Effectiveness of pharmacological agents in the management of non-infectious scleritis: a systematic review

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Background

- Non-infectious scleritis is a potentially sight-threatening condition characterised by inflammation of the sclera. It is associated with significant ocular comorbidities and a reduced quality of life. Approximately 40-50% have an underlying autoimmune condition.[1]
- Mild scleritis often responds to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), but more chronic and severe scleritis may require corticosteroids and/or immunomodulatory therapy (IMT) such as methotrexate, mycophenolate mofetil, and biologics such as rituximab.[2]
- No national or international guidelines exist for the treatment of non-infectious scleritis and there is wide variation in management. A systematic review of existing literature is therefore required to evaluate and summarise existing evidence; this may form the basis for evidence-based recommendations for future clinical practice.

Aim: To review existing literature to assess the effectiveness of pharmacological agents in the management of non-infectious scleritis.

Methods

Search strategy
- Electronic databases (MEDLINE, EMBASE, CINAHL, Cochrane Library, British Library, ProQuest, and registers of clinical trials) were searched using a comprehensive search strategy. Reference lists of relevant articles were also manually searched.
- Two reviewers independently screened all studies, and results compared to confirm agreement; discrepancies were resolved by a third independent reviewer. **Figure 1** outlines the literature search and study selection process.

Eligibility criteria
- *Population:* Participants of any age, gender or ethnicity with non-infectious scleritis. Only human studies included.
- *Intervention and comparator:* Any pharmacological agent compared to a placebo / same pharmacological agent at different dose / a different pharmacological agent.
- *Outcomes:* Disease activity, steroid dose sparing effect, adverse events and health-related quality of life.
- *Study Design:* Comparative studies only.

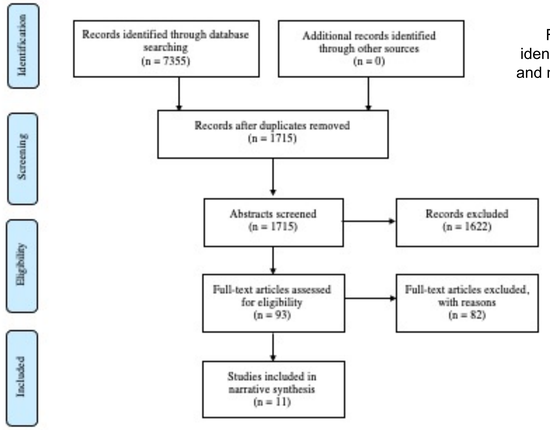


Figure 1: PRISMA Flow diagram Flow chart showing number of studies identified following initial database search and number excluded at each stage of the screening process.

Data extraction & Risk of bias assessment
- Study characteristics, population characteristics, intervention / comparator details and results were extracted.
- Bias was assessed using an adapted Cochrane Risk of Bias tool.[3]
- Data extraction and bias assessment were performed by two independent reviewers and results compared to confirm agreement; discrepancies were resolved by a third independent reviewer.

Data synthesis
- Studies were grouped by class of pharmacological agent. Data was tabulated and a narrative summary of evidence for each outcome of relevance was produced.

Results

Study characteristics
- 2 RCTs and 9 observational studies were included.
- 2/11 studies investigated the effect of NSAIDs, 1/11 corticosteroids, 7/11 IMTs and 1/11 a combination of agents from different classes.
- Sample sizes ranged from 3 to 126 patients.

Figure 2 shows the percentage of studies with high, unclear or low risk of bias.

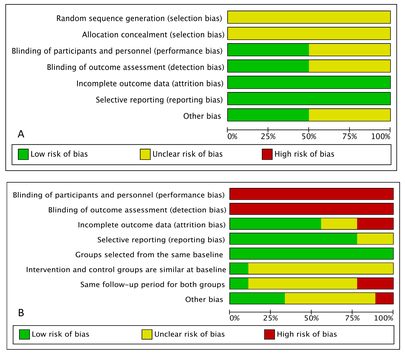


Figure 2: Risk of Bias summary for included studies. **A:** Bias assessment for randomised controlled trials **B:** Bias assessment for observational studies.

Summary of evidence
- There was limited evidence for a beneficial treatment effect with all classes of therapy (**Figure 3**). Due to wide variation in the reporting of outcomes across all studies, meta-analysis was not possible.

Drug	Summary of evidence for primary and secondary outcomes
NSAIDs	• Higher rate of remission in NSAIDs vs IMTs (85.7% vs 7.7- 50%) • Rates of inflammation control and steroid sparing of selective vs non-selective COX inhibitors were not significantly different (p=0.46-1.00 and p=0.25-1.00). • NSAIDs can be administered in combination with corticosteroids; results suggest a lower failure rate compared to NSAIDs alone. (1.41 vs 0.68 per 1000 person-years)
Steroids	• Iontophoretic delivery of dexamethasone phosphate showed promising results; the lowest dose of 1.2mA/min at 0.4mA was shown to be the most effective at reducing scleritis severity scores.
IMTs	• Cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, cyclosporin, rituximab, adalimumab and infliximab were evaluated across eight studies. • Sample sizes of studies were relatively low (n=3-104), and where statistical analysis was conducted, no statistically significant difference in efficacy was reported between studied agents.

Figure 3: Summary of evidence. Narrative summary of evidence for primary and secondary outcomes grouped by class of pharmacological agent.

Adverse events
- 9/11 studies reported adverse events; the most commonly reported side effect was gastrointestinal intolerance in NSAIDs (5.80-9.52%).
- Adverse events reported in patients receiving IMTs include hepatotoxicity (6%), nephrotoxicity (38%), leucopenia (12%) and haemorrhagic cystitis (12%). Rates of leucopenia and haemorrhagic cystitis were significantly higher with cyclophosphamide compared to other immunosuppressive agents (p<0.001).

Discussion

Key findings
- NSAIDs, corticosteroids and IMTs have all been shown to be effective at reducing disease activity. No agent was found to be more effective than another at reducing concurrent systemic steroid dose.
- Health-related quality of life was not reported by any of the included studies.

Limitations
- Small number of included studies in this review and small sample sizes
- Very few RCTs with most data extracted from observational studies; significant risk of bias with observational studies.
- Unable to perform meta-analysis due to methodological and clinical heterogeneity

Recommendations for future research
- Further high-quality double-masked RCTs are needed to inform future practice and enable development of evidence-based treatment protocols.
- Clinicians and researchers should be encouraged to adopt standardised outcome measures to reduce methodological heterogeneity.

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