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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 2017;■:1–17 © 2017 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