Anti-TNF therapy for eye involvement in spondyloarthropathy

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ABSTRACT

Approximately 40% of patients with ankylosing spondylitis or reactive arthritis will experience the sudden onset of a unilateral anterior uveitis sometime during the course of their spinal disease. In most instances, this inflammation resolves within several weeks and responds to corticosteroid and mydriatic eye drops without the need for additional therapy. A small percentage of patients with either Crohn's disease or psoriatic arthropathy will have a bilateral, chronic, anterior and/or posterior uveitis that is more refractory to therapy. A similar clinical challenge is occasionally encountered in patients with ankylosing spondylitis or reactive arthritis. In this manuscript, we review briefly the clinical manifestations of the uveitis associated with spondyloarthropathy and discuss several potential novel therapeutic approaches, primarily anti-tumor necrosis factor (TNF) therapy.

Clinical manifestations

The sudden onset of an anterior uveitis is a frequent association with HLA B27-related diseases (1). This eye inflammation is limited to the iris and/or ciliary body, and therefore is located predominantly anterior to the lens. It tends to be unilateral. It frequently recurs, however, sometimes in the contralateral eye. Characteristically the affected eye has a reduced intraocular pressure. Complications such as posterior synechiae (adhesions between the iris and the anterior surface of the lens) and even hypopyon (a collection of pus inferiorly in the anterior chamber) are frequent (2). While this pattern of eye inflammation is sometimes also seen in patients with Crohn's disease, ulcerative colitis, or psoriatic arthritis, those patients with Crohn's disease or psoriatic arthritis are more likely to develop eye inflammation which is bilateral, posterior to the lens (posterior uveitis) and chronic in duration (3, 4).

In general, anterior uveitis can be treated simply and effectively with topical corticosteroids. A mydriatic (dilating) eye drop is used in part to keep the pupil mobile and thus prevent the formation of posterior synechiae. Accordingly, novel therapies for this type of inflammation are not a major clinical priority. However, inflammation behind the lens represents a major cause of visual loss and can be a difficult clinical problem. Traditionally this type of inflammation is treated by some combination of periocular corticosteroid injections, oral corticosteroids, or systemic immunosuppressive therapy such as methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, cyclophosphamide, or chlorambucil.

In the last few years, several novel approaches have been attempted to treat posterior eye inflammation. Iontopheresis involves the application of a mild electrical current to promote the delivery of medication across the sclera (5). This is an approach being tested currently for posterior uveitis. In addition, polymer-containing devices have been developed to release medication slowly into the vitreous cavity. The device is inserted into the eye by a surgical procedure. A fluocinolone acetonide slow release implant, as well as a dexamethasone implant, are undergoing clinical trials (6). This approach is extremely promising for the treatment of posterior uveitis, although it can be complicated by the development of cataract, glaucoma, or surgical complications such as intraocular hemorrhage and retinal detachment. From the perspective of a rheumatologist who prescribes systemic treatments, the innovative therapy for inflammatory eye disease which is most germane is TNF blockade. We review the rationale for this approach based on animal models and discuss the clinical success with treating uveitis by TNF inhibitors.

Animal studies

Uveitis can be induced in laboratory

rodents by a variety of techniques. In most rat strains, a footpad injection of bacterial endotoxin will induce a polymorphonuclear leukocyte infiltrate in the anterior uveal tract within 24 hours of the injection (7). This model, known as endotoxin-induced uveitis (EIU), is highly reproducible and does not require direct ocular injection. The mouse response to systemic endotoxin is more mild intraocularly (8). Consequently some investigators inject endotoxin directly into the eye to induce inflammation in this animal. It is apparent that the systemic injection of endotoxin induces the local expression of TNF-alpha within the eye, as demonstrated by an up-regulation of mRNA encoding TNF alpha, and presence of the cytokine, in the iris and other intraocular tissues (9). Immunizing rats with an antigen that induces uveitis also upregulated TNFα gene expression locally in the eye of a susceptible strain (10).

Surprisingly, TNF inhibition fails to reduce the cellular infiltrate in EIU and in some instances actually enhances it (11). Strategies in animal studies for TNF inhibition have included the use of solubilized receptor (12) as well as the use of neutralizing antibodies (13) or even active immunization against TNF alpha. While these approaches do not address whether the inhibitor had adequate bioavailability within the eye, and leave some question as to whether the TNF alpha was adequately blocked, TNF receptor knock-out mice that lack both the P55 and P75 TNF receptors still develop EIU (14,15). On the other hand, TNF receptor knockout mice develop reduced inflammation if a reversed passive Arthus type inflammation is induced in the eye (16). Furthermore, TNF inhibition with antibody may reduce the severity of EIU in rabbits (17). Another observation that suggests TNF alpha is not a major mediator of EIU in the eye comes from studying the effect of interleukin 13 (IL-13) on the model. In this rat study, uveitis was induced by a foot pad injection of endotoxin and IL-13 was given subcutaneously. Although the IL-13 reduced the inflammation within the eye, it actually increased local concentration of TNF alpha in the eye (18).

The p55 TNF receptor-immunoglobulin fusion protein is partially effective in blocking a different animal model of uveitis called experimental autoimmune uveitis (EAU) (19). In this model, inflammation is induced by immunizing the rodent against a retinal antigen emulsified in adjuvant. Characteristically either arrestin or interphotoreceptor retinoid-binding protein is used as the antigen. In contrast to EIU, EAU is a lymphocyte-mediated disease. When TNF receptor fusion protein was used to treat rats 8 to 10 days after immunization with a retinal antigen, it successfully reduced tissue damage and delayed disease onset.

Anti-TNF therapy and uveitis

TNF inhibition has rarely been used to treat HLA B27-associated uveitis for the reasons noted above, namely, the disease is usually short lived and treatable with topical medications alone. A recent abstract reported treating 7 patients with HLA B27-associated iritis with a single infusion of 10 mg/kg of infliximab. Six of the patients entered remission although 3 of these developed a relapse within 4 months of the infusion (20). In this study infliximab was the only medication administered. It is not always possible to extrapolate from other clinical forms of uveitis to HLA B27-related disease just as the experience in animal models might suggest that EIU differs from the reversed passive Arthus-type uveitis or from EAU. However, TNF inhibition appears to be somewhat effective for the anterior uveitis associated with juvenile rheumatoid arthritis (21) and infliximab has demonstrated dramatic results in a small number of patients with the eye disease associated with Behcet's disease (22).

Despite these encouraging results, an occasional patient with either spondyloarthritis or psoriatic arthritis and joint disease responding to anti-TNF therapy has developed ocular inflammation while on an anti-TNF regimen (23). Since the eye is an extension of the brain, reports of TNF inhibition exacerbating or triggering demyelinating disease (24) are especially concerning to ophthalmologists. Certain subtypes of uveitis may occur in the association with neurological disease. For example, a form of uveitis known as pars plantis is associated with multiple sclerosis. Furthermore the effect of TNF inhibition on glaucoma or optic nerve health remains to be evaluated comprehensively. Thus TNF inhibition is a potentially exciting modality of therapy for the small subset of patients with HLA B27-associated uveitis who are especially refractive to other treatment, but its niche in the therapeutic armamentarium is far from established at the time of this writing.

At the time of this writing, two TNF inhibitors, etanercept and infliximab, are commercially available in the United States. No study has directly compared the efficacy of these two inhibitors for any disease to date. However, infliximab is approved for at least one indication, Crohn's colitis, while etanercept has not gained approval or shown efficacy for this indication (25). Infliximab may exert a greater effect on cells that synthesize TNF. The relative efficacy of these two inhibitors in the treatment of uveitis remains to be determined.

Additional approaches

Other innovative therapies are being tested for uveitis. A prospective trial including 10 patients with posterior uveitis assessed the efficacy of an antibody to the interleukin-2 receptor (26). Eighty percent of patients in this study were able to reduce other immunosuppressive drugs with the use of this medication. A second small study suggested that antibodies directed against the pan-lymphocyte antigen, CD 52, may also have beneficial effects in patients with recalcitrant uveitis (27). Potentially intraocular inflammation can be treated with the local administration of medication. As noted above, local delivery of corticosteroids is currently in clinical trial. There is certainly potential to deliver TNF inhibitors locally within the eye, possibly in combination with inhibitors of interleukin 1.

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