South African National Essential Medicine List
Primary Healthcare/ Adult Hospital Level of Care Medication Review Process
Component: Eye conditions

MEDICINE REVIEW

1. Executive Summary

Date: July 2023
Medicine (INN): Non-biologic corticosteroid-sparing agents: methotrexate, azathioprine, cyclosporine
Medicine (ATC): L01BA01 (methotrexate), L04AX01 (azathioprine) , L04AD01 (cyclosporine)
Indication (ICD10 code): H30.23
Patient population: Adult patients with non-infectious severe bilateral posterior uveitis and panuveitis.
Level of Care: Adult Hospital Level of care
Prescriber Level: Doctor prescribed
Motivator/reviewer name(s): Zahiera Adam, Prof Linda Visser, Dr Farah Moti

Key findings

- Inflammatory eye disease may be infectious or non-infectious in aetiology which could be restricted to the eye or associated with systemic disease. Uveitis is often classified anatomically based on the primary site of inflammation: anterior uveitis (iris and ciliary body), intermediate uveitis (vitreous), posterior uveitis (retina or choroid) and panuveitis (whole eye), with posterior segments of the eye generally associated with more severe disease.
- Corticosteroids are the mainstay of treatment for patients with non-infectious uveitis, although the optimal dose and/or duration of corticosteroid therapy is not clear. **However, the systemic and ocular side effects associated with prolonged use of corticosteroids is well-documented. Immunomodulatory drugs may be required to prevent complications from long-term corticosteroid use, or to manage steroid resistant disease.**
- The aim of this review is to compare the safety and efficacy of three non-biologic, disease-modifying anti-rheumatic drugs (DMARDs), namely methotrexate, azathioprine and cyclosporine for the management of non-infectious, severe posterior uveitis and panuveitis in patients who are refractory to corticosteroids or who require ongoing corticosteroids to maintain inflammation control.
- We identified three clinical guidelines (CG), of which, only one (Dick AD et al, 2018) was deemed to be of sufficient quality to report on (AGREE II score= 83%). A search of Pubmed, the Cochrane Library and Epistemonikos identified 3 systematic reviews (SRs), one of which has not been included (Karam M et al, 2022) as a full text reference could not be sourced. The pre-specified PICO included the use of 3 DMARDs as monotherapy (methotrexate, azathioprine and cyclosporine) as the intervention in adult patients with non-infectious posterior and panuveitis. However, following a review of the published literature, it was noted that no direct evidence that addressed the pre-specified PICO could be identified, and it was agreed that the PICO would be amended to better reflect trends in clinical practice i.e. the intervention was amended to include DMARDs in combination with corticosteroids.
- The CGs and SRs identified all recommend the use DMARDs for the management of non-infectious posterior and panuveitis – recommendations are informed primarily by observational studies and expert opinion.
- In the absence of robust RCT evidence, we summarised key efficacy and safety outcomes from cohort studies and case series as referenced in the guideline by (Dick AD et al, 2018).
- **Methotrexate:** has demonstrated efficacy with control of inflammation, steroid-sparing ability as well as the maintenance and improvement of visual acuity (Evidence level 2B, *Cohort studies)* (Dick AD et al, 2018).
- **Azathioprine:** is described as having moderate efficacy for control of inflammation and corticosteroid-sparing effects in patients with intermediate, posterior and panuveitis (Evidence level 2B, *Cohort studies)*. Evidence for improvements in visual outcomes is noted as lacking. Azathioprine demonstrated moderate efficacy in

inflammation control and a significant steroid-sparing effect in patients with severe uveitis secondary to Behçet's disease. Results from a SR (E Mayhew RG, 2022) suggests that corticosteroids with or without azathioprine results in little to no difference when compared to cyclosporine in the control of inflammation (RR 0.84, where < 1 favors cyclosporine A, 95% CI 0.70 to 1.02; I^2 = 0%), but is very uncertain.

- **Cyclosporine:** RCTs published between 1986 and 1993 generally used higher doses of cyclosporine (8 mg to 15 mg/kg/day) than is currently used in clinical practice. The more recently published studies between 2010 and 2021 used lower doses of cyclosporine which ranged from 3 mg to 5 mg/kg/day. Cyclosporine A plus oral steroid was not found to be superior to IV pulse of steroid plus steroid taper (Ono 2021) or azathioprine plus oral steroid (Cuchacovich 2010) for both efficacy and safety outcomes (low- or very low-certainty evidence).
- Overall, there is a paucity of data to recommend the use of one non-biologic DMARD over another in the management of non-infectious uveitis, based on either safety or efficacy. The few RCTs that were identified, included relatively small numbers of study participants in select patient groups. The heterogeneity in study design and reported outcomes do not readily support combined review through meta-analysis. Furthermore, application to the local setting is limited due to an under-representation of the African continent based on the geographic location of the included studies and the significant proportion of participants with Vogt-Koyanagi-Harada [VKH] disease in the key systematic review (SR) by (E Mayhew RG, 2022), as well as exclusion of HIV positive individuals in the SITE cohort study (Kempen JH et al, 2008).

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: The PHC/ Adult Hospital Level Committee suggests using methotrexate for the management of non-infectious posterior uveitis or panuveitis in patients who are refractory to corticosteroids or who require ongoing corticosteroids to maintain inflammation control. The recommendation is based on the limited observational data supporting the use of methotrexate for the management of non-infectious posterior uveitis or panuveitis.

Rationale: The potential harms with long term corticosteroid exposure is a concern as well as the risks of progression to blindness if inflammation is not controlled. Methotrexate is the cheapest of the DMARDs reviewed and is widely used for multiple indications already approved on the EML.

Level of Evidence: Low certainty

Review indicator: New RCT data for efficacy or safety.

NEMLC RECOMMENDATION (30 NOVEMBER 2023): NEMLC supports the recommendation by the ERC as above.

Monitoring and evaluation considerations

Research priorities

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BACKGROUND

Uveitis encompasses a broad spectrum of conditions which could range from relatively benign to sight threatening. The annual incidence of uveitis is estimated at 14–50 per 100 000 with a prevalence of around 38–200 per 100 000 general population (Durrani OM et al, 2004). To our knowledge, accurate local prevalence data is not available, however uveitis is stated to account for up to 25% of total blindness in the developing world (Rao, 2013).

Inflammatory eye disease may be infectious or non-infectious in aetiology which could be restricted to the eye or associated with systemic disease. Infectious uveitis may be caused by viruses including HSV and VZV (after ophthalmic shingles), syphilis and tuberculosis (TB) and antimicrobial therapy is guided by the underlying cause of the inflammation.

Non-infectious uveitis may be associated with systemic disease and could include the following aetiologies: sarcoidosis, Behçet's disease, ankylosing spondylitis, inflammatory bowel disease, juvenile idiopathic arthritis, seronegative arthropathy, reactive arthritis, multiple sclerosis and Vogt-Koyanagi-Harada syndrome. Uveitis may be further classified as follows (The Standardization of Uveitis Nomenclature (SUN) Working Group , 2005)

- Anatomically based on the primary site of inflammation: anterior uveitis (iris and ciliary body), intermediate uveitis (vitreous), posterior uveitis (retina or choroid) and panuveitis (whole eye)
- Onset of inflammation: sudden or insidious
- Duration of inflammation: Limited (</= 3 months duration) or Persistent (>3 months duration)
- Course of disease: Acute (Episode characterized by sudden onset and limited duration), Recurrent (Repeated episodes separated by periods of inactivity without treatment ≥3 months in duration), Chronic (Persistent uveitis with relapse in <3months after discontinuing treatment)

Non-infectious intermediate, posterior and panuveitis (NIIPPU) may be sight limiting if inflammation is not controlled. The pathophysiology of NIIPPU is not well understood and it is believed that both auto-inflammatory and autoimmune processes may be involved which often presents as a chronic course of disease (E Mayhew RG, 2022). NIPPU are generally managed with similar systemic therapies and are often grouped together in clinical studies even though the aetiologies are wide ranging. This does present significant heterogeneity challenges when reviewing published data.

Prompt therapy and rapid control of ocular inflammation are the key to maintaining good visual acuity. Corticosteroids are the mainstay of treatment for patients with non-infectious uveitis. However, the systemic and ocular side effects associated with prolonged use of corticosteroids is well-documented. Common systemic complications associated with long term corticosteroid use includes diabetes, systemic hypertension, osteoporosis and mood disorders, with cataracts and raised intraocular pressure noted as ocular complications. Lens opacity rarely improves following drug withdrawal and a persistently raised intraocular pressure may lead to open-angle glaucoma (Rossi DC et al, 2019).

It is not clear what the optimal dose and/or duration of corticosteroid use is to minimise the risk of ocular side effects. Based on a review conducted by (Dammacco R et al, 2022), daily corticosteroid use (equivalent to prednisolone 10mg

daily) for longer than one year leads to the onset of cataracts in approximately 75% of patients but even low doses of 5mg daily for 2 months in susceptible individuals may lead to the onset of posterior subcapsular cataracts.

Immunomodulatory drugs may be required to prevent complications from long-term corticosteroid use or to manage steroid resistant disease. In order to limit steroid side-effects, classic immunosuppressant agents have been widely used as steroid-sparing agents, particularly with steroid doses still over 10mg/day after six months of therapy (Jabs D et al, 2000).

RESEARCH QUESTION

How do the corticosteroid-sparing agents (methotrexate, azathioprine and cyclosporine) compare in terms of efficacy and safety for the management of non-infectious, severe posterior uveitis and panuveitis?

ELIBILITY CRITERIA FOR REVIEW

Population	Adult patients with non-infectious posterior uveitis or panuveitis
Intervention	Oral corticosteroids in combination with any one of the following DMARDs • Methotrexate (MTX), OR • Azathioprine (AZA), OR • Cyclosporine (CS)
Comparator	• Oral corticosteroids
Outcomes	**Efficacy** • Improved visual outcome and better resolution of disease **Safety** • Ocular and systemic side effects
Study designs	Clinical practice guidelines, systematic reviews of randomised controlled trials (RCTs), RCTs.

Note: While in the process of undertaking the literature screen and summary, a decision was taken to amend the pre-specified PICO (see Appendix 1) to better reflect clinical practice. More specifically, the intervention was amended to include the use of DMARDs (methotrexate, azathioprine and cyclosporine) in combination with oral corticosteroids for the management of severe posterior and panuveitis. As the original literature search was sufficiently broad, we did not deem it necessary to revise the literature search. Furthermore, the inclusion and exclusion criteria as stated in the pre-specified PICO were also retained.

METHODS

a. Data sources:

The websites of organisations identified by local experts as credible authorities for guideline development (European Society of Ophthalmology, Royal College of Ophthalmologists, American Uveitis Society) were searched for relevant guidelines. Additionally, a free text google search was undertaken to identify clinical guidelines/reviews from recognized clinical bodies/authorities within the ophthalmology specialty. Systematic reviews (SRs) and randomised controlled trials (RCTs) were sought in PubMed, the Cochrane Library, and Epistemonikos.

b. Search strategy:

A search for systematic reviews and meta-analyses was conducted on the 9 November 2022 from the following databases: Pubmed, the Cochrane Library and Epistemonikos. Details of the Pubmed search strategy and search terms are included Appendix 2.

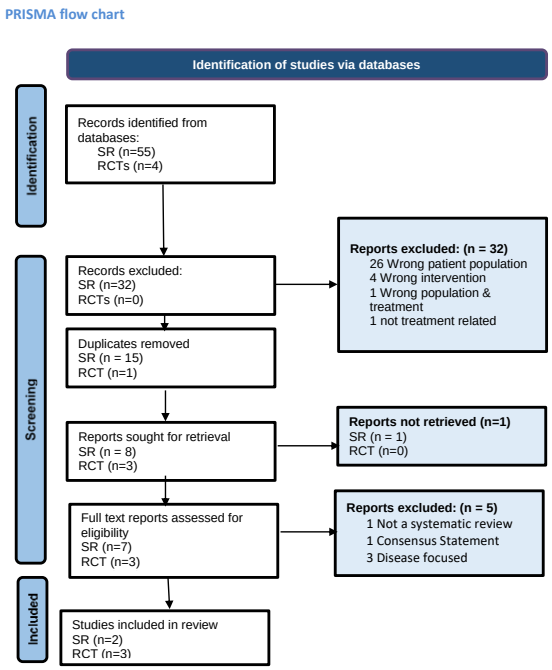
Screening, data extraction and analysis, evidence synthesis: Titles and abstracts were screened independently (ZA) and a spot check conducted by (FM). Full text screening was by (ZA) with spot checks by (FM). Eligible clinical guidelines were

appraised with the AGREE II tool and eligible systematic reviews were appraised using the AMSTAR II Checklist independently by two reviewers (ZA and VN), with discrepancies resolved following discussion.

RESULTS

Search results:

The literature search yielded 55 records – refer to the PRISMA diagram below for details on the screening process (see Appendix 2 for the list of excluded studies). Of the three SRs considered for inclusion, an AMSTAR II rating was completed for two studies, as a full text article by (Karam M et al, 2022), could not be sourced. The SR by (E Mayhew RG, 2022) was assessed as a high quality review and the (Gomez-Gomez A , 2020) SR was assessed as low quality based on the AMSTAR II assessment.



DESCRIPTION OF CLINICAL GUIDELINES, SYSTEMATIC REVIEWS AND RCTs IDENTIFIED

a. Guidelines

Search results from the list of organisations reviewed as follows:

- NICE guidance[1] – no relevant technology appraisals or clinical guidelines identified
- American Academy of Ophthalmologists (AAO)[2] - see table 1 below for guideline summary

Following a free text google search, the following clinical guidelines were identified.

- Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel (Jabs D et al, 2000)
- Scottish Uveitis National Managed Clinical Network Treatment Guidelines (Scottish Uveitis National Managed Clinical Network, Revised September 2010)

The guidelines that were identified and appraised were of variable quality, with AGREE II scores ranging from 8%-83% (Table 1). With the exception of the guideline by (Espinosa G et al, 2020) which specifically refers to non-anterior uveitis, the guidelines listed below have not excluded reference to anterior uveitis. The original scope of the guideline by (Dick AD et al, 2018) included only non-anterior uveitis, however, the guideline authors indicated that limited information was

[1] NICE guidelines | NICE guidance | Our programmes | What we do | About | NICE
[2] American Academy of Ophthalmology: Protecting Sight. Empowering Lives - American Academy of Ophthalmology (aao.org)

available when the searches were restricted to non-anterior uveitis. As the evidence assessed by the authors was deemed to be more broadly applicable, the guideline applies to the general management of non-infectious uveitis with reference to specific types of uveitis where relevant.

Table 1: Guidelines and recommendations for management of uveitis

Citation	Recommendation	AGREE II score
(Dick AD et al, 2018)* **American Academy of Ophthalmology Fundamentals of Care (FOCUS) Initiative**	<u>Determining factors for initiating DMARDs:</u> • To control persistent or severe inflammation (*impairment of visual function, bilateral disease, vitreous haze, macular or optic nerve disease, retinal vascular inflammation, macular oedema, exudative detachment, or ocular structural complications that threaten visual function)* • To prevent ocular structural complications that present a risk to visual function • Contra-indications or intolerance to other therapies • Need for corticosteroid-sparing effect to maintain disease remission (grade C recommendation) <u>Clinical criteria to adjust systemic therapy:</u> • 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 (grade B/C recommendation) <u>If the DMARD is not adequately effective:</u> • Before a change in therapy is considered, ensure medication adherence and exclude infectious uveitis and masquerade syndromes (grade B recommendation) • Dose escalation to the maximum tolerated therapeutic dose before considering an alternative (grade B recommendation) • If the initial DMARD is not effective transition to an alternative or additional agent. (grade A recommendation) • Choice of therapy to be individualised based on patient's history, aetiology and other systemic comorbidities (grade C recommendation) <u>Withdrawal of treatment:</u> • Treatment withdrawal should be individualised and informed by: patient preference, tolerance and risk to treatment, duration of disease control, aetiology (grade C recommendation) <u>Evidence to guide the selection of DMARDs:</u> • Data for the most commonly used non-biologic DMARDs are included in Appendix 7, although many studies did not distinguish between different aetiologies and subtypes of uveitis	83%
(Espinosa G et al, 2020)** **Recommendations statement on the immunosuppressive treatment of non-infectious, non-neoplastic, non-anterior uveitis**	• See Appendix 8 for a list of the 34 guideline recommendations	50%
(Jabs D et al, 2000)*** **Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel**	• Recommendations not listed due to low scoring on AGREE II assessment *Guideline authors support the use of DMARDs if there is no response after 2 to 4 weeks of high dose corticosteroids or if the patient's disease worsens while on high dose corticosteroids. DMARDs are also recommended where chronic suppression of disease requires more than 10mg/day of prednisone.*	33%
(Scottish Uveitis National Managed Clinical Network, Revised September 2010) **Uveitis NMCN Treatment Guidelines**	• Recommendations not listed due to low scoring on AGREE II assessment. *Guideline authors support the use of DMARDS for chronic immunosuppression (prednisone >7.5mg/day), lack of response to adequate doses of corticosteroids, reactivation during steroid dose tapering.*	8%

*Quality of evidence was defined using the Oxford Centre for Evidence-Based Medicine levels of evidence criteria grading:

- Level of evidence: 1a= Systematic reviews of RCTs, 1b=RCT, 2a= SR of cohort studies, 2b=cohort studies, 3a= SR of case-controls studies, 3b=case-control studies, 4=case series, 5=narrative (literature reviews, editorials.
- A=consistent kevel 1 studies, B=consistent level 2 or 3 studies or extrapolations from level 1 studies, C= level 4 studies or extrapolations from level 2 or 3 studies, D=level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

** The Jadad scale was used for clinical trials and the Oxford scale for the rest of the designs to assess the methodological quality of the included studies

***Recommendations were rated according to the strength and quality of available evidence. The categories have been adapted from Gross and associates[3]

[3] Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. Infectious Diseases Society of America. Clin Infect Dis 1994;18:421.

American Academy of Ophthalmology Fundamentals of Care (FOCUS) Initiative (Dick AD et al, 2018)

The Fundamentals of Care for Uveitis (FOCUS) initiative, was a global initiative organized to achieve consensus through evidence synthesis on optimal systemic treatment of patients with non-infectious uveitis. The initiative involved an international steering committee (ISC) comprising 9 international experts in uveitis, including 7 ophthalmologists and 2 rheumatologists. A further 130 uveitis specialists across 28 countries were included to provide input at a local level. The initiative was convened by AbbVie who are reported to have no involvement in the methodology, data collection, analysis or completion of the report.

The initiative included a literature search spanning January 1996 to August 2016 for relevant publications in English. The literature search included RCTs, prospective and retrospective studies, case series with >/=1 patients, peer reviewed articles, and conference abstracts. A systematic review was undertaken to support the final consensus statement. The authors noted that while the original scope of the analysis included only non-anterior uveitis, much of the evidence applied to a broader anatomical scope. As a result, most of the guideline statements apply generally to non-anterior uveitis unless explicitly stated otherwise.

While cohort studies were not included in our pre-specified PICO, a number of the recommendations in the Fundamentals of Care for Uveitis (FOCUS) initiative, were informed by cohort studies. In view of the lack of suitable RCT evidence identified from our literature search, we have reported on some of the key cohort studies that informed recommendations in the FOCUS initiative as detailed further below.

b. Systematic reviews

We identified two SRs for inclusion. A full text reference for the third SR (Karam M et al, 2022) could not be sourced.

- (E Mayhew RG, 2022)
- (Gomez-Gomez A , 2020)

Based on the AMSTAR II quality assessment of the two SRs identified**,** we focussed on the outcomes of the more recently published and high quality Cochrane review (E Mayhew RG, 2022). However, as significant overlap in RCTs was noted between the (E Mayhew RG, 2022) and (Gomez-Gomez A , 2020) SRs, a high level overview of the (Gomez-Gomez A , 2020) review is included even though the AMSTAR II assessment identified this as a low quality review. Furthermore, a gap analysis was conducted to assess for RCTs that were excluded from the Cochrane review (E Mayhew RG, 2022), which also cited the (Gomez-Gomez A , 2020) publication.

Edwards Mayhew *et al* (2022)

This recently published Cochrane review compared the effectiveness and safety of selected DMARDs (methotrexate, mycophenolate mofetil, tacrolimus and azathioprine) in the treatment of non-infectious intermediate, posterior and panuveitis (NIIPPU) in adults. The review included 11 RCTS (in which 7 studies n<50) and a total of 601 participants, which included a mix of adults, adolescents, and children (7 RCTs were in adults only). While our PICO is focussed on adult patients, the Cochrane reviewers (E Mayhew RG, 2022), acknowledge that they planned on including trials with adult participants only (age 18 and over), which was subsequently changed to include trials with a mix of adults, adolescents, and children but excluded trials where all participants were under 18 years old. As the majority of RCTs included in (E Mayhew RG, 2022) involved adults, we did not exclude this SR.

The reviewers compared each of the DMARDS under review with placebo or with standard of care (e.g. topical steroids with or without systemic steroids), or with each other. DMARDs with overlapping mechanisms of action (e.g. tacrolimus versus cyclosporine) were not compared. The review focussed on 4 critical outcomes which were assessed at 6 and 12 months follow-up: Proportion of participants achieving control of inflammation, Change in best corrected visual acuity (BCVA), Proportion of participants achieving a 2-line improvement in visual acuity and Proportion of participants with macular oedema, confirmed by optical coherence tomography (OCT). Other important efficacy, safety and cost effectiveness outcomes were also assessed at 6 and 12 months follow up. (Refer to Appendix 3 for types of outcome measures and how they were assessed by the Cochrane reviewers).

Note that this SR included the use of mycophenolate mofetil and tacrolimus which are outside the scope of our pre-defined PICO.

Gomez-Gomez (Gomez-Gomez A , 2020)

This systematic review was undertaken to evaluate the published evidence regarding the use of immunomodulatory drugs (including biologicals) in adult patients with non-infectious non-anterior (NINA) uveitis. NINA uveitis included intermediate (IU) and posterior uveitis (PU), panuveitis (PanU) and macular oedema (ME). This SR included a wider range of DMARDs compared to our stated PICO, including: methotrexate (MTX), cyclosporine A and G (CsA, CsG), azathioprine (AZA), cyclophosphamide (CYC), mycophenolate mofetil (MMF), tacrolimus, sirolimus, chlorambucil, interferon b (IFN-b), IFN-a and biologic therapies such as infliximab (IFX), adalimumab (ADA), golimumab, certolizumab), rituximab (RTX), secukinumab, sarilumab and daclizumab. Outcomes that were considered, included control of inflammation, steroid-sparing effects, visual acuity (VA), best corrected visual acuity (BCVA), and reduction of the number of uveitis flares and adverse events (AEs). Nineteen RCTs were included in the SR and the Jadad score was used to grade the quality of evidence.

This SR (Gomez-Gomez A , 2020) which is also cited in the more recently published Cochrane review by Mayhew (E Mayhew RG, 2022) discusses the evidence for each of the immunosuppressant drugs listed above. With specific reference to the DMARDs included in our PICO, we noted an overlap of five RCTS between the (Gomez-Gomez A , 2020) and (E Mayhew RG, 2022) SRs (refer to Appendix 4). Of the five overlapping studies, Gomez et al assessed 3 studies to be of good quality and 2 studies of low quality evidence (assessed based on the Jadad scale). Furthermore, a gap analysis identified three small RCTs (n < 30 in each study) that were included in the (Gomez-Gomez A , 2020) SR that were not included in the Cochrane review. Two of the three RCTS were assessed as not relevant to our PICO, due to wrong comparators, and the third study was a VKH only sub-analysis of the (Rathinam SR et al, 2014) study which was included in the Cochrane review (Refer to Appendix 5 for study details).

The authors of (Gomez-Gomez A , 2020) conclude that classical immunomodulatory drugs such as methotrexate, azathioprine and cyclosporine are effective in intermediate and posterior uveitis. The authors, however noted that although azathioprine is widely used for ocular inflammation (Pasadhika, S et al, 2009), no direct evidence could be extracted from the literature reviewed. Cyclosporine A was noted to improve visual acuity with enhanced efficacy when combined with prednisolone or ketoconazole. Furthermore, the authors state that while there is sufficient evidence for recommending the use of immunomodulatory drugs for the treatment of uveitis and/or as corticosteroid-sparing agents, no reliable conclusions can be drawn regarding the optimum treatment guideline.

c. <u>Randomised Controlled Trials (RCTs)</u>

Four RCTs were identified that were published subsequent to the literature search undertaken by the Cochrane reviewers (E Mayhew RG, 2022).

- (Kelly NK et al., 2021): Health- and Vision-Related Quality of Life in a Randomized Controlled Trial Comparing Methotrexate and Mycophenolate Mofetil for Uveitis.
- (Tsui E et al, 2022): Outcomes of Uveitic Macular Edema in the First-line Antimetabolites as Steroid-Sparing Treatment Uveitis Trial.
- (Kong CL et al, 2022): Comparison of CD4 Counts with Mycophenolate Mofetil versus Methotrexate from the First-line Antimetabolites as Steroid-sparing Treatment (FAST) Uveitis Trial.
- (Ono T et al., 2022): Comparison of combination therapy of prednisolone and cyclosporine with corticosteroid pulse therapy in Vogt-Koyanagi-Harada disease.

Three [(Kelly NK et al., 2021), (Tsui E et al, 2022), (Kong CL et al, 2022)] of the four RCTS identified are a secondary analysis of the original FAST trial (Rathinam SR et al, 2019). The original FAST trial has been included in the Cochrane SR and involved the randomisation of either methotrexate 25mg weekly (MTX) or mycophenolate mofetil 1.5g twice daily (MMF), orally in patients with with non-infectious intermediate, posteriori and pan-uveitis. As MMF is outside the scope of our pre-specified PICO, the FAST trial and the associated secondary analysis were excluded from this review.

The pre-print publication by (Ono T et al, 2021) has been included in the Cochrane review. Final publication of the study (Ono T et al., 2022) was subsequently available which we have not duplicated in our review. Furthermore, VKH is very infrequent among persons of African descent and applicability of these results to the local population is limited.

A subsequent Pubmed search for RCTs conducted on the 25th January 2023 (Appendix 2), was undertaken to identify any newly published studies since the literature search undertaken by the Cochrane reviewers (E Mayhew RG, 2022) in April 2021. The search yielded four RCTS, one of which was excluded as a duplicate as a pre-print of the article was included in the Cochrane review.

EFFECTIVENESS OF THE INTERVENTIONS

a. Guidelines

We have limited our reporting to the guideline by (Dick AD et al, 2018) in view of the relatively higher AGREE II score. With specific reference to the supporting evidence for methotrextate, azathioprine and cyclosporine, these were informed primarily by cohort studies as detailed below, with a more detailed summary of the reported efficacy and safety outcomes included in Appendix 6.

American Academy of Ophthalmology Fundamentals of Care (FOCUS) Initiative (Dick AD et al, 2018)

Evidence for Individual Systemic Non-corticosteroid Immunomodulatory Therapy Agents and Disease-Specific Recommendations

The quality of evidence was defined using the Oxford Centre for Evidence-Based Medicine levels of evidence criteria grading.

Drug	No. of Studies*	Disease Anatomic Locations†	Disease Entities or Cause	Outcomes: *Inflammation Control*	Outcomes: *Visual Acuity Stability or Improvement*	Outcomes: *Steroid Sparing*	Evidence Level	Recommendation Level
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.

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Efficacy

Methotrexate (MTX)

The AAO guideline cites two studies (Samson CM et al., 2001) (Gangaputra S et al. , 2009) in support of the efficacy of methotrexate for the management of uveitis with a grade B recommendation). According to the guideline authors, methotrexate has demonstrated efficacy with control of inflammation, steroid-sparing ability as well as the maintenance and improvement of visual acuity (Evidence level 2B, *Cohort studies)*. In the (Gangaputra S et al. , 2009) study, a discontinuation rate of 13% (50 out of 384 patients) due to ineffectiveness, was reported within 1 year of commencing methotrexate.

Azathioprine (AZA)

The AAO guideline team recommend a moderate efficacy rating for azathioprine (grade B recommendation) for control of inflammation and corticosteroid-sparing effects in patients with intermediate, posterior and panuveitis, based on the outcomes of two studies (Pacheco PA et al. , 2008) (Pasadhika, S et al, 2009)(Evidence level 2B, *Cohort studies*. Evidence for improvements in visual outcomes is noted as lacking. A third cohort study by (Saadoun et al, 2010) was cited in support of the reviewers comments that azathioprine demonstrated moderate efficacy in inflammation control and a significant steroid-sparing effect in patients with severe uveitis secondary to Behçet's disease (Evidence level 2B, *Cohort studies)*. A small cohort study (n=16) limited to patients with VKH by (Kim et al, 2007), included by the guidelines reviewers demonstrated control of inflammation and a steroid sparing effect with azathioprine (low-level evidence (EL 4)).

Cyclosporine (CS)

The AAO guideline stipulates a grade B recommendation for the calcineurin Inhibitors (tacrolimus and cyclosporine). Guideline authors indicate that the efficacy of cyclosporine for control of inflammation and improvements in visual acuity is supported by evidence level 2B (cohort studies with consistent level 2 or 3 studies or extrapolations from level 1 studies). Only the cohort study by (Kacmaz et al, 2010) reported on the safety and efficacy of cyclosporine (i.e. the other 3 studies cited by the reviewers included tacrolimus which is outside the scope of our PICO).

Safety

Overall mortality and cancer mortality

Although mortality is not included as a pre-specified outcome in the PICO, three of the cohort studies cited above, involving methotrexate (Gangaputra S et al. , 2009), azathioprine (Pasadhika, S et al, 2009) and cyclosporine (Kacmaz et al, 2010) were sub-studies of the larger SITE study (Kempen JH et al, 2008) which assessed overall mortality and cancer mortality.

The SITE study (Kempen JH et al, 2008), was a large retrospective cohort study involving 7957 US residents treated at five tertiary ocular clinics with non-infectious ocular inflammation to assess whether immunosuppressive drugs increase mortality (overall mortality and cancer mortality). The study period ran from 1979-2005 spanning over 66 802 person years. Patients with HIV infection were ineligible to participate in the SITE study. The primary outcomes included mortality and fatal malignancy, while secondary outcomes such as ophthalmological response and short-term toxicities of immunosuppressive therapy were reported in sub-studies over a shorter reporting period (Appendix 6).

For the primary outcomes, among the 2340 patients who received immunosuppressive drugs, 323 deaths were reported out of a total of 936 deaths. The overall mortality risk (adjusted for age, sex and race) in patients unexposed to immunosuppressive therapy was reported as a standardised mortality ratio of 1.02 95% confidence interval [CI] 0.94 to 1.11 with a cancer specific mortality ratio of 1.10, 95% CI 0.93 to 1.29). After adjusting for confounding, the antimetabolite immunosuppressive drugs were not associated with a substantial increase in overall mortality (fully adjusted hazard ratio 1.08, 95% CI 0.86 to 1.37) or cancer mortality (0.89, 0.54 to 1.48). Individually, azathioprine and methotrexate which were among the more commonly used antimetabolites were not associated with increased risk of overall or cancer mortality either. Similarly, the T cell inhibitor class of immunosuppressants did not demonstrate an increase in mortality risk i.e. (fully adjusted hazard ratio 0.81, 95% CI 0.59 to 1.11), and cancer mortality (0.78, 0.38 to 1.59). Individually, cyclosporine had overall and cancer-related mortality similar to that of the overall T cell class of drugs. Systemic corticosteroid therapy was not associated with increased overall (hazard ratio 1.13, 95% CI 0.96 to 1.33) or cancer mortality (1.02, 0.72 to 1.45) after adjusting for confounding.

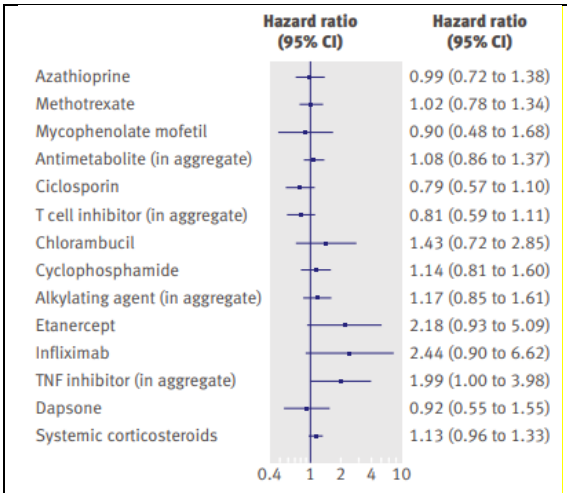


Fig 2 | Adjusted relative hazard of all cause mortality for each immunosuppressive agent and class of agents studied

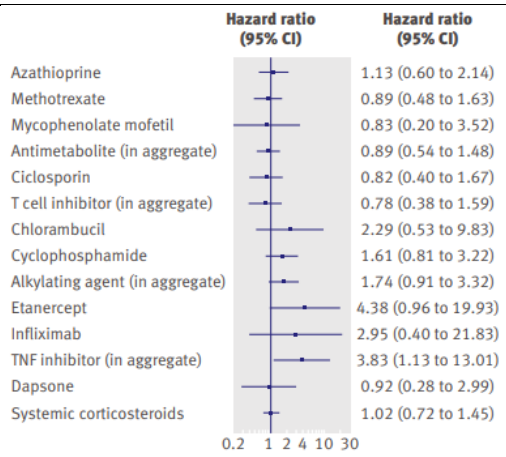


Fig 3 | Adjusted relative hazard of mortality attributed to cancer for each immunosuppressive agent and class of agents studied

According to the study authors, the tendency towards increased crude and demographic adjusted hazard ratios observed with antimetabolite therapy corresponded to greater use of these drugs in patients who had systemic inflammatory comorbidities and were older, as can be noted in the tables below:

Table 3 | Use of immunosuppressive drugs and risk of overall mortality*

Agent	Crude HR (95% CI)	P	HR adjusted for age, race, sex (95% CI)	P	HR fully adjusted model (95% CI)	P
No immunosuppressive agent	1.00		1.00		1.00	
Antimetabolite (any)	1.60 (1.33 to 1.91)	<0.0001	1.23 (1.02 to 1.47)	0.029	1.08 (0.86 to 1.37)	0.50
Azathioprine	1.73 (1.35 to 2.21)	<0.0001	1.13 (0.88 to 1.46)	0.33	0.99 (0.72 to 1.38)	0.97
Methotrexate	1.56 (1.25 to 1.95)	<0.0001	1.19 (0.95 to 1.49)	0.129	1.02 (0.78 to 1.34)	0.87
Mycophenolate mofetil	0.94 (0.53 to 1.67)	0.82	1.00 (0.56 to 1.78)	0.99	0.90 (0.48 to 1.68)	0.73
T cell inhibitor (any)	0.89 (0.69 to 1.14)	0.35	1.22 (0.95 to 1.56)	0.121	0.81 (0.59 to 1.11)	0.18
Ciclosporin	0.81 (0.63 to 1.05)	0.118	1.17 (0.90 to 1.52)	0.25	0.79 (0.57 to 1.10)	0.16
Alkylating agent (any)	2.36 (1.92 to 2.90)	<0.0001	1.26 (1.02 to 1.56)	0.031	1.17 (0.85 to 1.61)	0.34
Chlorambucil	1.33 (0.73 to 2.41)	0.35	1.97 (1.08 to 3.59)	0.027	1.43 (0.72 to 2.85)	0.30
Cyclophosphamide	2.54 (2.05 to 3.14)	<0.0001	1.19 (0.96 to 1.49)	0.116	1.14 (0.81 to 1.60)	0.45
TNF inhibitor (any)	1.45 (0.75 to 2.82)	0.27	1.96 (1.01 to 3.81)	0.048	1.99 (1.00 to 3.98)	0.050
Etanercept	1.78 (0.79 to 3.99)	0.16	2.04 (0.91 to 4.59)	0.085	2.18 (0.93 to 5.09)	0.072
Infliximab	1.31 (0.49 to 3.51)	0.59	2.25 (0.83 to 6.05)	0.110	2.44 (0.90 to 6.62)	0.080
Dapsone	3.45 (2.76 to 4.30)	<0.0001	0.98 (0.77 to 1.24)	0.85	0.92 (0.55 to 1.55)	0.77
No systemic corticosteroids	1.00		1.00		1.00	
Systemic corticosteroids	1.03 (0.90 to 1.19)	0.63	1.24 (1.08 to 1.43)	0.003	1.13 (0.96 to 1.33)	0.15

HR=hazard ratio; CI=confidence interval; TNF=tumour necrosis factor.
*For immunosuppressive agents, each comparison is of person time after exposure to the agent indicated compared with patients never exposed to any of the agents listed. For corticosteroids, the comparison is of person time after use of systemic corticosteroids versus person time before use of systemic corticosteroids. Fully adjusted models adjust for age, race, sex, smoking status, site of ocular inflammation, bilaterality of ocular inflammation, Charlson index score, and indicator variables for those systemic inflammatory diseases that were significantly associated with mortality in Cox regression. In addition to the agents listed, small numbers of patients taking leflunomide, tacrolimus, sirolimus, and adalimumab were included in the antimetabolite, T cell inhibitor, and TNF inhibitor groups, respectively.

Table 4 | Use of immunosuppressive drugs and risk of mortality caused by cancer*

Agent	Crude HR (95% CI)	P	HR adjusted for age, race, sex (95% CI)	P	HR fully adjusted model (95% CI)	P
No immunosuppressive drug	1.00		1.00		1.00	
Antimetabolite (any)	1.16 (0.76 to 1.76)	0.49	0.87 (0.57 to 1.32)	0.50	0.89 (0.54 to 1.48)	0.66
Azathioprine	1.73 (1.04 to 2.87)	0.034	1.06 (0.63 to 1.77)	0.83	1.13 (0.60 to 2.14)	0.70
Methotrexate	1.03 (0.60 to 1.76)	0.93	0.76 (0.44 to 1.32)	0.33	0.89 (0.48 to 1.63)	0.70
Mycophenolate mofetil	0.65 (0.16 to 2.66)	0.55	0.67 (0.16 to 2.76)	0.58	0.83 (0.20 to 3.52)	0.80
T cell inhibitor (any)	0.85 (0.51 to 1.44)	0.55	1.15 (0.68 to 1.95)	0.60	0.78 (0.38 to 1.59)	0.50
Ciclosporin	0.88 (0.52 to 1.48)	0.63	1.24 (0.73 to 2.10)	0.42	0.82 (0.40 to 1.67)	0.59
Alkylating agent (any)	2.36 (1.54 to 3.60)	<0.0001	1.21 (0.78 to 1.88)	0.39	1.74 (0.91 to 3.32)	0.092
Chlorambucil	1.02 (0.25 to 4.14)	0.97	1.54 (0.38 to 6.27)	0.55	2.29 (0.53 to 9.83)	0.26
Cyclophosphamide	2.54 (1.64 to 3.93)	<0.0001	1.14 (0.72 to 1.79)	0.58	1.61 (0.81 to 3.22)	0.17
TNF inhibitor (any)	2.06 (0.65 to 6.55)	0.22	2.44 (0.77 to 7.75)	0.132	3.83 (1.13 to 13.01)	0.031
Etanercept	2.47 (0.60 to 10.06)	0.21	2.51 (0.61 to 10.24)	0.20	4.38 (0.96 to 19.93)	0.056
Infliximab	1.42 (0.20 to 10.26)	0.73	2.13 (0.29 to 15.51)	0.45	2.95 (0.40 to 21.83)	0.29
Dapsone	1.92 (1.06 to 3.47)	0.031	0.55 (0.29 to 1.02)	0.056	0.92 (0.28 to 2.99)	0.89
No systemic corticosteroids	1.00		1.00		1.00	
Systemic corticosteroids	0.95 (0.70 to 1.28)	0.72	1.10 (0.81 to 1.49)	0.55	1.02 (0.72 to 1.45)	0.89

HR=hazard ratio; CI=confidence interval; TNF=tumour necrosis factor.
*For immunosuppressive drugs, each comparison is of person time after exposure to the agent compared with patients never exposed to any of the agents listed. For corticosteroids, the comparison is of person time after use of systemic corticosteroids versus person time before use of systemic corticosteroids. Fully adjusted models adjust for age, race, sex, smoking status, site of ocular inflammation, bilaterality of ocular inflammation, Charlson index score, and indicator variables for those systemic inflammatory diseases that were significantly associated with mortality in Cox regression. In addition to the agents listed, small numbers of patients taking leflunomide, tacrolimus, sirolimus, and adalimumab were included in the antimetabolite, T cell inhibitor, and TNF inhibitor groups, respectively.

Adverse reactions and discontinuation (Appendix 6)

Methotrexate (MTX)

In the study by (Samson CM et al., 2001), 18% (n=29) of the 160 participants discontinued therapy due to adverse effects. Potentially serious reactions were reported for 8 patients with persistent elevated liver enzymes and 3 with leukopenia. In the (Gangaputra S et al. , 2009) study, side effects were reported in 16% of participants (60 of 384 participants) which were generally reversible with dose reduction or discontinuation.

Azathioprine (AZA)

A discontinuation rate of 24% due to adverse effects in the first year of treatment, was reported in the (Pasadhika, S et al, 2009) study. Key reported side effects included (GI upset, bone marrow suppression, elevated LFTs, infection and allergic reactions. A further 15% discontinued therapy at one year but the reason was not specified. A similar side effect profile was noted in the study by (Saadoun et al, 2010) which included 157 patients with Behcet's disease i.e. side effects noted in 67 patients (42.6%) and mainly included gastrointestinal events (19.1%), cytopenia (18.4%), and infections (17.8%). There were 3 withdrawals due to toxicity during azathioprine therapy, 2 for hepatotoxicity and 1 for septicaemia.

Cyclosporine (CS)

In the study by (Kacmaz et al, 2010), a discontinuation rate of 10.7% (95% CI, 7.6–15.1) due to toxicity was reported (renal toxicity and hypertension most commonly reported) with a further 12.4% of participants discontinuing therapy where the reasons were reported as unknown. Discontinuation for toxicity was progressively more frequent with increasing age, particularly among patients aged between 55 and 64 years (adjusted RR = 3.25; CI, 1.54– 6.88) and patients aged more than 65 years (adjusted RR = 5.66; CI, 2.14–14.98, P =0.0005).

Comparative Studies of Antimetabolites (Mycophenolate Mofetil, Azathioprine, and Methotrexate)

The guideline authors also reported on comparative studies of antimetabolites which they state demonstrates moderate support of methotrexate and mycophenolate mofetil in steroid-sparing control (overall grade C recommendation), with no significant differences in uveitis control among these drugs. Azathioprine was reported to be associated with higher rates of side effects, laboratory test complications, and discontinuation of therapy relative to methotrexate and mycophenolate.

b. Systematic reviews

Edwards Mayhew *et al* (2022)

Refer to Appendix 7 for the summary of findings tables from the Cochrane review - 6 of the 15 outcomes measures included in Appendix 3 were assessed at 6 and 12 months and have been reported in the SoF table.

Methotrexate (MTX)
Nothing reported

Azathioprine (AZA)
Nothing reported.

Cyclosporine (CS)
The De Vries 1990 study compared cyclosporine with placebo, both in combination with oral steroid (0.3 mg/kg/ day). The Cochrane reviewers, however noted that the dose of cyclosporine A used in De Vries 1990 (10 mg/kg/day) is higher than that used in current clinical practice, indicating that the results of this study provide only indirect evidence on the effectiveness of cyclosporine A.

Indirect evidence

A. Cyclosporine (De Vries J et al, 1990)*:*

- Control of inflammatory activity: This was defined using a modified Hogan-Thygeson-Kimura scale which scored congestion, keratic precipitates, anterior chamber cells and flare, vitreous opacity, macular edema, optic disc edema, vasculitis, infiltrates, 'snowballs' and 'snowbanks', exudates, and hemorrhages.

Analysis 1.2. Comparison 1: DMARDs plus steroid versus steroid monotherapy, Outcome 2: Control of inflammation: high-dose cyclosporine A

Study or Subgroup	Cyclosporine A plus steroid Events	Total	Placebo plus steroid Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
De Vries 1990 (1)	1	14	1	13	0.93 [0.06 , 13.37]		? + + + ? ?

Footnotes
(1) At 12 month, CsA 10 mg/kg/day plus steroid 0-3 mg/kg/day

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

The effect of cyclosporine plus oral steroid versus placebo plus oral steroid on the control of inflammation (RR 0.93, where > 1 favors cyclosporine plus steroid, 95% CI 0.06 to 13.37;) is described by the Cochrane reviewers to be based on very uncertain evidence (Analysis 1.2 above).

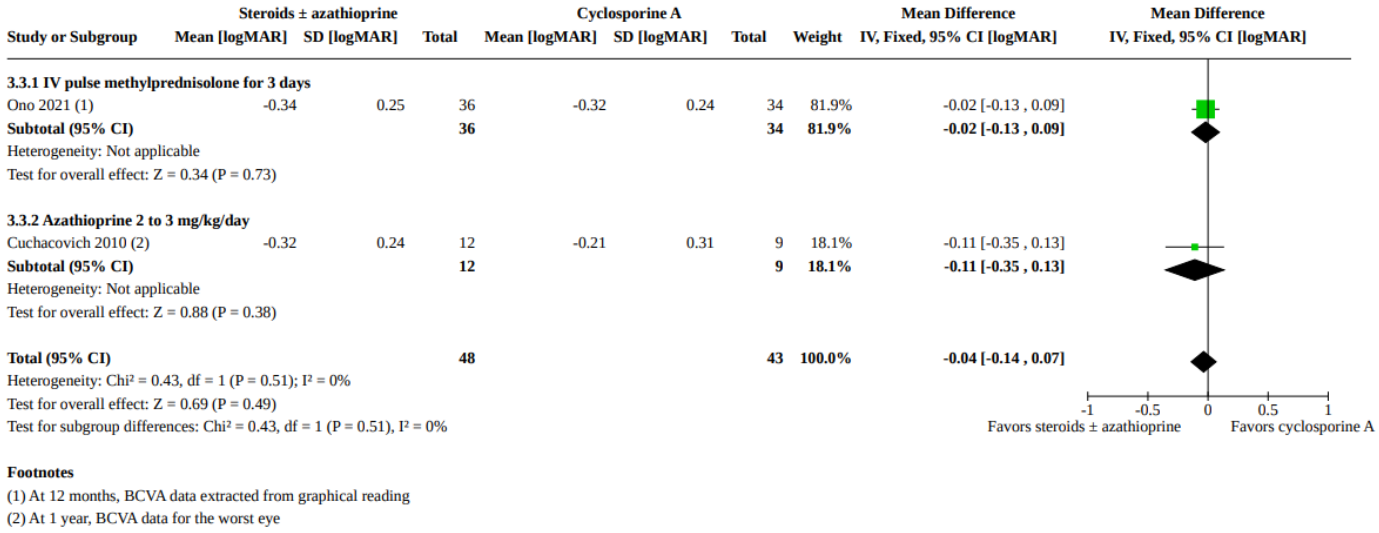
- Proportion of participants to achieve steroid-sparing control or to achieve reduction in oral steroid dose: The dose of oral steroid (0.3mg/kg/day) used by De Vries did not meet the Cochrane reviewers definition of steroid sparing control which was (</= 10mg/day).
- Proportion of participants experiencing complications requiring cessation of medication: As no events were reported for cyclosporine A (0 of 14 participants) or placebo (0 of 13 participants) a risk ratio was not estimatable.

B. Steroids with or without azathioprine versus cyclosporine A

This comparison by the Cochrane reviewers comparing steroids with or without azathioprine to cyclosporine A included 145 participants across four studies ((Cuchacovich M et al, 2010), (Nussenblatt RB, et al, 1991), (Ono T et al, 2021), (Wiederholt M et al, 1986), with Cuchacovich and Ono including only VKH patients. Note that the Nussenblatt (1991) and Wiederholt (1986) studies used high dose cyclosporine.

- Control of inflammation: Based on the analysis of two studies (Cuchacovich 2010; Ono 2021), the evidence may suggest the steroids with or without azathioprine results in little to no difference in control of inflammation at 12 months over cyclosporine, but is very uncertain (RR 0.84, where < 1 favors cyclosporine A, 95% CI 0.70 to 1.02; I2 = 0% (very low certainty). Note that all 112 participants had VKH.
- Change in BVCA: From the analysis of two trials (Cuchacovich 2010; Ono 2021), the evidence is very uncertain whether the steroids with or without azathioprine improve vision over cyclosporine (RR -0.04, where < 0 favours comparators, 95% CI -0.14 to 0.07; I2 = 0%.

Figure 5: analysis 3.3. comparison 3: Steroids with or without azathiprine vs cyclosporin A, outcome 3: change in BVCA



- Proportion of participants achieving steroid-sparing control: The reviewers report that the evidence is very uncertain as to whether there is a difference in the proportion of participants achieving steroid-sparing control between AZA and CsA (RR 0.64, where < 1 favors cyclosporine, 95% CI 0.33 to 1.25), very low certainty. This analysis was based on the (Cuchacovich M et al, 2010) study involving only VKH patients with evidence downgraded one level due to data imprecision and two levels due to risk of bias.
- Proportion of participants experiencing any adverse effects: Over the course of 12 months, 6 out of 9 patients on cyclosporine and 8 of 12 patients on azathioprine experienced any adverse event resulting in a RR=1 (95% CI 0.54 to 1.84), as reported in the (Cuchacovich M et al, 2010) study.

In view of the paucity of both efficacy and safety data, the Cochrane reviewers were unable to formulate any recommendations on which DMARD/s should be considered for the management of NIPPU. The authors noted the heterogeneity of studies (both in design and outcome measures*) and small sizes of the trials. While data on head to head comparisons of different DMARDs is lacking, the authors concluded that methotrexate is probably slightly more efficacious than mycophenolate *(not included in our PICO)* in achieving control of inflammation, including steroid-sparing control (moderate-certainty evidence), except for the VKH subgroup where there is insufficient evidence to preferentially consider one drug over another (very low-certainty evidence). No significant differences in safety outcomes were noted between methotrexate and mycophenolate. The Cochrane reviewer's (E Mayhew RG, 2022) further concluded that the findings from their review was similar to that from (Gomez-Gomez A , 2020) cited below, as well as the SR by (Pato E, et al, 2011), identified in our literature search and for which for which a full text of the reference could not be sourced.

*Example: The use of topical and systemic corticosteroids varied considerably across included studies. Regimens for oral corticosteroids also varied considerably with doses ranging from 10-100mg daily with variable dose tapering regimens. Steroid tapers were generally aimed to achieve a dose of 5 to 10mg daily.

Furthermore, the authors concluded that while oral steroids are efficacious and are accepted as the standard of care, there is a need for steroid-sparing medication. Results of the SR did however not yield any clear recommendations on the relative safety or efficacy of the DMARDs considered, and little practical advice could be given to clinicians on a proposed treatment algorithm.

CONCLUSION

International guideline recommendations support the use of DMARDs for the management of non-infectious uveitis, informed primarily by observational data and/or expert opinion. Despite the well-documented limitations of the published literature (appendix 8) and low quality of evidence, the literature consistently supports a favourable risk:benefit recommendation for the use of DMARDs for the management of non-infectious uveitis where corticosteroids are ineffective or tolerance is a concern.

Although blindness remains a significant consequence of severe non-infectious uveitis if inflammation is not controlled, a review of the literature does not provide for preferential consideration of any of the non-biological DMARDs under consideration or clear guidance for an algorithmic approach to the use of these agents.

In the absence of any further evidence to recommend one non-biologic DMARD over another, we recommend:

- For patients with non-infectious posterior or panuveitis requiring corticosteroid-sparing control, methotrexate should be considered (moderate certainty evidence), with dose tapering of corticosteroids to the lowest possible dose to control inflammation or discontinuation of corticosteroids when possible.
- For patients with non-infectious posterior or panuveitis refractory to oral corticosteroid therapy, methotrexate may be considered as add on therapy, with consideration of a steroid tapering based on individual patient response.

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
CERTAINTY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** **Methotrexate** High ☐ Moderate ☐ Low ☒ Very low ☐ **Azathioprine** High ☐ Moderate ☐ Low ☒ Very low ☐ **Cyclosporine** High ☐ Moderate ☐ Low ☐ Very low ☒ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	**MTX** Retrospective case series and cohort studies demonstrating moderate efficacy with control of inflammation, steroid-sparing ability and maintenance and/or improvement in VA. Low or very low certainty of evidence as observational data. No critical appraisal from source document available **AZA** Retrospective and prospective observational studies demonstrating moderate efficacy with control of inflammation, steroid-sparing ability. Low or very low certainty of evidence as observational data. No critical appraisal from source document available **CYC** The effect of cyclosporine plus oral steroid versus placebo plus oral steroid on the control of inflammation (RR 0.93, where > 1 favors cyclosporine plus steroid, 95% CI 0.06 to 13.37;) is described by the Cochrane reviewers to be based on very low certainty evidence. Doses used in RCTs no longer used in clinical practice. Evidence level – all 2B by guideline reviewers in (Dick AD et al, 2018).

EVIDENCE OF BENEFIT

What is the size of the effect for beneficial outcomes?

Methotrexate, Azathioprine, Cyclosporine

Large	Moderate	Small	None
☐	☐	☐	☐

Size of effect cannot be quantified as the evidence is primarily informed by non-RCT and non-comparative studies.

Due to the heterogeneity of outcomes reported in the cohort studies and the lack of a comparative treatment arms, the size of the beneficial effect cannot be quantified. However in view of the risks with long term corticosteroid use and the risk of blindness from uncontrolled inflammation, we consider the balance of benefit and harm to be favourable with the use of DMARDs.

MTX

(Samson CM et al., 2001)

- Control of inflammation = 76.2%
- Steroid-sparing effect = 56%
- Visual acuity maintained or improved = 90%
- Discontinuation within 1 year due to ineffectiveness 13% (n= 50);

(Gangaputra S et al. , 2009)

- Complete suppression of inflammation sustained for ≥28 days achieved within 6 months: Response rate ranged from 39% to 77% depending on type of inflammation or anatomical location.
- Corticosteroid-sparing effects (sustained suppression of inflammation with prednisone ≤10 mg/d) within 6 months: Response rate ranged from 21%-51% depending on type of inflammation or anatomical location.
- Overall, success within 12 months: 66% for sustained control and 58.4% for corticosteroid sparing ≤10 mg).
- Overall rate of remission = 11% (n=43)

AZA

(Pacheco PA et al. , 2008)

- Complete response =92%
- Remission at 12 months =85% (n=23)
- Relapse = 12% (n=3)

(Pasadhika, S et al, 2009)

- Sustained control of inflammation (for at least 28 days) by 12 months: 62% (95% CI, 50-74%)
- Complete inactivity of inflammation (for at least 28days) within 6 months ranged from 20% (95% CI, 3-80%) to = 69% (95% CI, 41-93%) depending on type of inflammation or anatomical location.
- Corticosteroid-sparing (patients on prednisolone >10mg reduced at 12 months to </=10mg per day: 46.9% (95% CI, 36.9 - 58.0)

CYC

(Kacmaz et al, 2010)

- Control of inflammation for at least 28 days at 1 year = 51.9% (45.5–58.5)
- Controlled inflammation (no activity at 12 months) ranged from 20.0% (3.1–79.6) to 62.3% (29.6–93.3) depending on type of inflammation or anatomical location.
- Corticosteroid-sparing at 1 year = 36.1% (95% CI, 30.5–42.2).

CERTAINTY OF EVIDENCE OF HARM

What is the certainty/quality of evidence?

Methotrexate

High	Moderate	Low	Very low
☐	☐	X	☐

Azathioprine

High	Moderate	Low	Very low
☐	☐	X	☐

Cyclosporine

High	Moderate	Low	Very low
☐	☐	X	☐

High quality: confident in the evidence
Moderate quality: mostly confident, but further research may change the effect

MTX

Retrospective case series and cohort studies demonstrating low or very low certainty of evidence as observational data. No critical appraisal from source document available.

AZA

Retrospective and prospective cohort studies demonstrating low or very low certainty of evidence as observational data. No critical appraisal from source document available.

CYC

RCTs data based on doses no longer used in clinical practice. Retrospective cohort study demonstrating low or very low certainty of evidence as observational data.

	Low quality: some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **Methotrexate, Azathioprine, Cyclosporine** Large ☐ Moderate ☐ Small ☐ None ☐ Size of effect cannot be quantified as the evidence is primarily informed by non-RCT and non-comparative studies.	**MTX** **(Samson CM et al., 2001)** • Discontinuation due to side effects = 18% • Potentially serious adverse reactions = 8.1% • n=8 with persistent elevated liver enzymes and n=3 with leukopenia **(Gangaputra S et al. , 2009)** • Discontinuation within 1 year due to side effects 16% (n=60), generally reversible with dose reduction or discontinuation **AZA** **(Pacheco PA et al. , 2008)** • None of the patients (n=27) needed discontinuation of AZA **(Pasadhika, S et al, 2009)** • Estimated discontinuation in first year due to adverse effects =24% (Gi upset, bone marrow suppression, elevated LFTs, infection, allergic reaction) and a further 15% were discontinued with reasons not specified **CYC** **(De Vries J et al, 1990)** • As no events were reported for cyclosporine A (0 of 14 participants) or placebo (0 of 13 participants) a risk ratio was not estimatable. **(Kacmaz et al, 2010)** • Discontinuation at 1 year due to toxicity=10.7% (95% CI, 7.6–15.1) with renal toxicity and hypertension most common. A further 12.4% of participants discontinued treatment with reasons unknown.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** **Methotrexate** Favours intervention ☐ Favours control ☒ Intervention = Control *or* Uncertain ☐ **Azathioprine** Favours intervention ☐ Favours control ☒ Intervention = Control *or* Uncertain ☐ **Cyclosporine** Favours intervention ☐ Favours control ☒ Intervention = Control *or* Uncertain ☐	Based on the evidence included in this review, we are uncertain if the desirable effects outweigh the undesirable harms. Based on expert opinion and what we know generally with the use of corticosteroids and DMARDs from other inflammatory conditions, the desirable effects of inflammation control and steroid sparing effects do outweigh the undesirable harms of continuing with long term oral corticosteroids or the risks of blindness from uncontrolled inflammation.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☐ No ☒	While oral corticosteroids may be used for the control of inflammation, DMARDs are intended when there is concern with the long term use of corticosteroids, where corticosteroids are contraindicated or ineffective.
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	Methotrexate and azathioprine are currently listed on the EML albeit for different indications.

RESOURCE USE	**How large are the resource requirements?** Based on drug acquisition costs only **Methotrexate** More intensive: [ ] Less intensive: [X] Uncertain: [ ] **Azathioprine (dose dependent)** More intensive: [ ] Less intensive: [ ] Uncertain: [X] **Cyclosporine** More intensive: [X] Less intensive: [ ] Uncertain: [ ]	**COSTS:** Min-max doses as stated in (Jabs D et al, 2000) Based on 70kg patient – dose rounded to nearest whole tablet/capsule MHP List 1 Jul 2023. Excludes monitoring costs and costs related to treatment of adverse effects. **Prednisone oral** **Dose:** 1mg/kg/day to max 80mg/day **Cost per patient per annum: R932-R1 065** **Methotrexate oral** **Dose:** 7.5 mg to 25 mg per week + folic acid 5mg daily **Cost per patient per annum: R303-832** **Azathioprine oral** **Dose:** 1mg – 4mg/kg/day **Cost per patient per annum: R737-R2 211** **Cyclosporine oral** **Dose:** 2.5 mg to 10 mg/kg/ day **Cost per patient per annum: R11 502-R40 258**
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [ ] Major: [ ] Uncertain: [X] **Is the option acceptable to key stakeholders?** Yes: [X] No: [ ] Uncertain: [ ]	Methotrexate, azathioprine and cyclosporine are already used in clinical practice for the management of panuveitis and posterior uveitis but this condition has been omitted from the AH EML. Patients with concomitant systemic disease are also treated with these medicines.
EQUITY	**Would there be an impact on health inequity?** Yes: [ ] No: [X] Uncertain: [ ]	Methotrexate, azathioprine and cyclosporine are already used in clinical practice for the management of uveitis. Inclusion on the EML will improve equity of access, allow for standardisation of care and avoid potential delays with initiating treatment.

Version	Date	Reviewer(s)	Recommendation and Rationale
1.0	July 2023	ZA	Methotrexate supported for the management of non-infectious posterior uveitis or panuveitis in patients who are refractory to corticosteroids or who require ongoing corticosteroids to maintain inflammation control.

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Appendix 1: Pre-specified PICO that was subsequently amended.

Population	Adult patients with non-infectious posterior uveitis or panuveitis Inclusion criteria: *Adult patients with severe posterior uveitis and panuveitis treated with the following non-biological DMARDs (methotrexate, azathioprine, cyclosporine).* *Note: The pre-specified PICO was limited to posterior and panuveitis (based on anatomical classification). Intermediate uveitis which affects the vitreous forms part of the back two thirds of the eye and is defined as part of the posterior segment. Although the condition may be classified by anatomic location, it is not clear if they are truly separate conditions and treatment recommendations across these anatomic locations generally overlap. A number of eligible studies in patients with posterior and panuveitis included patients with intermediate uveitis and have therefore been included in our review.* Exclusion criteria: • *Studies where the sole therapeutic focus for uveitis included: biologicals, injections intended for intra-ocular or peri-orbital administration (e.g. intravitreal corticosteroids), mechanistic target of rapamycin (mTOR) inhibitors (e.g. sirolimus), fingolimod, simvastatin, lens implants, zinc , colchicine, dapsone, diltiazem, NSAIDS* • *Studies that focused on related immunological aetiologies where ocular manifestations were not specifically and independently analysed e.g. rheumatoid arthritis, multiple sclerosis* • *Studies related to the management of uveitis requiring surgical intervention or other therapeutic modalities: cataract management in patients with uveitis, pre and post-surgical management of inflammation, glaucoma, neoplastic-related ocular inflammation, diabetic macular oedema* • *Studies on the management of uveitis other than non-infectious posterior and/or panuveitis: e.g. anterior uveitis, infection-related uveitis, HLAB27, Fuchs heterochromic uveitis, spondyloarthropathy uveitis* • *Studies in patient under 18 years of age*
Intervention	• Methotrexate (MTX), OR • Azathioprine (AZA), OR • Cyclosporine (CS) *The non-biologic, disease-modifying anti-rheumatic drugs (DMARDs) methotrexate and azathioprine were selected for review because they are the agents most utilized in clinical practice due to their cost and perceived efficacy i.e. they are already available on the EDL, albeit for non-ophthalmology indications. Cyclosporine was also selected as there have been anecdotal reports of the use of cyclosporine by specialists in tertiary state facilities for specific cases of severe uveitis due to the perceived efficacy of cyclosporine for select presentations of severe posterior uveitis and panuveitis e.g. Behçet's disease and Vogt-Koyanagi-Harada (VKH) disease.*
Comparator	• Oral corticosteroids
Outcomes	**Efficacy** • Improved visual outcome and better resolution of disease **Safety** • Ocular and systemic side effects
Study designs	Clinical practice guidelines, systematic reviews of randomised controlled trials (RCTs), RCTs and, if the latter is unavailable, systematic reviews of non-randomised/ observational studies.

Appendix 2: Database search

Pubmed Search strategy for SR and MA (conducted 9 November 2022)

Search	Query	Results
#9	Search: **#1 AND #4** Filters: **Meta-Analysis, Systematic Review**	11
#8	Search: **#1 AND #3** Filters: **Meta-Analysis, Systematic Review**	11
#7	Search: **#1 AND #2** Filters: **Meta-Analysis, Systematic Review**	14
#6	Search: **#1 AND #2** Filters: **Systematic Review**	14
#5	Search: **#1 AND #2**	798
#4	Search: **cyclosporine**	61,406
#3	Search: **azathioprine**	24,450
#2	Search: **methotrexate**	59,185
#1	Search: **uveitis**	41,709

Search terms for Cochrane Library and Epistemonikos: 'uveitiis' and 'panuveitis'

Pubmed search strategy for RCTs (conducted on 25 January 2023)

Search	Query	Results
#12	Search: **#7 AND #10** Filters: **Randomized Controlled Trial**	1
#11	Search: **#9 AND #10** Filters: **Randomized Controlled Trial**	3
#13	Search: **#5 AND #10** Filters: **Randomized Controlled Trial**	0
#10	Search: **uveitis** Filters: **Randomized Controlled Trial**	510
#9	Search: **methotrexate** Filters: **Randomized Controlled Trial, from 2021 - 2023**	165
#8	Search: **methotrexate** Filters: **from 2021 - 2023**	4,597
#2	Search: **methotrexate**	59,578
#7	Search: **cyclosporine** Filters: **Randomized Controlled Trial, from 2021 - 2023**	49
#6	Search: **cyclosporine** Filters: **from 2021 - 2023**	2,284
#3	Search: **cyclosporine**	61,606
#5	Search: **azathioprine** Filters: **Randomized Controlled Trial, from 2021 - 2023**	21
#4	Search: **azathioprine** Filters: **from 2021 - 2023**	1,225
#1	Search: **azathioprine**	24,542
#0	Search: **Clipboard**	4

Appendix 2: Excluded studies – Title and abstract screen

No	Author	Date	Reason for Exclusion
TITLE & ABSTRACT REVEIW			
1	Angeles-Han ST	2019	Wrong patient population
2	Welzel T,	2021	Wrong patient population
3	Jari M	2020	Wrong patient population
4	Simonini G	2013	Wrong patient population
5	Maese J	2018	Wrong patient population
6	Gómez-Gómez A (PMID: 29049193)	2017	Wrong patient population
7	Jachiet M	2016	Wrong patient population
8	Halyabar O,	2019	Wrong patient population
9	Tallouzi MO	2019	Wrong patient population
10	Urruticoechea-Arana A	2019	Wrong treatment
11	Leccese P	2019	Wrong patient population
12	Hatemi I	2015	Wrong patient population & treatment
13	Yilmaz U,	2022	Wrong patient population
14	Demir S,	2019	Wrong patient population
15	Taylor J,	2014	Wrong patient population
16	Gómez-Gómez A (PMID: 29049193)	2017	Wrong patient population
17	Hutchison DM	2022	Wrong patient population
18	Ozguler Y	2018	Wrong patient population
19	Yilmaz U	2020	Wrong patient population
20	Christopher J B	2016	Wrong intervention
21	Brady CJ	2021	Wrong intervention
22	Barry RJ	2018	Wrong intervention
23	Rebton WD	2022	Wrong patient population
24	Leung TG	2014	Wrong patient population
25	Davies GR	2007	Wrong patient population
26	Horn J	2020	Wrong patient population
27	Shuster AK	2016	Wrong patient population
28	Hu K	2021	Wrong patient population
29	Lim BX	2016	Wrong patient population
30	Juthani VV	2017	Wrong patient population
31	Kroom F	2015	Wrong patient population
32	Denniston AK,	2015	Not treatment related
FULL TEXT REVIEW			
33	Rossi DC	2019	Not a systematic review
34	Espinosa G	2020	Consensus Statement
35	Saenz A	2000	Disease focused (Behcet's)
36	Hatemi G	2008	Disease focused (Behcet's)
37	Dammacco R	2022	Disease focused (RA)

Appendix 3: Types of outcomes measures considered in the 2022 Cochrane review and how they were defined or measured. (Key time points for these outcomes include follow-up at 6 and 12 months.)

CRITICAL OUTCOMES	Reported in SoF tables (Appendix 8) (Y/N)
Proportion of participants achieving control of inflammation, defined as a two-step reduction in vitreous haze grade/score or decrease to grade 0 (Jabs 2005; Nussenblatt 1985); or clinically comparable study definition	Y
Change in best corrected visual acuity (BCVA), measured as a continuous outcome on a logMAR (logarithm of the minimum angle of resolution) chart (or equivalent)	Y
Proportion of participants achieving a 2-line improvement in visual acuity (Snellen chart)	Y
Proportion of participants with macular edema, confirmed by optical coherence tomography (OCT) (macular thickness, at the center point ≥ 240 µm) or by fluorescein angiogram (macular leakage ≥ 0.44 disc areas) or by slit-lamp biomicroscopy through a dilated pupil	Y
IMPORTANT OUTCOMES	
Mean time to relapse	
Reduction in cumulative hazard of disease relapse	
Proportion of participants with change in anterior chamber flare and cells, as defined by the SUN Working Group	
Mean change in central macular thickness (CMT), measured in microns on OCT imaging	
Change (resolution, yes/no) in other activity domains, including vitreous cells; vitreous 'snow-balls'; chorioretinal inflammatory lesions; and retinovascular inflammation	
Proportion of participants to achieve steroid-sparing control	Y
Proportion of participants to achieve reduction in oral steroid dose (to < 10 mg/day)	
Cost-effectiveness, e.g. the incremental cost-effectiveness ratio (ICER)	
Mean change in vision-related quality of life, measured using the Visual Function Questionnaire 25 (VFQ-25), or other validated questionnaire (Mangione 2001)	
Mean change in general health-related quality of life (HRQoL), measured using the EuroQoL five dimensions questionnaire (EQ-5D), or other validated questionnaire	
Adverse events: ◦ Proportion of participants experiencing any adverse effects, including ocular and systemic complications ◦ Proportion of participants experiencing complications or requiring cessation of medication, such as bone marrow suppression (absolute neutrophil count [ANC] < 1500 cells/ µL), hepatotoxicity (elevation in liver enzyme alanine transaminase [ALT] > 45 IU/L in men and ALT > 35 IU/L in women), as well as severe allergic reaction ◦ Proportion of participants experiencing ocular complications, including elevated eye pressure (≥ 21 mmHg), lens opacity, hypotony, choroidal neovascular membrane	Y (requiring cessation of medication)

Appendix 4: Characteristics of RCTs included in the Cochrane review (E Mayhew RG, 2022)

CITATION	STUDY DESIGN	POPULATION	INTERVENTION	COMPARISON	OUTCOMES MEASURED	Y= RCT included in (Gomez-Gomez A , 2020) & QUALITY RATING
(Cuchacovich M et al, 2010)	RCT	Adults N=21 VKH=100%	AZA + prednisone (n = 12) • Azathioprine dosed 2 mg to 3 mg/kg body weight/day for at least 1 year • Prednisone maintenance dose of either 5 mg or 10 mg/day for 1 year	CsA + prednisone (n = 9) • CSsA 3 mg to 5 mg/kg body weight/day for at least 1 year • Prednisone maintenance dose of either 5 mg or 10 mg/day for 1 year	Change in logMAR BCVA at 54 weeks	
(Deuter C, et al, 2018)	RCT	Adults N=41 VKH=nil	mycophenolate mofetil in combination with topical or oral steroid therapy (n=22) Tapering of oral prednisolone continued over approximately 3 months to a maintenance dose of 5 mg/day, plus • EC-MPS (Myfortic;Novartis, Basel, Switzerland) at a dose of 720 mg/day during the first week and 1440 mg/day from week 2 onwards.	Standard of care (n=19) Started on oral prednisolone (at an initial dose of 1 mg/kg bodyweight at the screening visit, followed by slow tapering over 3 months to maintenance dose of 5 mg/day.	Median time from study entry to the first relapse. Definition of relapse (at least 1 of the following): deterioration of BCVA ≥ 3 lines compared to best BCVA from baseline; at least 2-step increase of vitreous haze compared to lowest grade of vitreous haze from baseline or increase from 3+ to 4+; at least 2-step increase of anterior chamber cells compared to lowest grade of anterior chamber cells from baseline or increase from 3+ to 4+; new onset or worsening of pre-existing cystoid macular edema, proven by Optical Coherence Tomography (OCT); new onset or worsening of retinal vasculitis (sheating and/or leakage of retinal vessels), proven by fluorescein angiography (FA)	
(De Vries J et al, 1990)	RCT	Adults N=27 VKH=nil	cyclosporine in combination with oral steroid therapy (n = 14) • cyclosporine in a single dose of 10 mg/kg/day with dose reduction of 25% of dose of cyclosporine allowed, combined with • low dose of prednisone (0.3-20 mg/kg/day)	Placebo in combination with oral steroid therapy: (n=13) • placebo, with dose reduction of placebo allowed, combined with • low dose of prednisone (0.3-20 mg/kg/day)	Best corrected visual acuity: "best corrected visual acuity was determined at 6 m with charts which contain Landolt C optotypes ranging in unequal steps from a visual angle of 10' (that is visual acuity 20/ 200) to one of 0 5' (visual acuity 20/10). When the visual acuity of a patient was below 20/200 a second ordinal scale was used, namely, finger counting (FC), hand movements (HM), light perception (LP), and no light perception (NLP). In order to make comparisons between the two measurement scales the visual acuity of each eye was given a rank number. For example, visual acuities of hand movements in one eye and 20/80 in the other were given the rank	Y *(Ref 22)* Jadad (good quality)

					numbers 2 and 8 respectively."	
(Lee R et al, 2012)	RCT (non-inferiority)	Median age 31.3 N=35 VKH=nil	tacrolimus monotherapy +/- in combination topical steroid therapy (n = 16) All trial recruits started tacrolimus either before, or at the time of, enrolment in conjunction with 10 mg or more prednisone daily. Participants whose disease was inactive for 4 weeks while taking 10 mg prednisone daily in the presence of target tacrolimus levels (trough serum level of 8 ng to 12 ng/mL) were allocated randomly to: Intervention: tacrolimus and prednisone tapered rapidly and discontinued over 2 weeks	tacrolimus dual therapy in combination with oral steroid therapy +/- topical steroid therapy (n = 19) Comparator: tacrolimus and oral prednisone (10 mg/day for 3 months then tapering to a minimum of 7.5 mg/day).	Change in logMAR VA between randomization and study completion/withdrawal	
(Murphy C et ak, 2009)	RCT	Adults N=37 VKH=nil	cyclosporine in combination with oral steroid therapy (n = 18) 2.5 to 5.0 mg/kg daily, adjust based on clinical response and blood level up to 100 to 225 ng/L or lower with remission • Oral prednisone dosage not specified	tacrolimus in combination with oral steroid therapy (n = 19) 0.03 to 0.08 mg/kg daily, adjust based on clinical response and blood level up to 8 to 12 ng/L or lower with remission • Oral prednisone dosage not specified	logMAR BCVA • Binocular indirect ophthalmoscopy (BIO) score • Treatment failures and relapses	Y *(Ref 24)* Jadad = good quality
(Nussenblatt RB, et al, 1991)	RCT	Adults and children (10-61 years) N=56 VKH=5.4%	cyclosporine A (n = 28) 10 mg/kg of body weight/day as a starting dosage. Dosage of each therapeutic alternative depended on the clinical status of the participant. The dosage of cyclosporine could be as high as 15 mg/kg of body weight/day, but only for a short interval.	prednisolone (n = 28) Participants were given a dose of prednisolone (64 mg) that was pharmacologically equivalent to 80 mg of prednisone if they weighed 70 kg or more, or the equivalent of 60 mg of prednisone (42 mg of prednisolone) if they weighed less than 70 kg. Maximal dose of prednisolone was the prednisone equivalent of 80 mg/day for all participants in that therapeutic alternative	Treatment success at three months: • improvementin visual acuity of 15 letters [three lines] or more in at least one eye or an improvement of at least two increments on the vitreal haze scoring scheme, no more than 20 mg/day of prednisone); or • lack of treatment failure (failure reached if after maximal therapy of one week, visual acuity in one eye decreased 10 letters from baseline value, or if disease appeared to be progressing into the macula, or if there was uncontrolled systemic hypertension, diabetes, ulcer, or impaired hepatic function	Y *(Ref 23)* Jadad = low quality
(Nussenblatt RB et al, 1993)	RCT Parallel group (4-arm)	Adults Mean age: 33.8 N=32 VKH=3.1%	Cyclosporine A in combination with oral steroid therapy •15 mg prednisone orally which could be increased to 30 mg/day plus • escalating doses of cyclosporine A (2.5, 5, 7.5, or 10 mg/kg body weight/day) in two divided doses 12 hours apart, diluted in juice Intervention: cyclosporine G in combination with oral steroid therapy		Therapeutic success: visual acuity improvement of 2 lines or more over baseline or a decrease of two increments to the vitreous inflammation in either eye) at 16 weeks	Y *(Ref25)* Jadad = low quality

			• 15 mg prednisone orally which could be increased to 30 mg/day plus • escalating doses of cyclosporine G (2.5, 5, 7.5, or 10 mg/kg body weight/day) in two divided doses 12 hours apart, diluted in juice			
(Ono T et al, 2021)	RCT (non-inferiority trial parallel group VKH=100%	Adults (N=70)	Cyclosporin A combination with prednisolone (n = 34) Cyclosporine (3 mg/kg/day) was administered daily with • Oral prednisolone at "a daily dose of 1 mg/kg or 60 mg (the smaller dose was adopted for each patient) for 1 week, followed by 50 mg for another week. The dose was then reduced every 2 weeks with the following dosages: 40, 35, 30, 25, 20, 17.5, 15, 12.5, 10, 7.5, 5, and 3 mg, after which oral prednisolone was completely discontinued." However, acute hyponatremia, nausea, and vomiting were observed in the first participant in the combination group. Then, for safety purposes, the combination therapy protocol was changed to cyclosporine initiation when oral prednisolone reached a daily dose of 35 mg (4 weeks after prednisolone initiation) until completion of the oral prednisolone administration.	corticosteroid pulse therapy (n = 36) V methylprednisolone 1000 mg (or 500 mg in certain cases, such as elderly cases) for the first 3 days, then • Switch to oral prednisolone in the same dosing schedule as the other arm above.	ncidence of a composite of recurrence (serous retinal detachment by OCT; recurrence of systemic VKH symptoms) or worsening (two-step increase in AC cells and vitreous haze, or an increase from grade 3+ to 4+ according to SUN criteria)	
(Rathinam SR et al, 2014)	RCT parallel grp VKH=53.8%	Adults N=80	methotrexate in combination with topical or oral steroid therapy (n = 41) • Maintenance dose: 25 mg a week oral methotrexate • Induction dose for the first two run-in weeks: 15 mg a week oral methotrexate	mycophenolate mofetil in combination with topical or oral steroid therapy (n = 39) • Maintenance dose: 1 g twice daily oral mycophenolate mofetil • Induction dose for the first two run-in weeks: 500 mg twice daily oral mycophenolate mofetil	• Ttreatment success as defined "achieving corticosteroid-sparing control of inflammation in both eyes at the 5- and 6-month visits. This was defined by the following: ◦ ≤ 0.5 + anterior chamber cells, ≤ 0.5 + vitreous cells, ≤ 0.5 + vitreous haze, and no active retinal or choroidal lesions; ◦ ≤ 10 mg of oral prednisolone daily and ≤ 2 drops of prednisolone acetate 1% (or equivalent) a day; ◦ ≤ no declaration of treatment failure because of intolerability or safety concerns."	Y *(Ref 26)* Jadad = good quality
(Rathinam SR et al, 2019)	RCT parallel grp VKH=43.1%	Adults N=216	methotrexate in combination with topical or oral steroid therapy (n = 107) • Initial dose 15 mg by mouth weekly for 2 weeks, then increased to maintenance dose of 25 mg by mouth weekly; dose reductions allowed for intolerability	: mycophenolate mofetil in combination with topical or oral steroid therapy (n = 109) Initial dose 500 mg, twice a day, for 2 weeks, then increased to maintenance dose of 1.5 mg by mouth, twice a day; dose reductions allowed for intolerability	Proportion with treatment success - defined by the following: less than or equal to 0.5 + anterior chamber cells by SUN criteria, less than or equal to 0.5 + vitreous haze clinical grading using the NEI scale, and no active retinal or choroidal lesions; and • no more than 7.5 mg of oral prednisone daily and less	

					than or equalto 2 drops of prednisolone acetate 1% (or equivalent) per day; and • no declaration of treatment failure due to intolerability or safety concerns.	
(Wiederholt M et al, 1986)	RCT parallel grp	Adults N=8 VKH= not reported	cyclosporine in combination with topical steroid therapy (n = 4 Cyclosporine A treatment was carried out with the drinking solution "Sandimmun" or cyclosporine in castor oil, diluted in milk and given in 2 doses, twice a day; ~8 mg/kg per day. After 1 week dose was changed so that concentration of cyclosporine A was ~400-800 ng/mL. Levels were determined 12 hours after the last intake.	standard of care (e.g. topical steroids, with or without systemic steroids) (n = 4) Prednisolone given in a tablet form of 80 mg to 100 mg per day for 2 weeks and then reduced in alternating therapy (every other day) within three months	Visual acuity	

Appendix 5: Summary of 3 small RCTs identified in (Gomez-Gomez A , 2020) and not included in the Cochrane review (E Mayhew RG, 2022)

Citation	Study and size	Comparison & intervention	Description	Reason for exclusion
(de Smet MD, 1992)	RCT (n=10)	Cyclosporine +/- ketoconazole	Patient with endogenous uveitis in clinical remission attributable to treatment with cyclosporine and prednisone. were randomly assigned to ketoconazole or placebo to assess relapse of disease over a 3 month follow up	Wrong comparator
(Ozyazgan Y, 1992)	RCT (n=23)	cyclosporin A versus pulsed cyclophosphamide	Cyclosporin A 5 mg/kg/day versus monthly 1 g intravenous boluses of cyclophosphamide was conducted among 23 patients with Behçet's syndrome and active, potentially reversible uveitis. The trial was unmasked after a mean of 12 (SD 2) months for the cyclosporin A group (n = 12) and a mean of 10 (SD 3) months for the cyclophosphamide group (n = 11). During the initial 6 months the visual acuity significantly improved ($p < 0.001$) in the cyclosporin A group whereas this was not observed in the cyclophosphamide group. The subsequent follow-up of patients up to 24 months suggested that the initial improvement in visual acuity with cyclosporin A was not sustained.	Wrong comparator
(Shen E, 2016)	Sub-analysis of RCT (n=27)	25 mg oral methotrexate weekly or 1 g mycophenolate mofetil twice daily, with a corticosteroid taper.	Twenty-seven patients were randomized to methotrexate and 16 to mycophenolate mofetil; 30 had acute VKH. The odds of achieving corticosteroid-sparing control of inflammation with methotrexate were 2.5 times (95% CI: 0.6, 9.8; P = .20) the odds with mycophenolate mofetil, a difference that was not statistically significant. The average improvement in visual acuity was 12.5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. On average, visual acuity for patients with acute VKH improved by 14 more ETDRS letters than those with chronic VKH (P < .001), but there was no difference in corticosteroid-sparing control of inflammation (P = .99). All 26 eyes with a serous retinal detachment at baseline resolved, and 88% achieved corticosteroid-sparing control of inflammation. The majority of patients treated with antimetabolites and corticosteroids were able to achieve corticosteroid-sparing control of inflammation by 6 months. Although patients with acute VKH gained more visual improvement than those with chronic VKH, this did not correspond with a higher rate of controlled inflammation.	VKH = 100% *Sub-analysis of the* (Rathinam SR et al, 2014) study

Appendix 6: Summary of studies included in the AAO guideline for methotrexate, azathioprine and cyclosporine.

	Study description	Efficacy outcomes	Adverse effects	Comments
METHOTREXATE				
(Samson CM et al., 2001) Methotrexate therapy for chronic non-infectious uveitis	Retrospective non-comparative interventional case series at 1 institution in US (1985-1999). n=160 Panuveitis = 15%, Intermediate and posterior uveitis = 20% Anterior disease = 65%	Control of inflammation = 76.2% Steroid-sparing effect = 56% Visual acuity maintained or improved = 90%	Discontinuation due to side effects = 18% Potentially serious adverse reactions = 8.1% (n=8 with persistent elevated liver enzymes and n=3 with leukopenia)	Patients were typically started on MTX 7.5mg orally, once a week with 1 mg/day folic acid. MTX was increased at dose increments of 2.5 to 5mg every six weeks as needed until a therapeutic response was achieved. Average maintenance dose of 12.3mg per week (range, 7.5-40mg weekly). Concomitant cyclosporine therapy n=14. Other immunosuppressant n=2.
(Gangaputra S et al. , 2009) Methotrexate for non-infectious ocular inflammation *Sub-study of SITE study*	Retrospective cohort study across 4 clinics in US (1979-2007). n=384 (639 eyes) Anterior uveitis = 32.8% Intermediate uveitis 9.9% Posterior or panuveitis= 21.4% Scleritis =14.6% Ocular mucous membrane pemphigoid = 15.1% Other forms of ocular inflammation = 6.3%	Complete suppression of inflammation sustained for ≥28 days achieved within 6 months: Anterior uveitis =55.6% Intermediate uveitis = 47.4% Posterior or panuveitis =38.6% Scleritis =56.4% Ocular mucous membrane pemphigoid =39.5% Other forms of ocular inflammation=76.7% Corticosteroid-sparing effects (sustained suppression of inflammation with prednisone ≤10 mg/d) within 6 months: Anterior uveitis=46.1% Intermediate uveitis -41.3% Posterior or panuveitis =20.7% Scleritis =37.3% Ocular mucous membrane pemphigoid =36.5% Other forms of ocular inflammation =50.9% Overall, success within 12 months: 66% for sustained control 58.4% for corticosteroid sparing ≤10 mg) Remission 11% (n=43)	Discontinuation within 1 year due to : Ineffectiveness 13% (n= 50); Side effects 16% (n=60), generally reversible with dose reduction or discontinuation	Duration of therapy: methotrexate monotherapy for a median of 0.73 years (interquartile range, 0.31–1.59)
AZATHIOPRINE				
(Pacheco PA et al. , 2008) Azathioprine in the management of autoimmune uveitis	Prospective, open-label observational study (1998-2004) n=27	Complete response =92% Remission at 12 months =85% (n=23) Relapse = 12% (n=3) **Secondary outcomes:**	*Predetermined indications for withdrawal of AZA were leukocyte count <3500/mm3, platelet count <105/mm3, Hb <7g/dL or LFT*	Patients were judged to require a second-line agent on the basis of either the diagnosis of active disease resistant to a dose of 30 mg/day of prednisolone, or

	Anterior uveitis (n=3) Pars planitis (n=1) Idiopatic panuveitis (n=4) VKH (n=8) Behcet disease (n=3), Choroidoretinopathies (n=8) Pred + AZA Prednisolone was started at a dose of 0.5 mg/kg/day for 4 weeks and tapered to a maintenance dose of 5–10 mg/day during the next 3 months, titrated against disease activity; if the inflammatory activity continued beyond 4 weeks then the dose was tapered more gradually. Prednisolone was then continued for 1 year at a maintenance dose of 5–10 mg/day. AZA was given in a dose of 2–3 mg/kg body weight/day for 1 year	Improved BVCA = 59% (n=16) Maintained BVCA = 22% (n=6) BVCA worse =19% (n=5) *Statistically significant improvement in BVCA* Corticosteroid –sparing: Median daily dose reported as: Baseline: 45 mg/day (range, 25–60). At 1 month: 35 mg/day (20–40); At 3 months: 15 mg/day (10–30); At 6 months, 5 mg/day (5–10).	*increase to more than double baseline.* Ineffective: n=1 Adverse effects: None of the patients needed discontinuation of AZA	disease in remission, but requiring a maintenance dose > 20 mg/day prednisolone to remain in remission. All study participants were caucasian patients. 2 patients with Behcets received additional immunosuppressive treatment
(Pasadhika, S et al, 2009) Azathioprine for Ocular Inflammatory Diseases *Sub-study of SITE study*	n=145 Uveitis =63% of which *Anterior dx =23%* *Intermediate =20%* *Posterior/panuveitis=57%* Scleritis = 11% MMP = 23% Other =3% (three with peripheral ulcerative keratitis and two with orbital inflammation).	*Success in achieving complete inactivity of inflammation sustained for at least 28 days varied by the site of ocular inflammation.* Sustained control of inflammation (for at least 28 days) by 6 months: 41% (95% confidence interval (CI), 31-52% Sustained control of inflammation (for at least 28 days) by 12 months: 62% (95% CI, 50-74%) Complete inactivity of inflammation (for at least 28days) within 6 months: Anterior uveitis=24% (95% CI, 10-52%) Intermediate uveitis = 69% (95% CI, 41-93%) Posterior or panuveitis patients = 44% (95% CI, 28-64%) MMP =43% (95% CI, 26-66%) Scleritis =20% (95% CI, 3-80%) Corticosteroid-sparing (patients on prednisolone >10mg reduced at 12 months to </=10mg per day: 46.9% (95% CI, 36.9 - 58.0) </=5mg per day: 40.6% (95% CI, 30.8 - 52.2) 0mg per day =9.5% (95% CI, 5.2 - 17.1) *Posterior or panuveitis : 7% (95% CI, 2-21%) of participants completely discontinued prednisone while maintaining sustained control of inflammation for at least 28 days.*	Discontinuation (median follow up of 230 days)=68% Estimated discontinuation in first year: Ineffectiveness =17% (further 9% has add on therapy) Adverse effects =24% (Gi upset, bone marrow suppression, elevated LFTs, infection, allergic reaction) Not specified=15% Remission (at end of study period) =14%	Patients with HIV infection and those with infectious ocular inflammation were excluded At the inception of azathioprine therapy, 48% of patients were receiving systemic prednisone > 10 mg daily. Patients with intermediate uveitis and mucous membrane pemphigoid generally were more likely to achieve both control of inflammation and corticosteroid-tapering success than the other groups. Prior use of antimetabolites other than azathioprine was associated with an approximate 60% lower likelihood of control of inflammation. Intermediate uveitis responded significantly better to azathioprine than anterior uveitis, with 89.8% achieving complete control of inflammation sustained for at least 28 days and 68.2% meeting corticosteroid-sparing objectives before 12 months of therapy. *This pattern of*

				response was not observed in our study of patients treated with methotrexate, (Gangaputra study) suggesting that azathioprine might be especially effective for intermediate uveitis.
(Saadoun et al, 2010) Azathioprine in Severe Uveitis of Behcet's Disease	Retrospective cohort study at one site in France (1970-2006) in patients with Behcet's Disease n=157 Active posterior uveitis or panuveitis, had to receive corticosteroids and azathioprine Oral AZA 2.5 mg/kg/day initiated in association with oral prednisone (0.5–1 mg/kg/day)	Partial or complete response) of ocular lesions =92.9% After a mean +/-SD followup of 71.5 +/- 68.6 months: Complete responders = 51.6% Partial responders =41.4% Non-responders =7% Visual acuity : In better eye progressed from 4.49 to 6.8/10 (P< 0.0001) Worse eye progressed from 4.18 to 6.45/10 (P<0.0001) Loss of useful vision (baseline) =37.6% Loss of vision (end of followup) =19.6% (P< 0.01) Steroid-sparing: The mean +/- SD oral prednisone threshold decreased significantly from 55.3+/- 13.8 mg/day (range 25– 80) to 10.5 +/- 6.5 mg/day (range 5–25; P< 0.001). Non-responders (n=14) Relapse rates: Cumulative relapse rate at 1yr=11% Cumulative relapse rate at 5yrs=32.6%	Side effects of azathioprine were noted in 67 patients (42.6%) and mainly included gastrointestinal events (19.1%), cytopenia (18.4%), and infections (17.8%). There were 3 withdrawals due to toxicity during azathioprine therapy, 2 for hepatotoxicity and 1 for septicemia.	Thirty-one patients (19.6%) had been previously treated by another regimen (i.e., cyclophosphamide, cyclosporin, chlorambucil, and interferon [IFN] alfa-2a) The median duration of azathioprine therapy was 3.4 years (range 1–5 years)
(Kim et al, 2007) Use of low dose azathioprine in VKH	Retrospective case series at a single centre in Seoul (1999-2005) N=34 (VKH) All patients were treated with high-dose systemic corticosteroid therapy with either oral prednisone (1.0 mg/kg/day) or intravenous methylprednisolone (1000 mg/day) followed by oral corticosteroids over 6 months. Topical corticosteroids and cycloplegics were also used for the control of anterior segment inflammation.	*Acute uveitic* Corticosteroid sparing=86.5% Median time to corticosteroid sparing = 4 months (range, 1–8) *Chronic recurrent group* Corticosteroid sparing=90% Median time to corticosteroid sparing =2.5 months (range 1–9) *There were no significant differences in recurrence rate, cumulative corticosteroid dose, and ocular complication rates*	Adverse effects of AZA GI discomfort n=3 Mildly elevated LFTs n=2 All patients showed improvement after the dose was decreased or azathioprine therapy was discontinued	In 2 patients, cyclosporine (2.5–5.0 mg/kg/day) was added due to insufficient control of inflammation.

	Azathioprine at 1.0– 2.5 mg/kg/day was added in the following cases: (1) If serous retinal detachment associated with acute visual disturbance was persistent or recurred despite high-dose systemic corticosteroid therapy with slow tapering (2) Chronic recurrent uveitis with posterior involvement nonresponsive to corticosteroid therapy 3) Intolerable side effects of systemic corticosteroid therapy. According to the time phase when azathioprine was given, patients with azathioprine therapy were divided into 2 groups: *Acute uveitic phase (evidence of bilateral diffuse choroiditis such as serous retinal detachment).* *Chronic recurrent phase (phase when there was recurrent or chronic uveitis in patients with a history of early manifestations of VKH disease and ocular depigmentation).* Patients receiving AZA=47.1% Corticosteroid only =52.9%	*between the azathioprine therapy group and corticosteroid group.*		
CYCLOSPORINE				
(Kacmaz et al, 2010) Ciclosporin for ocular inflammatory diseases *Sub-study of SITE study*	Retrospective cohort study across 4 clinics in the US (1979-2007) N=373 (681 eyes) Anterior uveitis = 20.1% Intermediate uveitis=26.5% Posterior or panuveitis =45.8% Scleritis = 4.0% Ocular mucous membrane pemphigoid=1.6% Other forms of ocular inflammation =1.9% including lichen planus of conjunctiva, peripheral ulcerative keratitis, and idiopathic orbital pseudotumor	Control of inflammation for at least 28 days at 1 year = 51.9% (45.5–58.5) Controlled inflammation (no activity at 12 months) Anterior uveitis = 54.3% (40.0–69.9) Intermediate uveitis= 51.8% (40.4–64.2) Posterior or panuveitis = 51.7% (42.6–61.6) Scleritis = 62.3% (29.6–93.3) Ocular mucous membrane pemphigoid= 20.0% (3.1–79.6) Other forms of ocular inflammation = 33.3% (5.5–94.6) Corticosteroid-sparing at (spanning at least 28 days with corticosteroid tapered to </=10mg) at 6 months Anterior uveitis=28.5% Intermediate uveitis = 24.1% Posterior or panuveitis patients = 16.2% Scleritis =52.8% Ocular mucous membrane pemphigoid= 20%	Discontinuation at 1 year Toxicity=10.7% (95% CI, 7.6–15.1) Renal toxicity and hypertension most common Unknown=12.4%	Compared with patients aged 18 to 39 years, discontinuation for toxicity was progressively more frequent with increasing age, particularly among patients aged between 55 and 64 years (adjusted RR = 3.25; CI, 1.54–6.88) and patients aged more than 65 years (adjusted RR = 5.66; CI, 2.14–14.98, P =0.0005). Cyclosporine doses of 151 to 250 mg/day (approximately 2–3.5 mg/kg/day assuming an average body weight) were associated with an increased likelihood of control of inflammation (adjusted relative risk [RR]= 1.89; CI, 1.15–3.09) with respect to 150 mg/day or less, but the likelihood of corticosteroid-sparing success was similar across all dosage groups. Doses more than 250

		Corticosteroid-sparing at 1 year = 36.1% (95% CI, 30.5–42.2). Only 8.2% of the total population were able to discontinue corticosteroids completely at 12 months		mg/day were not associated with further therapeutic advantage. Approximately half of patients continued taking cyclosporine throughout the available follow-up, with 65 patients (17%) subsequently starting another immunosuppressive drug along with cyclosporine and 126 patients (34%) continuing cyclosporine as the only noncorticosteroid immunosuppressive drug for the remainder of (variable) follow-up

Appendix 7: Summary of findings table from the Cochrane review (E Mayhew RG, 2022)

SUMMARY OF FINDINGS

Summary of findings 1. Non-biologic disease-modifying antirheumatic drugs (DMARDs) versus steroid for NIIPPU

Non-biologic disease-modifying antirheumatic drugs (DMARDs) versus steroid for NIIPPU

Patient or population: NIIPPU

Setting: ophthalmology clinics (Netherlands, Germany)

Intervention: DMARDs (CsA, EC-MPS plus steroid)

Comparison: control (placebo plus steroid or steroid alone)

Outcomes	Anticipated absolute effect (95% CI)*		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk with control	Assumed risk with DMARDs				
Proportion of participants achieving control of inflammation (higher number of events is better) Follow-up: 0 to 12 months	21 events per 100 participants	**59 events per 100 participants** (2 to 100)	**RR 2.81** (95% CI 1.10 to 7.17)	41 (1 RCT)	⊕### **Very low**[a,b]	One study comparing CsA plus steroid with placebo plus steroid also reported this outcome but used CsA doses no longer in practice (De Vries 1990); thus, we did not include it in meta-analysis.
Change in BCVA (lower logMAR indicate better vision) Follow-up: 0 to 6 months	Right eyes MD -0.03 logMAR (95% CI -0.96 logMAR to 0.90 logMAR); Left eyes MD -0.10 logMAR (95% CI -0.27 logMAR to 0.07 logMAR)		-	82 eyes (1 RCT)	⊕### **Very low**[a,b]	
Proportion of participants achieving a 2-line improvement in visual acuity (Snellen chart) (higher scores indicate better vision)	No data were reported for this outcome		-	-	-	-
Proportion of participants with confirmed macular edema	No data were reported for this outcome		-	-	-	-

(lower number of events is better) Follow-up: 0 to 6 months					
Proportion of participants achieving steroid-sparing control (higher number of events is better) Follow-up: 0 to 12 months	No data were reported for this outcome	-	-	-	-
Proportion of participants experiencing complications or requiring cessation of medication (lower number of events is better) Follow-up: 0 to 12 months	See comment	-	41 (1 RCT)	⊕### **Very low**[b,c]	One event reported in DMARDs group (RR 2.61, 95% CI 0.11 to 60.51). Another study reported this outcome but used CsA doses no longer in practice (De Vries 1990).

***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**

BCVA: best-corrected visual acuity; **CI:** confidence interval; **CsA:** cyclosporin A; **DMARD**: disease-modifying antirheumatic drug;**EC-MPS:** enteric-coated mycophenolate sodium; **logMAR:** logarithm of the minimum angle of resolution;**MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio; **SD:** standard deviation

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence:
High certainty: further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low certainty: we are very uncertain about the estimate

[a]Downgraded (-2) for risk of bias (unclear risk of bias for the randomization process, deviations from intended interventions, and high risk of bias overall)
[b]Downgraded (-1) for imprecision (small sample size)
[c]Downgraded (-2) for risk of bias (unclear risk of bias for the randomization process and missing outcome data, and high risk of bias for measurement of outcome, selection of the reported result, and high risk of bias overall)

Summary of findings 2. Methotrexate versus mycophenolate for NIIPPU

Mycophenolate versus methotrexate for NIIPPU
Patient or population: NIIPPU
Setting: ophthalmology clinics (India, United States, Australia, India, Mexico, Saudi Arabia)
Intervention: methotrexate

Comparison: mycophenolate

Outcomes	Anticipated absolute effect (95% CI)*		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk with mycophenolate	Assumed risk with methotrexate				
Proportion of participants achieving control of inflammation§ (higher number of events is better) Follow-up: 0 to 6 months	55 events per 100 participants	**67 events per 100 participants** (55 to 88)	**RR 1.23** (1.01 to 1.50)	261 (2 RCTs)	⊕⊕⊕⊝ **Moderate**[a]	
Change in BCVA (lower logMAR indicate better vision) Follow-up: 0 to 6 months	The mean BCVA score across the control group ranged from -0.12 to -0.19 logMAR	**The mean logMAR was 0.01 higher (worse) on average** (0.04 lower to 0.05 higher logMAR)		490 eyes (2 RCTs)Φ	⊕⊕⊕⊝ **Moderate**[a]	
Proportion of participants achieving a 2-line improvement in visual acuity (Snellen chart) (higher scores indicate better vision) Follow-up: 0 to 6 months	No data were reported for this outcome		-	-	-	-
Proportion of participants with confirmed macular edema (lower number of events is better) Follow-up: 0 to 6 months	46 events per 100 participant eyes	**23 events per 100 participant eyes** (9 to 60)	**RR** 0.49 (0.19 to 1.30)	35 eyes (1 RCT)†	⊕⊝⊝⊝ **Very low**[b,c]	
Proportion of participants achieving steroid-sparing control§ (higher number of events is better) Follow-up: 0 to 6 months	55 events per 100 participants	**67 events per 100 participants** (55 to 88)	**RR 1.23** (1.01 to 1.50)	261 (2 RCTs)	⊕⊕⊕⊝ **Moderate**[a]	
Proportion of participants experiencing complications or requiring cessation of medication (lower number of events is better)	7 events per 100 participants	**7 events per 100 participants** (3 to 17)	**RR 0.99** (0.43 to 2.27)	296 (2 RCTs)	⊕⊕⊝⊝ **Low**[a,d]	

Follow-up: 0 to 6 months

***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**

BCVA: best-corrected visual acuity; **CI:** confidence interval; **logMAR:** logarithm of the minimum angle of resolution;**MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio; **SD:** standard deviation; **VKH:** Vogt-Koyanagi-Harada

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence:
High certainty: further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low certainty: we are very uncertain about the estimate

[3]Study primary outcome of steroid sparing control of inflammation defined as ≤ 0.5 + anterior chamber cells, ≤ 0.5 + vitreous cells, ≤ 0.5 + vitreous haze, and no active retinal or choroidal lesions; ≤ 2 drops of prednisolone acetate 1% a day in both studies and daily prednisolone ≤ 10 mg in one study and ≤ 7.5 mg/day in the other study
[b]Visual acuity of uveitic eyes only
[f]Subgroup of VKH participants' eyes with macular edema at baseline

[a]Downgraded (-1) for imprecision (small sample size)
[b]Downgraded (-1) for indirectness (single study subgroup of VKH in India)
[c]Downgraded (-2) for serious imprecision (small sample size)
[d]Downgraded (-1) for risk of bias (both studies have some concern for risk of bias in outcome measurement)

Summary of findings 3. Steroids with or without azathioprine versus cyclosporine A for NIIPPU

Steroids with or without azathioprine versus cyclosporine A for NIIPPU						
Patient or population: NIIPPU **Setting:** ophthalmology clinics (Germany, Japan, Chile, USA) **Intervention:** Steroids with or without azathioprine (oral steroids, IV steroids, or azathioprine) **Comparison:** cyclosporine A (CsA)						
Outcomes	**Anticipated absolute effect (95% CI)***		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk with cyclosporine A	**Assumed risk with steroids ± azathioprine**				

Proportion of participants achieving control of inflammation (higher number of events is better) Follow-up: 0 to 12 months	87 events per 100 participants	**73 events per 100 participants** (61 to 88)	**RR 0.84** (0.70 to 1.02)	112 (2 RCTs)[a]	⊕⊝⊝⊝ **Very low**[a,b,c]	Two other studies reported this outcome but used CsA doses no longer in practice (Nussenblatt 1991; Wiederholt 1986).
Change in BCVA (lower logMAR indicate better vision) Follow-up: 0 to 12 months	The mean BCVA score across the CsA group ranged from -0.32 to -0.21 logMAR	**The mean logMAR was 0.04 lower (better) on average** (-0.14 to 0.07 logMAR)	-	91 eyes (2 RCTs)[a]	⊕⊝⊝⊝ **Very low**[a,b,c]	
Proportion of participants achieving a 2-line improvement in visual acuity (Snellen chart) (higher scores indicate better vision) Follow-up: 0 to 6 months	See comment	-	-	-	-	One study reported this outcome but used CsA doses no longer in practice (Wiederholt 1986).
Proportion of participants with confirmed macular edema (lower number of events is better) Follow-up: 0 to 6 months	See comment	-	-	-	-	One study reported this outcome but used CsA doses no longer in practice (Nussenblatt 1991).
Proportion of participants achieving steroid-sparing control (higher number of events is better) Follow-up: 0 to 12 months	78 events per 100 participants	**50 events per 100 participants** (26 to 97)	**RR 0.64** (0.33 to 1.25)	21 (1 RCT)[a]	⊕⊝⊝⊝ **Very low**[a,b,c]	
Proportion of participants experiencing complications or requiring cessation of medication (lower number of events is better) Follow-up: 0 to 12 months	7 events per 100 participants	**6 events per 100 participants** (1 to 24)	**RR 0.85** (0.21 to 3.45)	91 participants (2 RCTs)[§]	⊕⊝⊝⊝ **Very low**[a,b,c]	One other study reported this outcome but used CsA doses no longer in practice (Nussenblatt 1991).

***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**

BCVA: best-corrected visual acuity; **CI:** confidence interval; **CsA**: cyclosporin A; **IV:** intravenous**logMAR:** logarithm of the minimum angle of resolution;**MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio; **SD:** standard deviation; **VKH:** Vogt-Koyanagi-Harada

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence:
High certainty: further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low certainty: we are very uncertain about the estimate

[a]Downgraded (-2) for risk of bias (one or more studies with unclear or high risk of bias overall, randomization process, deviations from intended interventions)
[b]Downgraded (-1) for imprecision (small sample size)
[c]Downgraded (-1) for indirectness (VKH not representative of all NIIPPU)
[§]Only VKH participants

Appendix 8: Key Limitations of the published literature

1. Lack of standardisation - disease and outcomes

While the SUN working group (The Standardization of Uveitis Nomenclature (SUN) Working Group , 2005) has made progress with standardizing the approach to reporting clinical data in uveitis research, studies conducted prior to this publication, lacked standardization with the anatomic classification of uveitis. This does present limitations with undertaking the determination of effect sizes, particularly given the small sizes of most studies. Lack of standardised nomenclature also impedes the extrapolation of results to any select population cohorts.

A SR by (Denniston et al, 2015) investigated the heterogeneity of outcome measures used in recent clinical trials (n=104 clinical trials) for intermediate, posterior, and panuveitis. According to this review, current study designs prioritize clinician-observed measures of disease activity and measurement of visual function as outcome measures which prevents comparison of studies and meta-analyses, and weakens the evidence available to stakeholders. Furthermore, even when the same outcome was used, there was often variation in the way it was measured, analysed, and reported, with many of the tools used to monitor outcomes were reliant on subjective scoring either by patients or healthcare providers. In assessing the degree of consensus or otherwise in the choice of primary outcome measures related to uveitis, 74% included one or more variables related to disease activity as primary outcome measures; 52% included visual acuity as a primary outcome measure and 4% included one or more variables of disease-associated tissue damage or complications as primary outcome measures. None of the studies identified by (Denniston et al, 2015), included a measure of patient reported visual function as a primary outcome measure. A subsequent publication by (Kelly NK et al., 2021) assessing VR-QoL and HR-QOL measures has been identified, and included in this review.

Following a five year consensus process which included patient, caregiver, and healthcare professional representatives, a list of 16 outcomes of sufficient importance to be included in a 'core outcome set' (COS), for non-infectious uveitis of the posterior segment (NIU-PS) in clinical trials was published by (Tallouzi MO et al, 2021). It remains to be seen whether these outcomes will be adopted for use in clinical trials going forward, however any benefits from adoption will likely only be realised in decades to come. The authors note that further work is required to determine and validate the optimal measurement tool for each of the recommended outcome measures.

2. Lack of standardisation – drug doses

As most DMARDs are used off-label for the management of uveitis, there is a of lack standardisation with recommended doses of DMARDs. The reported doses of methotrexate range from 7.5 mg to 25 mg per week, and cyclosporine doses ranged from 2.5 mg to 15 mg/kg/ day (higher doses reported in the older cyclosporine studies that have now fallen out of clinical practice). Head to head studies have also been incongruent where high doses of one DMARD e.g. methotrexate 25mg was compared to standard dose mycophenolate mofetil 2grams.

The dosing regimens of corticosteroid comparators also varied considerably with doses ranging from 10-100mg daily with variable dose tapering regimens, although steroid tapers were generally aimed to achieve a dose of 5 to 10mg daily.

3. Heterogeneity of studies

Most studies on uveitis involve different anatomic locations and usually included patients with variable underlying systemic disease.

4. Age cohorts

Similar to our review, the Cochrane SR (E Mayhew RG, 2022) intended to include only adults in their population cohort. The Cochrane methodology was subsequently revised to include trials with a mix of adults, adolescents, and children but excluded trials where all participants were under 18 years old. Most RCTs in the Cochrane review included only adult participants, except for (Cuchacovich M et al, 2010), which included one child aged five years, and the two FAST trials, (Rathinam SR et al, 2014) and (Rathinam SR et al, 2019) w which included participants 16 years of age and older.

5. Combination therapy

There is a lack of good quality studies with head to head comparisons of DMARDs. In the small number of head to head studies many included combination therapy with corticosteroids or other immunomodulatory therapies limiting the ability to assess the efficacy of any single DMARD.

6. Therapeutic management – uveitis vs underlying disease

Our review as well as that of the two SRs included above, focussed on the management of the anatomical classification of ocular manifestations of uveitis which is associated with of a wide range of underlying immune-mediated aetiologies. The indication of the DMARD, the course of the disease and the response to treatment could be different regarding the ocular and the systemic manifestations of the underlying conditions. According to (Denniston et al, 2015), the option of syndrome-specific clinical trials has not been possible, despite making "biological sense", because of logistic challenges, particularly around recruitment. This does then follow that the authors of both SRs included in this review [(E Mayhew RG, 2022) and (Gomez-Gomez A , 2020)], acknowledge the limitations with being able to develop a treatment algorithm for the management of uveitis. Instead, it is recommended that treatment strategies be informed on a case by case basis tailored to individual patient's needs.

Furthermore, many of the underlying systemic conditions associated with uveitis follow a relapsing and remitting course. One such example is Behcet's disease with eye involvement, where visual acuity regresses during an acute attack but often improves with time even if untreated. Reliance on small RCTs or case series with a measure of visual acuity over time for such conditions may inaccurately imply efficacy of drug treatment (Hatemi G et al, 2009).

7. Comprehensiveness of included studies

Given that patients with bilateral posterior and panuveitis are a subgroup of patients included in most studies, there is a risk of relevant articles being missed with any given search strategy, due to indexing, particularly if the study population has not been included in the title or abstract of the publication.

8. Generalisability to the local population

While the Cochrane review (E Mayhew RG, 2022) included studies spanning a wide geographic region [USA, Western Europe, Mexico, Chile, Australia, Japan, Saudi Arabia, and India], no studies from the African subcontinent were included. The prevalence of certain aetiological conditions such as VKH disease is reportedly higher in population cohorts with pigmented skin, such as Asians, Middle Easterners, Hispanics and Native Americans. VKH is very infrequent among persons of African descent (Rao NA et al, 2010), who were most likely under-represented in the Cochrane review (E Mayhew RG, 2022) given the sizeable populations of VKH in a number of the RCTs cited. The high proportion of VKH in some of the included RCTs may make the results of this SR less generalizable to our local population. The SITE cohort study (Kempen JH et al, 2008) excluded people living with HIV.