the North American RENAISSANCE study. Both studies included patients with heart failure stages II-IV and an ejection fraction < 30, in order to analyse the effects of different dosages of etanercept. Although no clinical improvement was shown, no differences were found between etanercept and placebo at the standard dosage.

The warning issued meant that patients with these conditions did not start biological therapy unless there was no other option. Therefore, there are only a few reports in clinical practice that analyse the risk of heart failure in patients receiving these agents. The German RABBIT registry [39] evaluated the incidence of and risk factors for heart failure and found a small increase in heart failure at three years in patients with previous cardiovascular disease compared with those without. The increase was greater in patients with more inflammation during the follow-up. The study concluded that TNF antagonists may be more beneficial than prejudicial when the risk of heart failure is weighed against the reduction in inflammation, especially when there are no other concomitant treatments, such as glucocorticoids or NSAID COX2. Thus, evidence suggests that TNF blockade does not increase the risk of worsening of previous heart failure.

Immunogenicity

Another safety aspect related to biological therapies is the risk of development of autoantibodies. Although rates of 30-80% of antinuclear antibodies, 3-15% of anti-DNA antibodies, 0-15% of anti-cardiolipin antibodies and 0-70 % of anti-histones have been described after biological treatment, especially with infliximab and etanercept, no association with specific clinical syndromes, such as systemic erythematosus lupus or other connective tissue diseases, has been found. The development of other antibodies, such as anti-drug antibodies, has also been analysed. The most important antibodies induced by biological agents are neutralizing antibodies. Two types of antibodies have been described: human anti-human antibodies (HAHA), most commonly induced by adalimumab; and, human anti-chimera antibodies (HACA), induced by infliximab. Clinically, the development of these anti-drug neutralizing antibodies is associated with different adverse events, such as infusion reactions, and may require drug withdrawal. A loss of efficacy has also been observed associated to the development of this type of antibodies [40,41].

Malformations and miscarriage in pregnancy

One of the main safety aspects of any drug is the teratogenic risk. Although TNF blockers were initially classified as category C of the US Food and Drug Administration (FDA) classification [42], they are currently classified as category B, while non-TNF antagonist biological agents are still classified as category C. Current recommendations for patients under biological therapy are to plan pregnancies once the inflammatory condition is controlled and, if possible, the biological agent should be withdrawn before the pregnancy, taking the half-life of the drug into account. However, in some patients it is not possible to withdraw the biological drug without a relapse in the underlying condition: these cases present a real challenge. A review of the FDA database from 1999 through December of 2005 found congenital anomalies in infants exposed to anti-TNF therapy, with a large number of them being part of the VACTERL spectrum (vertebral abnormalities, anal atresia, cardiac defect, trachea-oesophageal, renal, and limp abnormalities) [43]. This review led to an alert on the congenital risk of these drugs, although the risk is difficult to quantify, as there is no comparison of the incidence of these congenital abnormalities in the general population. The results of the ongoing PIANO (Pregnancy in IBD and Neonatal Outcomes) registry may provide more information on this risk [44]. However, data from other registries suggest that, fortunately, the risk of malformation in these patients is low. The British registry analysed 130 pregnancies in women receiving biological drugs during more than ten years, and found genetic malformations in only four cases [45]. However, studies on the exact incidence of malformation associated with biological drugs and in the general population are required.

Certolizumab is the only TNF antagonist that has no Fc portion and, as a consequence, it is not expected to be actively transported across the placenta like other agents such as infliximab or adalimumab. In one study of 10 patients with Crohn's disease receiving certolizumab during pregnancy up to 2 weeks prior to delivery, high levels of the drug were found in the maternal serum but low levels in the infants and their cord blood on the day of birth [46].

The results of the certolizumab safety database for all medically-confirmed cases of pregnancy through March 6, 2012 were recently reported [47]. Of the 139 cases of direct exposure with known outcomes, 103 resulted in live births, 21 pregnancies ended in spontaneous miscarriage and 15 in elective termination, results similar to those reported in the general population in the US. In the 103 live births, there were two reports of congenital disorders: one baby had mild, unilateral hydronephrosis on antenatal ultrasound and was described as healthy upon birth, and the other baby had vesicoureteric reflux. The rate of congenital disorder in the US general population is 3% [48]. Although these results may hold some promise, the recommendation to avoid biological exposure during pregnancy still holds, given the lack of controlled clinical trials.

Other adverse events

Some other emerging adverse events deserve to be commented. One of the most frequent adverse events observed in clinical practice is the development of cutaneous lesions. As these tend to be local, they have not been paid much attention in spite of their frequency. In addition to the development of infections or malignant skin lesions, as commented above, other conditions such as cutaneous autoimmune disorders have frequently been described [24]. The first reported immune-mediated condition induced by biological therapy was psoriasis [49], with more than 200 cases described to date [50]. Other autoimmune diseases associated with biological therapy are cutaneous lupus erythematosus [51]; alopecia areata [52]; cutaneous vasculitis (mainly leukocytoclastic) [53]; vitiligo [54]; relapsing polychondritis [55]; localized scleroderma [56]; and other immune-mediated skin diseases, such as granuloma annulare [57], lichen or lichenoid reactions [58], and pemphigus [59]. These immune-mediated conditions are confined to the skin, suggesting this may be a possible target for adverse events associated with biological therapy, especially TNF antagonists. The prognosis is usually favourable; however, in the most extensive cases biological withdrawal may be required [60].

Diverticulitis with the risk of gastrointestinal perforation has been specifically associated with tocilizumab [61], a humanized anti-interleukin-6 (IL-6) receptor antibody that is an emerging drug in uveitis patients and has demonstrated good results in uveitic macular oedema [62]. However, the reported risk of lower gastrointestinal perforations is more related to patients receiving concomitant glucocorticoid treatment. To minimize the risk, treatment with tocilizumab in patients with previously-diagnosed diverticular disease is not recommended.

Arthralgia is another frequent, although generally mild, adverse event associated with tocilizumab. In a study based on FDA reports of patients reporting side-effects of tocilizumab, made in August 2013, 4.19% had arthralgia [63], and in 73.64% of cases this occurred in the first month of treatment. Arthralgia was more frequent in females (81.75%) and in patients aged 50-59 years (41.92%). Although the exact mechanism is not known, it has been suggested that it may be a consequence of an increase in serum IL-6 levels observed between 7 and 14 days after tocilizumab administration [64] due, probably, to a blockade of IL-6 clearance [65]. The arthralgia is normally self-controlled after the continuous administration of tocilizumab, probably due to control of the underlying inflammatory condition that goes with lower IL-6 levels. Meanwhile, the symptoms may be controlled by the use of NSAIDs or, in moderate-severe cases, with a short course of low-dose glucocorticoids, and it is usually not necessary to discontinue biological treatment.

In conclusion, although there is a wide possible spectrum of adverse events related to biological therapy, overall these drugs have a reasonable safety profile, especially compared with the risk of the non-treated underlying inflammatory condition. Moreover, most adverse events may be minimized by appropriate screening before starting biological therapy and adequate surveillance during treatment coupled with early diagnosis and treatment of possible adverse events. As most experience of biological therapy comes from patients with rheumatic conditions, most safety data is based on these groups. Future studies on the specific incidence of adverse events in non-infectious uveitis patients may clarify the exact rate and type of these events in this population.

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Emerging Therapies: Fingolimod, Secukinumab, and Efalizumab

Marc Figueras-Roca* and Marina Mesquida

Uveitis and Medical Retina Unit, Ophthalmology Department, Hospital Clínic de arcelona, Barcelona, Spain

***Corresponding author:** Marc Figueras-Roca, Uveitis and Medical Retina Unit, Ophthalmology Department, Hospital Clínic de arcelona, Barcelona, Spain, E-mail: mafiguer@clinic.ub.es

Introduction

This chapter is intended to provide a short glimpse on recent emerging therapies that could play an important role in the field of non-infectious uveitis in the next years to come. Both secukinumab and fingolimod are quite new therapies that are being examined and analyzed by worldwide physicians, which means controversy has been found regarding its clinical use in ocular inflammation. Efalizumab had a promising starting in the fields of uveitis but unfortunately clinical trials were stopped because of safety concerns. Efalizumabis presented a possible emerging therapy in the new clinical trials to come whenever its safety concerns are resolved. Our aim is to give basic knowledge of these new drugs such as their molecular basis, clinical evidence, and preliminary conclusions.

Secukinumab

Molecular basis

Both affected subjects and experimental models have proven the core role of auto reactive T cells in the pathogenesis of non-infectious uveitis, thus allowing immunosuppressive (IS) medication to become a central therapeutic agent [1,2]. Several molecular agents and cytokines have been described in the proinflamatory reactions involving immune-mediated diseases, and, of them, interleukin-17A (IL-17A), secreted by T-helper (Th) 17 cells, is one of the main ones [3,4]. Increased levels of IL-17A have been described in the peripheral blood of subjects with uveitis such as Vogt-Koyanagi-Harada syndrome and Behçet disease, compared with unaffected subjects (or quiescent uveitis) [5,6]. Moreover, it has already been stated than IL-17A inhibition in animal models of uveitis suppresses disease activity [7]. In addition, from a strategic point of view, agents targeting IL-17A act selectively in the inflammatory cascade at the level of a key cytokine, thereby preserving other immune functions of IL-17A-expressing agents [8]. This selective targeting differs from other therapeutic agents such as IL-23/12 inhibitor therapies that are believed to block both the generation and maintenance of T- helper 1 cells (Th1) and T- helper 17 cells (Th17), thus impacting numerous T-helper activities far beyond IL-17A [8,9] (Figure1). Nowadays, inhibition of IL-17A can be achieved with secukinumab (AIN457, Novartis), a fully human monoclonal antibody that binds selectively and with high-affinity to this cytokine, therefore preventing initiation of the inflammatory cascade and consequent activation of neutrophiles, macrophages, epithelial cells and other inflammatory agents [10,11].

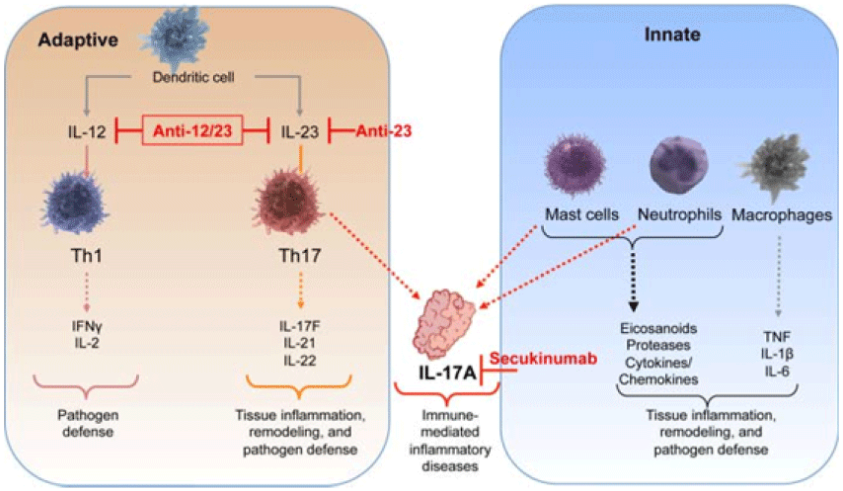

Figure 1: Adapted from: Patel DD, Lee DM, Kolbinger K, Antoni C. *Effect of IL-17A blockade with secukinumab in autoimmune diseases.* Ann Rheum Dis 2013; 116-123.

Clinical evidence

Secukinumab was first reported to show clinical efficacy and safety in active chronic non-infectious uveitis by Hueber et al. in 2010 [12], based on the results of an open-label proof-of-concept clinical study. Sixteen patients with non-infectious uveitis refractory to

corticosteroid therapy received intravenous secukinumab (10 mg/Kg) at baseline and 3 weeks afterwards, and 11 out of 16 patients responded and improved visual acuity, with reduction of intraocular inflammation that allowed stopping corticosteroid therapy. Disease activity was reduced in a similar manner to that achieved with infliximab therapy (antibody against tumor necrosis factor-alpha) thus setting the basis on future clinical trials [13]. Moreover, it was also reported that secukinumab induced clinically relevant responses in patients with other autoimmune diseases such as rheumatoid arthritis and psoriasis [12]. Since then, 3 major clinical trials with secukinumab have been promoted and analyzed, comparing this drug versus placebo in the treatment of non-infectious uveitis [14]. These studies were named SHIELD (patients with Behçet's disease with posterior uveitis or panuveitis), INSURE (patients without Behçet's disease and active non-infectious uveitis) and ENDURE (patients without Behçet's disease and quiescent non-infectious uveitis). Secukinumab was administered subcutaneously in a dosage of 300 mg or 150 mg in a once a week or once every two weeks regime depending on the trial arm of each study. Primary endpoints were set at the reduction of clinical disease activity (varying from rate of relapses, vitreous haze or time to first reactivation depending on the study) and secondary endpoints at the reduction of concomitant IS medication. In the SHIELD study, no statistically significant differences were observed between either of the secukinumab treatment groups and the placebo group for the rate of uveitis recurrence in the study eye [14]. There was a larger proportion of patients with no recurrences and a smaller proportion of patients with 3 or more recurrences in the secukinumab treatment groups compared with the placebo group, but the differences were not statistically significant. There were also no differences found in the mean duration of exacerbations. However, SHIELD study did show statistically significant reductions in the IS concomitant treatment from baseline with secukinumab versus placebo, a difference that was maintained taking into account events such as differences in the rate or duration of the exacerbations [14]. After completion of the SHIELD trial, having showed insufficient evidence for the efficacy of secukinumab, INSURE trial was terminated early. In the same line, ENDURE and INSURE trials were also terminated early because an interim data analysis did not show sufficient evidence of efficacy.

It can be argued that extended and intensive use of concomitant IS medication in all study groups may have played a role in the results of these studies, not allowing secukinumab to achieve clinical goals in the setting of an already deeply immune modulated subject. Discussion on the promotion of its clinical use in lightly treated patients can be taken into consideration. Moreover, another potential reason for these results is that Behçet's disease patients were selected using quite aggressive criteria (2 or more exacerbations in the past 6 months and needing IS therapy) thus their outcomes could not be the same that those in patients with milder forms of uveitis or quiescent ones.

Conclusion

Secukinumab is thought to have a role to play in non-infectious uveitis. Being a most favored immune modulatory agent due to its capacity of selectively blocking some IL-17A effects, it seems reasonable to think that more investigation on this promising drug is expected.

Fingolimod

Molecular basis

Fingolimod (Gilenya™, Novartis) is a drug structurally analogue to sphingosine-1-phosphate (S1P), a natural lysophosholipid that plays an important role in several pathways of immune and vascular biology. It modulates immune cascade by preventing T cells release from secondary lymphoid organs, therefore reducing the population of peripheral T lymphocytes [15]. It has been mainly developed and indicated in the context of multiple sclerosis, with widespread acceptance because of its more tolerable oral dosage regime, although new uses in other autoimmune diseases are being explored. Its active metabolite is fingolimod-phosphate (FP), which acts by binding to isoforms 1-3-4-5 of the S1P receptor, thus inducing internalization and degradation of the S1P1 receptor. Such lymphocytes with the S1P1 receptor, some already sensitized to auto antigens, are therefore withhold within the lymph node and are unable to access peripheral circulation and thus end up not accessing their target tissue to participate in the autoimmune response. Moreover, Fingolimod seems to preferentially suppress a subset of T cells (naive and central memory), allowing ongoing cell-based immunity to continue undisturbed while modulating the autoimmune activity associated with the target disease [16]. In addition, several studies indicate that S1P activation enhances endothelial barrier integrity through acting on both the cytoskeleton and intercellular junctions [17,18]. This may explain the pathophysiology of fingolimod's most characteristic ocular adverse event - macular edema-based on that, although FP is a structural analogue to S1P, it behaves biochemically as a functional antagonist due to receptor down-regulation, thus deteriorating endothelial barrier integrity. Regarding adverse events, macular edema is thought to affect 1-4% of fingolimod-treated patients on a dose-depending regime [19]. It commonly resolves when discontinuing the drug. Patients with multiple sclerosis treated with fingolimod and with a history of past uveitis are thought to bare an increased risk to develop macular edema (up to 20%), making them a subgroup of patients at least controversial whether to use fingolimod as therapy [20].

Clinical evidence

Fingolimod's efficacy in preventing inflammation has been successfully described in diverse conditions including relapsing-remitting multiple sclerosis [21], post transplantation inflammation [22,23] and ocular inflammation [24-26]. Clinical evidence in ophthalmic systems has been mainly based on published studies regarding its efficacy in experimental autoimmune uveoretinitis. These studies have shown that fingolimod-treated specimens had statistically significant less macrophage and T-cell infiltration than untreated ones and, moreover, this reduction was also accompanied by a reduction in early anatomical damage to the analyzed retinas. Regarding these data, authors suggest that oral fingolimod could embrace an important role in the acute treatment of non-infectious uveitis whether as a rescue therapy for patients resistant to other treatments or as an adjunct therapy to prevent structural damage [26].

Conclusion

Reported findings in experimental models regarding fingolimod use in autoimmune uveitis provide a solid basis where to develop and promote extensive clinical trials to evaluate its efficacy in non-infective uveitis. Although its benefits being extensively proven in multiple sclerosis studies, given the unique anatomical and structural characteristics of ocular tissues, results from specific designed trials are to be waited and analyzed before general recommendations could be set.

Efalizumab

Molecular basis

Efalizumab (Raptiva; Genentech) is a humanized form of a murine IgG1 antibody targeted against CD11a, a subunit of lymphocyte function–associated antigen 1 (LFA-1) [27]. LFA-1, which expression is increased in memory T-cells, and intercellular adhesion molecule 1 (ICAM-1), expressed on endothelial cells at inflamated sites, are both thought to bear important roles in the pathogenesis of autoimmune diseases; therefore existing studies have shown that inhibition of molecular adhesion function, for example, CD11a, decreases histologic and clinical expression of endotoxin-induced uveitis [28,29]. In the same way, *in vitro* studies have pointed out that efalizumab is able to inhibit T-cell activation, recruitment and adhesion without decreasing its population [30]. Efalizumab was approved for use in moderate to severe plaque psoriasis in adults [31-33].

Clinical evidence

Based on its approved application for plaque psoriasis and taking into account its uveitis usefulness rationale, an open-label, prospective and non-comparative clinical trial (phase I/II) was carried out to evaluate efalizumab in non-infectious uveitis [34]. The study recruited 6 patients with non-infectious uveitis and cystoid macular edema (CME) who were treated with weekly subcutaneous efalizumab for 16 weeks. No serious adverse events, including serious infections attributable to the study medication, were reported by the patients. All participants showed a reduction in CME (mean reduction of 128+/-105 micrometers), as evidenced by optical coherence tomography, and all patients experienced an improvement in visual acuity (mean best-corrected visual acuity improvement was 6.7+/-6.9 ETDRS letters (worse eye) and 1.7+/-5.2 letters (better eye). Three patients were able to reduce their concomitant IS medications by 50%, and 5 out of 6 participants maintained clinical quiescence of their uveitis during the study. Despite its promising results in ocular inflammatory disease, efalizumab was finally taken off the market due to safety concerns: 3 consecutive cases of progressive multifocal leukoencephalopathy were reported in long-term users (older patients using efalizumab for more than a year), none of them suffering from uveitis [34].

Conclusion

Efalizumab had its clinical use slowed down (if not stopped) due to safety concerns despite its promising results in available trials in uveitis. Since these described serious adverse events were limited to non-uveitic long-term users of this drug, decisions would be taken in order to promote clinical trials addressed to a much more selected group of patients. Nonetheless, widespread use of efalizumab for non-infectious uveitis is nowadays not possible.

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