Outcomes of Changing Immunosuppressive Therapy after Treatment Failure in Patients with Noninfectious Uveitis

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Purpose: To evaluate the outcomes of changing immunosuppressive therapy for noninfectious uveitis after failure.

Design: Retrospective cohort study.

Participants: Patients with noninfectious uveitis managed at 2 tertiary uveitis clinics in the United Kingdom and Australia.

Methods: Participants with a history of using immunosuppressive therapy were identified in clinics, and notes were reviewed by doctors trained in uveitis therapy. Each treatment episode/course (starting or changing a therapy) was identified, and demographic details, clinical characteristics, drug used (second-line immunosuppressive agent [ISA] or biologicals), and drug doses were obtained.

Main Outcome Measures: For each treatment episode, the reasons for changing therapy, corticosteroid-sparing effects, and control of inflammation were determined.

Results: A total of 147 patients were identified who underwent 309 different treatment episodes. Fifty-five percent of patients eventually required a change in treatment after their first treatment episode/course. Forty-five episodes involved switching from one ISA to another, with 50% to 100% of these patients achieving "success" (prednisolone $\leq$10 mg and sustained control) with the new ISA. A combination of ISAs were used in 53 episodes, with "success" being achieved in 50% to 71% of these patients. Biological agents were used in 45 episodes, the most common one being infliximab, which achieved success in 80% of patients.

Conclusions: Our data suggest that control of inflammation can be achieved after switching or combining ISAs. *Ophthalmology 2014;121:1119-1124 © 2014 by the American Academy of Ophthalmology.*

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Systemic corticosteroids are the mainstay of treatment for uveitis resistant to local therapy, bilateral disease, and the more severe forms of uveitis. In some patients, corticosteroids are unable to control inflammation at a dose of 10 mg/day, or preferably 7.5 mg/day or less,[1] whereas in others the side effects of long-term treatment are severe and limit the duration of therapy. These patients require additional immunosuppressive agents (ISAs) to control their disease and to minimize the corticosteroid dose they require.[1] Such nonbiologic ISAs include T-cell inhibitors (cyclosporine A [CSA] and tacrolimus), antimetabolites (azathioprine [AZA], methotrexate [MTX], and mycophenolate mofetil [MMF]), and alkylating agents (cyclophosphamide and chlorambucil); ISAs have been reported to become ineffective in up to 17% of patients within the first year.[2–6] An expert uveitis panel published a comprehensive set of guidelines on the use of ISAs, but there is no consensus on whether to change ISAs or add a biologic in such patients. There are a limited number of reports describing the outcomes of switching or adding an ISA after failure of an ISA.[7]

The objectives of this study were to determine the outcome of individual immunosuppressive therapies (both ISAs and biologicals) in producing a corticosteroid-sparing effect after treatment has failed (because of side effects or ineffectiveness) with a previous agent(s) in a large cohort of patients.

Methods

A retrospective review of the clinical records of all patients who attended the uveitis clinics of Susan Lightman at Moorfields' Eye Hospital (London, UK) and Peter McCluskey at St. Vincent's clinic (Sydney, Australia) for the management of noninfectious uveitis from January 2010 to August 2012 was undertaken. Ethical approval was obtained from the Moorfields' Eye Hospital research board under the program of research on causes of visual loss in uveitis (LIGS 10201).

Data Collection, Follow-Up, and Outcome Measures

Patients who were currently using or had previously used immunosuppressive drugs or biologics were identified. Patient medical records were reviewed, and information from each treatment episode/course (defined as starting or changing an ISA or biologic) was collected. The following information was collected: age; sex;

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uveitis subtype; any associated medical condition (e.g., sarcoidosis); duration of disease and follow-up; prednisolone dose and disease activity (based on the Standardization of Uveitis Nomenclature workshop grading system)[8] at the start of treatment episode; baseline and final best-corrected visual acuity (VA); any decrease/gain in best-corrected VA by ≥2 Early Treatment Diabetic Retinopathy Study (ETDRS) lines due to inflammation; ocular complications; maximum dose of ISA; reasons for changing treatment; and corticosteroid-sparing effect of ISA or biologics (defined as time to reach a prednisolone dose ≤7.5 or ≤10 mg with maintained inactivity spanning at least 28 days).[5] Patients were followed up until their last recorded visit to the clinic. Visual acuity was recorded using Snellen VA charts and converted to approximate ETDRS scores, which are more intuitively interpretable than logarithm of the minimum angle of resolution units.[9] Other associated features of uveitis were documented, such as increased vitritis, new-onset macular edema, vasculitis, or optic neuropathy/swelling.

The definition of remission was based on the clinician's evaluation of the patient, noting that the treatment could be reduced or stopped because there was no disease activity for at least 6 months after starting the agent; this definition also included no relapse within 6 months after stopping the agent. Ineffectiveness was based on the clinician's impression that a change in therapy was needed because the agent failed to improve inflammation or recurrent relapses occurred while on the treatment regimen.

Statistical Analyses

All data were entered into a Microsoft Excel 2007 spreadsheet (Microsoft Corp., Redmond, WA) and analyzed using the Excel PivotTable function and GraphPad Prism v5.01 (GraphPad Software, La Jolla, CA).

Results

The demographics and uveitis phenotypes of the patients are detailed in Table 1. We identified a total of 147 patients who underwent a total of 309 different treatment episodes; 30 episodes were a reduction of treatment (reducing from a combination of therapies to a single therapy), 56 episodes were a switch from one systemic therapy to another, 87 episodes were an increase in treatment (increasing from a single therapy to a combination of therapies), and 9 episodes were due to the reintroduction of a treatment that had been stopped. A total of 127 episodes involved the use of a single agent as the first treatment episode.

Continuation and Change of Treatment

Figure 1 shows that 55% of patients eventually required a change in treatment after their first treatment episode/course. Some patients subsequently underwent up to 8 treatment courses/episodes, highlighting that is difficult to achieve remission in these patients with a single course of treatment.

Visual Acuity Changes across Treatment Courses

Figure 2 shows the last recorded ETDRS-equivalent VA in all eyes for each consecutive treatment course and reveals a decline in VA after consecutive treatment courses. There may be a trend for patients to lose vision with increasing courses of treatment. However, up to 22% of patients gained 2 or more ETDRS lines of VA after treatment (Fig 3). The causes of visual loss are shown in Table 2.

Effectiveness of Single Immunosuppressive Agents after Failure of Other Agents in Comparison with Their Use as Initial Agents

Of the 127 treatment episodes involving the use of a single agent during the first treatment episode, MMF (44%) was the most commonly used initial agent, followed by CSA (25%), AZA (16%), MTX (13%), and alkylating agents (2%). The mean doses used for each of these initial ISAs are summarized in Table 3 (available at www.aaojournal.org). However, these agents failed (stopped because of ineffectiveness or side effects) in 40% to 75% of patients (Table 4), with the highest proportion for those given CSA. Remission (stopping treatment because of maintained inactivity) was not achieved in many patients, but a greater proportion of patients taking AZA managed to achieve this (35%). A greater proportion of patients taking AZA had systemic disease and a longer duration of disease and posterior uveitis than those taking the other ISAs (Table 1). A statistical comparison of baseline factors between ISAs was not possible because it would violate the rule of independent samples (because some patients may have multiple ISAs).

Of the 56 episodes that involved switching from one therapy to another, 45 involved switching from one ISA to another, whereas the other 9 involved switching between biological agents or switching an agent in an ISA combination regimen. Table 3 (available at www.aaojournal.org) shows the summary and outcomes of ISAs used after the failure of other ISAs, comparing them with ISAs used as initial therapy. The most commonly used ISAs after ISA failure were MTX (18 episodes) and MMF

Table 1. Baseline Characteristics of All Patients and First Treatment Episode for Commonly Used Immunosuppressive Agents

Characteristic	All Patients (n = 147)	Initial Agent Used (No. of Episodes)			
		MTX (n = 16)	*AZA (n = 20)*	*MMF (n = 56)*	*CSA (n = 32)*
Age (yrs), median (range)	37 (5–75)	31 (10–59)	37 (20–64)	42 (5–75)	33 (17–54)
Female sex (%)	55	69	40	43	34
Site of inflammation (%)					
Anterior uveitis	16	54	10.5	5.5	10
Intermediate uveitis	20	13	10.5	32	13
Posterior uveitis	64	33	79	62.5	77
Systemic disease	53	63	95	38	63
Duration of disease (mos), median (range)	31 (0–528)	38 (0–156)	74 (0–364)	46 (0–249)	20 (0–95)
Ocular complications (%)	67	63	60	73	69

AZA = azathioprine; CSA = cyclosporine A; MMF = mycophenolate mofetil; MTX = methotrexate.