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# Guidance on Noncorticosteroid Systemic Immunomodulatory Therapy in Noninfectious Uveitis

## *Fundamentals Of Care for UveitiS (FOCUS) Initiative*

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***Topic:*** An international, expert-led consensus initiative to develop systematic, evidence-based recommendations for the treatment of noninfectious uveitis in the era of biologics.

***Clinical Relevance:*** The availability of biologic agents for the treatment of human eye disease has altered practice patterns for the management of noninfectious uveitis. Current guidelines are insufficient to assure optimal use of noncorticosteroid systemic immunomodulatory agents.

***Methods:*** An international expert steering committee comprising 9 uveitis specialists (including both ophthalmologists and rheumatologists) identified clinical questions and, together with 6 bibliographic fellows trained in uveitis, conducted a Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol systematic review of the literature (English language studies from January 1996 through June 2016; Medline [OVID], the Central Cochrane library, EMBASE, CINAHL, SCOPUS, BIOSIS, and Web of Science). Publications included randomized controlled trials, prospective and retrospective studies with sufficient follow-up, case series with 15 cases or more, peer-reviewed articles, and hand-searched conference abstracts from key conferences. The proposed statements were circulated among 130 international uveitis experts for review. A total of 44 globally representative group members met in late 2016 to refine these guidelines using a modified Delphi technique and assigned Oxford levels of evidence.

***Results:*** In total, 10 questions were addressed resulting in 21 evidence-based guidance statements covering the following topics: when to start noncorticosteroid immunomodulatory therapy, including both biologic and nonbiologic agents; what data to collect before treatment; when to modify or withdraw treatment; how to select agents based on individual efficacy and safety profiles; and evidence in specific uveitic conditions. Shared decision-making, communication among providers and safety monitoring also were addressed as part of the recommendations. Pharmacoeconomic considerations were not addressed.

***Conclusions:*** Consensus guidelines were developed based on published literature, expert opinion, and practical experience to bridge the gap between clinical needs and medical evidence to support the treatment of patients with noninfectious uveitis with noncorticosteroid immunomodulatory agents. *Ophthalmology 2018;125:757-773 © 2018 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

*Supplemental material available at www.aaojournal.org.*

Uveitis is one of the leading causes of vision loss, and patients are at a high risk of ocular complications, including glaucoma, macular edema, and cataract.[1–14] Recurring flares may lead to cumulative eye damage and increasing risk of impaired vision or blindness, with the associated patient, societal, and economic burdens.[1–14] Despite predictable and serious side effects associated with long-term use, often at high doses, oral corticosteroids remain a mainstay of treatment for noninfectious uveitis (NIU).[8,14–18] Local (periocular or intravitreal) corticosteroid injections may limit systemic effects; however, they are also associated with local adverse effects such as elevated intraocular pressure, glaucoma, and cataract.[7–9,12,13]

Consensus guidelines for systemic treatment of NIU were published last in 2000, reflected the opinions of only 12 United States physicians, and predated the use of biologic



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therapy.[16] More recent nonsystematic reviews related to efficacy of biologics and the care of patients receiving immunosuppressants deliver more contemporaneous guidance.[19,20] Although few treatments have been approved for the indication of uveitis treatment by governing bodies, treatment with biologic and other systemic noncorticosteroid immunomodulatory agents has become widespread in patients whose uveitis is not controlled with corticosteroids alone. Furthermore, the Multicenter Uveitis Steroid Treatment Trial 7-year follow-up study demonstrated that systemic therapy (corticosteroid-supplemented immunomodulatory therapy and biologics) improved visual outcomes, controlled inflammation, and reduced macular edema compared with an intravitreous fluocinolone acetonide implant in patients with intermediate uveitis, posterior uveitis, or panuveitis.[21] Therefore, new evidence-based guidelines are needed to facilitate a move toward optimized treatment by ophthalmologists and others in the care of patients with NIU.

Herein we report the outcomes of the Fundamentals of Care for UveitiS (FOCUS) global initiative organized to achieve consensus through evidence synthesis on optimal systemic treatment of patients with NIU. The primary output of this expert-led initiative was to disseminate clear, relevant, evidence-based, and practical information for systemic therapy for clinicians managing uveitis in daily practice. This work did not look to provide consensus-management algorithms, including the use of depot corticosteroids, nor were pharmacoeconomic issues addressed in the analysis. Three principal areas of clinical focus were considered to support understanding and to address clinical guidance and evidence gaps effectively: (1) *optimal timing for treatment escalation* in relation to cycles of treatment in-class before moving to a new treatment class, recognizing treatment success and failure, and identifying patients for step-up therapy; (2) *transitioning treatment to a noncorticosteroid immunomodulator or immunomodulatory agent, including biologic agents* in relation to what treatment to choose, which to exclude, and why; when to initiate this treatment; the appropriate dosing strategies; and how best to monitor against treatment goals (including measures of disease activity and treatment response and monitoring timeframes); and (3) *multidisciplinary team collaboration* in relation to management, treatment plans, and decisions and for patient safety and shared treatment goals across the multidisciplinary team.

## Methods

An international steering committee (ISC) comprising 9 international experts in uveitis, including 7 ophthalmologists and 2 rheumatologists, was convened by AbbVie, Inc (AbbVie Inc, North Chicago, IL) to define the clinical care gap and areas of clinical focus. In addition, 130 uveitis specialists, including thought-leading ophthalmologists and rheumatologists involved in local professional societies or guideline committees from 28 countries with a commitment to improving standards of patient care in their countries, were selected with guidance from the ISC through the network of AbbVie local affiliates to act as national faculties and to provide input at the local level. There was no AbbVie involvement in the methodology, data collection and analysis, or completion of this report.

In total, 57 draft clinical questions were developed by the ISC to align with each of the 3 identified areas of clinical focus. The national faculty members subsequently ranked these questions by clinical importance. Sixteen questions of highest importance were discussed by the ISC and were refined into 9 final questions. Six clinical uveitis fellows (E.C., N.H., S.B.-S., S.S., J.S., L.R.S.) were nominated by ISC members to conduct detailed literature searches and to assess the evidence relating to each question in concert with members of the ISC.

### Eligibility Criteria for Considering Studies for This Review

A transparent, rigorous, and clearly defined literature-search methodology was defined, building on the process first outlined by the Standardization of Uveitis Nomenclature Working Group,[1] using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol.[22]

### Search Methods for Identifying Studies

The literature search process to support the consensus statement development and agreement is shown in Appendix 1 (available at www.aaojournal.org), and additional methodologic details are provided in Appendix 2 (available at www.aaojournal.org). In brief, a systematic review of English-language publications from January 1996 through August 2016 was performed.

### Study Selection

Identified publications were reviewed further, and in some cases, older studies were included in the analysis if they contained data of significance. More recent publications are cited herein, but were excluded from consensus recommendations because they were not included in the summary of evidence reviewed before the consensus meeting in November 2016.

### Data Collection and Risk of Bias Assessment

The quality of evidence was defined using the Oxford Centre for Evidence-Based Medicine levels of evidence criteria grading.[23] Answers were developed based on the literature searches and were documented for each clinical question using standardized opinion-based language to avoid creating recommendations. A note was made if the evidence level could not be substantiated fully.

### Data Synthesis and Analysis

Preliminary evidence statements that initially were developed by the ISC and bibliographic fellows underwent a rigorous discussion process by 27 national faculties in local meetings. The ISC reviewed several hundred detailed comments and incorporated key points into the final proposed evidence statements wherever possible. Finally, the ISC, bibliographic fellows, and representatives from the national faculties met in November 2016 (in London, United Kingdom) to refine and discuss the final statements. A modified Delphi technique process was used to reach consensus on the final evidence statements associated with the agreed definitive clinical questions. The voting system and flow used to reach consensus are shown in Appendices 3 and 4, respectively (available at www.aaojournal.org).

## Results

During the international consensus meeting, the final 10 clinical questions were discussed, updated, and summarized according to

the 3 clinical areas of focus (Appendix 5, available at www.aaojournal.org). Although the original scope of the analysis included only nonanterior NIU, limited information was available when the searches were restricted, and much of the evidence was more broadly applicable. Consequently, most of the statements apply generally to NIU; data that apply to a specific type of uveitis are specified below.

## Focus Area 1: Optimal Timing for Treatment Escalation

**Question 1. Which Factors Determine When Any Form of Noncorticosteroid Systemic Immunomodulatory Therapy Should Be Introduced into the Management of Noninfectious Uveitis?** Statement 1: Noncorticosteroid systemic immunomodulatory therapy (NCSIT) may be introduced for the management of NIU to control persistent or severe inflammation or to prevent ocular structural complications that present a risk to visual function. Indications for introducing NCSIT also include contraindications or intolerance to other therapies or a need for corticosteroid-sparing effect to maintain disease remission. Biologic therapy generally is considered for patients whose disease is inadequately controlled by standard (corticosteroids and NCSIT) drug therapy (evidence level [EL] 4). Grade C recommendation.

Statement 2: Indicators of severe inflammation include impairment of visual function, bilateral disease, vitreous haze, macular or optic nerve disease, retinal vascular inflammation, macular edema, exudative detachment, or ocular structural complications that threaten visual function. Recurrent or chronic disease may be considered as severe disease. Associated systemic disease also may influence the treatment approach (EL 4). Grade C recommendation.

Indications for the introduction of NCSIT in the management of noninfectious adult uveitis can be either the uveitis type and severity or therapeutic needs (Table 1). Although macular edema is a common cause of visual loss in NIU[43,44] and the most common cause of moderate visual loss,[45] few studies have defined a diagnosis of macular edema as an independent indicator for starting NCSIT. There was a significant association of central macular thickening of 240 μm or more on OCT with worse vision in the Multicenter Uveitis Steroid Treatment Trial.[46]

Therapeutic indications for NCSIT most commonly include failure of regional corticosteroids[24,27–29,33,35,36,38,39] or systemic corticosteroids.[20,24–33,35,36,38–40,47,48,57,61–63,66,67] Lack of tolerance to corticosteroids is a prominent reason for systemic noncorticosteroid therapy[20,26,29,30,34,40,48,57] or need for corticosteroid-sparing effect.[20,29,35,41,48,49,55] Other indications for the use of NCSIT may include disease that severely impairs essential activities of daily living and, consequently, quality of life.[59,60]

Contraindications to corticosteroid therapy include behavioral patterns (noncompliance), health-related factors (e.g., history of tuberculosis or hepatitis), and reproductive status (Appendix 6, available at www.aaojournal.org). It should be noted that these contraindications should be evaluated within the context of the overall benefit versus the risk of any therapy.[68]

**Question 2. What Are the Essential Data and Clinical Information That Should Be Collected about Patients before Deciding on Noncorticosteroid Systemic Immunomodulatory Therapy for Noninfectious Uveitis?** Statement 1: Collection of historical, laboratory, and clinically relevant nonocular imaging data should take place before initiation of NCSIT for the treatment of NIU. These data are used to assess baseline vital organ system functions and to test for active or latent infectious diseases (EL 4). Grade C recommendation.

Statement 2: Support for pretreatment testing in NIU patients can be derived from experience with nonuveitic diseases that are treated with NCSIT (EL 4). Grade C recommendation.

Table 1. Indications for Initiating Systemic Therapy

| |
|---|
| Ocular and anatomic |
| Onset and course as defined by SUN Working Group criteria |
| Acute disease that is sight threatening[24–26] |
| Chronic persistent inflammation[20,25,27–32] |
| Exudative retinal detachment[33,34] |
| Posterior and macular involvement[35–37] |
| Binocular sight-threatening disease[20,25,27,31,33,36] |
| Therapeutic |
| Regional failure to respond to:[20,24,27–31,33,35,36,38–42] |
| Periocular steroid injections[42] |
| Topical corticosteroids in JIA-associated uveitis[30,41] |
| Systemic failure[20,24,25,27–30,36,37,40–53] |
| Active uveitis while taking doses of 30 mg or 0.5 mg/kg prednisone per day or more[54] |
| Relapse of uveitis after reduction of the oral corticosteroid dose to less than 7 to 10 mg/day prednisone[34,49,55,56] |
| Steroid intolerance[20,24–26,28–30,34,36,40,44,47,48,51,57] |
| Need for steroid-sparing effect[20,25,28,29,31,34,35,39,41,48,49,51,55,56] |
| Severity (in adults)[20,24,25,28,29,33–36,39–42,55,57,58] |
| Visual acuity worse than 20/100 (18)[34] |
| Increase in vitreous haze of grade ≥2[34,55] |
| Relapse of cystoid macular edema[34] |
| Disease that impacts quality of life[59,60] |
| Severity (in JIA) includes prognostic factors for visual loss, such as:[28,29,38,50,51,54,56–58,61–65] |
| Poorer presenting visual acuity |
| Posterior uveitis |
| Uveitic complications of glaucoma |
| Advanced cataract |
| Macular edema |
| Synechiae |
| Severe band keratopathy |
| Ocular hypotony |
| Rubeosis iridis |

JIA = juvenile idiopathic arthritis; SUN = Standardization of Uveitis Nomenclature.

Before deciding on NCSIT, it is recommended (grade C recommendation) that clinicians should determine baseline vital organ function and screen for infectious diseases that may be reactivated or exacerbated by immunosuppression. In addition, age, exposure to immunosuppressive therapy, and a family history of malignancy may be associated with a greater risk of malignancy.[69] However, it should be noted that positive and negative predictive values of screening tests used depend on the accuracy of the diagnostic test, the pretreatment prevalence of the abnormality in uveitis patients, and the frequency of emergent disease during treatment. History of malignancy or testing for tuberculosis or human immunodeficiency virus is important before initiating biologic therapy. Published after the literature review process, Wakefield et al[19] formulated expert guidelines on the assessment of uveitis patients before initiating NCSIT, including both biologic and nonbiologic immunomodulatory therapy, which also may provide useful guidance. In addition, using or adapting screening procedures as they are performed in inflammatory disorders, such as rheumatoid arthritis, ankylosing spondylitis (AS), psoriasis, psoriatic arthritis (PsA), ulcerative colitis, and Crohn's disease, may support decision making in NIU.[70]

**Question 3. What Are the Clinical Criteria Used When Deciding to Adjust Systemic Therapy?** Statement: There is significant heterogeneity regarding the criteria used to judge

disease activity in NIU, but deterioration (or lack of response) in measures of visual function, anterior chamber cells, anterior chamber flare, vitreous haze, chorioretinal lesions, retinal vascular lesions, or macular or optic nerve involvement are among the parameters that can be influential in decisions to adjust therapy (EL 4). The overall level of evidence supporting criteria used to assess disease activity and adjusting of systemic therapy (including withdrawal of therapy) support a grade B/C recommendation.

Although there is considerable heterogeneity,[20,31,33,35,49,71] clinical criteria with the strongest evidence supporting their usefulness in adjusting systemic therapy (where the eye is the major organ affected in systemic disease and decisions are led by the ophthalmologist) are visual acuity (VA) and ocular inflammation, as defined by Standardization of Uveitis Nomenclature Working Group criteria.[1] A recent Delphi panel developed the Uveitis Disease Activity Index to assess global ocular inflammatory activity in patients with uveitis;[72] however, this has not yet been validated as a method to assess the need for therapeutic adjustment. Given that uveitides comprise several distinct diseases, assessments that are more specific to different forms of disease also may be desirable.

**Question 4A. If the Noncorticosteroid Systemic Immunomodulatory Agent Is Not Adequately Effective, What Should Be Considered First?** Statement: Treatment nonadherence, infections, and masquerade syndromes must be considered in any patient with NIU before a change in therapy is considered (EL 3A). Grade B recommendation.

The goal of treatment in uveitis must be to suppress ocular inflammation and achieve inactive disease state or drug-induced remission. In any patient who is not benefiting adequately from immunomodulatory therapy, defined according to the Standardization of Uveitis Nomenclature Working Group criteria as either a 2-step increase in the level of inflammation or an increase to the maximum grade (worsening) or as a lack of 2-step decrease in the level of inflammation and inability to decrease to inactive disease despite therapy,[1] the diagnosis should be reconsidered (Table 2), with special attention paid to the possible role of infection, masquerade, or patient nonadherence. Masquerade syndrome represents the presence of a condition, such as intraocular malignancy or retinal degeneration, which may mimic inflammation. The incidence has been suggested to be as high as 2.5% of cases of NIU in a tertiary referral clinic.[73] Appropriate diagnosis for malignancy, such as lymphoma, could include diagnostic vitrectomy, cerebrospinal fluid for cytologic analysis, and brain imaging by magnetic resonance imaging. The differential diagnosis for inflammation not responsive to corticosteroids and immunomodulatory therapy also includes infections, such as syphilis, tuberculosis, and a variety of viral causes.

**Question 4B. If the Noncorticosteroid Systemic Immunomodulatory Agent Is Not Adequately Effective or Adequately Tolerated, What Should the Next Approach Be?** Statement 1: Dose escalation of the NCSIT to the maximum tolerated therapeutic dose may be considered before introducing an alternative medication (including introduction of a biologic agent) or other approach in the management of NIU (EL 2A; see Appendix 7 for supporting evidence, available at www.aaojournal.org). Grade B recommendation.

Statement 2: Patients with NIU may be transitioned to an alternative or additional agent (EL 1B; see Appendix 7 for supporting evidence) if the initial NCSIT is controlling the disease inadequately. Grade A recommendation.

Statement 3: Therapy choice for patients with NIU that is refractory to NCSIT must be individualized based on multiple factors, including the patient's history, underlying cause of uveitis, other systemic comorbidities, or a combination thereof (EL 4; see Appendix 7 for supporting evidence). Grade C recommendation.

Table 2. Management of Patients with an Inadequate Response to Noncorticosteroid Systemic Immunomodulatory Therapy

| Considerations for Management of Patients with an Inadequate Response to Noncorticosteroid Systemic Immunomodulatory Therapy |
|---|
| 1. Consider differential diagnosis |
| 2A. Dose escalation of current therapy |
| 2B. Transition to alternative noncorticosteroid systemic agent |
| 2C. Local or regional therapies |
| 2D. Nonmedical therapy (vitrectomy, cryotherapy, etc.) |
| 2E. Biologic therapy |
| 3. Therapies should be individualized based on history, cause of uveitis, and patient preference |
| Currently limited evidence exists to support adding an additional agent; safety and cost implications should be considered. |

Optimizing the dosage of the noncorticosteroid systemic agent often is the first option before introducing a novel medication or approach. Escalating the dose can increase efficacy and may be tried in an individual patient, especially given variability in absorption and metabolism. Patients may be transitioned to an alternative agent if the initial NCSIT is not working or there are other reasons for discontinuing (EL 1B). For example, this may be from mycophenolate to methotrexate, or vice versa. There are limited published data to support adding another agent, and the safety and cost implications should be considered with this approach.

Nonmedical or surgical treatment in some cases may be considered as a primary option, particularly in cases where NCSIT is ineffective (EL 4). Pars plana vitrectomy has been studied as a surgical treatment option in patients with persistent inflammation and macular edema.[74] Peripheral cryotherapy represents another surgical treatment option, especially for active pars planitis. It should be noted that surgical interventions can have late sequelae, such as cataractogenesis.[75,76] In addition, because the surgery does not address the underlying immune-mediated cause of the inflammation, many experts regard the intervention as likely to be of temporary benefit.

Patients' understanding of their ocular disease process often is incomplete, which may influence adherence to therapy.[77] Although a dearth of information exists on factors influencing patient adherence in uveitis therapy, this must be an important consideration in any patient who fails to improve with noncorticosteroid systemic therapy (EL 3A). The ultimate choice for therapy must be individualized based on multiple factors, such as the patient's history (e.g., history of hepatitis), underlying cause of uveitis, patient preference, cost, and convenience (EL 4).

**Question 5. When Should Noncorticosteroid Systemic Immunomodulatory Therapy Be Withdrawn?** Statement: The decision to withdraw NCSIT for NIU should be individualized based on shared decision making that incorporates considerations such as patient preference, tolerance of and risk resulting from the current treatment, duration of disease control, and the specific cause of uveitis (EL 4; see Appendix 7 for supporting evidence). Grade C recommendation.

Inadequate clinical response is cited as the most frequent cause for discontinuation of therapy, followed by inefficacy (no clinical drug effect noted), then adverse drug reactions (EL 2A).[78] Cost and desire for fertility are also considerations, and all of these factors can be used to guide withdrawal decisions.[79] Although the data on sustained remission after withdrawal of biologic therapy are

limited, there are some supportive data in juvenile idiopathic arthritis and even more limited data from Behçet's disease (EL 3A).[80–85]

Any decision to withdraw systemic therapy in patients achieving remission involves a classic risk–benefit analysis that considers the risk that the inflammation will recur and the benefits resulting from not being subjected to systemic immunosuppression. A discussion about when to withdraw NCSIT also frequently arises in other conditions, such as organ transplantation or rheumatic diseases. We hesitate to extrapolate these observations directly to uveitis because prognosis and disease course vary greatly and because the potential for irreversible structural damage arguably is greater with intraocular inflammation. The decision to withdraw systemic therapy must be individualized based on shared decision making that incorporates considerations such as patient and physician preference, tolerance of and risk resulting from the current treatment, disease severity, and the specific cause of uveitis (EL 4).

## Focus Area 2: Transitioning Treatment to Noncorticosteroid Systemic Immunomodulatory Therapy, Including Biologics

**Question 6. What Evidence Is Available to Guide the Selection of Noncorticosteroid Systemic Immunomodulatory Therapy for Noninfectious Uveitis, Excluding Biologics?** Statement: Effective noncorticosteroid, nonbiologic immunomodulatory therapies for the treatment of NIU include mycophenolate mofetil (EL 2B), tacrolimus (EL 2B), cyclosporine (EL 2B), azathioprine (EL 2B), and methotrexate (EL 2B). Grade B recommendation (see Appendix 7 for supporting evidence).

A number of agents have been evaluated for treating NIU (Table 3). Although many studies did not distinguish between different subtypes and causes of uveitis, data for the most commonly studied and used agents are described below, including mycophenolate preparations, tacrolimus, cyclosporine, azathioprine, and methotrexate. Other agents, such as chlorambucil,[86] cyclophosphamide,[87,88] and leflunomide have been used. However, the level and amount of evidence are limited and do not meet the criteria for this report. There is limited evidence of benefit from local therapies, such as intravitreal sirolimus[89–92] and methotrexate,[93] as an alternative treatment strategy in NIU. However, there is no evidence comparing outcomes for these local therapies with systemic noncorticosteroid therapy (overall grade C recommendation for local sirolimus and methotrexate). Intravitreal sirolimus may be moderately effective in reducing inflammation and is associated with low risk of adverse events (AEs) in patients with active NIU.[89–92]

*Mycophenolate Preparations.* Evidence of inflammation control, steroid-sparing effect, and VA improvement in most patients supports a grade B recommendation for mycophenolate mofetil for NIU (Table 3). The evidence for other mycophenolate preparations is not robust (EL 4) and supports a grade C recommendation. Overall, mycophenolate preparations generally were well tolerated, with low rates of discontinuation resulting from AEs.[94–96]

Mycophenolate preparations also have demonstrated moderate efficacy alone[97] and in combination with cyclosporine[98] for control of birdshot chorioretinopathy. The grade C recommendation for the use of mycophenolate derivatives (alone or with cyclosporine) reflects the low-level evidence for this drug combination. Mycophenolate mofetil also has been evaluated in acute Vogt-Koyanagi-Harada (VKH) disease,[99] and in a comparative study (vs. methotrexate) in patients with acute or chronic VKH disease[100] in combination with high-dose oral corticosteroids. These studies support the use of mycophenolate mofetil and methotrexate for control of inflammation and maintenance of VA, with no evidence of superiority of one drug over the other (grade C recommendation).

*Calcineurin Inhibitors: Tacrolimus and Cyclosporine.* There is some evidence to support the efficacy of the calcineurin inhibitors tacrolimus and cyclosporine (EL 2B) for control of inflammation in NIU as well as improvements in VA,[101–104] supporting a grade B recommendation. Similar effects were seen in improvements in VA with tacrolimus and cyclosporine. However, tacrolimus may be slightly better tolerated versus cyclosporine (6% vs. 37% of patients reported AEs), and discontinuations were lower.[103]

*Azathioprine.* Azathioprine as a single agent alongside corticosteroids demonstrated control of inflammation and corticosteroid-sparing outcomes in patients with intermediate and posterior uveitis and panuveitis. However, there is a lack of evidence for improvement in visual outcomes.[105,106] In one study, approximately 17% of patients discontinued therapy because of ineffectiveness and 24% stopped therapy because of AEs within the first year,[106] although a second study did not report discontinuations because of AEs,[105] demonstrating moderate efficacy for azathioprine in NIU (grade B recommendation).

Azathioprine demonstrated moderate efficacy in inflammation control and a significant steroid-sparing effect in patients with severe uveitis secondary to Behçet's disease.[55] Therapy was well tolerated, with only 2% of patients discontinuing therapy. Azathioprine also has been evaluated in patients with acute and chronic VKH disease (alongside high-dose steroids in the acute phase) and demonstrated control of inflammation (85.5% in acute VKH disease and 90% in chronic VKH disease), with a median time to steroid-sparing effect of 4 months.[107] However, this single study in a small cohort of patients (n = 16) constitutes low-level evidence (EL 4).

*Methotrexate.* Evidence from 2 studies demonstrates the efficacy of methotrexate in inflammation control, steroid-sparing ability, and maintenance and improvements of VA in patients with NIU[47,108] and supports a grade B recommendation for methotrexate in NIU.

*Comparative Studies of Antimetabolites (Mycophenolate Mofetil, Azathioprine, and Methotrexate).* Comparative studies of antimetabolites demonstrate moderate support for efficacy of methotrexate and mycophenolate mofetil in steroid-sparing control of NIU (overall grade C recommendation),[71,109] with no significant differences in uveitis control among these drugs. Rates of side effects, laboratory test complications, and discontinuation of therapy were reported to be higher with azathioprine compared with mycophenolate mofetil and methotrexate.[110]

**Question 7. Which Biologic Should Be Used for the Treatment of Noninfectious Uveitis?** Statement 1: The use of adalimumab for the treatment of NIU is supported (EL 1B; see Appendix 7 for supporting evidence). Grade A recommendation.

Statement 2: The use of infliximab for the treatment of NIU is supported (EL 2B; see Appendix 7 for supporting evidence). Grade B/C recommendation.

Statement 3: There is no evidence to support the use of etanercept in NIU (EL 2B). Grade B recommendation.

Statement 4: The use of subcutaneous secukinumab in nonanterior NIU is not supported (EL 2B). Grade B recommendation.

Statement 5: The use of interferon alfa-2a in nonanterior NIU is supported (EL 2B). There is limited evidence to support the use of pegylated interferon alfa in nonanterior NIU in patients with Behçet's disease (EL 2B). Interferon β demonstrated efficacy in the

Table 3. Evidence for Individual Systemic Noncorticosteroid Immunomodulatory Therapy Agents and Disease-Specific Recommendations

| Drug | No. of Studies* | Disease Anatomic Locations† | Disease Entities or Cause | Outcomes | | | Evidence Level | Recommendation Level |
|---|---|---|---|---|---|---|---|---|
| | | | | *Inflammation Control* | *Visual Acuity Stability or Improvement* | *Steroid Sparing* | | |
| Mycophenolate preparations‡ | 13 | Anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis | NIU | Yes | Yes | Yes | 2B§ | B§ |
| | | | BCR | Yes | No | Yes‖ | 2B/3 | C |
| | | | VKH disease | Yes | Yes | Yes¶ | 2B/3 | C |
| Azathioprine** | 4 | Anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis | NIU | Yes | No | Yes | 2B | C |
| | | | BD | Yes | Yes | Yes | 2B | B |
| | | | VKH disease | Yes | No | Yes | 4 | C |
| Methotrexate†† | 5 | Anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis | NIU | Yes | Yes | Yes | 2B | B |
| | | | VKH disease | Yes | Yes | Yes | 2B/3 | C |
| Cyclophosphamide | 2 | Anterior, intermediate, and posterior uveitis | NIU | Yes‡‡ | No | Yes‡‡ | 4 | C |
| Calcineurin inhibitors: tacrolimus/ cyclosporine | 4 | Anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis | NIU | Yes | Yes | Yes | 2B | B |
| Chlorambucil | 1 | Panuveitis | Sympathetic ophthalmia | Yes | Yes | Yes | 4 | C |
| Evidence for noncorticosteroid local therapy | | | | | | | | |
| Methotrexate | 1 | Anterior uveitis, intermediate uveitis, and panuveitis | NIU | Yes | | No | 4 | C |
| Sirolimus | 4 | Intermediate uveitis, posterior uveitis, and panuveitis | NIU | Yes | Yes | Yes | 2B | C |

BCR = birdshot chorioretinopathy; BD = Behçet's disease; NIU = noninfectious uveitis; VKH = Vogt-Koyanagi-Harada.

*Some older studies identified in the literature search were excluded based on quality of reporting, consistency in reporting steroid-sparing effect (prednisone ≤10 mg), use of Standardization of Uveitis Nomenclature criteria, and adherence to Standardization of Uveitis Nomenclature criteria for reporting improvement or failure to improve.

†Data are consolidation of all anatomic locations covered in the associated publications. Some publications may cover some anatomic locations and some may cover others.

‡Seven studies with mycophenolate mofetil, 1 study with mycophenolate sodium, and 1 study in combination with cyclosporine; 2 studies in BCR; and 2 in VKH disease, including 1 study with methotrexate as comparator (no evidence of superiority of either drug) and 1 with methotrexate and azathioprine as comparators.

§Evidence level 4 and grade C recommendation for mycophenolate sodium.

‖Data not available for combination with cyclosporine.

¶One hundred percent steroid-sparing control of inflammation with mycophenolate mofetil alone.

**Includes study with mycophenolate mofetil and methotrexate as comparators.

††Includes 1 study with methotrexate and mycophenolate mofetil as comparators and 1 study in VKH disease with mycophenolate mofetil as comparator.

‡‡One study reported only on the entire cohort and not on uveitis patients within the cohort.

treatment of pars planitis in a small pilot randomized controlled trial (RCT; EL 2B). Grade B recommendation.

Several biologic therapies have been evaluated for the management of NIU across uveitis subtypes, disease causes, and anatomic locations, with the level of evidence varying considerably. Data on the most commonly used biologics are described below, with a comprehensive list in Table 4.

*Adalimumab.* Adalimumab is recommended for the treatment of nonanterior NIU in adults (grade A recommendation). Evidence supporting the use of adalimumab for the treatment of nonanterior NIU in adults is derived from 2 multinational RCTs[49,111] that evaluated the efficacy and safety of adalimumab in adult patients with active nonanterior NIU despite high-dose corticosteroids[111] and adult patients with inactive nonanterior NIU controlled by corticosteroids.[49] In these studies, adalimumab significantly lowered uveitic flare and loss of VA. A further RCT evaluating adalimumab in severe forms of nonanterior NIU in adults demonstrated that adalimumab is superior to placebo in improving VA and reducing flares.[112]

Adalimumab is indicated in the United States for the treatment of noninfectious uveitis, intermediate uveitis, posterior uveitis, and panuveitis in adult patients[113] and in Europe for the treatment of noninfectious uveitis, intermediate uveitis, posterior uveitis, and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid sparing, or in whom corticosteroid treatment is inappropriate.[114] Although adalimumab for treating anterior uveitis was not included in the recommendation, its use in the prevention of acute anterior uveitis was described in some of the supporting literature. For example, it has been shown to reduce the rate of anterior uveitis flares and recurrences in AS.[115–119]

Further, since the consensus meeting in November 2016, data from a randomized study, SYCAMORE,[120] evaluating the efficacy of adalimumab in combination with methotrexate in juvenile idiopathic arthritis-associated anterior uveitis have been published. This study reported a strong beneficial effect with adalimumab plus methotrexate, with significant relative risk reduction and delay in time to treatment failure compared with methotrexate alone (hazard ratio, 0.25; 95% confidence interval, 0.12−0.49; $P < 0.0001$). A significant steroid-sparing effect also was observed ($P = 0.04$), with a significant number of patients in the adalimumab plus methotrexate group reducing or discontinuing topical glucocorticoids ($P = 0.02$).

*Infliximab.* Evidence derived from prospective, noncomparative, open-label trials supports the use of infliximab for the treatment of NIU in adults (EL 2B, 3B, and 4), particularly in Behçet's disease.[121,122] Overall, there is moderate evidence supporting the use of infliximab in Behçet's disease, pediatric NIU,[123] and other uveitis entities[40,124] (grade B/C).

In Behçet's disease, infliximab provided complete remission in 30% to 85.7% of patients,[121,122,125–128] with a good response (investigator opinion) in 76.7% of cases and a significant decrease in the number of uveitis attacks.[129] There was no significant difference in reduction of total inflammatory score versus intravenous methylprednisolone or intravitreal triamcinolone; however, reduction in inflammation was more rapid with infliximab (2 weeks).[130] Improvements in macular edema[131] and best-corrected VA (BCVA) were statistically significant after infliximab treatment.[127,132–134] Infliximab treatment also resulted in a decrease in or discontinuation of, or both, systemic anti-inflammatory agents in patients with Behçet's-associated uveitis.[127,132] Quality of life (relief from uveitis attacks and extraocular manifestations) improved significantly in patients with Behçet's disease with infliximab.[126]

*Adalimumab and Infliximab in Anterior Uveitis Associated with Ankylosing Spondylitis.* Although it was not part of the original analysis, which focused on nonanterior NIU, we believed that it was important that information on the use of tumor necrosis factor inhibitors in anterior uveitis be included in the manuscript because it is the most common extra-articular manifestation in AS. A recent meta-analysis described a cumulative incidence of approximately 1 in 4 patients,[135] and another recent study reported acute anterior uveitis incidence in 30% to 40% of individuals with AS, with prevalence approaching 60% in patients with AS for more than 50 years.[136] International organizations that recently issued recommendations for the treatment of spondyloarthritis all have suggested that adalimumab and infliximab are preferred biologic agents for treatment and prevention of uveitis as an extra-articular manifestation of spondyloarthritis.[137–140]

*Etanercept.* There is no evidence to support the use of etanercept in refractory nonanterior NIU (EL 2B). Etanercept 25 mg administered subcutaneously twice weekly (as monotherapy or with methotrexate) did not provide control of ocular inflammation or steroid-sparing effect when compared with placebo in 2 RCTs.[141,142] There is secondary evidence, not evaluated in our methodology, that infers etanercept may alter the rate of uveitis in patients with spondyloarthropathy.[118,119] In addition, there are also reports of paradoxical occurrences of uveitis after etanercept administration in patients with AS-related acute anterior uveitis.[116]

*Secukinumab.* In patients with Behçet's disease and active or quiescent NIU, secukinumab, dosed subcutaneously, does not demonstrate control of ocular inflammation or decrease uveitis recurrence.[143] There was no significant reduction in inflammatory attacks, decrease in vitreous haze, or improvement in BCVA.[143] However, intravenous dosing in patients with active, noninfectious, nonanterior uveitis provided some control in 72.7% of patients at 6 months as well as some steroid-sparing effect.[144]

*Interferons.* In adult NIU (including that associated with Behçet's disease) or other uveitis entities, interferon alfa-2a administered subcutaneously without concomitant steroids was effective in controlling NIU (grade B recommendation).[78,85,145–158]

Interferon alfa-2a has demonstrated efficacy in control of uveitic flares in patients with Behçet's disease as well as in patients with other uveitis entities.[145–150,152–158] Relapse rate also decreased significantly (from 1.39−3.61 relapses/person annually to 0.05−0.8 relapses/person annually).[159] Visual acuity improved or remained stable and resolution of macular edema was observed in all those patients with macular edema at baseline.[85,145,148,150,152–156] Significant reductions in mean oral prednisolone dose also were achieved.[147,148,152]

There is very limited evidence to support the use of pegylated interferon alfa for NIU (EL 2B). In one randomized study, there was no difference from placebo in relapse rates. However, there was a significant steroid-sparing or immunosuppressant-sparing effect.[160]

Interferon β administered subcutaneously (2 weeks at 22 μg 3 times weekly then 44 μg every 3 weeks) has demonstrated efficacy in the treatment of pars planitis in a randomized pilot study (EL 2B). Patients showed a significant increase in BCVA at 3 months versus methotrexate, with mean improvement in BCVA of 0.31 logarithm of the minimum angle of resolution versus 0.09 logarithm of the minimum angle of resolution, respectively. Vision-related quality of life also improved compared with those receiving methotrexate.[28]

**Question 8. How Do You Assess Patient Safety While Noncorticosteroid Systemic Immunomodulatory Therapy Is Being Administered?** Statement: Support for safety monitoring while administering treatment derives from experience with uveitis and nonuveitic diseases that are treated with NCSITs.

There was significant variability in level of knowledge, along with low self-ratings regarding specific indications and toxicities for certain medications, in a survey of 51 United States ophthalmologists;[161] therefore, we included an additional statement with

Table 4. Evidence Supporting Use of Biologics and Recommendation

| Originator Biologic | No. of Studies | Anatomic Location* | Disease Entities or Cause | Outcomes | | | Evidence Level (No. of Publications) | Recommendation Level |
|---|---|---|---|---|---|---|---|---|
| | | | | *Inflammation Control* | *Visual Acuity Stability or Improvement* | *Steroid Sparing* | | |
| **Anti–tumor necrosis factor** | | | | | | | | |
| Infliximab | 24 | Anterior, posterior, retinal vasculitis | BD | Yes | Yes | Yes | 2B (3), 3B (2), 4 (8) | B |
| | | Anterior uveitis, intermediate uveitis, posterior uveitis, panuveitis | Pediatric NIU (uveitis entities include JIA, BD, sarcoidosis, VKH disease) | Yes | Yes | Yes | 2B (1), 4 (2), 5 (1) | C |
| | | Anterior uveitis, intermediate uveitis, posterior uveitis, panuveitis | Other uveitis entities (including BD, BCR, sarcoidosis, idiopathic vasculitis, VKH disease) | Yes | Yes | Yes | 2B (2), 3B (1), 4 (4) | B |
| Adalimumab | 15 | Anterior uveitis, intermediate uveitis, posterior uveitis, panuveitis | NIU (including different uveitis entities: BD, idiopathic uveitis, sarcoidosis, BSRC, TINU, VKH disease, pars planitis; other: HLA-B27, JIA) | Yes | Yes | Yes | 1B (4), 2B (4), 4 (5), 5 (2) | A |
| Golimumab | 2 | Anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis | NIU | Yes | Yes | Yes | 4 | C |
| Etanercept | 2 | Anterior, intermediate, posterior uveitis | NIU, sarcoidosis | ✗ | ✗ | ✗ | 2B | B |
| Certolizumab | No studies fulfilling inclusion criteria | | — | — | — | — | — | D |
| **Anti-interleukin 1** | | | | | | | | |
| Anakinra/canakinumab | 1 | Anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis | BD | Yes | — | — | 4 | C |
| Gevokizumab | 1 | Posterior uveitis, panuveitis, and/or retinal vasculitis | BD | Yes | — | — | 2B | C |
| **Anti-interleukin 2** | | | | | | | | |
| Daclizumab | 7 | Anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis; retinal vasculitis | NIU (including different uveitis entities such as: idiopathic anterior uveitis and panuveitis; MCP; scleritis, idiopathic panuveitis; sarcoid panuveitis; HSV-associated anterior scleritis; idiopathic keratouveitis) | Yes | Yes | Yes | 2B (5) and 4 (2) | B |
| **Anti-interleukin 6** | | | | | | | | |
| Tocilizumab | 2 | Anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis; also note retinal vasculitis with and without uveitis | NIU (including different uveitis entities) | Yes | Yes | ✗ | 4 | C |

Table 4. (Continued.)

| Originator Biologic | No. of Studies | Anatomic Location* | Disease Entities or Cause | Outcomes | | | Evidence Level (No. of Publications) | Recommendation Level |
|---|---|---|---|---|---|---|---|---|
| | | | | *Inflammation Control* | *Visual Acuity Stability or Improvement* | *Steroid Sparing* | | |
| Sarilimumab | Ongoing CT, no results | | NIU (including different uveitis entities) | — | — | — | — | D |
| **Anti-interleukin 17** | | | | | | | | |
| Secukinumab | 4 (2 publications) | Intermediate uveitis, posterior uveitis, panuveitis | NIU (including different uveitis entities: Behçet's uveitis noninfectious; non-Behçet's uveitis; quiescent, non-infectious, non-Behçet's uveitis) | Yes | ✗[†] | Yes | 1B (1) and 2B (3) | B |
| **Anti-CD-20** | | | | | | | | |
| Rituximab | 1 | Anterior uveitis, posterior uveitis, and retinal vasculitis | BD | Yes[‡] | — | — | 2B | C |
| **Anti—CD-52** | | | | | | | | |
| Alemtuzumab | 1 | Not specified | BD | Yes | — | Yes | 2B | C |
| **Interferons** | | | | | | | | |
| Interferon alfa-2a and -2b | 15 | Anterior uveitis, intermediate uveitis, posterior uveitis or panuveitis or retinal vasculitis | BD and other uveitis entities including pars planitis, VKH disease, idiopathic panuveitis, uveopapillitis | Yes | Yes | Yes | 2B (6), 3B (1), 4 (6), 5 (2) | B |
| Pegylated interferon alfa-2b | 1 | Nonanterior uveitis | BD | — | — | Yes[§] | 2B | C |
| Interferon β | 1 | Intermediate uveitis or uveitis associated with multiple sclerosis | Patients with primary intermediate uveitis or uveitis associated with multiple sclerosis | Yes[‖] | Yes | — | 2B | C |
| **Others** | | | | | | | | |
| Intravenous immunoglobulins | 1 | Posterior uveitis | BCR | — | Yes | — | 2B | C |

BCR = birdshot chorioretinopathy; BD = Behçet's disease; BSRC = birdshot retinochoroidopathy; CT = clinical trial; HLA = human leukocyte antigen; HSV = herpes simplex virus; JIA = juvenile idiopathic arthritis; MCP = multifocal choroiditis and panuveitis; NIU = noninfectious uveitis; TINU = tubulointerstitial nephritis and uveitis; VKH = Vogt-Koyanagi-Harada; ✗ = No; — = no data.
*Data are consolidation of all anatomic locations covered in the associated publications. Some publications may cover some anatomical locations and some may cover others.
[†]Not significant compared with placebo or different doses of secukinumab.
[‡]Not statistically significant in comparison with cyclophosphamide.
[§]In patients who were receiving corticosteroids at baseline, the corticosteroid requirement was significantly lower in the pegylated interferon-alfa-2b group compared with the noninterferon group.
[‖]Improvement not significant compared with the methotrexate arm.

an emphasis on clearly addressing patient safety screening and monitoring. It should be noted that a limitation of this statement was that it arose from a different process to the remaining statements and was not supported by the evidence synthesis. Nevertheless, because it has implications across all the other questions and statements, we considered it important to include a statement about monitoring for adverse effects from medication.

An interdisciplinary panel of 12 uveitis specialists and rheumatologists convened in 2000 to outline best practices and guidelines for use of immunosuppressive drugs, including recommendations for duration of corticosteroid therapy and optimal tapering schedules, as well as thresholds for prescribing immunomodulatory therapy.[16] Patients should be made aware of the systemic side effects of oral corticosteroid therapy, and blood pressure and blood sugar should be monitored every 3 months while receiving the medication, along with bone-mineral density and serum-lipid monitoring.[16] The panel also outlined the side effects of different classes of immunomodulatory medications, as well as dosages and indications, providing suggested frequencies of laboratory monitoring.[16] With the introduction and availability of new classes of immunosuppressive agents, these recommendations have been expanded to include biologic agents such as tumor necrosis factor inhibitors, and place emphasis on careful assessment of patients before commencing immunosuppressive or biologic therapy, or both, and on monitoring and preventing viral or bacterial infection, cardiovascular side effects, and metabolic and bone diseases and on reducing iatrogenic side effects in a manner no different from their use in other disease states.[19] We also recognize that guidelines and guidance for safety screening and monitoring of patients vary globally in relation to treatment with noncorticosteroid immunomodulatory agents or biologics, as well as across different disease states, and it is likely that similar consideration to local practices may be applied in NIU.[162–165] Appendix 8 (available at www.aaojournal.org) outlines recommended monitoring and management practices associated with treatments for NIU.

## Focus Area 3: Collaboration across the Multidisciplinary Team

**Question 9. How Would You Discuss the Therapeutic Options (Pros and Cons) and Make a Shared Decision with the Patient?** Statement: Shared decision making is an appropriate strategy in caring for patients with NIU, but there are limited data to guide this interaction. Discussions regarding the choice of therapy should be tailored to fit the needs and expectations of individual patients and their healthcare professionals. Availability of information in multiple formats is desirable (EL 4). Grade C recommendation.

When reviewing treatment options with patients, it is important to emphasize the chronic nature of uveitis as a condition requiring ongoing treatment, during which potential adverse effects from therapy may manifest at varying stages.[166] Best–worst scaling has been used as an estimate for patient preferences in the treatment of uveitis in a patient survey from the Multicenter Uveitis Steroid Treatment Trial follow-up study of patients with nonanterior NIU and outpatients with predominantly anterior NIU at 2 United States ocular inflammation subspecialty clinics. Patient outcome preference of local versus systemic corticosteroid therapies for NIU was evaluated,[167] and not meeting vision requirements for driving, development of glaucoma, and need for eye surgery were ranked as more salient concerns than high blood pressure and cholesterol, cataracts, or systemic infections by patients.[167] Understanding and sharing outcomes relevant to patients may inform them on how best to weigh the risks and benefits of therapeutic options and may provide specific markers for them to assess the impacts of therapy on their lives.

An additional sampling of the rheumatology literature provides further insight for shared decision making for uveitis therapy. For example, low-literacy decision aids for rheumatoid arthritis patients improved knowledge of the treatment while reducing decision-making conflict.[168] One shortcoming of the uveitis literature regarding shared decision making is the absence of specific metrics for defining how to arrive at a decision with the patient. The Outcome Measures in Rheumatology Clinical Trials Working Group[169] determined 7 domains for assessment of shared decision-making: (1) identifying the decision, (2) exchanging information, (3) clarifying views, (4) deliberating, (5) making the decision, (6) putting the decision into practice, and (7) assessing the effect of the decision.

It should be noted that shared decision making also can have negative aspects,[170] including impact on time, that limit the ability to discuss each option thoroughly and the opportunity for patient reflection. Individual biases also impact discussion (e.g., experiencing a patient having an AE could bias that provider's advice, and anecdotal evidence may influence a patient more than results from a controlled study). In summary, shared decision making in uveitis is important, and efforts should be made to involve patients by making information relevant and understanding their view of the impact of their treatment on their lives.

**Question 10. How Do We Ensure Effective Communication between Internists or Rheumatologists and Ophthalmologists to Optimize Safe Prescribing and Monitoring of Systemic Therapy?** Statement: Patients with uveitis may benefit from the input of more than one medical speciality. Communication among healthcare professionals fosters optimal diagnosis and therapy. The optimal methods to enable this communication require further investigation (EL 4). Grade C recommendation.

Communication between physicians has been identified as a potential deficiency in the healthcare system. A survey of specialist and primary care physicians revealed that a significant number expressed dissatisfaction with how information regarding a patient referral was conveyed.[171] Multiple cross-sectional surveys of physicians have demonstrated that a lack of coordinated care between primary care physicians and specialists negatively impacts patient care, and this further impacts the patient–physician relationship by reducing patient confidence in their care.[172]

A dearth of literature exists regarding optimal communication between ophthalmologists and rheumatologists or internists with respect to shared monitoring of efficacy and side effects. Thus, although interdisciplinary management has near universal support, few practical guidelines exist to help actualize this dialog. Although it is difficult to quantify its benefit, the authors believe that an interdisciplinary clinic—for example, one that combines rheumatologists with ophthalmologists at the same physical location—is an effective approach to optimize communication among specialists. Obstacles to this communication paradigm include the challenge to use time efficiently for all practitioners and issues regarding the division of compensation for the care provided.[173]

An alternative or supplementary approach is found in the rheumatology literature, which offers some empirical guidance on the use of biological nurse specialists for monitoring therapeutic outcomes and safety, which may have applications for patients who are managed between ophthalmologists and rheumatologists in an interdisciplinary setting. The biological nurse specialist has emerged as an important component of patient care in rheumatology, assuming responsibilities such as monitoring disease-activity metrics, training patients to self-administer subcutaneous

medications, coordinating nurse specialists and consultants from other disciplines, and managing telephone-advice helplines.[174] In addition, a Spanish Delphi consensus offered guidance on comanagement of PsA with dermatologists,[175] stating that generally the rheumatologist manages PsA with the dermatologist, referring to the dermatologist after detection of worsening psoriasis. The specialists also confer on any change in patient treatment that affects the course of PsA or psoriasis.

In summary, multidisciplinary collaboration comes in many forms, with the benefits from such interactions documented in peer-reviewed literature. Their specific applications to the interdisciplinary relationship among ophthalmologists, rheumatologists, and internists for management of uveitis need further and more specific study in the coming years.

## Discussion

Noninfectious uveitides are rare, sight-threatening inflammatory diseases often associated with comorbid, systemic, immune-mediated inflammatory diseases. The most commonly used treatment options, corticosteroids, are associated with significant side effects, and long-term use is not recommended to achieve the treatment goal of uveitis quiescence. Systemic immunosuppressants generally are used off-label as second-line therapy for patients whose uveitis is not sufficiently controlled with corticosteroids.[16] However, prospective, randomized, placebo-controlled trials are uncommon and few treatments are approved.[71,109,110]

The goal of the FOCUS initiative was to support optimal management of NIU across relevant specialties, with the ultimate aim of improving patient outcomes. This program included an academically rigorous process, supported by a large number of uveitis specialists worldwide, including both rheumatologists and ophthalmologists who collaborate in the care of patients with NIU, and represents a broad range of clinical opinion from diverse geographical regions and a variety of clinical practices. Most studies on interventions for uveitis include patients with diverse forms of uveitis. However, we recognize that the therapeutic approach for Behçet's disease, as an example, may differ from the approach for a disease such as sarcoidosis. Accordingly, when data were available to support a statement, we have endeavored to indicate if a specific entity should influence clinical decision making. We further recognize that regional differences such as the prevalence of tuberculosis should influence clinical advice. Although we consider a recurrence an indicator of severity, we acknowledge that the nature of the uveitis disease, associated systemic disease, and frequency of recurrence are all important in any decision to initiate NCSIT.

A limitation of the program was greater representation from Western European countries and the United States compared with Eastern Europe and Asia. In addition, this was not a full systematic or Cochrane review, and the level of evidence in some cases was not robust and did not meet the criteria for inclusion for some therapies analyzed. Furthermore, some evidence had to be drawn from literature outside of uveitis treatment or drawn from the expert opinions, and subsequent consensus around those opinions was provided by the experts involved in the initiative. Furthermore, the focus of the initiative was NCSIT with only brief analysis of local, surgical, or other management approaches. Finally, it should be acknowledged that clinical practice varies depending on local factors, such as the availability of medications or demographics of patients; because this was intended as a global initiative, local adaptation and application should be considered.

The initiative also has highlighted the lack of randomized, prospective studies in NIU in general, and especially for specific subsets of uveitis, such as VKH disease or birdshot chorioretinopathy. In addition, or even as a consequence, it is not possible to identify which treatment would be appropriate for which patient. However, the initiative has identified clearly the opportunities to collaborate with colleagues and to identify optimal methods of communication and comanagement of patients.

As novel approaches to treatment and management of patients with NIU are identified, future opportunities to update this initiative may be offered, affording the possibility to adapt recommendations to fit local clinical practices along with the generation of guidelines with greater specificity toward different uveitides or specific medications. In addition, measuring any improvement in patient outcomes as a result of these recommendations would continue to validate the findings in meeting the aim of the initiative.

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## Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
**AE** = adverse event; **AS** = ankylosing spondylitis; **BCVA** = best-corrected visual acuity; **EL** = evidence level; **ISC** = International Steering Committee; **NCSIT** = noncorticosteroid systemic immunomodulatory therapy; **NIU** = noninfectious uveitis; **PsA** = psoriatic arthritis; **RCT** = randomized controlled trial; **VA** = visual acuity; **VKH** = Vogt-Koyanagi-Harada.

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