Use of Immunomodulatory Treatment for Non-Infectious Uveitis: an International Ocular Inflammation Society report of real-world practice

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PRECIS

An international group of uveitis-specialised ophthalmologists prioritises the use of methotrexate as a conventional systemic immunomodulatory drug and adalimumab as a biologic systemic immunomodulatory drug for the treatment of non-infectious uveitis.

ABSTRACT

Background: Non-infectious uveitis is a diverse group of inflammatory conditions that collectively account for substantial blindness worldwide. Expert guidelines and results of clinical trials guide treatment, but real-world clinical care is impacted by additional factors. In 2023, an international group of uveitis-specialised ophthalmologists formed the *International Study Group for Systemic Immunomodulatory Drug Treatment of Non-Infectious Uveitis* to report current practice.

Methods: 221 Study Group members from 53 countries completed a 30-item questionnaire on their management of non-infectious uveitis including: indications for and investigations prior to initiating systemic immunomodulatory drugs, use of conventional and biologic drugs, and follow-up of treated patients.

Results: Major indications to initiate systemic immunomodulatory drugs were: uveitis not controlled with oral prednis(ol)one (n=208, 94.1%), specific uveitis diagnosis (n=197, 89.1%), and patient intolerance of oral prednis(ol)one (n=186, 84.2%). All members (n=221, 100%) performed pre-treatment screens including blood chemistry (n=217, 98.2%), blood examination (n=207, 93.7%), and Quantiferon assay (n=196, 88.7%). Eight conventional and 14 biologic drugs were prescribed: methotrexate was the preferred conventional drug overall (n=126, 57.0%), and for 9 of 11 uveitides, and adalimumab was the preferred biologic drug overall (n=216, 97.7%), and for 11 of 11 uveitides. When drugs were combined, methotrexate plus adalimumab was most popular (n=158 of 188 members, 84.0%). Patients with inactive uveitis were typically evaluated and screened for drug toxicity every 6 to 12 weeks (n= 161, 72.9%, and 165, 74.7%, respectively).

Conclusion: Our report describes practice patterns of a large international group of uveitis specialists treating non-infectious uveitis with systemic immunomodulatory drugs.

KEYWORDS: uveitis, treatment, management, prednisone, prednisolone, conventional, biologic, immunomodulatory, immunosuppressive, drug, medication

KEY MESSAGES

What is already known on this topic?

New randomised controlled clinical trials, cohort studies and expert evidence-based recommendations have been published on the use of systemic immunomodulatory drugs for non-infectious uveitis. However, real-world implementation is dictated by many practical factors, and there are no international studies of current clinical practice.

What does this study add?

The *International Study Group for Systemic Immunomodulatory Drug Treatment of Non-Infectious Uveitis* prioritises the use of methotrexate as a conventional systemic immunomodulatory drug and adalimumab as a biologic systemic immunomodulatory drug for the treatment of non-infectious uveitis.

How might this study affect research, practice or policy?

Results of this work may be a useful practice guide, providing information on when and how to initiate systemic immunomodulatory drugs for non-infectious uveitis, selection of conventional and biologic drugs, and monitoring for drug effectiveness and safety.

INTRODUCTION

Non-infectious uveitis represents a diverse group of autoimmune, autoinflammatory, and other inflammation-based conditions that occur inside the eye and may be associated with systemic inflammatory disease.[1] Although uncommon, uveitis collectively accounts for substantial blindness: according to a study published in 2004, an estimated 70% of patients with uveitis suffer loss of vision and approximately 20% meet the criteria for legal blindness over a mean follow-up interval of 3 years.[2] More recently published reports across several countries show that vision impairment from uveitis continues to be of major concern.[3-5] Vision loss often occurs secondary to complications of the inflammation, including macular oedema, choroidal neovascularisation, glaucoma, and hypotony.[6] Analysis of a United States-based health insurance database has highlighted the high work-loss costs associated with non-infectious uveitis.[7] A new systematic review has identified multiple studies reporting suboptimal quality of life across populations of patients with non-infectious uveitis.[8]

There have been major international efforts over the past 20 years to develop better treatment approaches for non-infectious uveitis, beginning around 2005, when the Standardization of Uveitis Nomenclature (SUN) Working Group published criteria for describing the disease.[9,10] As examples, the multicentre Systemic Immunosuppressive Therapy for Eye diseases (SITE) Cohort Study documented the effectiveness of standard conventional immunosuppressive drugs,[11-14] and the VISUAL family of studies established the effectiveness of the biologic approach of tumour necrosis factor-alpha (TNF-α) blockade.[15-17] In line with these and other clinical trials, different groups have published

evidence-based recommendations to define best practice in the use of systemic immunomodulatory treatments for non-infectious uveitis.[18-20]

While expert recommendations exist, real-world practice is dictated by other factors, including the practical availability of different drugs including generics, and individual clinician experience. An additional consideration for randomised controlled clinical trials is that enrolees represent a skewed population. Representing a large group of uveitis clinician specialist members of the *International Ocular Inflammation Society*, *The International Study Group for Systemic Immunomodulatory Drug Treatment of Non-Infectious Uveitis* was formed to produce a report on real-world practice by uveitis experts. This report describes the results of the project completed by this group, focusing on their use of conventional and biologic systemic immunomodulatory drugs.

MATERIALS AND METHODS

A subset of members from the *International Ocular Inflammation Society* (IOIS) formed the *International Study Group for Systemic Immunomodulatory Drug Treatment of Non-infectious Uveitis*. The IOIS is an independent global scientific society focused on the study of ocular inflammatory diseases. Between 2022 and 2023 the IOIS had 821 members, consisting of ophthalmologists, other health practitioners, and research scientists.

The IOIS sent an electronic communication to its members on 31 August 2023, inviting uveitis-specialised post-fellowship ophthalmologists to join the Study Group and complete an online questionnaire to outline their current practice patterns of systemic immunomodulatory drug use for treatment of non-infectious uveitis. The online

questionnaire included 30 items and was developed using SurveyMonkey software (surveymonkey.com) by co-authors JAB, BB, LBF, PJM, JET, and JRS. A reminder was sent out to all IOIS members prior to the questionnaire link closing on 30 September 2023. The link was reopened for one week on 6 November 2023 to allow more IOIS members to join the group and complete the questionnaire, and closed again on 12 November 2023.

A total of 221 uveitis-specialised post-fellowship ophthalmologists joined the *International Study Group for Systemic Immunomodulatory Drug Treatment of Non-infectious Uveitis*. These IOIS members were based in the following 53 countries: Argentina, Australia, Austria, Bangladesh, Belgium, Brazil, Cambodia, Canada, Chile, China, Colombia, Czech Republic, Dominican Republic, Egypt, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Iran, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Malaysia, Mexico, New Zealand, Palestine, Philippines, Portugal, Republic of Korea/South Korea, Russia, Serbia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Thailand, Tunisia, Turkey, Ukraine, United Arab Emirates, United Kingdom, USA, and Venezuela.

Study Group members reported on their clinical management of non-infectious uveitis including: treatment with oral prednis(ol)one; indications for and investigations prior to initiating systemic immunomodulatory therapy; use of conventional and biologic systemic immunomodulatory drugs, and their combinations; follow-up and investigations for patients having systemic immunomodulatory therapy; and considerations for performing cataract surgery. Members answered questions based on the standard clinical scenario and their knowledge as a uveitis expert, recognising there were exceptional circumstances in which they would make different management decisions, and they might be addressing situations

that were uncommon due to their practice setting and location. The survey questions are available in online supplemental table 1.

RESULTS

Members of the *International Study Group for Systemic Immunomodulatory Drug Treatment of Non-infectious Uveitis* reported on their uveitis patient load in 2022, the year prior to the project: 100 patients or less (n=26, 11.8%), 101 to 500 patients (n=108, 48.9%), 501-1000 patients (n=57, 25.8%), and more than 1000 patients (n=30, 13.6%). Most Study Group members used the SUN Working Group grading scheme to assess the severity (n=216, 97.7%) and activity (n=201, 91.0%) of the uveitis. Standard first-line systemic treatment of non-infectious uveitis is with oral prednis(ol)one; a majority of Study Group members used an initial maximum daily dose of 1 mg/kg to achieve control of the inflammation (n=170, 76.9%), and continued this maximum dose for 4 weeks or less (n=207, 93.7%). Of the 84 clinicians (38.0%) who used prednis(ol)one past 6 months, maximum long-term doses were 10 mg or less (n=77 of 84: 91.7%). The use of oral prednis(ol)one to treat non-infectious uveitis is summarised in table 1.

Table 1. Treatment of non-infectious uveitis with oral prednis(ol)one (N = 221 Study Group members responding, unless otherwise stated).

Clinical Variable	**N (%)**
Maximum initial daily dose of prednis(ol)one	
2 mg/kg	6 (2.7)
1.5 mg/kg	32 (14.5)
1 mg/kg	170 (76.9)
0.5 mg/kg	13 (5.9)
Maximum time used at maximum dose	
< 2 weeks	74 (33.5)
2 weeks	81 (36.7)
4 weeks	52 (23.5)
> 4 weeks	14 (6.3)
Long-term (> 6 months) treatment with prednis(ol)one	
Yes	84 (38.0)
No	137 (62.4)
Maximum long-term daily dose of prednisolone (n=84 members responding)	
5 mg	36 (42.9)
10 mg	41 (48.8)
15 mg	6 (7.1)
20 mg	1 (1.2)

When using systemic immunomodulatory drugs to treat non-infectious uveitis, Study Group members commonly co-managed the disease with another medical specialist (n=152, 68.8%), who was often a rheumatologist (n=142 of 152: 93.4%). Indications to initiate a systemic immunomodulatory drug included: uveitis not controlled with a course of oral prednis(ol)one (n=208, 94.1%), specific uveitis diagnosis (n=197, 89.1%), patient intolerance of oral prednis(ol)one (n=186, 84.2%), and/or contraindication to locally delivered corticosteroid (n=159, 71.9%). All 221 Study Group members (100%) performed screening tests prior to initiating a systemic immunomodulatory drug, frequently including blood chemistry screen (n=217, 98.2%), complete blood examination (n=207, 93.7%), and the Quantiferon assay (n=196, 88.7%), and almost all members (n=216, 97.7%) gave a course of

oral prednis(ol)one while the drug was taking effect. Considerations when initiating treatment with systemic immunomodulatory drugs are presented in table 2.

Table 2. Considerations when initiating a systemic immunomodulatory drug (N = 221 Study Group members responding, unless otherwise stated).

Clinical Variable	**N (%)**
Co-management of systemic immunomodulatory drug treatment	
Yes	152 (68.8)
No	69 (31.2)
Co-managing practitioner (n=152 members responding)	
With adult and/or paediatric rheumatologist	142 (93.4)
With general internist and/or paediatrician	54 (35.5)
With adult and/or paediatric immunologist	31 (20.4)
With other medical specialist(s)*	26 (17.1)
Indication to commence systemic immunomodulatory drug	
Uveitis not controlled after course of oral prednis(ol)one	208 (94.1)
Specific uveitis diagnosis	197 (89.1)
Patient intolerance of oral prednis(ol)one	186 (84.2)
Contraindication to local (periocular or intraocular) corticosteroid injection or implant	159 (71.9)
Other indication(s)**	45 (20.4)
Pre-commencement investigations	
Blood chemistry screen (including serum creatinine and liver enzymes)	217 (98.2)
Complete blood examination	207 (93.7)
Quantiferon assay	196 (88.7)
Chest X-ray	184 (83.3)
Hepatitis B and C serology	160 (72.4)
HIV serology	127 (57.5)
Vaccine history	96 (43.4)
Urine chemistry	97 (43.9)
Urine microscopy	48 (21.7)
MRI brain	30 (13.6)
Bone scan	13 (5.9)
Adjunctive therapy at commencement of systemic immunomodulatory drug	
Course of oral prednis(ol)one	216 (97.7)
Locally injected corticosteroid	5 (2.3)

*26 Study Group members listed one or more adult or paediatric medical practitioners working in other specialities including dermatology, gastroenterology, general practice, infectious diseases, neurology, and pulmonology.

**45 Study Group members listed one or more other indications including anticipated requirement for long-term prednis(ol)one, bilateral inflammation, chronic course, paediatric patients, patient preference, recurrent course, severe inflammation, and systemic disease requirements.

A complete list of the systemic immunomodulatory drugs used by Study Group members to treat patients with non-infectious uveitis is provided in table 3. Eight conventional drugs were reported: almost all members had used methotrexate in their clinical practice (n=217, 98.2%), and other commonly prescribed conventional drugs included azathioprine (n=198, 89.6%), mycophenolate (n=192, 86.9%), and cyclosporine (n=168, 76.0%). Each of these drugs were selected as a most common first-choice conventional drug, with methotrexate being the preferred first choice for 126 members (57.0%). Fourteen biologic drugs were used, with nearly all Study Group members having used adalimumab to treat their patients (n=218, 98.6%). A majority of Study Group members had also utilised infliximab (n=176, 79.6%), rituximab (n=139, 62.9%), and tocilizumab (n=130, 58.8%). For 216 clinicians (97.7%), adalimumab was the most common first-choice of a biologic drug. Most Study Group members would trial a systemic immunomodulatory drug for 3 to 6 months (n=181, 81.9%) before declaring the drug ineffective and switching to an alternative agent. Although the widely used step-ladder approach involves starting with a conventional systemic immunomodulatory drug, many members (n=133, 60.2%) had utilised a biologic drug ahead of a conventional drug in their clinical practice, for reasons that included specific uveitis diagnoses (n=121 of 133: 91.0%) and contraindications to the available conventional drugs (n=95 of 133: 71.4%).

178 **Table 3**. Conventional and biologic systemic immunomodulatory drugs used to treat non-
179 infectious uveitis (N = 221 Study Group members responding, unless otherwise stated).
180

Clinical variable	N (%)
Conventional systemic immunomodulatory drugs used	
Methotrexate	217 (98.2)
Azathioprine	198 (89.6)
Mycophenolate	192 (86.9)
Cyclosporine	168 (76.0)
Cyclophosphamide	97 (43.9)
Tacrolimus	56 (25.3)
Leflunomide	21 (9.5)
Chlorambucil	19 (8.6)
First-line systemic immunomodulatory conventional drug	
Methotrexate	126 (57.0)
Mycophenolate	44 (19.9)
Azathioprine	33 (14.9)
Cyclosporine	18 (8.1)
Biologic systemic immunomodulatory drugs used	
Adalimumab	218 (98.6)
Infliximab	176 (79.6)
Rituximab	139 (62.9)
Tocilizumab	130 (58.8)
Golimumab	76 (34.4)
Certolizumab	54 (24.4)
Interferon-alpha 2a	44 (19.9)
Anakinra	36 (16.3)
Abatacept	31 (14.0)
Etanercept	25 (11.3)
Interferon-alpha 2b	20 (9.0)
Ocrelizumab	19 (8.6)
Canakinumab	9 (4.1)
Sarilumab	9 (4.1)
First-line systemic immunomodulatory biologic drug	
Adalimumab	216 (97.7)
Infliximab	3 (1.4)
Rituximab	2 (0.9)
Time of drug trial	
< 2 months	9 (4.1)
2 months	22 (10.0)
3 months	88 (39.8)
4 months	32 (14.5)
5 months	1 (0.5)
6 months	60 (27.1)
> 6 months	9 (4.1)

Use of biologic before conventional systemic immunomodulatory drug	
Yes	133 (60.2)
No	88 (39.8)
Indicator for first-line biologic systemic immunomodulatory drug (n=133 members responding)	
Specific uveitis diagnosis	121 (91.0)
Contraindications to available conventional immunomodulatory drugs	95 (71.4)
Standard practice	7 (5.3)
Other indication(s)*	27 (20.3)

*26 Study Group members listed one or more other indications including monocular patients, ocular complications, patient-related considerations, severe inflammation, situations requiring rapid action, and vision-threatening inflammation.

Study Group members provided their first-line conventional and biologic systemic immunomodulatory drugs for specific types of non-infectious uveitis, presented in table 4. Methotrexate was the most common first-line conventional drug for 9 of 11 uveitides, including juvenile idiopathic arthritis-associated uveitis (n=206, 93.2%), HLA-B27-positive uveitis (n=177, 80.1%), sarcoid uveitis (n=138, 62.4%), tubulointerstitial nephritis and uveitis syndrome (n=129, 58.4%), pars planitis (n=122, 55.2%), multifocal choroiditis-punctate inner choroiditis spectrum disease (n=87, 39.4%), serpiginous choroiditis (n=84, 38.0%), sympathetic ophthalmia (n=71, 32.1%), and Vogt-Koyanagi-Harada syndrome (n=70, 31.7%). For some types of non-infectious uveitis, a different conventional drug was more commonly used first: azathioprine (n=115, 52.0%) for Behçet uveitis, and mycophenolate (n=88, 39.8%) for birdshot chorioretinopathy. Adalimumab was the most common first-line biologic drug for 11 uveitides: juvenile idiopathic arthritis (n=215, 97.3%), HLA-B27-associated uveitis (n=213, 96.4%), multifocal choroiditis-punctate inner choroiditis spectrum disease (n=211, 95.5%), tubulointerstitial nephritis and uveitis syndrome (n=210, 95.0%), birdshot chorioretinopathy (n=206, 93.2%), sarcoid uveitis (n=205, 92.8%), Vogt-Koyanagi-Harada syndrome (n=204, 92.3%), pars planitis (n=204, 92.3%), serpiginous choroiditis (n=201, 91.0%), sympathetic ophthalmia (n=198, 89.6%), and Behçet uveitis (n=160, 72.4%).

202 **Table 4**. First-choice conventional and biologic systemic immunomodulatory drugs used to
203 treat different types of uveitis (N = 221 Study Group members responding).
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Uveitis type	Conventional systemic immunomodulatory drug		Biologic systemic immunomodulatory drug	
	Drug	**N (%)**	**Drug**	**N (%)**
HLA-B27-positive	Methotrexate	177 (80.1)	Adalimumab	213 (96.4)
	Mycophenolate	17 (7.7)	Infliximab	5 (2.3)
	Cyclosporine	14 (6.3)	Golimumab	2 (0.9)
	Azathioprine	12 (5.4)	Etanercept	1 (0.5)
	Leflunomide	1 (0.5)		
Sarcoidosis	Methotrexate	138 (62.4)	Adalimumab	205 (92.8)
	Mycophenolate	37 (16.7)	Infliximab	13 (5.9)
	Azathioprine	31 (14.0)	Rituximab	2 (0.9)
	Cyclosporine	15 (6.8)	Etanercept	1 (0.5)
Behçet disease	Azathioprine	115 (52.0)	Adalimumab	160 (72.4)
	Methotrexate	38 (17.2)	Infliximab	51 (23.1)
	Cyclosporine	33 (14.9)	Rituximab	4 (1.8)
	Mycophenolate	29 (13.1)	Interferon-alpha 2a	4 (1.8)
	Cyclophosphamide	4 (1.8)	Tocilizumab	2 (0.9)
	Tacrolimus	2 (0.9)		
Vogt-Koyanagi-Harada syndrome	Methotrexate	70 (31.7)	Adalimumab	204 (92.3)
	Mycophenolate	68 (30.8)	Infliximab	11 (5.0)
	Azathioprine	48 (21.7)	Rituximab	4 (1.8)
	Cyclosporine	33 (14.9)	Tocilizumab	2 (0.9)
	Tacrolimus	1 (0.5)		
	Cyclophosphamide	1 (0.5)		
Pars planitis	Methotrexate	122 (55.2)	Adalimumab	204 (92.3)
	Mycophenolate	46 (20.8)	Infliximab	9 (4.1)
	Azathioprine	34 (15.4)	Tocilizumab	4 (1.8)
	Cyclosporine	17 (7.7)	Rituximab	2 (0.9)
	Tacrolimus	1 (0.5)	Interferon-alpha 2a	2 (0.9)
	Cyclophosphamide	1 (0.5)		
Birdshot chorioretinopathy	Mycophenolate	88 (39.8)	Adalimumab	206 (93.2)
	Methotrexate	69 (31.2)	Infliximab	10 (4.5)
	Azathioprine	36 (16.3)	Tocilizumab	3 (1.4)
	Cyclosporine	27 (12.2)	Rituximab	1 (0.5)
	Cyclophosphamide	1 (0.5)	Interferon-alpha 2a	1 (0.5)
Multifocal choroiditis-Punctate inner choroiditis	Methotrexate	87 (39.4)	Adalimumab	211 (95.5)
	Mycophenolate	69 (31.2)	Infliximab	8 (4.1)
	Azathioprine	44 (19.9)	Anakinra	1 (0.5)
	Cyclosporine	21 (9.5)	Tocilizumab	1 (0.5)
Sympathetic ophthalmia	Methotrexate	71 (32.1)	Adalimumab	198 (89.6)
	Mycophenolate	66 (29.9)	Infliximab	18 (8.1)
	Cyclosporine	41 (18.6)	Rituximab	3 (1.4)
	Azathioprine	36 (16.3)	Golimumab	1 (0.5)
	Cyclophosphamide	4 (1.8)	Tocilizumab	1 (0.5)
	Tacrolimus	2 (0.9)		
	Chlorambucil	1 (0.5)		
Serpiginous choroiditis	Methotrexate	84 (38.0)	Adalimumab	201 (91.0)
	Mycophenolate	61 (27.6)	Infliximab	12 (5.4)
	Azathioprine	51 (23.1)	Interferon-alpha 2a	5 (2.3)
	Cyclosporine	22 (10.0)	Golimumab	2 (0.9)
	Chlorambucil	2 (0.9)	Rituximab	1 (0.5)
	Tacrolimus	1 (0.5)		

Juvenile idiopathic arthritis-associated	Methotrexate Azathioprine Mycophenolate Cyclosporine	206 (93.2) 5 (2.3) 5 (2.3) 5 (2.3)	Adalimumab Infliximab Golimumab Anakinra	215 (97.3) 4 (1.8) 1 (0.5) 1 (0.5)
Tubulointerstitial nephritis + uveitis syndrome	Methotrexate Mycophenolate Azathioprine Cyclosporine Cyclophosphamide	129 (58.4) 52 (23.5) 29 (13.1) 10 (4.5) 1 (0.5)	Adalimumab Infliximab Tocilizumab Rituximab Etanercept Interferon-alpha 2a	210 (95.0) 7 (3.2) 1 (0.5) 1 (0.5) 1 (0.5) 1 (0.5)

Most Study Group members (n=188, 85.1%) combined systemic immunomodulatory drugs in their clinical practice. A total of 61 different combinations of systemic immunomodulatory drugs were reported, the most common being the combination of methotrexate and adalimumab (n=158 of 188 members responding, 84.0%). A list of the drug combinations used by 5% or more Study Members is presented in online supplemental table 2.

Study Group members often evaluated patients with inactive non-infectious uveitis on stable immunomodulatory drug treatment every 6 to 12 weeks (n= 161, 72.9%). Routine investigations, including blood chemistry (n=213, 96.4%) and complete blood examination (n=195, 88.2%), were commonly checked to monitor patients for any drug toxicity. Members obtained these routine tests frequently, with approximately one-half repeating the investigations every 12 weeks (n=116, 52.5%). Most Study Group members required that the uveitis was inactive for at least 2 years before considering cessation of the systemic immunomodulatory drug (n=199, 90.0%). When cataract surgery was indicated, there was general agreement within the Study Group that the uveitis should be inactive for at least 3 months prior to the operation (n=210, 95.0%). All Study Group members employed a range of perioperative measures to reduce the likelihood of the inflammation flaring post-operatively, including oral prednis(ol)one (n=174, 78.7%), periocular corticosteroid injections (n=105, 47.5%), intravitreal corticosteroid injections or implants (n=84, 38.0%),

225 conventional systemic immunomodulatory drugs (n=62, 28.1%), and biologic systemic
226 immunomodulatory drugs (n=47, 21.3%). The management of patients with inactive non-
227 infectious uveitis, and considerations for cataract surgery are outlined in table 5.
228

Table 5. Evaluation of inactive non-infectious uveitis and considerations for cataract surgery (n=221 study group members responding).

Clinical variable	N (%)
Routine evaluation of uveitis	
< 6 weekly	19 (8.6)
6-10 weekly	55 (24.9)
12 weekly	106 (48.0)
14-16 weekly	23 (10.4)
> 16 weekly	18 (8.1)
Routine systemic immunomodulatory drug monitoring	
Blood chemistry screen	213 (96.4)
Complete blood examination	195 (88.2)
Urine chemistry	45 (20.4)
Urine microscopy	19 (8.6)
Chest x-ray	14 (6.3)
Other test(s)*	13 (5.9)
Frequency of routine drug monitoring	
< 6 weekly	17 (7.7)
6-10 weekly	49 (22.2)
12 weekly	116 (52.5)
14-16 weekly	24 (10.9)
> 16 weekly	15 (6.8)
Time of inactivity before drug cessation	
< 2 years	57 (25.8)
2 years	142 (64.3)
3 years	17 (7.7)
> 3 years	5 (2.3)
Time of uveitis inactivity before cataract surgery	
< 3 months	11 (5.0)
3-4 months	173 (78.2)
5-6 months	35 (15.8)
> 6 months	2 (0.9)
Perioperative prophylaxis for cataract surgery	
Oral prednis(ol)one	174 (78.7)
Topical corticosteroid	167 (75.6)
Periocular corticosteroid injection**	105 (47.5)
Intravitreal corticosteroid injection or implant**	84 (38.0)
Conventional systemic immunomodulatory drug	62 (28.1)
Biologic systemic immunomodulatory drug	47 (21.3)
Intravenous corticosteroid	15 (6.8)
Other***	7 (3.2)

*13 Study Group members listed one or more other tests including drug-specific tests, erythrocyte sedimentation rate or C-reactive protein, hepatitis B or C serology, lipid tests, and interferon-gamma response assay.

** Study Group members reported giving periocular corticosteroid injections or intravitreal corticosteroid injections/implants both at the time of cataract surgery and/or in the lead-up to the surgery.

***7 Study Group members listed other treatments that included intracameral corticosteroid injections and topical non-steroidal anti-inflammatory drugs.

DISCUSSION

There have been a number of expert recommendations published on the use of systemic immunomodulatory drug treatment for non-infectious uveitis.[18-20] This report by the *International Study Group for Systemic Immunomodulatory Drug Treatment of Non-infectious Uveitis* provides a unique description of the current real-world approach taken by 221 uveitis-specialised ophthalmologists practising across 53 countries. Over 90% of these clinicians applied the SUN Working Group nomenclature when assessing uveitis, and approximately two-thirds of them co-managed systemic immunomodulatory drug use with an internist, most commonly a rheumatologist. There was a remarkably consistent approach by the Study Group overall, including in the use of prednis(ol)one, the selection of conventional and biologic immunomodulatory drugs, and indications for treatment, pre-treatment screening and drug monitoring.

To achieve rapid control of non-infectious uveitis, treatment with oral glucocorticoid in the form of prednis(ol)one is a decades-old approach that remains common today.[18,21] However, the protean and multi-system adverse events of prednis(ol)one are well recognised, and thus long-term use has generally been avoided.[22] In using prednisolone, the majority of Study Group members limited the initial dose to 1 mg/kg/day, given for under one month, and did not continue the drug past 6 months. Recent rheumatological literature suggests long-term use of low-dose prednisolone may have a place in the treatment of non-infectious inflammatory disease. For example, results of the Glucocorticoid LOw-dose in RheumatoId Arthritis (GLORIA) randomised clinical trial supported 2 years of adjunctive prednisolone 5 mg/day in patients with established rheumatoid arthritis: compared with placebo, prednisolone-treated patients experienced improved disease control with a 1.24-

fold higher risk of complications, mostly non-severe infections.[23] Although the role of long-term low-dose prednis(ol)one for non-infectious uveitis has not been explored systematically, the SITE Cohort Study considered 10 mg/day or less as corticosteroid-sparing.[11-14] Interestingly, approximately one-third of Study Group members prescribed prednis(ol)one past 6 months, with approximately equal proportions favouring doses of 5 mg or 10 mg daily.

For Study Group members, there were multiple common reasons for initiating systemic immunomodulatory drugs for non-infectious uveitis, including ongoing need for inflammation control after taper of oral prednis(ol)one, intolerance of oral prednis(ol)one, contraindication to local corticosteroid, and specific uveitis diagnoses. Study Group members, most of whom managed in excess of 100 patients with uveitis in the year, had broad experience in using these drugs, including 22 different conventional and biologic drugs. The majority used systemic immunomodulatory therapy for 2 years or more to maintain control of the inflammation.

Methotrexate was the most common first-choice conventional drug across Study Group members, both in general and for 9 of 11 specified types of uveitis. Selection of methotrexate is consistent with published literature. The SITE Cohort Study publications suggested superiority of anti-metabolite drugs – methotrexate, mycophenolate mofetil, and azathioprine – over the T-cell inhibitor – cyclosporine – for non-infectious uveitis.[11-14] In the recent First-line Antimetabolites as Steroid-sparing Treatment (FAST) randomised, comparative effectiveness clinical trial, treatment success was not significantly different between methotrexate and mycophenolate mofetil for all forms of non-infectious uveitis

involving the posterior segment, but significantly higher with methotrexate for posterior and pan- uveitis.[24] An earlier clinical study that used retention time to compare multiple conventional immunomodulatory drugs showed methotrexate to be superior to mycophenolate mofetil, azathioprine, cyclosporine, and cyclophosphamide for non-infectious inflammatory eye disease.[25]

Biologic immunomodulatory drugs have been developed to target pathogenic molecules or pathways, and with increasing understanding of the mechanisms of uveal inflammation, the potential spectrum of these agents for uveitis continues to expand.[26] More than half of the Study Group have initiated a biologic drug first when there were contraindications to available conventional drugs or for specific types of uveitis. To date within the uveitis field, TNF-α blocker, adalimumab, has been studied most extensively in randomised controlled phase III clinical trials: the VISUAL I and II trials showed effectiveness for controlling active or preventing flares of quiescent non-infectious intermediate, posterior or pan- uveitis in comparison to placebo,[15,16] while the Randomised controlled trial of the clinical effectiveness, SafetY and Cost effectiveness of Adalimumab in combination with MethOtRExate for the treatment of juvenile idiopathic arthritis-associated uveitis (SYCAMORE) demonstrated improvement in control of methotrexate-treated uveitis in the comparison with placebo.[27] These results have led to widespread regulatory approval of adalimumab for non-infectious uveitis, including by the US Food and Drug Administration and the European Medicines Agency.[28] Not unexpectedly therefore, adalimumab was the first-line biologic drug of choice across the Study Group, in general and for 11 specified uveitides. Notably however, TNF-α blockade has been associated with demyelination, and

thus adalimumab is contraindicated in patients who suffer from both uveitis and multiple sclerosis.[29]

Cataract contributes to the morbidity of non-infectious uveitis.[30] Although vision is often substantially improved postoperatively,[31] surgery for uveitic cataract is frequently presents technical challenges, and there is potential to exacerbate the inflammation – and associated cystoid macular oedema – thorough the surgical procedure.[32,33] Over 90% of the Study Group set the requirement for non-infectious uveitis to be inactive for at least 3 months prior to cataract surgery. This is consistent with the observation that the risk of cystoid macular oedema is increased significantly in eyes with active uveitis compared with inactive uveitis within 3 months of cataract surgery.[34] Study Group members frequently augmented anti-inflammatory therapy with glucocorticoid drugs around the time of surgery, including by topical, injected and oral routes.

Although not addressed in our work, an interesting related issue is geographic variation in immunomodulatory treatment for non-infectious uveitis, and the reasons behind any differences between countries. This issue would certainly be impacted by the availability of drugs, particularly the relatively more costly biologic drugs. The World Health Organization Model List of Essential Medicines represents the minimum drug requirements for a health-care system.[35] The current list includes most conventional drugs, as well as some biologic drugs, used by Study Group members to treat uveitis: considering those drugs used by at least one-half of the group, only mycophenolate and tocilizumab are not on this list.

Our work is limited by participation bias since the *International Study Group for Systemic Immunomodulatory Drug Treatment of Non-infectious Uveitis* was formed within one professional society and publicised through that society's electronic communication channel and at its bi-annual meeting. Further, as information was collated via electronic questionnaire, the findings that we present is limited by the items posed and the responses provided. However, with its large size and broad international coverage, the documented experience of the Study Group provides a current information regarding the real-world use of systemic immunomodulatory drugs for non-infectious uveitis that can be used by ophthalmologists in their everyday clinical practice. Our key findings are the prioritised uses of methotrexate as conventional drug and adalimumab as biologic drug in the management of this important inflammatory eye disease.

DECLARATIONS

Abbreviations

First-line Antimetabolites as Steroid-sparing Treatment (FAST), Glucocorticoid LOw-dose in RheumatoId Arthritis (GLORIA), International Ocular Inflammation Society (IOIS), SafetY and Cost effectiveness of Adalimumab in combination with MethOtRExate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE), Standardization of Uveitis Nomenclature (SUN), Systemic Immunosuppressive Therapy for Eye Diseases (SITE), Tumour necrosis factor-alpha (TNF-α).

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JAB, BB, LBF, PJM, JET, and JRS designed the questionnaire; JAB administered the questionnaire; JAB, JMM, and JRS collated the questionnaire responses; JAB, JMM, and JRS drafted the manuscript; JAB, BB, LBF, PJM, JET, JMM, and JRS reviewed and edited the draft.

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