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REVIEW ARTICLE

Anti-inflammatory treatment of uveitis with biologicals: new treatment options that reflect pathogenetic knowledge of the disease

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Abstract
Background Endogenous uveitis is a sight-threatening disease. In addition to corticosteroids, immunosuppressive agents are commonly used to treat patients with severe course. Immunosuppressive drugs act nonspecifically, rather than providing a specific interaction with the critical pathogenetic pathways of uveitis. Better knowledge of the basic mechanisms underlying uveitis and of the molecules that are important for regulating inflammation has helped to create new and more specific treatment approaches. Biological therapy for inflammatory diseases employs substances that interfere with specific molecules or pathways induced in the body during the inflammatory process.
Methods This review gives an overview on molecules that play a critical role in the pathogenetic process of uveitis, as has been observed in patients or the respective animal models, and summarizes the current experience with biologicals for the treatment of uveitis refractive to conventional immunosuppressives.

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Introduction

Endogenous uveitis manifesting as Behçet's disease, Vogt–Koyanai–Harada (VKH) disease, ocular sarcoidosis, juvenile idiopathic arthritis, or others is known to be a sight-threatening intraocular disease. Complications such as cystoid macular edema, glaucoma, vascular occlusion, and proliferative vitreoretinopathy are common causes of permanent loss of vision [1–4].

While corticosteroids are usually required to control acute inflammation, immunosuppressive agents, such as cyclosporine A, azathioprine, methotrexate, or mycophenolate mofetil, are needed to downregulate chronic inflammation and prevent recurrences. However, long-term treatment with immunosuppressive agents is frequently required, which goes hand-in-hand with a significant risk of severe side-effects, such as osteoporosis, infertility, diabetes, liver and kidney dysfunction, and secondary malignancy. Importantly, immunosuppressive drugs act nonspecifically rather than providing a specific interaction with the critical pathogenetic pathways of uveitis.

Biologicals

Biological agents are defined as substances produced from living organisms, or which consist of their products, which are applied for the diagnosis, prevention, and treatment of disease. Recently, biological agents have been introduced in the treatment of inflammatory diseases, aiming to stimulate or restore immune system function. They have been suggested as alternatives to classical immunosuppressive

drugs, in order to accelerate drug action and to avoid harmful side-effects.

Chronic inflammatory disease is caused by a dysregulation in the immune response. During the effector phase, humoral and cellular components of the immune response trigger a cascade of events that ultimately lead to tissue destruction. Knowledge of the underlying events from human disease and the respective animal models has defined therapeutic targets to specifically modulate the harmful cascade of events. The development of biologic agents has produced a novel therapeutic task force for specific immune interventions, such as in rheumatoid arthritis, multiple sclerosis, Crohn's disease, and many other chronic autoimmune diseases.

Biological therapy for inflammatory diseases employs substances that interfere with specific molecules or pathways induced in the body during the inflammatory process. Currently available biological agents include monoclonal antibodies, which are complete molecules or fragments, human–rodent chimeric or completely humanized forms, and recombinant forms of natural inhibitory molecules, such as receptor constructs, and immunomodulatory cytokines. The currently available biologicals are applied parenterally. Some of them are currently being introduced into treatment regimens for several chronic inflammatory eye diseases.

Material and methods

This review gives an overview on molecules that play a critical role in the pathogenetic process of uveitis, as has been observed in patients or the respective animal models, and summarizes the current experience with biologicals for the treatment of uveitis refractive to conventional immunosuppressives.

Results

Animal models

To establish new therapeutic targets for treating human uveitis, different experimental animal models are used which resemble the pathologic features of the human disease. There are two principal models: endotoxin-induced uveitis (EIU), representing an unspecific, innate efferent immune response (inflammation), and experimental autoimmune uveitis (EAU), which includes the afferent arm (antigen-specific activation of T cells) and the subsequent ocular inflammation.

Endotoxin-induced anterior uveitis (EIU), which can be induced in rats and mice via intraocular or systemic injection of lipopolysaccharides (LPS), is rather a model for endophthalmitis than for any autoimmune uveitis or acute anterior uveitis [5–7]. The inflammation ensues 4 hours after LPS injection, peaks after 24-48 h, and declines 96 h after disease induction. EIU is marked by a vasodilatation of the iris and vascular changes in the ciliary body, accompanied by an increased vascular permeability and breakdown of the blood–aqueous barrier [8–10]. The cells involved in EIU are monocytes/macrophages and polymorphonuclear neutrophils (PMNs), the key players of inflammation, while T and B cells are not involved. The inflammatory cells infiltrate the anterior chamber from ciliary body (cb) and iris in conjunction with protein extravasion into the aqueous humor. It has been shown that TNF-α is important for the induction of EIU, and that IL-6 produced in the eye plays a major role in the development of ocular inflammation [11, 12].

Experimental autoimmune uveitis (EAU), which can be induced in mice and rats by immunization with ocular proteins in adjuvants, serves as a model of human autoimmune uveitis [13]. While EAU in mice can only be induced with IRBP or an IRBP-derived peptide, a variety of retinal autoantigens and their peptides are pathogenic in rats. In addition to IRBP, S-antigen, rhodopsin, phosducin, and CRALBP can also be used to induce uveitis. Adoptive transfer of antigen-primed T cells also induces EAU in both rats and mice [14–19]. The ocular inflammation peaks about 14 days after immunization, or about 7 days after adoptive transfer of antigen-specific cells [19–21]. Serum antibodies do not appear to play a role in disease induction [22]. Histological signs of EAU include leukocyte infiltration, retinal granulomas, and folding and detachment of the retina [17]. The disease is mediated by CD4+ T cells, but retinal destruction is mainly caused by infiltrating activated macrophages [22, 23]. EAU in rats induced with a peptide from IRBP can have a relapsing-remitting course, which is useful for the investigation of therapeutic approaches [24, 25]. Therapies for uveitis patients such as cyclosporin A or oral tolerance induction were first developed or proven in rat and mouse models of EAU [26–30].

The T-cell populations that induce EAU belong to the Th1 and/or Th17 type in both rats and mice [24]. As it is difficult in an intact eye to induce an autoimmune response to the sequestered retinal autoantigens, which are separated by the blood–ocular barriers, antigenic mimicry has been proposed for extraocular activation of T cells. That is, peptides from environmental antigens such as viruses, bacteria, or others with similarity to ocular autoantigens could induce cross-reactive T cells [25, 26], which are able to pass the BRB due to their activated state and induce intraocular inflammation [32, 33].

Animal models have helped us to identify and test novel autoantigens for uveitis; they have enabled us to dissect

afferent and efferent immune responses in the eye, as well as to study the pathogenic mechanisms leading to uveitis. The initiating events of intraocular inflammation can only rarely be detected in patients, since the disease seen clinically represents only the efferent arm of the immune response.

For an overview of the immune response, see Fig. 1.

TNF-α inhibitors

TNF-α is synthesized by T helper cells and by activated macrophages, monocytes, neutrophils, and endothelial cells. It activates other cytokines, upregulates adhesion molecules, induces nitric oxide synthase (NOS), and increases cell-mediated immunity and granuloma formation [27]. TNF-α thus plays a role in all types of uveitis: in macrophage-mediated granulomatous uveitis (sarcoid, VKH, infectious uveitis such as tuberculosis or syphilis), as well as in uveitis mediated by neutrophilic and basophilic granulocytes (B27-associated iritis, Behçet's disease, SLE, juvenile idiopathic uveitis, and endophthalmitis). Furthermore, it activates neutrophils and renders them more adherent to vascular endothelia and more sensitive for IL-1 and IL-6. TNF-α also shows effects on many non-immune cells. In the brain, it induces fever and

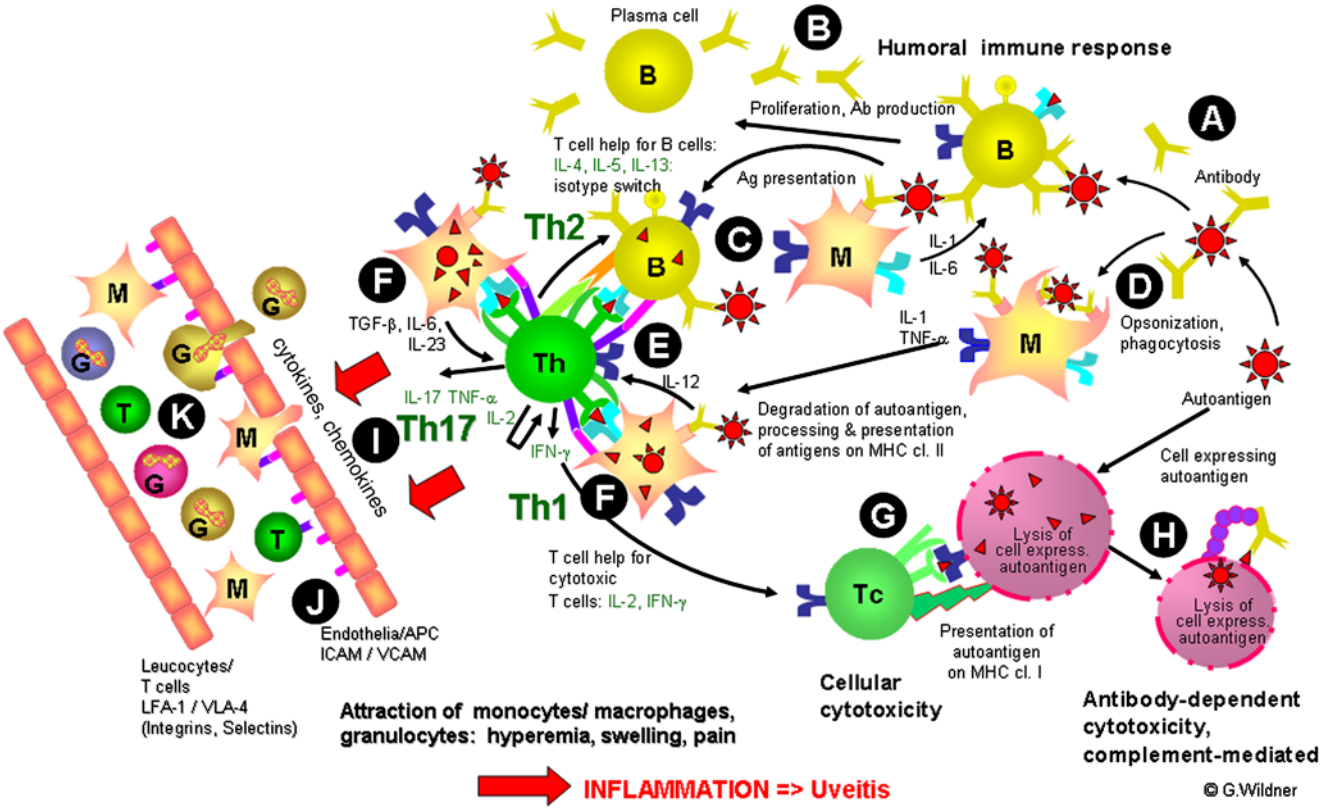

Fig. 1 Specific autoimmune response leading to inflammation. **a** An autoantigen is recognized and bound by antibodies. This leads to cross-linking of the surface immunoglobulins (antibodies, *Ab*) on the respective antibody-producing B cell. Here, the surface antibodies serve as B-cell receptors. Antigen binding stimulates the B cell to proliferate and to further mature to a plasma cell (**b**). B cells can also internalize the antigen, which is bound by their surface Ab, process it, and present peptides from this antigen on their MHC class II molecules, to seek T cell help (**c**). The help provided from a Th2 cell by cytokines such as IL-4, IL-5, and IL-13 enables the B cell to undergo isotype switch and subsequently produce antibodies of another IgG, IgA, or IgE type. Antibody-bound or "opsonized" antigen is easily sensed by macrophages via their surface Fc receptors (**d**); they subsequently phagocytose the complex. The bound antigen is also processed and presented to T cells as peptides (**e**). By secreting certain cytokines during antigen presentation to a naive T cell, antigen-presenting cells can determine the T-cell type (Th1 by IL-12 or Th17 by IL-6 and TGF-β) (**f**). These T cells can help cytotoxic T cells (if they are Th1 cells) to support lysis of cells that present intracellular antigen on their surface MHC class I molecules, a mechanism normally used to eliminate virus-infected cells but also found in autoimmunity (**g**). Cell lysis can also be obtained by binding of antibodies and complement factors (antibody-dependent cytotoxicity) (**h**). T-helper cells of all three types, Th1, Th2, and Th17, can recruit inflammatory cells such as granulocytes and monocytes/macrophages to the site of their antigen recognition, no matter if the antigen is a pathogen, an allergen, or an autoantigen. This recruitment is mediated by cytokines and chemokines (chemotactic cytokines) (**i**), which induce upregulation of cell adhesion molecules ("CAMs") on neighboring vascular endothelia (**j**) used to attract and catch leukocytes from the circulation (**k**). They finally migrate through the endothelium into the tissue to fight against pathogens (or, in autoimmune diseases, against their own tissue) with their highly effective "chemical weapons", causing the typical signs of inflammation

sleep, and in osteoblasts, fibroblasts, and myocytes the production of proteases, which lead to tissue destruction [28]. In addition to the proinflammatory activity of TNF-α, these latter effects are responsible for the destruction of bone and connective tissue in rheumatic diseases.

Due to its central role in inflammation, TNF-α is an important target for immune therapy. Nevertheless, despite its ability to activate immune or inflammatory responses, TNF-α is also important for the downregulation of immune responses by inducing apoptosis.

It is primarily produced as a membrane-bound surface molecule; the soluble form is created by proteolytic cleavage from the cell surface. For both soluble and transmembrane TNF-α, homotrimerization is important for receptor binding and biological function.

TNF-α acts on two receptors: (a) TNFR1 (p55, CD120a) is constitutively expressed on all nucleated cells, and (b) TNFR2 (p75, CD120b) can be induced on lymphocytes, endothelial cells, and neurons. TNFR1 contains a death domain; thus, activation of TNFR1 in general leads to apoptosis, while activation of TNFR2 confers resistance to cell death. Both receptors can be cleaved off the cell surface after TNF binding, thus transiently desensitizing cells to TNF activity. Soluble TNF receptors are also regarded as endogenous inhibitors of TNF because they still have the capacity to bind TNF-α [29, 30].

TNF receptors on cells are stimulated by both soluble and membrane-expressed TNF. While soluble TNF-α mainly stimulates TNFR1, membrane-bound TNF-α signals through both receptors, but activates TNFR2 more efficiently. Interestingly, signaling not only occurs via the receptors, but also through the membrane-bound TNF-α itself ("reverse signaling") [31]. Stimulating mTNF-α can provide costimulatory signals for both T and B cells, and reverse signaling in monocytes induced by TNFR2 on activated T cells activates and enhances TNF-α secretion. Reverse signaling cannot be achieved with anti-TNF antibodies (Fig. 2a), but etanercept does not block reverse signaling, and thus monocytes are still partially activated, in terms of cytokine release (Fig. 2b).

In addition to its role in the immune system, TNF-α can be both neurotoxic and neuroprotective, a feature that must be considered for anti-TNF-α therapies of ocular diseases. Under pathologic conditions, TNF-α induces demyelination and/or neuronal degeneration, either directly or indirectly via the production of other proinflammatory cytokines, nitric oxide, or oxygen radicals [32]. LPS stimulation of microglia is followed by autocrine activation through TNFR1: this positive feedback loop results in prolonged activation and neuronal and axonal damage even after the inflammatory cell infiltrates have disappeared, as has also been observed in neurodegenerative and ischemic disorders. On the other hand, microglia-produced TNF-α plays an important role in the development of the nervous system, modulating cell cycle and metabolism [33]. Furthermore, TNF-α protects neurons against hypoxia- or nitric oxide-

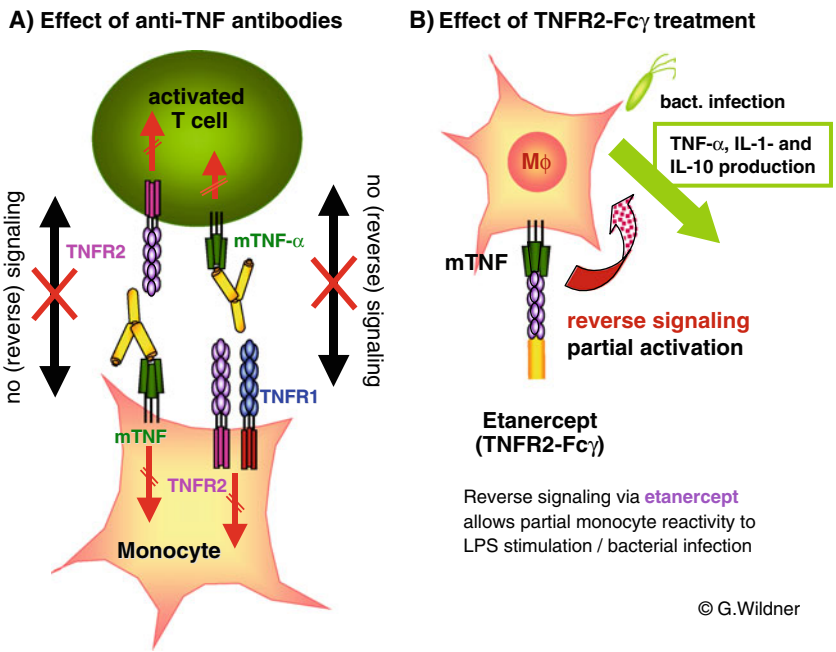

Fig. 2 TNF-α inhibition. **a** Effect of anti-TNF antibodies. Activated T cells and monocytes express TNFR2 for activation by TNF-α binding. They also bear membrane TNF, which confers activation after binding of TNFR2. TNF-specific antibodies prevent activation of TNFRs by binding TNF-α, but, on the other hand, they are not able to induce reverse signaling, blocking TNF-mediated activation on the sides of both T cells and monocytes. **b** Effect of TNFR-Fcγ treatment. In contrast to anti-TNF antibodies, etanercept, which contains the TNF-binding site of TNFR2, is still able to induce reverse signaling and thus does not completely impede monocyte reactivity to infections

Binding of therapeutic anti-TNF antibodies:

1. **Neutralization** of soluble TNF
2. **Blocking** of mTNF on T cells and monocytes
3. **Inhibition** of TNFR-signaling and reverse signaling via mTNF

induced damage by upregulating expression of the anti-apoptotic proteins Bcl-2 and Bcl-x [34]. Deprivation of TNF-α during anti-TNF-α therapies could thus result in adverse events such as exacerbation or initiation of acute neuropathies, multiple sclerosis, and uveitis [35, 36].

Infliximab

Infliximab is a chimeric monoclonal antibody of predominantly human origin with two murine antigen-binding sites. The usual dose is 3–5 mg/kg body weight (intravenous infusion), which can be escalated to 10 mg/kg. Infusions are repeated after 2 and 6 weeks and then every 8 weeks, but particularly in patients with uveitis the infusion frequency must be increased. Side-effects during infusion include dizziness and headaches. Infusion reactions to infliximab are rare but may be severe. Infliximab induces a strong immunosuppression, and thus inhibits defense of infections. Frequently, viral and respiratory infections develop and tuberculosis is reactivated [37]. Thus, before initiating anti-TNF therapy, tuberculosis must be excluded by chest X-ray and tuberculin skin testing. If results are positive, prophylactic INH (isoniazide) treatment is mandatory. Infliximab has also been associated with a higher incidence of death and hospitalization of patients with moderate to severe congestive heart failure [38]. Optic neuritis may develop [39].

Infliximab has been used to treat many different uveitis entities. In most of these studies, patients with chronic or relapsing uveitis were included who did not respond adequately to conventional therapy. Anterior uveitis associated with HLA-B27 seems to respond quickly to monotherapy with infliximab. Some of the patients experienced relapses after a median period of 5 months, which, however, might reflect the natural course of the disease [40, 41]. Moreover, in ankylosing spondylitis (AS) patients treated with infliximab for their rheumatic diseases, the frequency of anterior uveitis relapse is sharply reduced to 3.4 relapses per 100 patient years, compared to placebo-treated patients with 15.6 relapses per 100 patient years [42]. Another retrospective study found a reduction in anterior uveitis flares under treatment with TNF-α antibodies (infliximab and adalimumab) from 50.6 to 6.8 per 100 patient years [43].

Due to the severity of uveitis in Behçet's disease, several groups have used infliximab. A single infusion of infliximab rapidly induces uveitis inactivity [44, 45]. Long-term treatment for 1 to 3 years was successful in preventing uveitis relapses and improved visual acuity [46–50].

Infliximab has been and is used to treat juvenile idiopathic arthritis and associated uveitis. Heiligenhaus et al. have reviewed the literature for the effect of TNF inhibitors on juvenile uveitis, and found infliximab to be effective in 51 of 55 children. Most other reports document a good therapeutic effect on uveitis, but it seems that the effect fades in chronic treatment of longer than 1 year [51–54].

Adalimumab

Adalimumab is a human monoclonal anti-TNF-α antibody, which is injected subcutaneously at a dose of 40 mg every 2 weeks in adults with uveitis. In children the usual dose is in the range of 24 mg/m^2. Adalimumab is well-tolerated and after injection usually only mild local side-effects occur, if any. The side-effects with respect to the immunosuppression are basically the same as seen in infliximab, but with slightly reduced incidence and severity.

Many types of uveitis seem to respond to adalimumab. Among 31 patients reported by Callejas-Rubio et al., Diaz-Llopis et al., and Petropoulos et al., inflammation and visual acuity improved in 21 while reducing conventional immunosuppressive treatment. Relapses of anterior uveitis associated with AS are reduced significantly by treatment with adalimumab. In a series of eight AS patients, the number of relapses per 100 patient years was reduced from 60.5 to 0 [55]. Another series of 274 uveitis patients in a cohort of 1,250 AS patients demonstrated a reduction of uveitis flares from 15 to 7.4 per 100 patient years [56].

Uveitis in children with JIA also reponds to adalimumab. In 28 of 43 children, uveitis improved after initiating adalimumab treatment [51, 57, 58]. Tynjala et al. [57] also reported reduced frequency of uveitis flares.

Etanercept

Etanercept binds both TNF-α and TNF-β, preventing the interaction with the natural receptor on cell surfaces. Due to its long half-life of 98 to 300 hours, 25 mg of etanercept are administered subcutaneously twice a week only. Side-effects include a local reaction at the injection site, which usually does not require special care. Other undesired effects as a consequence of etanercept's antiinflammatory and immunosuppressive activity, which interferes with the host's defense against infections, include respiratory infections, reactivation of tuberculosis, and sepsis. Since patients with rheumatoid diseases have an increased risk of infections due to their disease, close monitoring is mandatory.

In patients with chronic or relapsing uveitis, etanercept was used with the aim of preventing relapses after disease has been brought under control by methotrexate [59]. With regard to the frequency of relapses and the final visual acuity, the authors did not find any significant difference between the treatment and placebo groups. Others found only limited effects of etanercept on uveitis in four of a total of 11 patients [60, 61]. The efficacy of etanercept in children with treatment-resistant uveitis with or without

underlying juvenile chronic arthritis is rather disappointing [54], and Smith et al. did not find any therapeutic effect in a small, double-blind and placebo-controlled trial of 12 children with pediatric uveitis, thus questioning the efficacy of etanercept in these patients [62]. Reiff et al. reported that uveitis was alleviated in ten of 16 eyes and relapses prevented in most of the children, but visual acuity did not improve much [63].

Etanercept is widely used for the treatment of AS due to its documented tolerability even for long-term administration. One important aspect for these patients is accompanying anterior uveitis. While Elewaut et al. found basically no effect of etanercept on uveitis flares per 100 patient years (54.6 in controls vs 58.5 in treated patients), Cobo-Ibanez et al. recorded increased uveitis flares (52 vs 82) and Braun et al. a decrease in flares (15.6 vs 7.9) in patients receiving etanercept [42, 55, 64].

New TNF-α blockers

Recently, two other TNF-α inhibitors (certolizumab-pegol and golimumab) for systemic use were introduced to the market, but no experience in the treatment of uveitis is available yet.

For the treatment of anterior uveitis, a new topical TNF blocker for topical use is under development (ESBA105CRD04). While this approach promises to avoid systemic side-effects, complications, and inconveniences during application, its efficaciousness cannot be evaluated at present.

General considerations for all TNF inhibitors

In past years, the important question of whether TNF inhibitors can induce uveitis did arise. A number of case reports linking the first attack of uveitis to TNF blockers in the treatment of rheumatic disease seem to burden etanercept in particular [65, 66]. In an attempt to clarify this question, Lim et al. analyzed two drug event databases in the USA and found that etanercept is indeed associated with a higher incidence of uveitis than adalimumab and infliximab [67]. The authors concluded that etanercept is less effective for the treatment of uveitis but does not seem to induce uveitis, and that if uveitis occurs under an etanercept regimen, it is possible to switch to another TNF blocker.

Interleukin-6 and anti-IL-6 therapy

Interleukin-6

Interleukin-6 (IL-6) is a pleiotropic and multifunctional inflammatory cytokine produced by T cells, monocytes, macrophages, and synovial fibroblasts which influences the immune response, hematopoiesis, acute phase response, and inflammation. IL-6 can amplify acute inflammation, and promote progression to a chronic state. The receptor complex contains the IL-6 receptor and the signal-transducing molecule gp130. In addition to the membrane receptor, a soluble form of IL-6R is released into blood and inflamed tissue. IL-6 can bind to both receptor types, mIL-6R and sIL-6R, and the IL-6/sIL-6R complexes then bind to gp130 to transduce the IL-6 signal into the cell [68, 69] (Fig. 3a).

Together with transforming growth factor β (TGF-β), IL-6 induces the differentiation of pathogenic Th17 cells (Figs. 1 and 4), while TGF-β in the absence of IL-6 induces CD4+CD25+ regulatory T cells [70, 71]. IL-6 not only induces inflammation, but also accelerates vascular permeability and angiogenesis by inducing vascular endothelial growth factor (VEGF) [72]. Systemically, IL-6 provokes fever, fatigue, C-reactive protein, and fibrinogen [69].

IL-6 and autoimmune disease

Several lines of evidence have shown that overproduction of IL-6 augments various inflammatory autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, systemic-onset juvenile idiopathic arthritis, and Castleman's disease [73, 74]. Observations in experimental autoimmune models of encephalomyelitis and type II

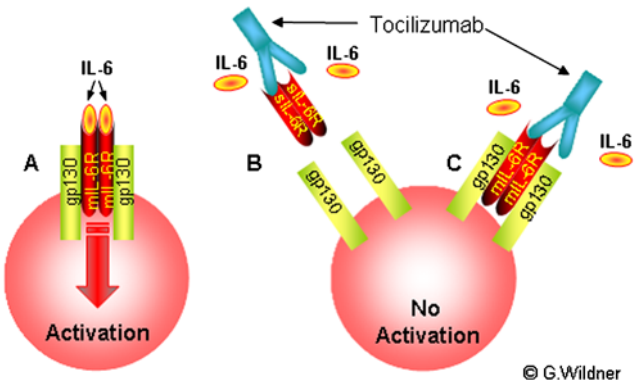

Fig. 3 Effect of tocilizumab (anti-IL-6R). **a** The membrane form of IL-6R is complexed with gp130, which transfers the intracellular signal after IL-6 binds to its receptor chains, leading to activation of the cell. **b**, **c** While gp130 is always membrane-bound, a soluble IL-6R exists which can bind IL-6. The complex of IL-6/IL-6R can then bind to gp130 on the cell surface, inducing an activating signal. Tocilizumab competes with IL-6 for binding to its receptor, the soluble (**b**) as well as the membrane-bound form (**c**), and thus blocks IL-6-mediated signaling

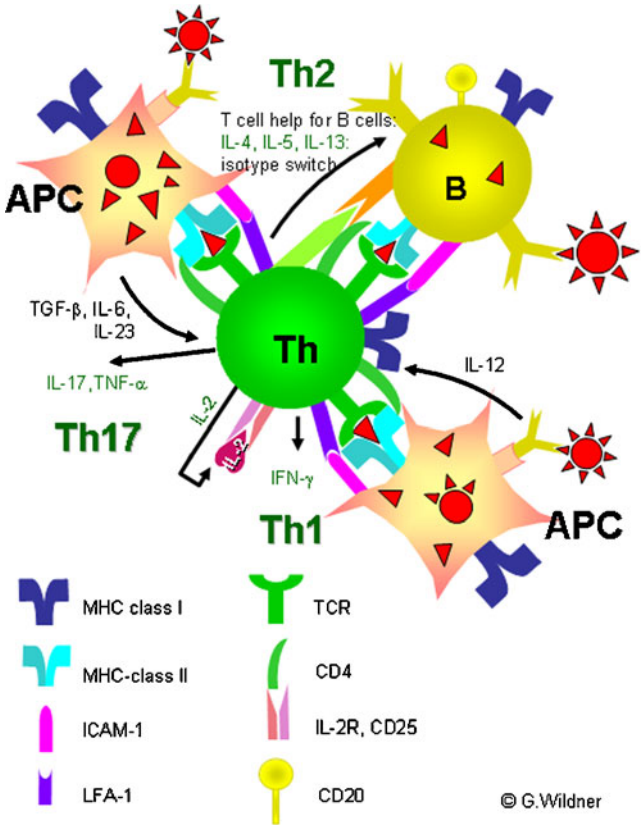

Fig. 4 Antigen presentation and T helper cell types. Antigen presentation, as described for Fig. 1, induces three different T helper cell types. The T cell receptor binds peptide antigen presented on MHC class II molecules of the respective antigen-presenting cell (APC). This complex is stabilized by the CD4 molecule on T helper cells, and many other receptor–ligand pairs, which form the "immune synapse", the contact region between T cells and their APCs. Among these additional interacting molecules, ICAM- and LFA-1 are potential targets for therapeutic intervention to prevent T cell activation. Once Th1 cells are activated, they secrete IL-2 and upregulate CD25, the IL-2 receptor. In addition to activating neighboring T cells, IL-2 also promotes autocrine activation of the secreting cell. Blocking CD25 can efficiently impede T-cell activation

collagen-induced arthritis suggest that IL-6 is involved in the induction of inflammation. IL-6 production induced by chronic inflammation activated polyclonal B cells and produced autoantibodies under experimental conditions and in patients [73, 75, 76].

IL-6 and uveitis

IL-6-deficient C57BL/6 mutant mice immunized with hIRBP1-20 showed lower uveitis scores than wild-type C57BL/6 mice. Furthermore, the systemic administration of recombinant anti-IL-6 receptor antibody reduced the uveitis score in wild-type mice during the entire course of uveitis. T cells from the draining lymph nodes produced lower amounts of IL-17, and IL-17 concentrations within the ocular fluid were lower than in the wild-type control mice, suggesting an impaired Th17 response after IL-6 blockade [77].

It has been previously shown that IL-6 is elevated in the vitreous body of patients with active intermediate and posterior uveitis [78]. In the undiluted vitreous fluid from 35 eyes of chronic uveitis patients that was collected during pars plana vitrectomy, IL-6 was higher than in 82 eyes of control patients. The IL-6 level was also increased in the aqueous humor from six patients during the acute onset of uveitis [77].

Anti-IL-6 receptor antibody tocilizumab

Anti-IL-6R antibodies have been effective in experimental models of arthritis and autoimmune encephalomyelitis [79, 80]. Tocilizumab is a recombinant humanized anti-IL-6 receptor antibody which specifically blocks both the membrane and the soluble IL-6R. Tocilizumab competitively inhibits the binding of IL-6 to these receptors, and prevents biological activity [68, 69, 81] (Fig. 3b).

Tocilizumab for the treatment of autoimmune disease

Clinical trials with tocilizumab have been promising in the treatment of several autoimmune diseases in patients who inadequately respond to conventional immunosuppression or TNF-α inhibitors. Tocilizumab was beneficial in patients with refractory rheumatoid arthritis, either as systemic monotherapy or combined with immunosuppressive drugs [69, 82]. This drug has also been effective in the treatment of patients with a severe systemic-onset form of juvenile idiopathic arthritis and vasculitis syndromes [83, 84]. Tocilizumab might represent a treatment option for uveitis as well.

IL-17 and anti-IL-17 antibodies (AIN457)

Interleukin-17

Naive CD4+ T cells differentiate into different T-cell populations after stimulation with antigen (Fig. 4). These subsets include T-helper 1 (Th1), Th2, and Th17 cells, in which cytokine production and effector functions differ [85, 86]. Th1 cells produce large amounts of IFN-γ and mediate cellular immunity. Th2 cells primarily produce IL-4, IL-5, and IL-13 and are involved in humoral immunity. Th17 cells preferentially produce IL-17, IL-21, and IL-22 [87, 88]. Under certain conditions, CD8+ T cells, γδ T cells, natural killer T cells, neutrophils, and monocytes also produce IL-17 [89, 90].

Th17 cell differentiation is induced by transforming growth factor-β and IL-6 or IL-21, and is accelerated by the

coordinated activities of IL-1 and TNF-α [70, 71]. IL-23 is required for the growth, survival, and effector functions of Th17 cells, and promotes IL-17, IL-21, and IL-22 production by this T-cell subset. IL-23 drives a pathogenic Th17 T cell population that induces autoimmune encephalomyelitis [91, 92]. In contrast, Th17 cell differentiation is negatively regulated by several different mediators, e.g., by IFN-γ, type 1 interferon, IL-2, IL-4, and IL-27 [87, 92–94].

IL-17 induces the production of antimicrobial peptides, cytokines, chemokines, and matrix metalloproteinases from fibroblasts, endothelial and epithelial cells, intercellular cell adhesion molecule 1 (ICAM-1), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (Cox2), and nuclear factor kB (NF-kB) ligand [90]. The stimulated cells in turn cause chronic inflammation by inducing the secretion of IL-6, IL-8, PGE2, MCP-1, and G-CSF [95].

IL-17 and autoimmune disease

Th17 cells are important effector cells in the development of several autoimmune diseases, allergic diseases (delayed-type hypersensitivity (DTH), contact hypersensitivity, and allergic airway inflammation), and host defense against infections [87, 90]. While experimental autoimmune encephalomyelitis (EAE), an experimental model for multiple sclerosis, was thought to be mediated by Th1 cells, recent experiments demonstrated that Th17, but not Th1 cells are involved in the development of the disease [96]. Accordingly, IL-17 mRNA expression is upregulated in multiple sclerosis lesions, and IL-17 expression is increased in the cerebrospinal fluid of multiple sclerosis patients [97, 98].

In patients with autoimmune rheumatoid arthritis, too, high levels of TNF, IL-1, IL-6, and IL-17 were measured in synovial fluid and serum [99]. More recent observations have shown that, although Th17 cells are critical for the development of arthritis, disease progression was impeded by the blockade of TNF, IL- 1, or IL-6 [100, 101].

In 2002, Hamzaoui et al. found a striking increase in IL-17 in the blood of patients with active systemic Behçet's disease and, recently, Chi et al. reported markedly elevated IL-17 production from peripheral blood mononuclear cells in patients with active Behçet's uveitis as compared to Behçet's disease patients without active uveitis and healthy controls [102, 103].

IL-17 and experimental autoimmune uveitis

There is significant evidence that Th17 cells can induce EAU. Depending on the method of induction, however, the relative impact of Th17 and Th1 cells differed.

When EAU was induced by immunization with IRBP and complete Freund's adjuvants, disease was significantly reduced in p19 (lacking IL-23 that is required for Th17 cell expansion) and p40 (lacking IL-12 and IL-23) knockout mice, while EAU was significantly increased in p35 knockout mice (lacking IL-12 that is required for Th1development) as compared to wild-type mice. EAU was reduced in mice after antibody blockade of IL-17 during disease induction or after disease onset. In contrast, antibody blockade of IL-23 reduced disease only when given during disease induction, most likely because this cytokine is required for expansion of pre-existing Th17 cells but not for lineage commitment [24]. Transfer of IRBP-specific CD4+ cells from mice polarized towards Th17 with IL-23, TGF-β, IL-6, and anti-IL-4 antibody also induced EAU. Disease was similar when the cells were transferred to IFN-γ deficient mice, showing that Th17 effector cells induce EAU in the absence of an IFN-γ response.

However, when EAU was induced in the animal model by transferring IRBP-specific CD4+ T cells obtained from the regional lymph nodes of IRBP/CFA-immunized mice that had been polarized towards Th1 with IL-12 and anti-IL-4 antibody, blockade with anti-IL17 had no effect on EAU.

Furthermore, when an IFN-γ producing Th1 cell line was used to induce EAU, severe disease without any detectable IL-17 was observed, showing that under some conditions IL-17 might be dispensable for EAU and possibly other types of autoimmunity. In line with this, when EAU was induced with IRBP-pulsed mature dendritic cells followed by pertussis toxin injection 2 days later (this is an induction protocol that favours a Th1-dominated response as opposed to the more common protocol that utilizes complete Freund's adjuvant that primes the T helper cells toward IL-17 production, i.e., Th17), disease was decreased in IFN-γ deficient mice, despite the presence of a Th17 response [24]. Therefore both a Th1 and a Th17 response seem to be capable of inducing EAU [24]. It seems to depend on the induction method of EAU, whether the resulting immune response and inflammation is dominated by IFN-γ (Th1) or IL-17 (Th17). Or in other (clinically minded) words: not all patients with uveitis might have IL-17 dominated disease (depending on thus far not known initiating factors), but those whose IL-17 levels are increased might benefit from anti-IL17 treatment. In fact, Th17 cells were detected in human peripheral mononuclear cells from healthy individuals, but the numbers were increased in uveitis patients during active disease [104].

Anti-IL-17 AIN457 antibody: description and mechanisms of action

AIN457 is a high-affinity human monoclonal anti-human IL-17 antibody of the IgG1 isotype. AIN457 binds to

human IL-17 and neutralizes the bioactivity of this cytokine. When administered intravenously, the molecule was shown to have only a limited potential for being distributed into normal and uninflamed tissues. Analysis of terminal phases of the serum concentration-versus-time profile did not reveal any signs of formation of anti-idiotypic (neutralizing) antibodies in Cynomolgus monkeys (Novartis, unpublished data).

Impact of anti-IL-17 antibody AIN457 on autoimmune disease

Recently, two clinical trials with intravenous AIN457 in patients with rheumatoid arthritis and psoriasis have shown rapid improvement in the clinical manifestations of disease as compared to placebo-treated controls (Novartis, unpublished data).

Impact of anti-IL-17 antibody AIN457 on autoimmune uveitis

In an open-label pilot study including 16 patients with active noninfectious uveitis not adequately responding to systemic immunosuppression, AIN457 was given at a dosage of 10 mg/kg intravenously at baseline and 3 weeks. Five patients had anterior, another one had intermediate, three had posterior, and another seven patients had panuveitis. Uveitis was of diverse etiologies, including idiopathic, HLA-B27-associated, Vogt–Koyanagi–Harada disease, sarcoidosis, and Behçet's disease. The preliminary data show that uveitis responded to treatment at 8 weeks in 12 of the 16 patients (Novartis, unpublished data). Currently, a multicenter randomized, double-masked, placebo-controlled study is underway in order to assess the rate of recurrent exacerbations in Behçet's patients with posterior or panuveitis treated with AIN457 versus placebo as an adjuvant to conventional immunosuppressive therapy.

IL-1 and treatment with IL-1 receptor antagonist

IL-1 and the IL-1 receptor antagonist (anakinra)

So far, 11 members of the IL-1 family of ligands have been described. In contrast to other cytokines, some of the IL-1 family members exert their function at both the receptor and nuclear level [105]. IL-1 plays a role in chronic inflammation and immune responses and is linked to the innate immune responses (Fig. 1). While some of the IL-1 members induce local and systemic inflammation (IL-1α, IL-1β, and IL-18), others protect against ongoing immune reactions (IL-1 receptor antagonist; IL-1Ra). IL-1Ra is a specific inhibitor of the activity of both IL-1α and IL-1β. IL-1 activity blockade, in particular of IL-1β is already well-established for clinical use. Anakinra is the truncated, N-terminally methionylated recombinant form of the human IL-1Ra, which can block receptor binding of IL-1α and IL-1β.

Anakinra in autoinflammatory and autoimmune disease

Recently, a group of certain diseases with a chronic inflammatory component have been defined as auto-inflammatory diseases that characteristically respond to IL-1 blockade rather than TNF-α inhibitors. Typical examples are adult-onset of Still's disease, systemic-onset juvenile idiopathic arthritis, macrophage activation syndrome, and Blau's syndrome. Anakinra has become the standard treatment for patients with systemic-onset juvenile idiopathic arthritis and for Still's syndrome in adults [106, 107].

Anakinra has also been shown to be effective in treating various other systemic and local inflammatory disorders. It is approved for therapy in typical autoimmune diseases, such as rheumatoid arthritis, and has been effective in Behcet's syndrome [108, 109].

IL-1 and anakinra in uveitis

IL-1 and IL-1Ra levels in the aqueous humor of patients with uveitis were found to be higher than in healthy controls. They were increased in patients with active disease in particular [110]. High levels of IL-1 and IL-1Ra have also been determined in experimental models of uveitis [111]. Indeed, anakinra has been shown to suppress intraocular inflammation in a rabbit model of IL-1 induced uveitis [112]. In a recent study, treatment with anakinra suppressed the development of experimental autoimmune uveitis and the IRBP-specific immune response, and also inhibited IL-1α, IL-1β, TNF-α and IFN-γ being produced in draining lymph node cells [113]. During immunomodulatory treatment of patients with idiopathic pars planitis and ocular Behcet's disease, the serum levels of IL-1Ra significantly increased, suggesting a potential role of IL-1Ra in the therapeutic effect [114]. Finally, Theol and colleagues reported that treatment of CINCA-associated uveitis with anakinra was successful [115].

CD-25 / IL-2R and Daclizumab

Daclizumab is a humanized monclonal antibody, which recognizes the α-chain of the human high-affinity IL-2 receptor (IL-2R), CD25. The IL-2Rα is expressed on activated T cells, but not on resting T cells or B cells, NK cells, and monocytes (Fig. 4).

Targeting the α-chain of the high-affinity IL-2R is thought to affect only activated T cells, the population that maintains the autoaggressive immune response, while leaving the pool of memory and naïve T cells untouched. In rodent experimental autoimmune uveitis, the autoaggressive Th1 cells express large numbers of IL-2R [11]. However, CD25 is also expressed by regulatory T cells of the CD4+CD25+Foxp3+ phenotype and on negative regulatory NK cells (CD56bright, IL-10-producing) [116]. While IL-2 is a characteristic cytokine of Th1 effector cells, the recently discovered Th17 cells, which have been shown to play an important role in many autoimmune diseases, are not affected by anti-IL-2R-targeted therapies [117].

Upon binding to CD25, daclizumab does not completely inhibit IL-2-induced intracellular signal transduction via the beta and gamma chains of the IL-2 receptor, i.e., JAK-1, JAK-3, and STAT-5 are still intracellularly activated [118].

Surprisingly, daclizumab therapy primarily affects T effector cells rather than regulatory T cells, although it is known that they strongly depend on IL-2. Nevertheless, the fate of CD4+CD25+ regulatory T cells under daclizumab therapy is contradictory [119]: on the one hand, daclizumab is used to enhance immune responses to vaccination by knocking out regulatory T cells [120, 121], while on the other it successfully treats autoimmune diseases, which are supposed to be caused by a dysregulation of Tregs. However, even if classical regulatory CD4+CD25+ T cells are impaired by daclizumab therapy, their function might be taken over by other regulatory cell populations such as IL-10-producing $CD56^{bright}$ NK cells [116].

Daclizumab for the treatment of autoimmune uveitis

In a nonhuman primate model, targeting IL-2 receptors effectively downregulated experimentally induced intraocular inflammation [122], offering the rationale for treating the first patients in a nonrandomized open-label pilot study [123]. Uveitis improved with daclizumab at 1 mg/kg bodyweight in 2-week intervals in eight of ten patients. After 24 weeks, the intervals between infusions were increased to 4 weeks. Within the first year patients did not need any other immunosuppressive or anti-inflammatory therapy other than daclizumab. Meanwhile, seven additional studies have reported clinical improvement in 42 of 64 uveitis patients treated with daclizumab with a follow-up of 1 to 2 years [51, 124–129]. Two of these studies reported an increase in average visual acuity from 68 to 79.6 and 69.2 to 78.2 letters [124, 126]. Side-effects included nausea, fatigue, muscle aches, rashes, edema, upper respiratory infections, cutaneous herpes zoster lesion, hepatic dysfunction, or leukopenia, but were considered to be nonhazardous.

In January 2009, authorization for marketing daclizumab in Europe was withdrawn, leaving basiliximab as the only anti-IL-2R agent. Unfortunately, publications on basiliximab in the context of uveitis are not available.

CTLA-4

In addition to T-cell receptor recognition of the peptide/MHC complex on antigen-presenting cells, costimulatory signals are needed to fully activate a naive T cell. Those costimulatory signals are mediated by CD28 binding to CD80 or CD86 (B7.1 and B7.2) on the surface of T cells and on APC. Upon TCR ligation, CTLA-4 or CD152, another ligand of CD80/CD86, is upregulated on the surface of T-helper cells. CTLA-4 has a higher affinity to CD80/86 than CD28 and, in contrast to the activating effect of CD28 signalling, the natural function of CTLA-4 is to terminate T cell activation [130]. Tregs constitutively express CTLA-4 [131, 132]. Abatacept and belatacept are fusion proteins of an IgG Fc part and the extracellular domain of CTLA-4. They inhibit interaction between CD28 on T cells with CD80/CD86 on APC, and thus impede T-cell activation [133, 134] (Fig. 5).

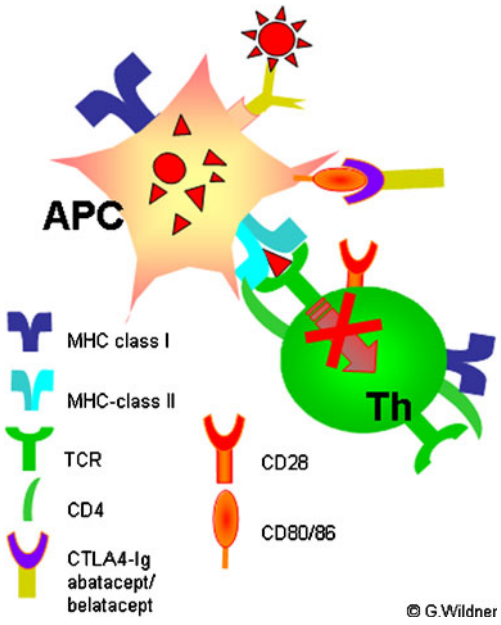

Fig. 5 Inhibitory effect of CTLA4-Ig on T-cell activation via blocking of antigen-presenting cells. In addition to MHC–peptide antigen recognition, T cells require interaction with additional molecules on the APC to become fully activated. The interaction between CD28 on T cells and CD80 or CD86 on APC induces one of the most important "second signals". CD80 and CD86 have a second high-affinity ligand, CTLA4, a molecule expressed on cytotoxic T cells. Abatacept or belatacept contain the CD80/CD86 binding site of CTLA4, coupled to the Fc part of an immunoglobulin. This construct blocks the costimulatory molecule on APC and thus prevents CD28 activation and costimulation, impeding T cell activation

The CTLA4-Ig construct (abatacept, belatacept) blocks the receptor on APCs and thus prevents costimulation of T cells, resulting in immunosuppression; in contrast, there are fully humanized therapeutic antibodies directed against CTLA-4 (ipilimumab and tremelimumab) which have the opposite effect. Abatacept and beletacept are used to treat autoimmune diseases [135] or to prevent kidney graft rejection, while the antibodies to CTLA4, ipilimumab and tremelimumab, block CTLA4, impeding the natural downregulation of T-cell activation, and are thus used as adjuvant therapy to activate the immune response against cancers [136].

A single case report has been published on abatacept (Orenica®). The drug was given to a patient with JIA-associated uveitis who showed a good therapeutic response. Inflammation and visual acuity improved, and other immunosuppressive treatments, including corticosteroids, could be reduced [137].

Cell-adhesion molecules (CAM) and treatment with anti-CAM antibodies

VCAM-1/VLA-4 and treatment with α4 integrin inhibitor

VCAM-1 and its ligand VLA-4

The vascular cell adhesion molecule (VCAM) belongs to the immunoglobulin gene superfamily. It is expressed on the surface of activated endothelial cells, dendritic cells, fibroblasts, and tissue macrophages, and facilitates entry of activated leukocytes through blood vessels into inflamed tissues via its ligand very late activation antigen-4 (VLA-4) (Fig. 1). VLA-4 belongs to a family of β1-integrins that have the CD19 β-chain in common. It is expressed on T and B lymphocytes, monocytes, natural killer cells, and eosinophils.

VCAM-1/VLA-4 and autoimmune disease

Cell adhesion molecules such as VCAM-1 and VLA-4 are essential to guide leukocytes to tissue sites in order to initiate and maintain local inflammation. While this is essential for removing infectious agents or foreign particles, it has deleterious effects if host structures are being targeted, such as in autoimmunity. Increased levels of VCAM-1 expression have been found in synovial tissue from rheumatoid arthritis (RA) patients [138]. A soluble form of VCAM-1 (sVCAM-1) inducing T-cell chemotaxis has been detected in synovial fluid of RA patients [139, 140]. Furthermore, high levels of VLA-4 expression in memory T cells and increased expression of the corresponding VCAM-1 have been found in inflamed intestine [141].

VCAM-1/VLA-4 and uveitis

In the EIU model in rabbits, VLA-4 blockade significantly reduced both disease scores and protein content in aqueous humor [142]. In addition, VCAM-1 expression was found to be significantly higher in iris biopsy specimens from patients with uveitis (mostly anterior uveitis) than in healthy individuals [143].

Natalizumab as anti-VLA-4 antibody

Natalizumab is a humanized monoclonal IgG4-antibody targeting the α4-integrin subunit of VLA-4. It blocks the binding of VLA-4 to VCAM-1 and interferes with an important molecular interaction for the entry of leukocytes into sites of inflammation.

Natalizumab for the treatment of autoimmune disease

Recent clinical trials used natalizumab to treat patients with multiple sclerosis, and showed significant amelioration of the disease. It substantially reduced the risk of the sustained progression of disability and the rate of relapses in patients with multiple sclerosis [144]. Natalizumab has also shown promise in the treatment of Crohn's disease [145].

Intercellular cell-adhesion molecule-1

Intercellular cell-adhesion molecule-1 (ICAM-1, CD54) is a member of the integrin family, and is expressed on the surface of vascular endothelium (Fig. 1), fibroblasts, dendritic cells, ocular cells such as keratinocytes, monocytes, and B and T cells. It binds to its ligands Mac-1 (also known as complement receptor 3, CD11b paired with CD18, the integrin β2) and lymphocyte function-associated molecule-1 (LFA-1, CD11a/CD18), which is expressed on granulocytes, monocytes, and leukocytes. In addition to its function in leukocyte trafficking, it is involved in interactions between lymphocytes and APCs, where it enables the formation of an immunological synapse (Fig. 4). This is important for the APC to provide sufficient costimulatory signals to activate lymphocytes. The expression of adhesion molecules is regulated by cytokines. IFN-γ, IL-1, and TNF-α are strong inducers of ICAM-1 expression.

ICAM-1 and autoimmune disease

The major role of ICAM-1 in cell migration implies that it may possibly be involved in autoimmune processes, too. Several studies revealed evidence for neutrophil recruitment to the colonic mucosa in inflammatory

bowel disease (IBD) that is mediated by ICAM-1. Furthermore, ICAM-1 levels were correlated with disease activity [146, 147]. Hence, ICAM-1 seemed a logical target in IBD such as Crohn's disease (CD) and ulcerative colitis (UC). Expression of ICAM-1 is also increased in the synovial tissue of RA patients and in the central nervous system of MS patients. In addition to its role in autoimmune diseases, ICAM-1 has been shown to be a major receptor in several infectious diseases.

ICAM-1 and uveitis

In EIU, ICAM-1 is first expressed on the ciliary body endothelium, followed by the vascular endothelium of the iris and the corneal endothelium. Treatment of rats with either anti-ICAM-1 or anti-LFA-1 antibody prevented development of EIU [148]. ICAM-1 and LFA-1 have also been shown to play a critical role in experimental autoimmune uveitis (EAU) [149]. ICAM-1 expression was observed on day 7 after immunization with IRBP on the vascular endothelium of the retina and the ciliary body. As in EIU, monoclonal antibodies against ICAM-1 or LFA-1 significantly reduced disease scores in an EAU mouse model.

Blockade of ICAM-1 expression by ISIS-2302

ISIS-2302 is a 20-nucleotide phosphorothioate antisense oligonucleotide designed to inhibit the expression of ICAM-1. Due to its complementary structure, it can bind ICAM-1-m-RNA to form a DNA:RNA heteroduplex, which is a substrate for hydrolysis by RNAse H [150, 151]. Thereby, it can block the ICAM-1 transcription and reduce expression levels.

ISIS-2302 for the treatment of autoimmune disease

ISIS-2302 has been used in clinical trials for the treatment of patients with active CD. However, it failed to demonstrate statistical significance as compared to a placebo group [152].

Efalizumab as LFA-1-antibody

Another inhibitor of the ICAM-1/LFA-1 axis is the humanized monoclonal IgG1 antibody efalizumab. It binds the CD11a chain of LFA-1, and therefore blocks interaction with ICAM-1.

Efalizumab for the treatment of autoimmune disease

Efalizumab has been shown to be effective for the treatment of psoriasis [153].

CD-20 and anti-CD20 antibody (rituximab) treatment

CD20 antigen

The surface antigen CD20 is expressed on pre-B and mature B cells, but it is not present on stem cells and plasma cells. After the antibody binds to the target antigen, B cells are depleted from the peripheral blood and also moderately from the lymph nodes and bone marrow.

B cells and autoimmune disease

There is significant evidence that B cells play potential roles in the immunopathogenesis of autoimmune disease. In rheumatoid arthritis, B cells are involved in the secretion of proinflammatory cytokines, antigen presentation and thus T cell activation, autoantibody production, and self-perpetuation, which eventually cause inflammatory tissue damage and cartilage loss [154–157].

Rituximab: description and mechanisms of action

The monoclonal antibody rituximab is directed against the CD20 antigen expressed on B cells. Rituximab is a monoclonal chimeric antibody, consisting of a variable region with a murine antibody fragment and the human IgG and k-constant regions. The cytotoxic mechanisms of anti-CD20 on B cells include complement-mediated cell lysis, cell-mediated cytotoxicity through natural killer cells and macrophages, and apoptosis [158, 159] (Fig. 6).

Anti-CD20 therapy for autoimmune disease affects the secretion of proinflammatory cytokines, antigen presentation, T-cell activation, and autoantibody production. As the treatment commonly has little impact on the extent of serum immunoglobulin levels and on the antibody-secreting cells in the bone marrow, the antibody-secreting plasma cells are presumably long-lived, and memory B cells are not targeted [160]. In addition, an immune complex decoy hypothesis has been proposed: rituximab could generate IgG-opsonized cells that bind to macrophages to divert them from pathogenic interactions with tissue-associated immune complexes [159].

Impact of rituximab on systemic autoimmune disease

Recent clinical studies have underlined the substantial impact of rituximab for the treatment of systemic autoimmune diseases. Rituximab was effective in treating active rheumatoid arthritis with an inadequate response to MTX or TNF-α inhibitors [161–163]. Rituximab has also been successful in the treatment of refractory systemic lupus erythematosus [164–166], and effective in treating refractory ANCA-associated vasculitis [167–169].

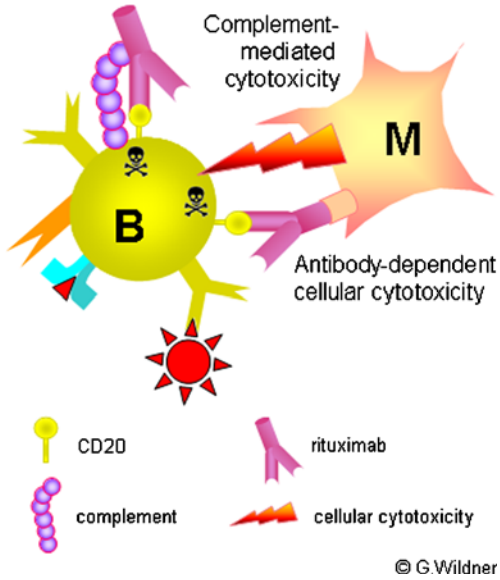

Fig. 6 Rituximab and B cells. CD20 is expressed on all B cells, except plasma cells. Binding of the CD20-specific therapeutic antibody Rituximab kills B cells either by complement fixation or mediates killing by macrophages, which bind to rituximab via their Fc receptors

However, the treatment protocols applied in these studies differ from each other in that infusions were given once weekly for 2 to 4 weeks, and the dosages were either fixed at 500 mg or 2,000 mg or were 375 mg/m^2 in other studies. In order to prevent an anaphylactic response to the chimeric antibody, intravenous methylprednisolone was given 30 min before each infusion at dosages of 100 to 250 mg. A sustained B-cell depletion of naïve and autoimmune cells was achieved, with peripheral blood CD20 cells being low or undetectable for up to 6 months, returning to pretreatment levels within 12 months [169]. Earlier repopulation of B cells was observed after rituximab monotherapy rather than after combination therapy with immunosuppressive agents, such as methotrexate.

Impact of rituximab on inflammatory eye disease

Rituximab has been successfully used for the treatment of refractory keratoconjunctivits, scleritis, peripheral ulcerative keratitis, and uveitis, also when associated with systemic diseases.

Sjögren's syndrome Extended improvement in submandibular flow rate, dry mouth score, IgM rheumatoid factors, fatigue, and health-related quality of life (SF-36) was observed in Sjögren's patients upon treatment and retreatment [170, 171]. In addition, keratitis refractory to immunosuppression improved with rituximab infusions [172–174].

Scleritis Rituximab improved Wegener's granulomatosis. Clinically, systemic disease resolved rapidly and ANCA levels were reduced. Associated necrotizing and non-necrotizing scleritis that persisted despite immunosuppression and TNF-α inhibitors also showed improvement [175–178].

Uveitis Rituximab may be helpful in selected patients with chronic uveitis refractory to corticosteroid and immunosuppression. In an adult with endogenous anterior uveitis, uveitis stabilized and the associated CME resolved with rituximab infusions. The treatment also had some steroid-sparing effect [179]. However, the B-cell depletion in the peripheral blood and the positive effect on uveitis was transient, as inflammation and CME recurred after 6-9 months. Retreatment with rituximab produced improvement. In selected patients with refractory JIA-associated uveitis not responding to immunosuppressive drugs and TNF-α inhibitors, a rituximab infusion improved uveitis activity (Heiligenhaus et al., submitted for publication).

In summary, one cycle of rituximab was effective for treating active disease and the subjective and objective symptoms for a prolonged period. Retreatment was required in selected cases, with favorable long-term response. Rituximab is an intriguing new modality for the treatment of sight-threatening ocular inflammatory disease. Indications and treatment protocols for initial and maintenance therapy must be studied in future trials.

Interferons

Interferon-α and interferon-β (IFN-α, -β) are type 1 interferons induced by viral infections, tumors, or foreign cells. They are produced by macrophages, IFN-α 2b preferentially by fibroblasts. Both IFNs bind to a specific cell surface receptor complex known as the IFN-α receptor (IFNAR) that consists of IFNAR1 and IFNAR2 chains.

IFN-α subtypes are preferentially produced by monocytes/macrophages, but also by T cells and mainly by plasmacytoid dendritic cells (PDC) during viral infections. This reaction is triggered by viral DNA or bacterial CpG motifs via TLR7 and/or TLR9. Thus, interferons have primarily been used for the treatment of chronic hepatitis B and C. The mechanism of action of recombinant IFN-α2a treatment, especially of patients with Behçet's disease, is not yet fully understood. It was shown that the capacity of PDC from Behçet's disease patients to secrete IFN-α was lower after stimulation with CpG in culture [180]; thus, IFN-α therapy might substitute the defective function of PDC in these patients.

The effect may also involve modulation of the immune system. NK (natural killer) cells and NKT cells, a cell population bearing NK receptors as well as T-cell receptors (of restricted variability), are stimulated with IFN-α. The original hypothesis was based on reports that NK/NKT cell activity is impaired and that numbers of cells are decreased in several autoimmune animal models and human diabetes [181]. NKT cells have an important regulatory function in both innate and adaptive immune responses [182]. It was possible to correct the deficiency of NK cells with IFN-α treatment. Later, IFN-α was reported to induce circulating IL-1 receptor antagonists. In this case, induction of an antiinflammatory status was suggested through modulation of the IL-1/IL-1receptor antagonist balance. Recent results suggest that host immunity is an important factor in the response to interferon therapy [183].

Side-effects of IFN-α therapies are commonly observed, and are dose-dependent. Most patients experience flu-like symptoms, which can effectively be treated with paracetamol (acetaminophen) and resolve with time. In addition, anti-thyroid antibody production has frequently been observed (40% of patients treated with IFN-a for HCV infection), sometimes leading to thyroiditis (15% of IFN-α treated patients), and anti-DNA-antibodies were increased in others [184, 185]. Since increased IFN-α production and anti-DNA antibodies are also found in patients with lupus erythematosus, it is a major concern that IFN-α treatment might have the potential to induce SLE. Depression is observed frequently, probably due to the presence of IFN-α receptors in the hypothalamus [186]. Furthermore, IFN-α stimulates expression of corticotropin-releasing factor. In humans, IFN-α injection increased cortisol levels, which are also correlated with subsequent development of depression. IFN-α decreases concentrations of serotonin and dopamine in the brain, and can also directly bind to opioid receptors.

In an uncontrolled prospective study, 50 patients with Behçet's disease and sight-threatening uveitis were treated with a daily subcutaneous dose of initially 6 million units recombinant human IFN-α2a, and followed for up to 5 years [187]. Forty-six patients responded well with increasing visual acuity and regressing intraocular inflammation. The overall activity of Behçet's disease was reduced to 50 %, and after a mean observation period of 3 years, 20 patients were able to discontinue treatment and were in remission for 7 to 58 months. The remaining patients were able to reduce their dose of IFN-α2a to 3 million units three times a week. These positive effects have also been observed by others [188–190]. The additional use of corticosteroids at initiation or during continued IFN-α2a treatment is controversial, but has been shown to be effective [191]. The use of IFN-α2a has been extended to the treatment of occlusive vasculitis, pediatric Behçet's patients, Vogt–Koyanagi–Harada's disease, and cystoid macular edema [192–194].

CD-52

CD-52 is a glycoprotein expressed on the surface of all mature lymphocytes and also found on dendritic cells and monocytes. Its precise function is still unknown.

Alemtuzumab as anti-CD52 antibody

Alemtuzumab (Campath-1H) is a humanized monoclonal antibody, which targets CD-52. Even a single treatment can substantially deplete the blood of lymphocytes, resulting in leukopenia that can last for several months.

Alemtuzumab for the treatment of autoimmune disease, uveitis, and cancer

Alemtuzumab has shown promising results in some patients with noninfectious refractory posterior uveitis [195]. Another study demonstrated its efficacy in Behcet's disease, although the effect on the associated uveitis was not specifically addressed [196]. In early multiple sclerosis, alemtuzumab has been shown to be superior to IFN-β1a [197].

An adverse effect of alemtuzumab is secondary autoimmunity, mainly Graves' disease and idiopathic thrombocytopenia purpura. This effect is driven by increased levels of IL-21, caused by antibody-induced lymphopenia, which is followed by enhanced lymphocyte proliferation [198]. Interestingly, increased IL-21 levels prior to treatment identified those patients who went on to develop these adverse effects. Furthermore, alemtuzumab has been evaluated in clinical trials as being effective in treating chronic lymphocytic leukemia [199].

Interleukin-15

IL-15 is secreted by mononuclear phagocytes, e.g., in response to viral infections. It is a crucial growth factor for NK cells, and seems to be important for inducing cytotoxic T cells, particularly of CD8+ memory T cells.

IL-15 and autoimmune disease

Patients with multiple sclerosis present increased numbers of peripheral blood mononuclear cells expressing IL-15 m-RNA, and the skin lesions in psoriasis express high levels of IL-15 [200]. Increased levels of IL-15 have been found in patients with rheumatoid arthritis, both in serum

and the synovial membrane. Elevated serum levels have also been found in patients with ulcerative colitis, and also in patients with Behcet's disease. However, the latter was not correlated with disease activity or treatment [201].

HuMax-IL-15 as anti-IL-15 antibody

HuMax-IL15 is a human monoclonal anti-IL-15 IgG1 antibody with the capacity to neutralize both exogenous and endogenous IL-15 activity in vitro.

HuMax-IL15 for the treatment of autoimmune disease

A phase I/II dose-escalation trial with HuMAX-IL15 in patients with RA showed substantial improvement in disease activity [202]. HuMax-IL15 was well-tolerated, and had no significant effects on the numbers of lymphocyte subsets.

Conclusions

Better knowledge of the basic mechanisms underlying uveitis and of the molecules that are important for regulating inflammation would help us to create new and more specific treatment approaches. In biological therapy, the therapeutic targets for immunomodulation specifically interact with molecules that play a critical role in the pathogenetic process of uveitis, as has been defined by observations in patients or the respective animal models of uveitis.

Recently, small case series have already shown that in selected patients biologicals are valid alternatives to classical immunosuppressive drugs in order to accelerate drug actions. Biological agents are currently used as rescue therapy for uveitis unresponsive to corticosteroids and classical immunosuppressives. Now, prospective randomized clinical trials are warranted to compare the benefit and risk between the diverse biologicals and the classical immunosuppressive drugs, in order to better define their place in the step-ladder approach for treating uveitis patients.

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