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REVIEW

Immunosuppressive Treatment of Non-infectious Uveitis: History and Current Choices

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Abstract Non-infectious uveitis is one of the leading causes of preventable blindness worldwide. Long-term immunosuppressive treatment is generally required to achieve durable control of inflammation in posterior and panuveitis. Although systemic corticosteroids have been the gold standard of immunosuppressive treatment for uveitis since first introduced in 1950s, its side effects of long-term use often warrant an adjuvant treatment to reduce the dosage/duration of corticosteroids needed to maintain disease control. Conventional immunosuppressive drugs, classified into alkylating agent, antimetabolites and T cell inhibitors, have been widely used as corticosteroid-sparing agents, each with characteristic safety/tolerance profiles on different uveitis entities. Recently, biologic agents, which target specific molecules in immunopathogenesis of uveitis, have gained great interest as alternative treatments for refractory uveitis based on their favorable safety and effectiveness in a variety of uveitis entities. However, lack of large randomized controlled clinical trials, concerns about efficacy and safety of long-term usage, and economic burden are limiting the use of biologics in non-infectious uveitis. Local administration of immunosuppressive drugs (from corticosteroids to biologics) through intraocular drug delivery systems represent another direction for drug development and is now under intense investigation, but more evidences are needed to support their use as regular alternative treatments for uveitis. With the numerous choices belonging to different treatment modalities (conventional immunosuppressive agents, biologics and local drug delivery systems) on hand, the practice patterns have been reported to vary greatly from center to center. Factors influence uveitis specialists' choices of immunosuppressive agents may be complex and may include personal familiarity, treatment availability, safety/tolerability, effectiveness, patient compliance, cost concerns and suggestions from related specialists such as rheumatologists and pediatricians. The focus of this review is to provide an overview of each treatment modality on safety/tolerability and effectiveness, which are believed to be the two most important factors affecting treatment decision making.

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INTRODUCTION of corticosteroids in early 1950s opened a new era of anti-inflammatory treatment for ocular inflammatory diseases.[1-2] Despite the favorable therapeutic results in early observations, corticosteroids were soon reported to induce increased intraocular pressure[3-4] and posterior subcapsular cataract,[5] and were later found to cause unintended side effect in any structure of the eye.[6] Systemic toxicities secondary to long-term immunosuppressive treatment with corticosteroid are even more formidable and may result in morbidities in multiple organ systems or even death.[7-8] Immunosuppressive agents, classified into alkylating agents, including cyclophosphamide (CTX) and chlorambucil (CHB); antimetabolites, including azathioprine (AZA), methotrexate (MTX) and mycophenolate mofetil (MMF); and T cell inhibitors, including cyclosporine A (CsA) and tacrolimus (FK506), [9-10] were later introduced into treatment of ocular inflammation, with the earliest reports date back to late 1960s.[9, 11] Initially, concerns about the low therapeutic index of immunosuppressive agents limited their use to the treatment of corticosteroid resistant or intolerant, or sight-threatening cases.[11-12] Equipped with improved knowledge on drug pharmacological mechanism and drug toxicity, as well as increased clinical experiences, immunosuppressive agents gradually gained recognition as the treatment of choice for a number of ocular inflammatory diseases.[12] When administered at properly adjusted doses and by experienced physicians with close monitoring, immunosuppressive agents appeared to produce fewer adverse effects than chronic use of systemic corticosteroids.[12] They now have been widely used as complementary treatments in settings when (1) corticosteroids are insufficient to control the disease (recalcitrant), (2) long-term immunosuppression is needed to achieve disease control but expected corticosteroid toxicity is high at dose required (greater than 10 mg/d), which is often the case for treatment of uveitis, or (3) contradictions to high-dose (or long-term use) of corticosteroids are present.[9, 13-14] Selected diseases, such as Behcet's disease with posterior segment involvement and mucous membrane pemphigoid with ocular involvement, are candidates for immunosuppressive drug therapy from the onset because of their poor natural history.[9]

Despite the above mentioned advances, challenges remain at least in the following aspects for conventional cytotoxic immunosuppressive agents. Firstly, some diseases such as birdshot chorioretinopathy, juvenile idiopathic arthritis-uveitis and serpiginous choroiditis respond poorly to these medications, even with combination therapy at maximum therapeutic doses.[10] Secondary, even in most experienced tertiary centers, corticosteroid-sparing success (sustained control of inflammation while tapering prednisone to 10 mg or less among those not meeting success criteria initially) was gained by 60%-70% of patients with ocular inflammation for CTX[15] and AZA,[16] and by 36% for CsA,[17] in a period of 12 months, suggesting the limited role of "corticosteroid sparing" for those most commonly used immunosuppressive drugs with regard to the whole patient population. Thirdly, macular edema, which can cause profound visual loss and is one of the major causes of legal blindness in patients with uveitis, may become refractory to all currently available immunosuppressive drugs.[18]

Biologics act as selective suppressors of immune responses by targeting specific molecules in effector mechanisms of autoimmunity and inflammation; they can be recombinant antibodies to, or antagonists of, particular cytokines or cell-surface receptors, and recombinant cytokines [such as interferons (IFNs)].[19] Since first reported in 1994,[20] a number of biologics have been investigated for their role in management of ocular inflammation, with majority of the publications related to uveitis.[21] Reported biologic agents for non-infectious uveitis include tumor necrosis factor (TNF) inhibitors (infliximab, etanercept and adalimumab), anti-interleukine (IL)-1β monoclonal antibody (gevokizumab), anti-IL-2R monoclonal antibody (daclizumab), anti-IL-6R monoclonal antibody (tocilizumab), anti-IL-17A antibody (secukinumab), anti-CD20 monoclonal antibody (rituximab), anti-CD52 monoclonal antibody (alemtuzumab), fusion protein of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) (abatacept) and IFNs (IFN-α and IFN β).[19,22] Biologics provide new hopes for the treatment of refractory uveitis and currently available evidences have shown a favorable safety and efficacy profile for most of the biologic agents.[22-23] A continuous emerging of new biologic agents into the armory of uveitis specialists for combating ocular inflammation, mainly from that of rheumatology colleagues, is expected. However, lack of large randomized controlled clinical trials, concerns about efficacy and safety of long-term usage, and economic burden of the patients and the society, which is perhaps the biggest limiting factor even in developed countries,[23-24] have limited the usage of biologics in non-infectious uveitis.

As systemic side effects are one of the major concerns for immunosuppressive treatment in uveitis, local administration of corticosteroids, conventional immunosuppressive drugs, as well as biologics represent another direction of drug development for uveitis.[25] Routes of local ocular drug administration used in uveitis include topical application, sub-conjunctival or sub-tenon injection, periocular (including