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Comparative efficacy of steroid-sparing therapies for non-infectious uveitis

Jared E. Knickelbein, **Meredith Kim**, **Elvira Argon**, **Robert B. Nussenblatt**^, and **Nida H Sen**

National Eye Institute, National Institutes of Health, Bethesda, MD

Abstract

Introduction: Non-infectious uveitis encompasses a group of inflammatory eye diseases that can cause irreversible vision loss if left untreated or undertreated. In cases requiring stemic treatment, a step-wise treatment approach is often employed starting with corticosteroids for severe active disease, followed by initiation of steroid-sparing therapies to maintain inflammatory control and avoid the abundant complications of long-term corticosteroid use.

Areas covered: We review the current high-quality evidence comparing the efficacy of various systemic steroid-sparing agents in the treatment of non-infectious uveitis. For studies to be included, they had to have a prospective, randomized, comparative design or a retrospective design including at least 100 patients.

Expert commentary: Given the rarity of uveitis and the heterogeneity of uveitic diseases, there are few randomized controlled studies that directly compare the relative efficacy of the various steroid-sparing immunosuppressive agents. Therefore, current treatment strategies are based mainly on data from observational series.

Keywords

Non-infectious uveitis; immunosuppression; methotrexate; mycophenolate; mofetil; azathioprine; cyclosporine; infliximab; adalimumab

1. Introduction

Uveitis is a group of heterogeneous inflammatory eye diseases encompassing several infectious and non-infectious pathologies that may result in severe vision loss [1]. While infectious etiologies require antimicrobial treatment, most non-infectious uveitides are thought to be autoimmune in nature, and therefore are treated with immunosuppression. Corticosteroids were first utilized in the treatment of non-infectious uveitis in the 1950s [2] and remain a mainstay of treatment, particularly in the rapid control of acute intraocular

Corresponding author: H. Nida Sen, MD, MHS, Laboratory of Immunology, National Eye Institute, NIH, 10 Center Dr., 10/10N109, Bethesda, MD 20892, senh@nei.nih.gov, Phone: 301-435-5139.

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Declaration of interest

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inflammation [3]. Due to the numerous side effects associated with long-term use of corticosteroids, Nussenblatt and colleagues conducted a randomized double-masked trial comparing cyclosporine to prednisolone in the treatment of non-infectious uveitis and demonstrated that cyclosporine offers an effective alternative [4]. Steroid-sparing agents, such as cyclosporine A, methotrexate, and mycophenolate mofetil, have since assumed an important role in the treatment of non-infectious uveitis [3]. However. clinical trials directly comparing the efficacy of various agents against one another are rare, and information regarding their use in uveitis is usually limited to small non-controlled series and case reports. Furthermore, the ability to synthesize evidence gathered from such studies is limited by the heterogeneous nature of uveitis [5]. Although all forms of uveitis are characterized by intraocular inflammation, they may or may not be associated with systemic disease, they may be caused by different immunopathological mechanisms, and they may respond differently to the same therapeutic approach. In addition, a lack of consensus over which outcome measures to use in clinical studies also limits the ability to draw comparisons across studies and to pool data for meta-analysis.

1.1 Purpose and methods

The purpose of this review is to identify the current high-quality evidence that demonstrates the relative efficacy of steroid-sparing treatments available for non-infectious uveitis. Each section will focus on a different method of comparison, including by anatomic location of inflammation, within pharmacologic class of therapy, and across pharmacologic classes. A Pubmed search of the English language literature was formed using the search terms “uveitis” and “clinical trial.” References of identified orts were also searched for relevant studies. For studies to be included, they had to have a prospective, randomized, comparative design or a retrospective design including a large number of patients (arbitrarily set at 100 patients).

2. Comparative efficacy of therapies for non-infectious uveitis by anatomic location

The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) cohort study, which reviewed the records of patients seen at four tertiary uveitis clinics in the United State from 1979 through 2007, is the largest retrospective study in uveitis to date [6]. The primary goal of the SITE study was to investigate the long-term risks of malignancy and mortality in patients with inflammatory eye diseases receiving immunosuppression. Information was also gathered pertaining to the effectiveness of various steroid-sparing immunosuppressive agents, and these results are discussed below. A summary of the findings is provided in table 1.

The effectiveness of methotrexate was analyzed in 384 patients with inflammatory eye diseases identified through the SITE study and was found to be moderately effective in controlling ocular inflammatory disease as a single agent [7]. Specifically, corticosteroid-sparing success, defined as sustained suppression of ocular inflammation with prednisone dose of ≤10mg/day, was attained by 6 months in 46.1%, 41.3% and 20.7% of patients with anterior, intermediate, and posterior or panuveitis, respectively. By 12 months, 62.6%,

68.8%, and 39.1% had achieved corticosteroidsparing success for these anatomic locations, respectively. Although these data suggest that methotrexate is particularly effective in the setting of anterior and intermediate uveitis, the authors cautioned that the difference could be due to varying rates of spontaneous remission of disease associated with the location of inflammation. Furthermore, variation in the dose of methotrexate would be expected to affect efficacy.

Mycophenolate mofetil as a single agent was studied in 236 patients enrolled in the SITE study [8]. Corticosteroid-sparing success was achieved by 6 months in 47.2%, 39.0%, and 41.2% of patients with anterior, intermediate, and posterior or panuveitis respectively. By 12 months, the steroid-sparing success rate increased to 53.1%, 49.2% and 60.3% for these anatomic locations, respectively. Although there was no statistical difference in the rate of response based on anatomic location of inflammation,cases of anterior and posterior or panuveitis seemed to respond more effectively to mycophenolate mofetil.

In a study of 373 SITE cohort patients treated with cyclosporine A as a single non-corticosteroid immunosuppressive agent, corticosteroid-sparing success was achieved by 6 months in 28.5%, 24.1%, and 16.2% of patients with anterior, intermediate, and posterior or panuveitis, respectively [9]. By 12 months, the steroidsparing success rate increased to 42.4%, 38.0%, and 32.3%. The rates of response by locations of inflammation were not statistically different. Patient age >55 years was associated with >3-fold risk of discontinuation due to toxicity.

Azathioprine as a single agent was studied in a cohort of 145 patients from the SITE study [10]. By 6 months, 16.6%, 47.0%, and 36.3% of patients with anterior, intermediate, and posterior or panuveitis respectively had achieved steroid-sparing success, which increased to 24.9%, 68.2%, and 44.0% by 12 months. Azathioprine was especially effective in cases of intermediate uveitis.

Based on these analyses from the SITE study, steroid-sparing success was attained most frequently in anterior uveitis with methotrexate and mycophenolate mofetil, in intermediate uveitis with methotrexate and azathioprine, and in posterior or panuveitis with mycophenolate mofetil (Table 1). In order to compare the efficacy of the various steroid-sparing immunosuppressive agents, we estimated the frequency counts in the SITE studies based on the sample number and percentages shown in table 1. In general, there were statistically significant differences between the immunosuppressive medications in attaining complete control at 6 and 12 months and achieving inactive or slightly active levels of inflammation at 6 and 12 months in anterior, intermediate, and posterior or panuveitis. In the SITE reports, inflammatory status was categorized as “active,” “slightly active,” or “inactive” based on the clinician’s notations at the time of each visit [7–10]. “Slightly active” inflammation was defined as “activity that is minimally present, described also by terms such as mild, few, or trace cells, and so on,” whereas inflammation was scored as inactive when described by terms such as “quiet,” “quiescent,” “no cells,” and “no active inflammation.”

When assessing steroid-sparing success at 6 and 12 months in patients with anterior uveitis, there were statistically significant differences between the immunosuppressive therapies for the proportion of patients using prednisone <10mg/day and ≤5mg/day. However, there was no difference between the medications for the proportions of patients able to taper off of prednisone. For patients with intermediate uveitis, there was no difference between the immunosuppressive therapies in the proportion of patients able to taper prednisone to ≤10mg/day, to ≤5mg/day, or to taper off of prednisone at six months; however, there were statistically significant differences between the therapies in the proportion of patients able to taper prednisone to ≤10mg/day and ≤5mg/day at 12 months. In patients with posterior or panuveitis, the proportion of patients able to taper prednisone to ≤10mg/day was statistically different between the medications at 6 and 12 months. The differences in the proportions of patients able to taper prednisone to ≤5mg/day was not significant at 6 months but was statistically significant at 12 months. The proportion of patients able to taper off of prednisone was significantly different at 6 months; however, this difference did not persist at 12 month.

3. Comparative efficacy of non-infectious uveitis therapies within pharmacologic classes

3.1 Antimetabolites

Methotrexate, azathioprine, and mycophenolate mofetil are antimetabolites, a class of corticosteroid-sparing agents that decrease inflammation by antagonizing or competing with a metabolite needed for nucleotide synthesis, thereby inhibiting the proliferation of rapidly dividing T and B lymphocytes [11]. A retrospective cohort study of 257 patients with inflammatory eye disease treated with an antimetabolite compared the efficacy of each medication by evaluating the ability to control inflammation and to taper prednisone to ≤ 10mg/day [12]. The median starting dose was 15mg/week for methotrexate (range 5–40mg/week), 2000mg/day for mycophenolate mofetil (range 1000–3000mg/day), and 150mg/day for azathioprine (range 50–300mg/day). Patients with posterior or panuveitis had a higher rate of corticosteroid-sparing success with mycophenolate mofetil compared to azathioprine and methotrexate. Mycophenolate mofetil was also found to have an improved side effect profile compared to azathioprine and a more rapid time to control of inflammation compared to methotrexate. The dose of antimetabolite undoubtedly contributes to treatment success. As mentioned above, antimetabolite doses were variable for all groups in this study. Therefore, care must be taken when drawing conclusions from the overall group data.

More recently, Rathinam and colleagues conducted a randomized clinical trial comparing methotrexate to mycophenolate mofetil in a cohort of 80 patients with non-infectious intermediate uveitis, posterior uveitis, or panuveitis treated at two centers in India [13]. Patients were randomized to receive either 25mg methotrexate weekly (n=41) or 1000mg mycophenolate mofetil twice daily (n=39) and were monitored for 6 months. While not statistically significant, 69% of patients treated with methotrexate and 47% of patients treated with mycophenolate mofetil achieved treatment success, defined as i) clinical scores for anterior chamber cells, vitreous cells, and vitreous haze of ≤0.5+ with no active retinal or choroidal lesions in both eyes, ii) ≤10mg of prednisone and ≤2 drops of prednisolone acetate

1% per day, and iii) no determination of treatment failure due to intolerability or safety (p=0.09). No differences were detected in time to corticosteroidsparing control of inflammation (p=0.44), best-corrected visual acuity (p=0.68), or resolution of macular edema (p=0.31) between the treatment groups.

3.2 T cell Inhibitors

Cyclosporine and tacrolimus decrease inflammation by interfering with signaling pathways involved in the function and proliferation of T cells, which are thought to play central role in the pathogenesis of certain non-infectious uveitis conditions, such as birdshot chorioretinopathy and VKH disease [14]. Although their mechanism of action is similar, tacrolimus has been associated with fewer adverse effects compared to cyclosporine A [15].

Murphy and colleagues conducted a randomized clinical trial comparing tacrolimus to cyclosporine in the treatment of 37 patients with intermediate or posterior uveitis [16]. Clinical efficacy was defined by an improvement in best-corrected logMAR visual acuity of at least 2 lines in either eye or a decrease in the vitreous haze score to 0 within three months of treatment initiation. Treatment success was achieved in 13 patients (68%) on tacrolimus and 12 patients (67%) on cyclosporine. Although tacrolimus and cyclosporine were found to be similarly efficacious in the treatment of intermediate and posterior uveitis, tacrolimus was associated with a more favorable safety profile.

Lee and colleagues conducted a randomized trial of tacrolimus versus tacrolimus and prednisone for the maintenance of disease remission in noninfectious uveitis [17]. Fifty-eight patients with sight-threatening posterior segment intraocular inflammation requiring second-line immunosuppression were treated with tacrolimus in conjunction with 10mg or more of prednisone daily. Tacrolimus was titrated to achieve a trough level of 8–12ng/mL while the prednisone was reduced to 10mg daily. Of the 35 patients who were able to sustain disease remission while reducing prednisone to 10mg daily, 16 were assigned to stop the prednisone completely, while 19 were instructed to continue the prednisone at 7.5 – 10mg per day for 9 months. There was no significant difference in the primary outcome measures of logMAR visual acuity and rate of patient withdrawal resulting from treatment inefficiency or intolerance, suggesting that corticosteroids can be withdrawn in tacrolimus-treated patients who are able to maintain control of posterior segment intraocular inflammation with 10mg prednisone daily.

3.3 Biologic Agents

The anti-tumor necrosis factor (TNF) antibodies infliximab and adalimumab, are biologic agents that decrease inflammation by blocking TNF-α, a potent pro-inflammatory cytokine released by monocytes, macrophages, and certain T cells in many immune responses [18,19]. A multicenter retrospective observational study of 160 patients with refractory non-infectious uveitis compared the efficacy of treatment with either infliximab or adalimumab [20]. The main etiologies of uveitis were Behçet’s diseas (36%), juvenile idiopathic arthritis (22%), spondyloarthoropathy (10%), and sarcoidosis (6%). Patients received either 5mg/kg of infliximab at weeks 0, 2, 6 and then every 5–6 weeks or adalimumab 40mg every two weeks. Both agents were found to be highly effective in controlling refractory uveitis. No

statistically significant difference was observed in the rate of complete response, defined as a decrease in the level of intraocular inflammation to grade 0, regression of retinal vasculitis, complete resolution of macular edema, and a corticosteroid dosage of ≤10mg/day at 6 months, between infliximab and adalimumab. Uveitis associated with Behçet's disease was highly associated with a complete response to anti-TNF therapy in this retrospective observation study.

The VISUAL I trial was a phase 3 multicenter, double-masked, randomized, placebo-controlled trial that investigated adalimumab as steroid-sparing therapy for noninfectious uveitis [21]. Participants had active intermediate, posterior, or panuveitis despite two or more weeks of systemic prednisone treatment (10–60mg per day). 217 patients were randomly assigned to receive either placebo (n=l10) or adalimumab n=107) at a loading dose of 80mg followed by biweekly dosing of 40mg. All participants received high-dose prednisone (60mg per day) followed by prednisone taper taper over 15 weeks. The primary outcome was the time to treatment failure, determined by assessment of new inflammatory lesions, best corrected visual acuity, anterior chamber cell grade, and vitreous haze grade, occurring at or after week 6. Treatment failure was observed significantly less in the adalimumab group compared to controls (hazard ratio, 0.50; 95% confidence interval, 0.36 to 0.70; $P<0.001$). Furthermore, several secondary outcomes, including change in anterior chamber cell grade, change in vitreous haze grade, and change in best-corrected visual acuity, were significantly better in the participants treated with adalimumab compared to controls.

VISUAL II was a multicenter, double-masked, randomized, placebo-controlled trial investigating adalimumab for the prevention of uveitic flares [22]. 229 patients with inactive non-infectious intermediate, posterior, or panuveitis controlled by 10–35mg of prednisone daily were randomly assigned to receive either placebo (n=114) or adalimumab (n=115) at a loading dose of 80mg followed by biweekly dosing of 40mg. All participating underwent a mandatory prednisone taper from week 2. The primary outcome measure was time to treatment failure, defined by new active inflammatory chorioretinal or inflammatory retinal vascular lesions, anterior chamber cell grade, vitreous haze grade and visual acuity. Treatment failure occurred in 55% of patients in the placebo group compared with 39% of patients in the adalimumab group. Time to treatment failure was significantly improved in the adalimumab group compared with the placebo group, and the rate of adverse events was similar between the two groups. The results of the VISUAL I and II trials have led to United States FDA approval of adalimumab for the treatment of non-infectious intermediate, posterior, and panuveitis.

4. Comparative efficacy of treatments across pharmacologic classes

There are relatively few studies comparing the efficacy of treatments for uveitis across different pharmacologic classes. In the past decade, a small number of studies have compared outcomes between the use of T cell inhibitors and antimetabolites. A prospective, randomized study examined the use of cyclosporine and azathioprine in 21 patients with VKH disease [23]. Patients were treated with either 3mg/kg/day of azathioprine or 3–5mg/kg/day of cyclosporine. Both groups were also simultaneously treated with prednisone,

which was tapered to 5–10mg/day over 3 months if inflammation decreased. At 54 weeks of treatment, patients were evaluated for visual acuity, ocular inflammation, and steroid-sparing effect. While both regimens were effective in reducing intraocular inflammation, patients treated with cyclosporine required significantly lower doses of prednisone, indicating improved steroid-sparing efficacy with cyclosporine compared to azathioprine in the treatment of VKH disease.

Teoh and colleagues conducted a retrospective cohort study of 100 patients with non-infectious uveitis treated with mycophenolate mofetil at a single academic center between 2000 and 2006 [24]. Results were compared to another Standardization of Uveitis Nomenclature (SUN)-compliant report from the same group describing the longterm efficacy of tacrolimus in the treatment of non-infectious uveitis [25]. Steroid-sparing effect was equivalent for both mycophenolate mofetil and tacrolimus, but patients taking mycophenolate mofetil required alternative immunosuppression less often. On the other hand, the rate of discontinuation of prednisone with tacrolimus was greater than that with mycophenolate mofetil. There was no difference in the rate of discontinuation due to intolerance.

A recent randomized trial compared the efficacy of interferon (IFN)-beta with methotrexate in the treatment of 19 patients with intermediate uveitis and associated macular edema [26]. At 3 months, patients treated with IFN-beta showed a mean improvement in logMAR visual acuity of 0.31 versus 0.09 in the methotrexate-treated group. All patients in the IFN-beta group also demonstrated improvement in macular edema, with mean decrease in central foveal thickness of 206μm, while patients treated with methotrexate experienced a mean increase of 47μm. Given the superiority of IFN-beta over methotrexate in the treatment of uveitis and associated macular edema, the trial was discontinued prematurely for ethical concerns.

5. Expert commentary

The treatment of non-infectious uveitis typically involves a stepwise approach, with corticosteroids playing a crucial role in the initial rapid control of acute inflammation [27]. Given the many side effects associated with the long-term use of systemic corticosteroids, a variety of traditional steroid-sparing agents, such as methotrexate, mycophenolate mofetil, and cyclosporine A, may be employed to optimize control and minimize recurrence of ocular inflammation, with the addition of biologic agents in particularly severe or refractory cases. Selection of a specific treatment regimen is dependent on a variety of factors, including anatomic location of inflammation and coexisting medical conditions. Ideally, these decisions are driven by data from highquality, randomized, clinical trials. Given the rarity of uveitis and the heterogeneity of uveitic diseases, there are few randomized controlled studies that directly compare the relative efficacy of the various steroid-sparing immunosuppressive agents. Therefore, current treatment strategies are based mainly on data from observational series.

Large retrospective cohort studies have suggested increased efficacy for mycophenolate mofetil compared to other antimetabolites in treating posterior uveitis or panuveitis

[7,9,10,12]. However, a recent randomized clinical trial showed that the efficacy of mycophenolate mofetil and methotrexate in treating intermediate uveitis, posterior uveitis, or panuveitis was not statistically different and actually favored methotrexate by 22% [13]. These findings exemplify the sometimes disparate results from retrospective observational studies versus randomized trials.

The SITE study group performed large retrospective cohort analyses of several immunosuppressive medications, including methotrexate, mycophenolate mofetil, azathioprine, and cyclosporine A, in patients with inflammatory eye disease[7–10] Based on the SUN criteria for predominant location of intraocular inflammation, efficacy results were presented for anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis. As discussed above, different medications appeared to be more effective for uveitis depending on the predominant location of inflammation. However, as these were separate cohorts within an index retrospective study, the efficacy of different medications was not directly compared statistically. Here, we presented statistical analyses (comparison of proportions) comparing the efficacy of the immunosuppressive agents analyzed in SITE. Overall, there were statistically significant differences between the medications in the proportion of patients who attained complete control as well as those who were inactive or slightly active at 6 and 12 months. In terms of steroid sparing success, there were also statistically significant differences between the steroid-sparing medications in the proportion of participants on prednisone ≤5–10mg/day but not in the proportion of patients completely off of prednisone. This may suggest differences in synergy between the various steroid-sparing agents when used in combination with systemic corticosteroids. However, the proportion of patients completely off prednisone was very low in all groups making statistical analysis less reliable.

The heterogeneity of uveitic diseases poses difficulty in interpreting these results for specific uveitis entities. For example, birdshot chorioretinopathy and serpiginous choroiditis are both considered posterior uveitis; however, the examination and imaging findings, and possibly the immunopathology, are markedly different between these two entities. Alternatively, intermediate uveitis is relatively uniform in its presentation allowing a more direct comparison of therapeutic options as exemplified by the randomized clinical trial showing superior efficacy of INF-beta (44μg subcutaneously three times per week) over methotrexate (20mg subcutaneously once weekly) in improving visual acuity and reducing macular edema [26].

The cellular and molecular pathogenesis of uveitic conditions remains incompletely understood. The precise immunopathology likely differs between uveitic entities, and this may have therapeutic implications. For instance, VKH disease is proposed to have a T cell-mediated pathology [28], theoretically making T cell inhibitors an ideal therapeutic option. Indeed, a small randomized comparative trial showed higher steroid-sparing efficacy with the T cell inhibitor cyclosporine compared to the antimetabolite azathioprine in the treatment of VKH disease [23].

Biologic agents that target particular inflammatory molecules are increasingly used to treat non-infectious uveitis, with the anti-TNF agents, infliximab and adalimumab, being most

common [29]. Infliximab is a chimeric monoclonal antibody against TNF-α composed of murine variable regions and human constant domains, while adalimumab is a fully humanized monoclonal antibody against TNF-α. Other major differences between infliximab and adalimumab include dosing schedules and the routes of administration (infliximab is given by intravenous infusion, while adalimumab is a self-administered subcutaneous injection). Low-dose methotrexate may be administered with both infliximab and adalimumab to prevent antibody production against the anti-TNF agent. Data directly comparing the use of infliximab and adalimumab is sparse, but based on one large retrospective study, efficacy appears to be similar between the two anti-TNF agents [20]. Furthermore, it is important to note that while anti-TNF agents have been quite successful in the treatment of uveitis, and adalimumab has recently been approved by the FDA for the treatment of uveitis, the failure rates in the VISUAL I and II trials at 12 months were approximately 60% and 40%, respectively [21,22].

6. Five-year view

Performing large, randomized, clinical trials in the field of uveitis is difficult given the relative rarity of the disease and often requires a multicenter approach. A prime example of the effectiveness of a multicenter approach is the Multicenter Uveitis Steroid Treatment (MUST) trial [30,31]. In addition, a large degree of heterogeneity exists between uveitic entities making clinical trial outcomes difficult to define. Using vitreous haze score as an outcome measure is reasonable in uveitis conditions, such as intermediate uveitis or Behçet's disease-associated panuveitis, in which vitreous inflammation is common. However, other uveitis entities, such as serpiginous choroiditis, rarely present with vitreous haze, making this outcome measure impractical. These limitations will have to be addressed to design and conduct meaningful clinical trials investigating treatment regimens in patients with non-infectious uveitis. For instance, a composite disease severity score, akin to those proposed for patients with systemic lupus erythematosus [32], that encompasses the main clinical features of the different uveitic conditions may be more appropriate for uveitis clinical trials. As a first step, a meeting of uveitis specialists, industry partners, and representatives from the United States Food Drug Administration was recently held at the National Eye Institute to begin discussions on how to overcome these hurdles [33]. Hopefully, these collaborative efforts will lead to adequate and well-controlled clinical trials providing further guidance on the best therapies, and possibly FDA-approved treatment options, for patients with non-infectious uveitis.

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8. References

1. Nussenblatt RB, Whitcup SM. Uveitis: Fundamentals and clinical practice(Mosby, Philadelphia, Pa, 2010).
2. Woods AC. Clinical and experimental observation on the use of ACTH and cortisone in ocular inflammatory disease. Am J Ophthalmol, 33(9), 1325–1349 (1950). [PubMed: 14771206]

3. Jabs DA, Rosenbaum JT, Foster CS et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol, 130(4), 492–513 (2000). [PubMed: 11024423]
4. Nussenblatt RB, Palestine AG, Chan CC, Stevens G, Jr, Mellow SD, Green SB. Randomized, double-masked study of cyclosporine compared to prednisolone in the treatment of endogenous uveitis. Am J Ophthalmol, 112(2), 138–146 (1991). [PubMed: 1867297]
5. Denniston AK, Holland GN, Kidess A et al. Heterogeneity of primary outcome measures used in clinical trials of treatments for intermediate, posterior panuveitis. Orphanet journal of rare diseases, 10, 97 (2015). [PubMed: 26286265]
6. Kempen JH, Daniel E, Gangaputra S et al. Methods for identifying long-term adverse effects of treatment in patients with eye diseases: the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study. Ophthalmic Epidemiol, 15(1), 47–55 (2008). [PubMed: 18300089]
7. Gangaputra S, Newcomb CW, Liesegang TL et al. Methotrexate for ocular inflammatory diseases. Ophthalmology, 116(11), 2188–2198 e2181 (2009). [PubMed: 19748676]
8. Daniel E, Thorne JE, Newcomb CW et al. Mycophenolate mofetil for ocular inflammation. Am J Ophthalmol, 149(3), 423–432 e421–422 (2010). [PubMed: 20042178]
9. Kacmaz RO, Kempen JH, Newcomb C et al. Cyclosporine for ocular inflammatory diseases. Ophthalmology, 117(3), 576–584 (2010). [PubMed: 20031223]
10. Pasadhika S, Kempen JH, Newcomb CW et al. Azathioprine for ocular inflammatory diseases. Am J Ophthalmol, 148(4), 500–509 e502 (2009). [PubMed: 19570522]
11. Kim EC, Foster CS. Immunomodulatory therapy for the treatment of ocular inflammatory disease: evidence-based medicine recommendations for use. Int Ophthalmol Clin, 46(2), 141–164 (2006).
12. Galor A, Jabs DA, Leder HA et al. Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. Ophthalmology, 115(10), 1826–1832 (2008). [PubMed: 18579209]
13. Rathinam SR, Babu M, Thundikandy R et al. A randomized clinical trial comparing methotrexate and mycophenolate mofetil for noninfectious uveitis. Ophthalmology, 121(10), 1863–1870 (2014). [PubMed: 24917273]
14. Kim JS, Knickelbein JE, Nussenblatt RB, Sen HN. Clinical trials in noninfectious uveitis. Int Ophthalmol Clin, 55(3), 79–110 (2015). [PubMed: 26035763]
15. Barbarino JM, Staatz CE, Venkataramanan R, Klein TE, Altman RB. PharmGKB summary: cyclosporine and tacrolimus pathways. Pharmacogenet Genomics, 23(10), 563–585 (2013). [PubMed: 23922006]
16. Murphy CC, Greiner K, Plskova J et al. Cyclosporine vs tacrolimus therapy for posterior and intermediate uveitis. Arch Ophthalmol, 123(5), 634–641 (2005). [PubMed: 15883282]
17. Lee RW, Greenwood R, Taylor H et al. A randomized trial of tacrolimus versus tacrolimus and prednisone for the maintenance of disease remission in noninfectious uveitis. Ophthalmology, 119(6), 1223–1230 (2012). [PubMed: 22381809]
18. Jared Knickelbein LK, Jesia Hasa, Padmini Kaushal, Sen H Nida and Robert Nussenblatt. Therapeutic options for the treatment of non-infectious uveitis. Expert Rev. Ophthalmol, Early Online, 1–15 (2015) (2015).
19. Sebbag M, Parry SL, Brennan FM, Feldmann M. Cytokine stimulation of T lymphocytes regulates their capacity to induce monocyte production of tumor necrosis factor-alpha, but not interleukin-10: possible relevance to pathophysiology of rheumatoid arthritis. Eur J Immunol, 27(3), 624–632 (1997). [PubMed: 9079801]
20. Vallet H, Seve P, Biard L et al. Infliximab versus adalimumab in the treatment of refractory inflammatory uveitis: Multicenter study from the french uveitis network. Arthritis Rheumatol, (2016).
21. Jaffe GJ, Dick AD, Brezin AP et al. Adalimumab in Patients with Active Noninfectious Uveitis. The New England journal of medicine, 375(10),932–943 (2016). [PubMed: 27602665]
22. Nguyen QD, Merrill PT, Jaffe GJ et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. Lancet, 388(10050), 1183–1192 (2016). [PubMed: 27542302]

23. Cuchacovich M, Solanes F, Diaz G et al. Comparison of the clinical efficacy of two different immunosuppressive regimens in patients with chronic vogt-koyanagi-harada disease. Ocul Immunol Inflamm, 18(3), 200–207 (2010). [PubMed: 20482399]
24. Teoh SC, Hogan AC, Dick AD, Lee RW. Mycophenolate mofetil for the treatment of uveitis. Am J Ophthalmol, 146(5), 752–760, 760 e751–753 (2008). [PubMed: 18455143]
25. Hogan AC, McAvoy CE, Dick AD, Lee RW. Long-term efficacy and tolerance of tacrolimus for the treatment of uveitis. Ophthalmology, 114(5), 1000–1006 (2007). [PubMed: 17467532]
26. Mackensen F, Jakob E, Springer C et al. Interferon versus methotrexate in intermediate uveitis with macular edema: results of a randomized controlled clinical trial. Am J Ophthalmol, 156(3), 478–486 e471 (2013). [PubMed: 23786783]
27. Foster CS, Kothari S, Anesi SD et al. The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. Surv Ophthalmol, 61(1), 1–17 (2016). [PubMed: 26164736]
28. Du L, Kijlstra A, Yang P. Vogt-Koyanagi-Harada disease: Novel insights into pathophysiology, diagnosis and treatment. Prog Retin Eye Res, 52, 84–111 (2016). [PubMed: 26875727]
29. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology, 121(3), 785–796 e783 (2014). [PubMed: 24359625]
30. Multicenter Uveitis Steroid Treatment Trial Research Kempene JH G, Altaweel MM, Holbrook JT, Jabs DA, Sugar EA. The multicenter uveitis steroid treatment trial: rationale, design, and baseline characteristics. Am J Ophthalmol, 149(4), 550–561 e510 (2010). [PubMed: 20097325]
31. Multicenter Uveitis Steroid Treatment Trial Research Kempen JH G, Altaweel MM et al. Benefits of Systemic Anti-inflammatory Therapy versus Fluocinolone Acetonide Intraocular Implant for Intermediate Uveitis, Posterior Uveitis, and Panuveitis: Fifty-four-Month Results of the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study. Ophthalmology, 122(10), 1967–1975 (2015). [PubMed: 26298715]
32. Mikdashi J, Nived O. Measuring disease activity in adults with systemic lupus erythematosus: the challenges of administrative burden and responsiveness to patient concerns in clinical research. Arthritis Res Ther, 17, 183 (2015). [PubMed: 26189728]
33. NEI/FDA Workshop on Clinical Trial Endpoints for Inflammatory Eye Diseases. Accessed May 25, 2016 https://arvo.box.Com/s/cormx606d6yv5njr82uwp8jdxf49vr8c.

7. Key issues

Non-infectious uveitis encompasses a group of inflammatory eye diseases that may require systemic immunosuppression to prevent and limit vision loss. Several steroidsparing immunosuppressive agents, including antimetabolites, T cell inhibitors, and anti-TNF agents, are used in the treatment of non-infectious uveitis. However, most of the data on these agents is from retrospective studies. Given the rarity of uveitis and heterogeneous manifestations of intraocular inflammation, and lack of good outcome measures, performing randomized clinical trials remains difficult. Nonetheless, well-conducted trials are emerging investigating the use of steroid-sparing immunosuppressive agents in patients with non-infectious uveitis. Despite recent advances, failure rates with individual biologic or nonbiologic immunosuppressives remain high. As outcome measures are refined to better assess the various disease entities encompassed in the large class of uveitic diseases, future clinical trials will be able to provide more valuable information for treating this potentially blinding group of diseases.

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Table 1.

Data from SITE studies on efficacy of steroid-sparing immunosuppressive agents in the treatment of non-infectious uveitis (adapted with permission from references 7–10).

	Azathioprine	MMF	MXT	CsA	Chi-Square[+]
Age (Median) [ranqe in years]	50.6 [9.2–86.4]	47.1 [8.1–84.2]	46.9 [0.4–93.5]	36.1 [5.5–81.5]	
Female (%)	67.6	63.6	72.9	62.7	0.0153
Caucasian (%)	76.6	66.9	73.2	73.7	0.157
# of patients (n)[*]	145	236	384	373	
Complete control at 6/12 months (%)					
- Total	40.8/62.2	53.1/73.1	49.4/66.0	33.4/51.9	<0.0001/<0.0001
-Anterior	23.7/34.6	55.2/72.4	55.6/67.2	30.4/54.3	<0.0001/<0.0001
- Intermediate	69.3/89.8	65.0/76.7	47.4/74.9	39.3/51.8	<0.0001/<0.0001
- Posterior/Pan	44.2/59.7	50.6/70.9	38.6/52.1	29.2/51.7	<0.0001/<0.0001
Inactive or slightly active at 6/12 months (%)					
- Total	56.8/72.7	77.5/91.2	62.8/74.3	60.8/76.4	<0.0001/<0.0001
-Anterior	28.2/42.6	84.9/100	69.7/71.6	52.8/85.8	<0.0001/<0.0001
- Intermediate	87.5/100	83.1/100	62.8/89.4	73.7/80.2	<0.0001/<0.0001
- Pan/Posterior	72.0/83.2	86.5/93.2	53.9/66.2	56.6/75.2	<0.0001/<0.0001
Steroid-sparing success at 6/12 months (%)					
Total					
- Prednisone	32.2/46.9	40.7/55.0	37.3/58.4	22.1/36.1	<0.0001/<0.0001
⩽10mg	20.6/40.6	27.3/43.7	32.6/52.9	18.1/30.0	<0.0001/<0.0001
- Prednisone ⩽5mg	05.2/09.5	04.4/12.1	05.1/18.8	03.6/08.2	0.629/0.0002
- Off prednisone					
Anterior (n)	21	48	126	75	
- Prednisone	16.6/24.9	47.2/53.1	46.1/62.6	28.5/42.4	0.0038/0.0017
⩽10mg	11.5/19.5	46.4/51.3	41.8/59.4	26.9/40.4	0.0041/0.0013

	Azathioprine	MMF	MXT	CsA	Chi-Square[+]
- Prednisone ⩽5mg	00.0/08.3	05.8/18.4	06.2/17.6	08.8/14.9	0.61[^]/0.756
- Off prednisone					
Intermediate (n)	18	28	38	99	
- Prednisone	47.0/68.2	39.0/49.2	41.3/68.8	24.1/38.0	0.0915/0.0060
⩽10mg	29.9/64.9	26.0/43.6	31.8/57.0	19.0/32.5	0.454/0.0068
- Prednisone ⩽5mg	00.0/00.0	00.0/13.8	07.4/15.0	03.7/09.2	0.443[^]/0.264[^]
- Off prednisone					
Posterior/Pan (n)	52	94	82	171	
- Prednisone	36.3/44.0	41.2/60.3	20.7/39.1	16.2/32.3	<0.0001/0.0001
⩽10mg	16.6/42.9	21.3/41.7	20.2/32.0	12.7/23.6	0.251/0.0064
- Prednisone ⩽5mg	07.1/09.9	02.6/09.1	03.0/11.9	00.7/03.9	0.0259[^]/0.105
- Off prednisone					

MMF, mycophenolate mofetil; MXT, methotrexate; CsA, cyclosporine A; D/c, discontinued; SE, side effects; GI, gastrointestinal; HTN, hypertension

[+] p values calculated by comparison of proportions unless noted otherwise.

[*] Total # of patients includes patients with scleritis, ocular cicatricial pemphigoid, and other ocular inflammatory diseases not otherwise included in this table.

[^] p value calculated by Fisher's exact test because of small sample size.