REVIEW ARTICLE

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Management of Sight-Threatening Uveitis

New Therapeutic Options

Matthias D. Becker,[1,2] *Justine R. Smith*,[3] *Regina Max*[1,4] and *Christoph Fiehn*[1,5]

1 Interdisciplinary Uveitis Center, University of Heidelberg, Heidelberg, Germany
2 Department of Ophthalmology, University of Heidelberg, Heidelberg, Germany
3 Casey Eye Institute, Oregon Health & Sciences University, Portland, Oregon, USA
4 Department of Internal Medicine, University of Heidelberg, Heidelberg, Germany
5 Centre of Rheumatic Diseases, Baden-Baden, Germany

Contents

Abstract

Over the past 2 decades therapy for the treatment of intraocular inflammation (uveitis) has developed into a highly differentiated approach with an increasing number of drug options. This paper primarily summarises literature from the past 5 years (2000 to May 2004), gives an update on systemic immunosuppressive therapy for non-infectious uveitis and speculates about new developments that could become relevant in the near future for the treatment of uveitis patients. The spectrum of immunosuppressive drugs has been notably expanded by tumor necrosis factor inhibitors, but with some limitations to uveitis. Behçet's disease is an example of uveitis where a multisystem disorder can affect the eye very severely. This clinical example has been used to investigate the utility of many different types of immunosuppressive therapies and the clinical approach is extensively discussed in this review. An accompanying table summarises the proposed mode of action, standard dosage, common adverse effects, as well as estimated cost of current treatment options.

Uveitis, a synonym for intraocular inflammation, accounts for approximately 50 different entities with either an infectious or autoimmune origin. Intraocular inflammation generally originates from the middle layer of the eye, termed the uvea. This structure consists of the iris, the ciliary body and the choroid. Primary uveitis ('idiopathic') is a term for intraocular inflammation of unknown cause (approximately 40% of patients seen in tertiary referral centres). Secondary uveitis (all cases with some explanation for the uveitis) accounts for inflammatory ocular conditions that are either associated with a systemic disease (e.g. ankylosing spondylitis or sarcoidosis), are of known infectious cause (e.g. toxoplasmosis or cytomegalovirus-retinitis) or are defined as ocular syndromes (e.g. Fuchs' uveitis syndrome, birdshot syndrome or serpiginous choroiditis). Masquerading syndromes, such as intraocular lymphoma, also have to be differentiated from primary or secondary uveitis.

The epidemiological distribution of the various categories of uveitis depends on multiple factors including geographic location, gender and race; however, epidemiological studies of uveitis are rare. A recent study determined the incidence and prevalence of uveitis in a large, well defined population in Northern California, USA.[1] The incidence of uveitis in this well defined population was calculated to be 52.4 per 100 000 person-years with a period prevalence of 115.3 per 100 000 persons. Despite studies that showed a peak incidence of uveitis in those from middle aged groups,[2-4] the incidence and prevalence of disease in this study were lowest in paediatric age groups, increased with age and were highest in patients ≥65 years. The prevalence of uveitis in this study was also reported to be higher in women than in men (not statistically significant) with primary ('idiopathic') uveitis being diagnosed in 48% of new cases (most of which were an initial episode of iritis) and in 33.9% of the prevalent cases. These incidence rates are approximately three times those of previous US estimates.[4,5] With the increasing age of the general population in Western countries, this higher incidence of uveitis could have tremendous impact on public health. Therefore, it is of importance to summarise currently known evidence for the treatment of sight-threatening ocular inflammation.

During the last decades several second-line disease-modifying antirheumatic drugs (DMARDs) have been added to the inventory of treatment for rheumatoid arthritis (RA). Because of the high inci-

dence and prevalence of RA in the general population,[6,7] several prospective randomised trials investigating different DMARDs and their combination have been undertaken. Results from these studies have been used to guide treatment of much rarer ocular inflammatory diseases, which are broadly summarised within the term 'uveitis'.

To date, there have been no published prospective, randomised trials investigating DMARDs in uveitis. In 2000, an expert panel of uveitis specialists conducted by Jabs et al.[8] published their guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders. This expert consensus is recommended for treatment decisions in the context of low-evidence clinical trials of heterogeneous ocular inflammatory disease groups. Song[9] has written another recommended review in the recent literature about standard immunosuppressive treatment (corticosteroids, methotrexate, ciclosporin [cyclosporine], azathioprine and combination therapy), which includes highly informative tables.

This review primarily summarises literature from the past 5 years, gives an update on systemic immunosuppressive therapy for non-infectious uveitis and speculates about new developments in the treatment of patients with uveitis. It updates the recent publication by Becker and Rosenbaum.[10] Table I summarises the proposed mode of action, standard dosage, common adverse effects and estimated cost of treatment (given in €) based on pharmacy prices in Germany.

1. Treatment of Uveitis

1.1 Corticosteroids

Because of their immediate efficacy, topical, periocular, intraocular and systemic corticosteroids remain the mainstay of primary immunosuppressive therapy in uveitis and have been recently reviewed by Rothova.[28] Because of the high rate of steroid-induced ocular and systemic adverse effects, independent of the administration route, with long-term treatment (>3 months), steroid-sparing drugs should be added to the treatment regimen and should ideally even replace the use of corticosteroids or allow the use of corticosteroids below the Cushing-threshold (<8mg prednisone equivalent per day). However, steroid-sparing agents do not have to be administered in every patient immediately. If the 'prednisone-threshold' during corticosteroid taper is below the Cushing-threshold some experts favour retaining this low-dose corticosteroid strategy before switching or adding steroid-sparing agents.

In contrast with their high frequency of use in uveitis, available medical evidence concerning the efficacy of corticosteroids in uveitis is limited compared with that available for immunosuppressives, which have been analysed in several studies.

Among other unwanted adverse effects, steroid-induced osteoporosis is of major concern and has recently been analysed in 129 adult patients in a retrospective multicentre study from England.[29] Bone density in these patients was abnormally low in 44.2% of patients, with 15.5% having definitive osteoporosis. Osteoporosis was far more common in males (20.6% in those <60 years) than in females (9.8%). Bone loss also correlated well with total corticosteroid dose, mean dose, duration of treatment and the presence of pre-existing risk factors. The risk of fracture was also found to be increased 2.5–3-fold compared with the control population. Therefore, patients undergoing long-term prednisone treatment should receive calcium and vitamin D supplementation according to the recently published recommendation of the American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis.[30] Moreover, the use of bisphosphonates should be considered, as these drugs play a major role in the treatment of steroid-induced osteoporosis. However, bisphosphonates should used with care since in rare cases these substances can themselves induce uveitis.[31]

1.1.1 Peri- and Intraocular Treatment of Uveitis with Corticosteroids

Several techniques have been advocated for periocular application of corticosteroids, including subconjunctival, sub-Tenon's capsule, transseptal, orbital floor and retrobulbar injections. However, each technique is associated with various complications

Table I. Overview of immunosuppressives discussed in this review, including information about mechanism of action, most common and relevant adverse effects, standard dose administration and price. All drugs are sorted according to calculated daily cost of treatment given in € and based on German pharmacy prices (2004 values)

Drug	Mechanism of action	Recommended dosage	Selected common adverse effects	Approximate maximum cost of maximal standard treatment per day (€)	References related to uveitis in the recent literature
Price range <€10/day					
Methotrexate	Methotrexate inhibits dihydrofolate reductase, thus impairing the synthesis of nucleic acids and proteins	10–25mg once per week	Liver toxicity, nausea/vomiting, alopecia, mouth ulcers	1	11-13
Sulfasalazine	Influence on leukotriene synthesis, arachidonic acid metabolism and lipoxygenation, unknown influence attributable to antimicrobial effects	Start at a dose of 500 mg/day and increase 500 mg/week to achieve a stable dose of 2 g/day (1g bid); in cases of a new flare, the dose can be increased 500 mg/week up to a total dose of 3 g/day	Azoospermia, hypersensitivity reaction	1	14,15
Cyclophosphamide	Alkylation of purines	2–3 mg/kg/day PO, 10–15 mg/kg IV pulsed over 3–4 weeks	Bone marrow depression, nausea/vomiting, secondary infections, haematuria, haemorrhagic cystitis, risk of malignancies	2	16
Leflunomide (Arava®)	Inhibitor of dihydroorotate dehydrogenase, the rate-limiting intracellular enzyme required for the *de novo* synthesis of pyrimidines	Loading dose of 100 mg/day for 3 days, then 20 mg/day PO	Elevation of liver enzymes, hypertension, reversible alopecia	3	NA
Chlorambucil	Alkylating agent	0.1 mg/kg/day, maximum 0.2 mg/kg/day (approximately 6–12 mg/day)	Bone marrow depression, opportunistic infections, increased risk of malignancy, sterility, no bladder toxicity	5	17

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Table I. Contd

Drug	Mechanism of action	Recommended dosage	Selected common adverse effects	Approximate maximum cost of maximal standard treatment per day (€)	References related to uveitis in the recent literature
Price range €10–50/day					
Mycophenolate mofetil (CellCept®)	Mycophenolic acid inhibits inosine monophosphate dehydrogenase (*de novo* synthesis of purines). T and B cells rely solely on this pathway for production of guanosine nucleotide (other cells can also use the salvage pathway alternatively)	1g bid	No major organ toxicity, diarrhoea/vomiting, leukopenia, sepsis	14	18-21
Interferon-β	Suppression of T-helper 1 or increase in T-helper 2 cytokines production: shifts the balance of cytokines in favour of a net anti-inflammatory response	Loading dose of 22μg three times per week, if insufficient response 44μg three times per week	Flu-like illness	17	NA
Ciclosporin (cyclosporine)	T-cell inhibitor	2–5 mg/kg/day	Nephrotoxicity, hypertension	23	22
Interferon-α	Suppression of T-helper 1 or increase in T-helper 2 cytokines production: shifts the balance of cytokines in favour of a net anti-inflammatory response	Initially, 6MU three times per week dose; frequency adjusted depending on the clinical response	Flu-like illness	29	23
Price range >€50/day					
Anakinra (Kineret™)	IL-1 receptor antagonist	100 mg/day SC	Risk of infection, local reaction	38	NA
Etanercept (Enbrel™)	Human TNFRp75-IgG1 fusion protein binds TNFα and TNFβ	25mg twice per week or 50mg once per week SC	Risk of infection, local reaction	64	24
Adalimumab (Humira™)	Human anti-TNF-α antibody	40mg every other week SC	Risk of infection	70	NA
Infliximab (Remicade™)	Chimeric murine-human anti-TNFα monoclonal antibody	3 mg/kg of bodyweight at 0, 2 and 6 weeks, then every 8 weeks; for incomplete response, maintenance dose may be gradually increased to a maximum of 10 mg/kg	Risk of infection, allergic/ anaphylactic reaction	144/day for a period of 6 weeks with three infusions	24,25
IV immunoglobulin	Anti-inflammatory effects that may be mediated by the inhibitory Fc receptor pathway	Different protocols, 0.4 mg/kg/day IV over 5 days	Allergic/anaphylactic reaction, nausea, vomiting, fever, headache	9100 per cycle (5 days)	26,27

bid = twice daily; **IL** = interleukin; **IV** = intravenous; **NA** = not applicable; **PO** = orally; **SC** = subcutaneous; **TNF** = tumour necrosis factor; **TNFR** = TNF receptor.

resulting from the injection itself, including blepharoptosis, orbital fat herniation, globe perforation, and even retinal and choroidal vascular occlusion. With the increased popularity of intravitreal corticosteroid injections, several recent studies have documented the safety and efficacy of intraocular application of corticosteroids either by injection or surgical implantation of depot devices.[32-36] Both of these techniques carry the risk of complications associated with the intravitreal procedure itself, including suprachoroidal placement of an implant, vitreous haemorrhage, retinal detachment and endophthalmitis.

Of the numerous corticosteroid adverse effects the one of major concern is steroid-induced intraocular pressure (IOP) elevation, which can often be treated by topical anti-glaucoma medication but which may also require surgical intervention. In addition to others,[37-41] one recent article has almost exclusively concentrated on this adverse effect.[42] This study retrospectively analysed 64 eyes of 64 patients to determine whether a history of IOP elevation from local corticosteroid administration could predict subsequent IOP elevation after posterior sub-Tenon's capsule corticosteroid injections. Patients were categorised as either historical corticosteroid responders or nonresponders after topical corticosteroid treatment in the same eye or after previous posterior sub-Tenon's corticosteroid injection of the fellow eye. Recurrent elevated IOP developed more often in historical responder eyes (4 of 9; 44%) than in non-responders (7 of 55; 13%) after posterior sub-Tenon's injection. A higher risk of IOP elevation was also seen in patients with uveitis (10 of 39 eyes; 36%) than in eyes without uveitis (1 of 25; 4%). All but one eye that developed IOP elevation from posterior sub-Tenon's injection was adequately controlled with topical antiglaucoma therapy. Since the risk of IOP elevation is not absolute, the authors concluded that in non-glaucomatous eyes, a history of corticosteroid-induced IOP elevation is a relative, not absolute, contraindication to posterior sub-Tenon's corticosteroid injection. If a pressure rise occurs it usually can be well controlled with topical antiglaucoma therapy. The use of sub-Tenon's depot corticosteroid injection must, therefore, be considered in the context of available alternative therapies and not solely based on the absence or presence of a previous steroid-induced pressure elevation.

Okada and coworkers[43] recently analysed the technique of trans-Tenon's retrobulbar triamcinolone infusion in 51 eyes of 37 patients who underwent this treatment for vitreitis, cystoid macular oedema (CME) or posterior retinal vasculitis using a long blunt canula via an incision made through conjunctiva and Tenon's capsule. The authors report on different clinical responses depending on the indication for treatment with response rates of 96% for vitreitis, 82% for CME and 33% for posterior retinal vasculitis, with an overall general clinical response rate of 86%. In this study, cataract progression occurred in 31% of the eyes and IOP elevation in 27%. Most of the eyes received concomitant topical corticosteroids. IOP elevation developed at 2–3 months after treatment in all patients and was controlled using a monotherapeutic pressure-lowering drug regimen that, in 13 eyes, could be discontinued by 6 months after the procedure. No progression of disc cupping or visual field loss was observed in any of the patients in this study. However, one patient in this study eventually underwent filtration surgery for refractory glaucoma in one eye.

CME can be a real challenge for clinicians. If it is longstanding it can severely affect visual acuity, even if treatment is successful. The treatment of uveitis[32] and/or uveitic CME[33,34,44] with intravitreal triamcinolone injections has drawn increasing interest in the recent literature. The efficacy of various methods of corticosteroid injection has always been a matter of debate with different studies giving mixed results.[45-48] The use of optic coherence tomography (OCT) allows a reliable quantification of CME in uveitis patients and has been used in several studies to document the success of treatment.[33,44] Antcliff and coworkers[33] injected triamcinolone 2mg into the vitreous cavity of six patients with CME resistant to conventional treatment with either periocular or systemic corticosteroids or immunosuppressives. This study achieved complete ana-

tomic resolution of CME in five of the six patients, beginning as soon as 1 week after injection. However, CME recurred between 6 weeks and 3 months after injection (as it does after periocular injection). Two patients with longer-term follow-up responded to one further orbital floor corticosteroid injection and had no CME 1 year later. None of the phacic patients developed lens opacities during follow-up. Notably, one patient developed raised IOP requiring a trabeculectomy. In contrast with the dramatic anatomic improvement seen in OCT, the mean improvement in visual acuity after 12 months was limited with an average final visual acuity score of 0.27 (range 0.14–0.42), probably because these end-stage eyes already had permanent damage resulting from long-term CME. The reduced dose of triamcinolone 2mg, used for intravitreal injections, reduced complications but was still sufficient to resolve CME.

In another study, Martidis and coworkers[44] injected a higher dose of triamcinolone (4mg) into the vitreous of two patients. These preliminary results showed prompt resolution of oedema with corresponding improved visual acuity. Young et al.[34] used triamcinolone 4mg injected into the vitreous, in six patients with CME who were unresponsive to periocular corticosteroids and who had not experienced a previous rise in IOP.[34] In most patients two injections were necessary to achieve a temporary CME resolution. Despite the negative history for corticosteroid-induced glaucoma, five of six patients had pressure rises of up to 30mm Hg or greater post-injection. Two of six patients developed cataract.

Resolution of CME is undoubtedly a question of adequate intraocular corticosteroid levels, which is positively correlated with the development of cataract and secondary glaucoma. The effect of intravitreal corticosteroid injections is temporally limited and has to be weighed against the irreversible damage that can be caused to the eye by both corticosteroids and the injection procedure. In a small cohort of 22 patients, Jonas et al.[49] were able to show that single or repeated intravitreal triamcinolone injections in the treatment of neovascular or oedematous diseases do not change the profile of surgical complications. In future analyses the short-term efficacy of intravitreal injections should be compared with the effect of intraocular slow-release devices (see section 1.1.2).

1.1.2 Intraocular Slow-Release Drug Delivery Devices

Fluocinolone acetonide sustained drug delivery devices have been tested in two large prospective multicentre ongoing trials over the past 3 years. A preliminary pilot study from Jaffe et al.[36] published in 2000 reported on seven eyes in five patients with severe uveitis implanted with either 2mg (six of seven) or 15mg (one of seven) devices.[36] At the final visit (average 10 months), no eye had clinically detectable inflammation and all seven eyes had a marked reduction in systemic, topical and periocular anti-inflammatory medication use. Four of seven eyes had increased IOP at the time of 6 weeks to 6 months after device implantation, which was controlled with topical medications.

Initial data from the clinical trials of the fluocinolone acetonide-containing Retisert™ [1] (Bausch & Lomb, Rochester, NY, USA) implant for posterior uveitis were presented at the meeting of the American Academy of Ophthalmology in 2003.[50] The results of 34-week data from the first phase III randomised, multicenter, double-blinded and controlled trial were analysed. In this trial, 278 patients with non-infectious posterior uveitis were randomised to receive either a Retisert™ 0.5 or 2mg implant in the affected eye, or in bilateral but asymmetric cases, in the more severely affected eye. At 34 weeks, the uveitis recurrence rate was significantly lower in those eyes with the implant (2.9%) than in fellow eyes (43.7%). There was also a significant improvement in visual acuity with 25.9% of the implant eyes improving three or more lines. The use of systemic corticosteroid or immunosuppressive therapy was also significantly decreased at 34 weeks. The most common adverse events at 34 weeks included cataract progression (13.5% of im-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

planted eyes had cataract surgery) and increased IOP (34.9% of the implanted eyes used pressure-lowering drops and 8.6% required filtering surgery).

If the implant technology (either with corticosteroid derivatives or other immunosuppressive compounds) shows that implanted patients can taper or even cease their systemic immunosuppressive therapy with a manageable risk of ocular adverse effects, uveitis could potentially become a surgically treatable disease. The risk of cataract progression and secondary glaucoma, as well as less common but potentially sight-threatening complications, must be weighed against the therapeutic benefit, including evaluation of quality of life in terms of reduced adverse effects associated systemic immunosuppressive therapy. There is a need for long-term data regarding outcomes after implantation, none of which, to date, have been US FDA approved.

1.2 Calcineurin Inhibitors

1.2.1 Ciclosporin (Cyclosporine)

Many studies were undertaken in the 1980s and 1990s to evaluate the clinical efficacy of ciclosporin in uveitis, one of the earliest immunosuppressive drugs. An excellent review summarising all studies of the use of ciclosporin in uveitis has recently been published by Hesselink et al.[22] The authors conclude that ciclosporin is an effective second-line agent. However, despite the use of low-dose regimens, ciclosporin toxicity (renal toxicity, hypertension) remains an important problem. This forms a major limitation to successful long-term treatment. In addition, a significant number of uveitis patients are refractory to this powerful immunosuppressant. Monitoring the serum ciclosporin concentrations levels of patients on this therapy is generally not recommended in current treatment guidelines and dosage should be titrated according to clinical anti-inflammatory response, blood chemistry and blood pressure.

1.3 Antimetabolites

1.3.1 Pulsed Low-Dose Oral Methotrexate

There is a growing body of evidence suggesting that the folate antagonist methotrexate should be used as a first-line corticosteroid-sparing drug or as additional treatment in the wide spectrum of ocular inflammation. Low-dose methotrexate (10–25 mg/week) is now widely used because of its sufficient clinical response, the low risk of adverse effects and the convenient weekly oral application. Methotrexate has been considered the standard against which newer DMARDs should be evaluated.[51] Basic drug mechanisms of methotrexate have been nicely summarised in a recent review from Kremer.[52]

Samson et al.[11] reviewed 160 adult and paediatric patients, retrospectively from 1985 to 1999, with chronic noninfectious uveitis unresponsive to conventional anti-inflammatory therapy who were treated with methotrexate. This is obviously the largest series of uveitis patients treated with a single corticosteroid-sparing immunosuppressive agent published to date. This group found that control of inflammation was achieved in 76.2% of patients and a corticosteroid-sparing effect in 56% of patients. Visual acuity was maintained or improved in 90% of their patients. Adverse effects requiring discontinuation of medication occurred in 18% of patients. Potentially serious adverse reactions occurred in only 8.1% of the patients in this study.

In a separate study, Kaplan-Messas and coworkers[12] evaluated the use of methotrexate as a first-line corticosteroid-sparing agent in 39 patients with uveitis and scleritis. In this study 79% of the patients showed full or partial control of the inflammation. However, 26% of their patients had to discontinue therapy because of methotrexate-related adverse effects. Combined with those patients who did not respond to methotrexate, 41% ultimately were switched to another immunosuppressive drug.

Bom et al.[13] reported on 11 patients in whom methotrexate was added to the treatment regimen as a first-line corticosteroid-sparing drug in 4 of 11 patients, as a second-line in 5 of 11 patients or third-line agent in 2 of 11 patients.[13] Control of inflam-

mation with reduction of corticosteroid dose was achieved in >50% of these patients. The number of relapses was reduced in 45%.

In a study by Smith and Rosenbaum,[53] methotrexate was also successfully used as a corticosteroid-sparing drug in the treatment of autoimmune inflammation of the orbit (orbital pseudotumour) in patients who did not respond to systemic corticosteroids and/or orbital irradiation.[53] This retrospective cohort study included 14 patients. Sixty-four percent of the patients showed clinical benefit after a median duration of 25 months. The authors stated that a trial of methotrexate should be considered for many patients with recalcitrant orbital inflammation before the institution of cyclophosphamide therapy.

Considered to have the best efficacy to toxicity ratio among available DMARDs, methotrexate is associated with an approximate 30% discontinuation rate in the first year, primarily due to toxicity. In a recent multicentre, randomised, double-blind, placebo-controlled trial including 434 patients with RA the question of adequate folate supplementation during methotrexate therapy was investigated.[54] Toxicity-related discontinuation of methotrexate occurred in 38% of the placebo group. Only 17% of the folic acid group (1 mg/day) and 12% of the folinic acid group (2.5 mg/week given 1 day post-methotrexate) stopped therapy because of adverse effects. The authors explained that differences between these groups were a result of a decreased incidence of elevated liver enzyme levels in the folate supplementation groups. This allowed significantly more patients to continue taking methotrexate. In the US and Europe, folic acid supplementation is widely used as a co-medication of methotrexate treatment.

1.3.2 Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an antimetabolite used widely in the treatment of solid organ transplant rejection and has shown efficacy in renal transplantation.[55] Its use in human inflammatory eye diseases has been described since 1998.[18,56] Several studies have shown favourable steroid-sparing outcomes in the treatment of ocular inflammatory disease with a low risk of adverse effects as mono- or combination therapy[18-21,56] in adults as well as in children.[57] Baltatzis and coworkers[20] demonstrated control of inflammation in 65% of 54 patients and achieved a corticosteroid-sparing effect in 54% of the patients. In a study by Lau et al.,[21] the efficacy of MMF was maintained during long-term management in 14 patients with uveitis and scleritis treated with MMF for a mean of 33 months in a follow-up study.[21] They previously reported the successful use of MMF in 11 patients in a follow-up period of 6 months[18] as a corticosteroid adjunct, either alone or in addition to ciclosporin. If MMF was combined with other immunosuppressants, ciclosporin was most commonly used in the published experience to compensate for insufficient clinical response to MMF. However, no randomised clinical trials have been published that show a benefit of MMF over ciclosporin so far, although, to the knowledge of the authors, trials are ongoing in two centres. In summary, the clinical experience and published work with MMF indicate that this drug is a valuable and safely used alternative to other immunosuppressive therapy with good clinical response and low risk of adverse effects.

1.4 Sulfasalazine

Anterior uveitis is the most common form of uveitis, and its association with human lymphocyte antigen (HLA)-B27 haplotype in the White population has been estimated to be approximately 50%.[58] Two Spanish groups showed that sulfasalazine has beneficial effect in preventing recurrences of anterior uveitis.[14,15] Benitez-Del-Castillo et al.[14] randomised 22 patients with HLA-B27-positive anterior uveitis associated with ankylosing spondylitis to either receiving sulfasalazine (10 patients) or no therapy (12 patients) over a 3-year period. They observed a statistically significant difference between the two groups regarding the number of recurrences of uveitis: 0.5 ± 0.53 (mean $\pm$ SD) in the sulfasalazine-treated group vs 1.33 ± 1.23 in the control group during the first year. Muñoz-Fernández and coworkers[15] also demonstrated in an open, prospective, longitudinal study with ten patients that monotherapy with sulfasalazine reduces the number of recurrences. The mean number of flares de-

creased from 3.4 ± 0.5 to 0.9 ± 0.1 during a 1-year period of sulfasalazine treatment in this study. This effect was more pronounced in those patients who were HLA-B27-positive (seven of ten patients). These results agree with our clinical experience that, in particular, HLA-B27-positive patients with recurrent anterior uveitis can benefit from the use of sulfasalazine. The use of anti-gastric coated drug formulations seems to ameliorate this anti-inflammatory effect.

1.5 Alkylating Agents

1.5.1 Cyclophosphamide

Because it is associated with a variety of potential toxic effects, including haemorrhagic cystitis, secondary malignancy and sterility, cyclophosphamide has only been used as a second-line immunosuppressive agent in the treatment of uveitis. Cyclophosphamide metabolites alkylate nucleic acids, and DNA replication and transcription are interrupted by the resultant cross-linking between chains. Cyclophosphamide in its parent form does not have direct cytotoxic effects; it must be bioactivated by cytochrome P450 (CYP) isoenzymes to be effective. CYP metabolism produces 4-hydroxycyclophosphamide, which spontaneously isomerizes to aldophosphamide, the active drug form. Aldophosphamide can break down both non-enzymatically to form acrolein (which is also cytotoxic) and to an inactive metabolite (carboxyphosphamide) by aldehyde dehydrogenase (aldehyde oxidase).

However, cyclophosphamide has a stronger immunosuppressive power than drugs such as methotrexate or MMF and seems to have a tolerable safety profile when used intravenously for a short period of time. Therefore, cyclophosphamide might be a reasonable choice for patients with ocular inflammatory disease who have failed other immunosuppressants, although its efficacy in this setting remains uncertain.

Durrani and coworkers[16] recently published a report including a large series of patients with severe or treatment-resistant autoimmune ocular inflammatory disease treated with intravenous cyclophosphamide. Patients were administered intravenous cyclophosphamide 1 g/m^2 body surface area. Eighty-three patients were analysed in a retrospective noncomparative interventional case series. Improvement of ocular inflammation occurred in 68% of patients in this study. Fifty-five percent of patients achieved complete quiescence. A corticosteroid-sparing effect resulted in all patients who were previously on systemic corticosteroids. Finally, cyclophosphamide allowed successful discontinuation of corticosteroids in 41% of patients studied. The primary goal of this study was to stabilise destructive inflammation and not to improve vision. Consequently, visual acuity was maintained in 66% but improved in 21% of eyes. The most common adverse effects observed were fatigue (63%), nausea (32%) and headache (22%), and none of the patients discontinued therapy as a result of adverse effects. Panuveitis with retinal vasculitis and ocular cicatricial pemphigoid were the most common disease entities treated in this study. Scleritis seemed to be the most responsive to treatment. However, it is not possible to discriminate the differential effect of cyclophosphamide on the different forms of ocular inflammation (intraocular vs ocular surface disease) that the authors included in this study.

1.5.2 Chlorambucil

Chlorambucil is a bifunctional alkylating agent of the nitrogen mustard type that has been found to be active against selected human neoplastic diseases. The group headed by Tessler has gained special experience in treating uveitis patients with chlorambucil.[17] They recently published a retrospective, noncomparative interventional case series of 53 patients.[17] After a mean duration of 16 weeks of chlorambucil therapy and with an average follow-up of 4 years, 47% of patients had at least two lines and 33% had at least three lines of improvement in visual acuity. By the time the chlorambucil regimen was stopped, 78% of the patients had discontinued oral corticosteroids and 77% were still in remission with no recurrence. However, there is a notable safety profile in this study: secondary amenorrhoea developed in 26% of the females. One male patient developed impaired spermatogenesis and two had erectile dysfunction. Twelve percent of the patients

in this series developed cutaneous herpes zoster. No patient in this series developed a malignancy during the observation period. The authors concluded that in patients with severe ocular inflammation unresponsive to corticosteroids and/or a corticosteroid-sparing agent, or in patients with progressive sight-threatening disease despite other therapies or in patients in whom blindness is a real possibility without immunosuppressive treatment, therapy with chlorambucil should be considered. Interestingly, chlorambucil seemed to place many of the treated patients in this study in sustained remission.

Serpiginous choroiditis is one of the most difficult uveitis entities to treat. Typically, it is a bilateral, progressive choroiditis of unknown origin. It can lead to significant morbidity if the loss of choriocapillaris and consecutive atrophy of the overlying retinal pigment epithelium results in scarring of the fovea, as recently summarised.[59] If the disease has already destroyed the fovea of one eye despite immunosuppressive therapy, the clinician should consider using an alkylating agent, as described in a recent retrospective multicentre study. This study, performed by Akpek et al.,[60] analysed nine patients receiving either oral cyclophosphamide or chlorambucil. All patients who were no longer receiving alkylating agents (seven of nine patients) were in drug-free remission with a median follow-up time of 6.5 years. Two patients still taking cyclophosphamide were reported to be quiescent. However, significant adverse effects were noted, including bladder carcinoma. Again, however, sustained remission was achieved in most patients with alkylating agents and should be considered as a final treatment option.

1.6 Biological Treatments

'Biological' is the popular term for a new generation of pharmaceuticals designed to specifically target molecular or cellular mediators of disease. As stated by Moreland et al.,[61] "biologic agents can be broadly defined, but generally include monoclonal antibodies directed against selected cell surface markers or recombinant forms of natural inhibitory molecules". Biologicals are proteins produced by recombinant DNA or monoclonal antibody technology that is used in a therapy based on the understanding of the molecular mechanisms.

Over the past 3 decades the development of clinically relevant animal models has facilitated research aimed at better understanding the pathogenesis of immune-mediated uveitis. In many patients, CD4+ T cells probably play the critical role in an inflammatory process that also involves other leukocytes, particularly macrophages and neutrophils, as well as cell adhesion molecules, cytokines and chemokines, eicosanoids, free radicals and enzymes.[62,63] This new knowledge and the recognition of the potentially severe adverse effect profile of the more conventional treatments described elsewhere in this review has provided stimulus for the development of biological therapeutic alternatives. In this section, we describe biological treatments that have been attempted in uveitis as well as other novel therapies for uveitis.

1.6.1 Treatments Targeting Lymphocyte Subsets

Given the key role of CD4+ cells in many forms of immune-mediated uveitis, it is not surprising that the first treatment with a biological agent involved an anti-CD4 antibody. In a report published in 1994 by Thurau and colleagues,[64] a patient with refractory bilateral idiopathic posterior uveitis was treated with murine-human anti-CD4 monoclonal antibody. The treatment, which was well tolerated, reduced the frequency and severity of disease relapses over a subsequent 2-year period. At the time of that report, availability of the antibody had become restricted and no further patients were treated. In a series published by Dick and coworkers[65] in 1995, alemtuzumab (Campath-1H), a humanised monoclonal antibody directed against the pan-lymphocyte surface antigen, CD52, was used to treat six adults with refractory, non-infectious uveitis. The therapy, which was given intravenously over 5 days, resulted in improvement or stabilisation of inflammation. Although these treatments targeted T cells or T-cell subsets and proved efficacious for uveitis, recent clinical research has focused on other biological targets, i.e. the inflammatory cytokine, tumour necrosis factor (TNF)-α, and the receptor for cytokine,

interleukin (IL)-2. One reason for this might have been that alemtuzumab induces a prolonged lymphopenia, as shown in studies with RA patients.[66] However, to date it has not been shown that this predisposes to an unusual spectrum of infections or is associated with an excess of mortality or morbidity.

1.6.2 Tumor Necrosis Factor Antagonists

TNFα is an inflammatory cytokine[67] that is produced by a number of different cell subtypes, mainly macrophages-monocytes but also lymphocytes and neutrophils. Activities of the molecule are mediated via two cell surface receptors, TNFRp55 and TNFRp75. Examples of these activities include the activation of neutrophils and macrophages, dendritic cell migration and maturation, activation of natural killer cells and the up-regulation of adhesion molecules on the vascular endothelium. Up-regulation of TNFα in both serum and ocular fluids is described in animals[68] and humans[69] with active uveitis. However, studies of the effects of blocking TNFα in experimental uveitis have been contradictory. In rodents with uveitis induced by systemic injection of endotoxin, inflammation did not improve or, in some cases, was exacerbated by treatments to block the cytokine.[70] In contrast, experimental autoimmune uveoretinitis, a CD4+ cell-mediated response directed against retinal S-antigen (S-Ag), was ameliorated by a TNFRp55-IgG fusion protein.[71] Following successful use of TNF antagonists to control various systemic inflammatory diseases, clinician researchers naturally considered the possibility of such therapy in patients with uveitis.[72] Studies published to date describe experience treating uveitis with subcutaneous etanercept (human TNFRp75-IgG1 fusion protein), intravenous infliximab (chimeric murine-human anti-TNFα monoclonal antibody) and an intravenously administered lenercept (human TNFRp55-IgG1 fusion protein) produced by the Therapeutic Antibody Centre (University of Oxford, Oxford, UK). Use of adalimumab, a fully humanised anti-TNFα antibody recently introduced onto the market, in uveitis has not been reported in published studies.

Etanercept

In one of the first studies published on the use of TNF blockade in uveitis, Reiff and coworkers[73] treated ten children with juvenile idiopathic arthritis-associated uveitis or idiopathic uveitis who had not responded to treatment with topical corticosteroids and oral methotrexate and/or ciclosporin with etanercept 0.4 mg/kg twice weekly. Within 3 months, and after withdrawal of one patient due to noncompliance, decreased anterior chamber cellular activity was observed in 10 of 16 affected eyes and Snellen visual acuity improved in 4 of the 10 eyes with visual loss at baseline. Dose escalation did not improve this response rate. In a subsequent letter to the editor, Reiff[74] reported that four of the original ten patients continued treatment and had sustained improvement for at least 1 year.

Smith and colleagues[24] performed a retrospective study which included patients with inflammatory eye disease treated with TNF blockade in combination with various other immunosuppressive agents for a median of 11 months. Eight of nine patients with uveitis were treated with etanercept; while articular benefit was universal in all patients with concurrent joint symptoms, only two of the eight patients experienced reduction in intraocular inflammation. A ninth patient of uveitis responded to treatment with infliximab. In two patients with uveitis, inflammation first developed while the patients were receiving treatment, leading the authors to speculate that in some patients inflammation may worsen or even be precipitated by TNF blockade.

In a small randomised controlled trial involving 20 adults with various forms of immune-mediated uveitis controlled on methotrexate, conducted by Foster et al.,[75] individuals received either etanercept 25mg twice weekly or placebo. Methotrexate was tapered, and a successful outcome was defined as complete absence of flare-ups during the 24-week study period. No significant difference in relapse rate was found between groups for patients who completed the study. However, as the authors acknowledged, the power to detect a significant difference was limited.

Infliximab

Infliximab has received more recent attention for the treatment of uveitis than etanercept.

Sfikakis and colleagues[25] reported the results of using a single infusion of infliximab 5 mg/kg to treat five adult patients with Behçet's uveitis who had relapsed while they were receiving other systemic immunosuppression.[25] In all patients, there was reduction in inflammation within 24 hours, with complete resolution of the uveitis by 7 days after treatment.

El-Shabrawi et al.[76-78] have published three case series of adults with HLA-B27-associated uveitis. In one series presented as a letter to the editor,[77] three patients with disease unresponsive to systemic or local corticosteroids and methotrexate were treated with one or more infusions of infliximab, leading to a resolution of the inflammation and improvement of visual acuity that occurred for up to 2 months. In a subsequent series,[76] seven adult patients with acute-onset HLA-B27-associated uveitis received an infusion of infliximab 10 mg/kg as sole treatment. In six of seven patients inflammation resolved after approximately 1 week on average; a second infliximab infusion and topical corticosteroids were required for resolution of one case. Four patients experienced recurrent inflammation 1–6 months later. A recently published letter to the editor by the same authors[78] described a total of eight patients with other forms of uveitis as well as HLA-B27-related disease. To explain less impressive clinical responses in three of four patients with non-HLA-B27-related uveitis, the authors suggested differential efficacy of TNF blockade in different forms of uveitis.

Joseph and colleagues[79] treated five adults with sight-threatening uveitis that was refractory to other immunosuppressive agents (i.e. three patients with Behçet's disease and two patients with idiopathic uveitis) with three doses of infliximab according to a standard loading schedule (5 mg/kg at 0, 2 and 6 weeks) and low-dose methotrexate.[79] Treatment was judged successful by 6 weeks and at 6 months in four patients, according to inflammatory parameters, although three patients required follow-up infusions. One patient did not respond to treatment as they developed more florid inflammation, necessitating intravenous methylprednisolone, and subsequently the patient developed clinical evidence of ocular and systemic tuberculosis.

Lenercept

Lenercept has now been used to treat patients with active chronic relapsing posterior segment intraocular inflammation, not improved by prednisolone or at least one immunosuppressive agent.

In a study of the effects of therapy on the phenotype of peripheral blood CD4+ cells in 15 patients (i.e. 13 patients with idiopathic uveitis and 2 with ocular Behçet's disease), Greiner and colleagues[80] found the fraction of peripheral blood CD4+ cells expressing IL-10 was significantly increased by treatment; in 15 patients and 17 treatment periods, this increase was significantly correlated with improvement of LogMar visual acuity. For eight infusions in this patient group, visual acuity improved significantly within the first 4 weeks of treatment. Doses of other immunosuppressives were reduced during 11 of 17 treatment periods. Further details of the effect of treatment on clinical parameters are promised.

Summary

Overall, the results of TNF blockade for uveitis appear promising, but there is a well recognised need for randomised controlled clinical trials to definitively assess the efficacy of such treatment. Available literature suggests infliximab and lenercept may be more effective for uveitis than etanercept. Additionally, it appears that certain uveitis subtypes (e.g. Behçet's disease and HLA-B27-associated uveitis) may be especially responsive to this mode of therapy. In addition to its high cost, potential complications are clearly an important consideration in prescribing TNF blockade. Some risks, although uncommon, are potentially life-threatening, including opportunistic infections, autoantibody formation and autoimmune conditions, and demyelinating disease. Injection site and infusion reactions are reported for etanercept and infliximab, respectively. Information pertaining to drug adverse effects comes primarily from relatively large treatment studies of patients with RA, and the

possibility that patients with uveitis are a different patient group with different potential risks must be considered. At this time, treatment with TNF antagonists remains experimental and should be reserved for patients with refractory disease.

1.6.3 Therapy Directed Against Interleukin (IL)-2 Receptors

IL-2 is a cytokine[81] that is synthesised primarily by activated T cells, particularly CD4+ T-helper cells. Acting via the cell surface receptor, IL-2R, it plays an essential role in the cellular immune response, by promoting proliferation and differentiation of T-helper cells. It has other activities which include differentiation of natural killer cells, antibody production by B cells and activation of macrophage-monocyte populations. CD4+ cells from animals with experimental autoimmune uveoretinitis[82] and humans with uveitis[83] express IL-2R. The receptor consists of three subunits: α, β and γ. The α subunit conveys specificity to this receptor. Currently, there are two commercially available antibodies directed against that subunit, daclizumab (humanised anti-IL2R monoclonal antibody) and basiliximab (chimeric human-murine anti-IL2R monoclonal antibody). These drugs were first tested in the prevention of renal transplantation rejection.

In two publications, Nussenblatt and colleagues[84,85] have described their experience treating patients with various forms of intermediate and posterior uveitis with daclizumab for up to 4 years, the longest period any group of patients has been treated with this agent. The initial publication describes an open-label, noncomparative study in which ten adult patients taking a minimum of prednisone 20mg, ciclosporin and/or antimetabolites were treated with intravenous daclizumab 1 mg/kg/dose (with frequency adjusted according to an initial loading and subsequent maintenance schedule).[84] Other immunosuppression was weaned over 8 weeks; the primary endpoint was loss of ten letters of ETDRS (Early Treatment Diabetic Retinopathy Study) visual acuity. At the end of 1 year, eight of ten patients achieved this endpoint, and one patient did not because of loss of vision and another as a result of recurrence of inflammation. There was a significant increase in vision in the worst affected eye. Two patients required ongoing, low-dose prednisone for adrenal insufficiency, not for uveitis. In the second report,[85] seven of the original ten patients continued to be classified as treatment successes, although an attempt to increase the dosage interval in selected patients was generally not successful. A group of five new patients as well as six of the original subjects were transitioned to a subcutaneous injectable form of drug, obviating the need for hospitalisation for drug administration; uveitis remained controlled in all patients. Papaliodis and coworkers[86] treated 14 patients with daclizumab 1 mg/kg/dose, including 11 patients with uveitis, for an average of 45 weeks. This retrospective noncomparative case series included patients with refractory immune-mediated uveitis or who were intolerant of conventional medications. Six patients showed improvement in inflammation and in three patients inflammation worsened in at least one eye, according to a standard grading system. Visual acuity improved in four patients, two of whom had cataract surgery, and worsened in at least one eye in five patients. Because of the small numbers of patients in these studies it is difficult to draw conclusions about drug adverse effects; however, larger studies in renal transplant recipients suggest that daclizumab is generally well tolerated.[81] As is the case for the TNF antagonists, randomised controlled clinical trials are necessary to establish the role of therapy targeting IL-2R in the treatment of uveitis.

1.7 Other Novel Treatment Options

Several other therapies, including the induction of oral tolerance, intravenous immunoglobulin (IVIg) and interferon (IFN)-α, may hold promise for treatment of recalcitrant uveitis.

1.7.1 Intravenous Immunoglobulin

IVIg has anti-inflammatory effects that may be mediated by the inhibitory Fc receptor pathway.[87] Several studies have addressed the use of this agent for treating patients with uveitis. Two reports from LeHoang and colleagues[26,88] detailed efficacy of IVIg in patients with birdshot retinochoroidopathy,

allowing reduction in prednisone dose, improving visual acuity and visual field, and decreasing macular oedema in a proportion of patients when present by 50%. Seider and coworkers[89] reported excellent results from treating four patients with ocular Behçet's-related intraocular inflammation that was refractory to corticosteroids and/or ciclosporin treated for 1 year with IVIg.[89] Good visual acuities were maintained in all patients, with no recurrence of inflammation within the year following treatment. Rosenbaum and coworkers[27] treated ten patients with active bilateral uveitis who had not responded to corticosteroids and other more conventional immunosuppressive therapy.[27] Overall, five of ten patients had improvement in terms of visual acuity and/or requirement for other immunosuppressive medication. This report highlighted potential concerns of using IVIg, including high cost, the requirement for intravenous infusion and, albeit rare, potentially life-threatening toxicities including thrombosis and transmission of infectious agents.

1.7.2 Immunomodulatory Treatment with Type 1 Interferons

Biological effects of IFNs have been known since the early 1970s. Type 1 IFNs (IFNα and IFNβ) have an amino acid sequence homology of 30% and share the same receptor, although there is an additional IFNβ receptor. Therefore, the therapeutic effect of type 1 IFNs is quite similar. In contrast, type 2 IFN (IFNγ) has a different amino acid structure and receptor. IFNβ-1a ('1' indicates a closely related protein within the β-family; 'a' indicates that the synthetic product has the same primary structure as the natural substance) and IFNα-2a are the most commonly used IFNs clinically. Several studies show that IFNβ treatment shifts the balance of cytokines in favor of a net anti-inflammatory response, by either suppressing T-helper 1 or by increasing T-helper 2 cytokine production or both.[90,91] IFNβ also suppresses the IFNγ-mediated expression of major histocompatibility complex class II on astrocytes and microglia *in vitro* and reduces the antigen-presenting capacity of these cells.[92,93]

We (MDB, CF) have also used IFNβ to treat uveitis associated with multiple sclerosis (MS), which was refractory to GC treatment, in a retrospective, multicentre observational case series.[94] In this study 13 patients (8 female, 5 male) with proven MS and associated uveitis from five uveitis centres who were treated with IFNβ-1a were included. Visual acuity, cell count in the aqueous humor and vitreous, as well as the presence of CME were observed. Seven patients had documented CME before IFN treatment (n = 13 eyes). Median duration of treatment was 24.6 months (range 7.9–78.7). Visual acuity improved in 17 eyes (comparing visual acuity before therapy and at last follow-up); while ten eyes (36%) improved ≥3 Snellen lines. Aqueous cell count improved by 1.2 ± 1.1 grades in all eyes. Vitreous cell count improved by 1.7 ± 1.4 in all eyes. Only two patients still had minimal CME on last follow-up angiographically. CME resolved after or during IFN treatment in nine eyes. As shown in the models of experimental allergic encephalomyelitis (EAE) and uveitis, the neurological and ophthalmological manifestations seem to share similar pathogenic mechanisms. Treatment of MS-associated uveitis with IFN appears to have beneficial effects on visual acuity, intraocular inflammation activity and the presence of CME.

1.7.3 Oral Tolerance Induction

Oral tolerance induction is a natural immune mechanism that could be another interesting approach for the treatment of autoimmune uveitis. From animal experiments we know that the uptake of soluble autoantigen via the gut mucosa generates a specific systemic tolerance which inhibits delayed-type hypersensitivity reactions to the ingested antigen. The pathoimmunological mechanisms involved are not yet well understood but are thought to involve the recognition of tolerogenic epitopes, the generation of suppressor T cells and an altered regulation of selected cytokines. Whole proteins as well as peptides have been found to be potent oral tolerogens capable of down-regulating immune responses.[95,96] Peptides that mimic an S-Ag epitope because of a few amino acid and/or structural homologies have been used to induce oral tolerance

and suppress experimental uveitis in rats.[97] This was shown for peptide B27PD, derived from the sequence of HLA-B antigens that mimics a highly pathogenic and immunogenic retinal S-Ag peptide, PDSAg (aa 341-354).[97] These studies also showed that peptides from these antigens, representing single epitopes, are sufficient to prevent the disease induced by intact protein.

The promising results of the animal models and the apparent lack of adverse effects lead to the initiation of clinical trials for oral tolerance induction in humans. The first trial was a prospective, randomised, double-blind clinical phase I/II study, conducted at the US National Eye Institute in the mid-1990s, and studied the possibility of inducing immunological tolerance to retinal antigens by oral administration of these antigens.[98] Treatment arms of 10–15 patients each included retinal photoreceptor S-Ag, a mixture of retinal soluble antigen, S-Ag plus the mixture of soluble antigen and placebo. The antigen was given three times a week initially and reduced to once weekly after 8 weeks. After commencement of treatment, an attempt was made to wean patients off other systemic immunosuppression; the primary study endpoint was time to relapse of uveitis. While the antigen was non-toxic, there was no significant difference in the primary endpoint between groups. However, although not quite statistically significant, the S-Ag-treated group appeared to be tapered off their other medication more successfully than the placebo group. This study demonstrated another interesting trend: those patients who had received a defined purified antigen (S-Ag) responded better than the patients receiving a mixture of different retinal antigens.

In a second prospective, uncontrolled open trial conducted by Thurau et al.[99,100] in Munich, Germany, nine patients were treated with a specific 14-mer peptide, B27PD, which is cross-reactive with a corresponding peptide from retina S-Ag that has been shown to be effective for the treatment of experimental autoimmune uveoretinitis. Nine patients with chronic anterior, intermediate or posterior uveitis were included. Within 6 weeks of oral peptide treatment all patients responded with a decrease in uveitis activity. In seven patients the dose of systemic corticosteroids could be reduced. Visual acuity remained unchanged or increased in 14 of 16 eyes. To date no larger study of oral tolerance therapy has been undertaken. Certainly a major obstacle to such therapy is the labour-intensive preparation of the antigen: 0.5mg of S-Ag (approximately five doses of treatment) requires extraction from 1000 bovine retinas. Therefore, the need for a genetically engineered antigen or synthetic peptide approach is obvious.

Oral tolerance induction with a peptide derived from the patient's own HLA-antigens and cross-reactive with the organ-specific autoantigen as a potent therapeutic approach needs further evaluation.

2. A Clinical Example: Behçet's Disease

Behçet's disease is a multisystem disorder that can affect the eye severely. It is a rare disease in tertiary referral uveitis clinics in North America and Western Europe, but common in clinics in Turkey and Japan. The uveitis in a patient with Behçet's disease can cause severe inflammation with occlusive vasculitis which represents a real threat to visual outcome. Therefore, many attempts with different drugs have been undertaken to prevent ocular recurrences in patients with Behçet's disease. There is no entity in the recent uveitis literature that has been more extensively studied with different treatment regimens including azathioprine,[101] ciclosporin,[102] colchicine[103] and chlorambucil.[104] Of special interest is the treatment with IFN and infliximab, which is described here.

Herpes simplex virus type 1 is thought to play a role in the pathogenesis of Behçet's disease. Therefore, IFNα was introduced 1986 for its antiviral activity with encouraging results.[105] Feron et al.[106] used IFNα for the first time in patients with ocular Behçet's disease in 1994. The group headed by Kötter and Zierhut[107] has the widest published experience in treating patients with Behçet's disease with IFN. They recently published an update to their pilot study from 1998:[107] an open, noncomparative prospective study including 50 patients.[23,108] In this

study, the drug was administered by subcutaneous injection, initially at a dose of 6 million units daily, with dose and frequency adjusted depending on the clinical response. A response rate of 92% was reported, with significant improvements in both visual acuity and posterior uveitis score. More than one-third of patients were off treatment and disease-free after an average of 2.5 years. Adverse effects experienced by all patients were a flu-like illness (i.e. fatigue, headache, arthralgia and fever) and injection site reactions. Less common adverse effects were leucopenia, alopecia, depression and fibromyalgia. Development of autoantibodies was observed, and 3 of the 50 patients developed Hashimoto's thyroiditis. The IFN treatment also seems to be beneficial for extraocular manifestations of Behçet's disease, although less for oral ulcerations. This group recently published their successful 5-year results from 15 eyes of nine patients.[109] Other groups have published smaller case series supporting therapeutic effects of IFNα in this subtype of uveitis.[110-113]

Sfikakis et al.[25] reported on five patients with recurrent panuveitis successfully treated with infliximab at immediate onset of relapse. Interestingly, infliximab had a very rapid onset of clinical response. This has also been observed in other case series recently presented as abstracts[114,115] or published.[116,117]

In summary, it seems reasonable to divide the treatment strategy for Behçet's disease into two arms: one should focus on therapy in the phase of sudden-onset severe intraocular inflammation which requires emergency ocular therapy and one should focus on prevention of further recurrences with the goal of drug-free remission. The first strategy could be achieved by the use of infliximab, which seems to be highly effective within days of initiating treatment. The use of IFNα could target the second strategy.

3. Future Treatment Options for Uveitis

Most of the immunosuppressive treatments used in uveitis have been extensively explored in patients with RA and other rheumatic diseases. Therefore, even today it is worthwhile looking at new developments already used in rheumatology and expect reports on their use in uveitis in the near future.

3.1 Leflunomide

Large placebo-controlled studies comparing leflunomide with sulfasalazine[118] or methotrexate[119] in the treatment of RA suggest that the drugs have comparable efficacy. After 2 years >80% of the patients who received methotrexate or leflunomide in a blinded, randomised, controlled trial (the ULTRA [Utilisation of Leflunomide in the Treatment of Rheumatoid Arthritis] trial) had no new articular erosions.[119] The combination of leflunomide and methotrexate appears to be more effective than methotrexate and placebo, resulting in a better clinical outcome of arthritis. The primary drawback of this combination is its potential for hepatotoxic effects.[120]

However, to date no study has been published about the use of leflunomide in uveitis. This may be partly due to the different dosages required (daily with leflunomide vs weekly with methotrexate) to achieve comparable efficacy to methotrexate.

3.2 Adalimumab

The TNF inhibitors etanercept and infliximab have been extensively discussed elsewhere in this review. While etanercept is a construct of a p75TNF-receptor with an immunoglobulin backbone, infliximab is a chimeric monoclonal antibody with a complete human Fc-part and murine sequences in the Fab section of the antibody. In contrast, adalimumab is a fully human monoclonal antibody directed against TNFα. It is hoped that the absence of murine amino acid sequences might reduce the rate of drug reactions and prevent loss of effectiveness due to the induction of antibodies against the drug, which is observed in some patients treated with TNF antagonists and is responsible for the loss of effectiveness in some patients.[121]

In a randomised, double-blind, 52-week, placebo-controlled study for the treatment of RA, the response rate for adalimumab 40mg administered every other week was similar to adalimumab 20mg

every week.[122] Both strategies were significantly more effective than the combination of methotrexate with placebo. At week 52, there was statistically significantly less radiographic progression in the patients receiving adalimumab either 40mg or 20mg weekly than in the placebo group. Adalimumab was generally well tolerated in this and previous studies. Adalimumab is now approved for the treatment of RA and trials for the use of adalimumab in uveitis are in preparation.

3.3 Anakinra

Anakinra is the recombinant form of the naturally occurring IL-1 receptor antagonist and differs from it only in one single amino acid sequence.[123] IL-1 is a proinflammatory cytokine with various effects on cellular immune response and seems to play an important role in the degradation of bone and cartilage in RA. Therefore, anakinra was evaluated in clinical trials for the treatment of RA and showed a good inhibitory effect on bone and joint erosion, although its effect on pain and joint inflammation was less impressive in comparison to those of the TNF inhibitors.[124,125] Anakinra is now approved for the treatment of RA. So far, no reports about its efficacy in uveitis are available.

3.4 Rituximab

Rituximab is a monoclonal antibody directed against the B-cell antigen CD20 and is approved for the treatment of B-cell lymphomas. Rituximab effectively depletes the pool of peripheral blood leucocytes of B lymphocytes, an effect that can be detected many months or even longer after a single infusion of the antibody. As B cells play a role in the pathogenic immune response of autoimmune diseases, rituximab is also a candidate for use in these disorders. Indeed, a recent controlled trial in patients with severe RA showed a significantly better response to rituximab combined with cyclophosphamide and intermediate-dose corticosteroids compared with the latter two drugs alone.[126]

Moreover, several small uncontrolled studies and case reports imply that rituximab may be effective in systemic lupus erythematosus[127] and systemic vasculitis.[128] Although it leads to a prolonged depletion of B cells in the peripheral blood it does not seem to predispose to an increased frequency of infectious complications.[129] In conclusion, rituximab, the use of which at this time has not been reported in uveitis, is an interesting drug for further studies on the treatment of severe, refractory autoimmune diseases.

3.5 Alefacept

Alefacept is a lymphocyte function-associated antigen (LFA)-3/IgG_1 fusion protein which blocks the binding to CD2 and, therefore, targets the memory effector T-cell population in immune response. Clinical trials have shown that it is effective against plaque psoriasis and it has been approved in the US for this indication.[130] Small studies have been performed for the evaluation of alefacept in psoriatic arthritis[131] and RA.[132] Although the patients showed a good clinical response with reduction of arthritis disease activity, more studies are awaited before the potency of this new drug for the treatment of a broader range of autoimmune diseases can be judged. No data are available to date about a possible effect of alefacept on uveitis.

3.6 Cytotoxic T-Lymphocyte-Associated Antigen (CTLA)4-Ig

Cytotoxic T-lymphocyte-associated antigen (CTLA)4-Ig is a fusion protein consisting of CTLA4 and human IgG_1. CTLA4-Ig binds to CD28, which is expressed on antigen-presenting cells and, therefore, blocks T-cell costimulatory pathways. CTLA4-Ig has been shown in controlled clinical trials to be effective in the treatment of patients with active RA.[133] Further studies are going on and experimental data imply that CTLA4-Ig might be a candidate drug for the treatment of other autoimmune diseases, including uveitis.

3.7 Blocking IL-6 Activity

IL-6 is a cytokine that is involved in inflammation, although its definitive role is still a matter of debate. Controlled clinical trials evaluated the effect of tocilizumab (MRA), a monoclonal antibody di-

rected against the IL-6 receptor, in the treatment of active RA.[134,135]

Tocilizumab showed a favourable effect on disease activity in RA patients with or without concomitant methotrexate in both studies. Therefore, tocilizumab belongs to the prime candidates for approval in RA and should be evaluated for other autoimmune diseases such as uveitis in the future.

3.8 Others

A variety of other compounds are currently being investigated in autoimmune diseases and have a potential relevance for uveitis. They include golimumab (CNTO 148), a fully human anti-TNFα antibody that is currently in phase I trials, the anti-CD2 receptor antibody splizumab, the complement cascade inhibitor eculizumab and the anti-α-4 integrin antibody natalizumab. All of these drugs interfere with immunological mechanisms that are involved in the pathophysiology of autoimmune inflammation such as uveitis. Future trials are awaited with interest.

4. Cost of Treatment

The socioeconomic impact of uveitis is highlighted by the fact that 70–90% of patients are affected during their active working life, costing an annual $US242.6 million in the US alone (based on data from 1996).[136] Considering that all therapy offered to uveitis patients, including corticosteroids, is 'off-label', good evidence is required to argue with health insurance companies about necessity, efficacy and cost of treatment. Cost-utility analysis may help to make rational healthcare decisions, as recently reviewed by Brown et al.[137] However, there are currently no cost-utility data available for immunosuppressive therapy in uveitis.

Estimated prices of drugs described in this review are given in table I. Three groups of price ranges can be identified: the first price range covers prices below €10 per day and includes corticosteroids, methotrexate, sulfasalazine, cyclophosphamide, leflunomide and chlorambucil. Depending on the specific diagnosis, a large percentage of uveitis patients at uveitis tertiary referral centres should primarily be treatable with corticosteroids, methotrexate and sulfasalazine at very low cost and with a tolerable safety profile. Failure of primary immunosuppressive treatment or certain specific indications, such as Behçet's disease, could be indications for the second price range between €10 and €50 per day. This group includes mycophenolate, ciclosporin and IFNs. The third price range is a daily price of over €50 per day. This includes all biological drugs, IVIg and other experimental therapies.

5. Conclusions

The developments in anti-inflammatory therapy for uveitis patients in the past decade have been enormous. In contrast with some other common sight-threatening ocular diseases, such as age-related macular degeneration, the majority of patients with uveitis can expect to receive treatment that will positively alter the course of their eye disease. Besides corticosteroids as primary systemic treatment, the most popular corticosteroid-sparing drug in the treatment of uveitis patients is methotrexate. If this and other drugs of similar potency (such as MMF or ciclosporin) are not effective then other drugs such as biologicals or cyclophosphamide may be alternatives to consider.

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Correspondence and offprints: Assoc. Prof. *Matthias D. Becker*, Interdisciplinary Uveitis Center, University of Heidelberg, Im Neuenheimer Feld 350, Heidelberg, 69120, Germany.
E-mail: Matthias.Becker@uveitiscenter.de