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The effectiveness of pharmacological agents for the treatment of Uveitic Macular Oedema (UMO): a systematic review

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Abstract
To conduct a systematic review of effectiveness of pharmacological therapies for treatment of Uveitic Macular Oedema (UMO).

Method/Design
Comparative studies of pharmacological therapies in patients with UMO were identified in Cochrane CENTRAL/MEDLINE/EMBASE/CINAHL/trials registers (February 2017). PROSPERO registration: CRD42015019170.

Results
Thirty-one studies were included. Corticosteroids were the most frequently studied (n=20). Corticosteroids (all forms) were consistently of greater/equal efficacy to active comparators; for anti-VEGF (n=4) improvement in best-corrected-visual-acuity (BCVA) and central-macular-thickness (CMT) was mostly less than local corticosteroid injection; for interferon (n=1) improvement in BCVA and CMT was greater than the comparator of methotrexate; for topical indomethacin (n=1) improvement in BCVA and CMT was greater than placebo. Non-steroidal anti-inflammatory drugs, carbonic anhydrase inhibitors and vitamin E (n=5) were not effective for these outcomes.

Conclusion
The review highlights areas where the evidence base is still lacking, and appropriately focused trials are needed to inform best treatment to tackle this sight-threatening condition.

Keywords
Systematic review, macular oedema, macular edema, uveitis, management, pharmacological agents, treatment, meta-analysis.
Introduction

Uveitis describes a group of disorders characterised by intraocular inflammation. Uveitis is the fifth commonest cause of visual loss in the developed world and accounts for about 10–15% of total blindness [1,2] and up to 25% in the developing world [3,4]. Although uveitis may affect any age group, it peaks in the working-age population with no significant gender difference [5]. 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 [1,2,5,6].

Macular Oedema (MO) is a leading cause of sight-loss in uveitis, due to its impact on the ‘central vision’ [1,7]. Uveitis may be classified anatomically as anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis [8-10]. MO is more common in those forms of uveitis, that affect the more posterior structures in the eye, namely intermediate, posterior or panuveitis; collectively these are sometimes referred to as posterior segment-involving uveitis. Less commonly MO occurs in association with anterior uveitis [11].

The treatment of Uveitic Macular Oedema (UMO) is a major priority in tackling sight-loss in uveitis [10], and is the focus of this study. In current clinical practice, the mainstay of treatment for UMO is corticosteroid, delivered by various routes including: systemic (oral, intravenous and intramuscular); local which includes periocular injection (sub-Tenon and orbital floor injection) and intraocular (intravitreal injection or implant) [10,12,13]. Other classes of intervention include non-corticosteroid immunomodulatory agents (e.g. T cell inhibitors (e.g. cyclosporine, tacrolimus), anti-metabolites (e.g. azathioprine, methotrexate, mycophenolate), alkylating agents (e.g. cyclophosphamide) and biological agents (e.g. interferons, antitumor necrosis factor (anti-TNF)) [14-17]. Most of these agents are only used systemically (oral, intravenous, or subcutaneous), while intravitreal use has been reported for both methotrexate and anti-TNF agents [16-19]. Other treatments that have been used in UMO include non-steroidal anti-inflammatory drugs (NSAID), anti-vascular endothelial growth factor (anti-VEGF), carbonic anhydrase inhibitor (e.g. acetazolamide), and vitamins [10,20].
Whilst there have been narrative reviews on the management of UMO [10], one systematic review published in 2011, has been undertaken to date. The review included RCTs only and had some methodological limitations (lack of steps to minimise bias in the review process) [21]. Currently there are no consensus guidelines to direct treatment of UMO, therefore, it is timely to review the literature to summarise the available evidence for the pharmacological agents used for the treatment of UMO.

**Method**

Protocol was registered with PROSPERO database ref (CRD42015019170), and published prior to study commencement [22]. The review and its findings are reported in accordance with the PRISMA guidelines [23].

**Search strategy**

MEDLINE, EMBASE, CINAHL, Cochrane Library and registers of clinical trials were searched from inception to February 2017 [22]. Reference lists of included studies and identified reviews were also searched. The search strategy for each bibliographic database is shown Supplementary Table 1. There was no restriction placed on either language or year of publication, however, for conference abstracts, only those within three years of the search date were considered.

**Selection Criteria**

Studies were included if meeting the following criteria:

- **Study design:** Randomised controlled trials (RCTs) and other comparative studies where the comparator group was from a concurrent time-period (e.g. non-randomised controlled trials, comparative observational studies).

- **Participants:** Participants of any age, gender or ethnicity with a diagnosis of UMO. Studies on a population broader than UMO were only included if data specific for the UMO subgroup was reported separately.

- **Intervention and comparator:** Any pharmacological agent compared to no use of a pharmacological agent or to another pharmacological agent.

**Selection process**
Search results were entered onto EndNote x7 (Clarivate Analytics). Duplicate entries were removed. Titles and abstracts were screened to remove irrelevant records based on the study design, population and intervention. Full texts were retrieved for the remaining potentially relevant studies and assessed against the selection criteria. Details of articles excluded at the full text selection stage were recorded along with the reason for exclusion. Translation in part or wholly of non-English language articles was undertaken to aid selection and reviewing.

Two reviewers independently selected, appraised and extracted data from included articles, with disagreements resolved by discussion and referral to a third reviewer if required. Attempts were made to contact authors for missing information.

**Data Extraction**

The following data were extracted using standardised forms:

- **Study characteristics**: authors, publication year, journal, study design, setting, sample size, length of follow up, analysis,
- **Participant’s characteristics**: patient’s selection/recruitment criteria, demographic data, type of uveitis (anatomical categorisation, syndrome/aetiological classification), comorbidity and co-medication,
- **Intervention and comparator**: type, dose, frequency and route of administration, underlying care.
- **Outcomes**: Best corrected visual acuity (BCVA) (the primary outcome of this review) adverse events, health-related quality of life (QoL), central macular thickness (CMT), assessment of UMO leakage using Fundus fluorescein angiographic (FFA), clinical assessment of UMO, vitreous haze and anterior chamber cells.

**Quality assessment**

The Cochrane risk of bias tool was used to guide appraisal of all studies [24]. For randomised crossover studies, additional criteria such as washout period and carry over treatment effect were used. For controlled observational studies, the domains in the risk of bias tool for RCTs were used as a minimum assessment (again accepting that the studies were not randomised), and noting that the
most relevant criteria for assessment in this area relate to how the groups were selected: differences in patient characteristics, loss to follow-up, and biases and confounding in outcome assessment [24].

Analysis
Data were grouped together from the same study design and by each intervention and comparison, with data tabulated and a narrative synthesis of evidence conducted for each outcome of relevance to the review. Multiple time point data were available within the same study and between studies and considered in the ranges ≤3 months, >3 and ≤6 months and >6 months’ at the end of interventions. The potential for meta-analysis was considered where there was more than one study of the same design in the same population for the same comparison presenting the same type and time point of data for each outcome. No meta-analysis was deemed feasible.

Results
Database searches identified 3891 records, of which 1151 were duplicates. After screening titles and abstracts, full selection criteria were applied to 81 articles which yielded 31 included studies [13,25-55]; of these two studies [50,53] were identified through cross-checking bibliographies of recent reviews [10,21] and two studies through screening references of included studies [29,51]. The study selection process is shown in details of excluded studies are shown in Figure 1. Details of excluded studies are shown in Supplementary Table 2.
Of the 31 included studies, there were 23 randomised control trials [13,26-34,38,39,42-50,52,54] three randomised crossover trials [35,36,55], and one internally randomised controlled study (by eye within an individual) [37], and four retrospective cohort studies [39-41,51]. Eighteen studies enrolled UMO patients [13,29-31,33-41,43,48,49,51,54] and 13 studies had UMO as a subgroup of all enrolled patients [25,27,28,32,38,42,44-48,50,53]. The most frequently encountered class was corticosteroids agents (n=20), followed by immunomodulatory agent (n=8), anti-VEGF (n=4), NSAIDs (n=3), carbonic anhydrase inhibitor (n=3) and vitamins (n=1). Study characteristics, presented by comparison, and outcomes measured are shown in Table 1.
<table>
<thead>
<tr>
<th>Author/year</th>
<th>Design</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuppermann 2007 [25,26]</td>
<td>RCT</td>
<td>CRVO, Irvine-Gass syndrome and DMO</td>
<td>Dexamethasone 350 µg or 700µg implant (DDS)</td>
<td>Observation</td>
<td>*The proportion of patients achieving 10 letters improvement in BCVA at the day 90 of follow up (ETDRS). The proportion of patients achieved 15 letters improvement in BCVA, the proportion of patients achieved 2 and 3 grade levels of improvement in fluorescein angiogram leakage. Adverse events</td>
</tr>
<tr>
<td>Lowder 2011 [42]</td>
<td>RCT</td>
<td>Uveitis/UMO</td>
<td>Dexamethasone 350 µg or 700µg implant (DDS)</td>
<td>Sham</td>
<td>*BCVA (Snellen chart), CMT, Safety measures, IOP and cataract progression</td>
</tr>
<tr>
<td>Shin 2015 [43]</td>
<td>RCT</td>
<td>UMO</td>
<td>Intravitreal Triamcinolone a Acetonide 4mg</td>
<td>Sham</td>
<td>*BCVA (ETDRS), CMT, IOP and cataract progression</td>
</tr>
<tr>
<td>Pavesio 2010 [50]</td>
<td>RCT</td>
<td>Uveitis/UMO</td>
<td>Fluocinolone Acetonide implant 0.59</td>
<td>Standard of Care</td>
<td>*Uveitis recurrence rate, BCVA (LogMAR), macular leakage Safety outcomes (IOP, Lens opacity and adverse events)</td>
</tr>
<tr>
<td>Tomkins-Netzer 2015 [29]</td>
<td>RCT</td>
<td>UMO</td>
<td>Systemic prednisolone (1mg/kg/day up to 60mg/day)</td>
<td>Fluocinolone Acetonide implant 0.59mg</td>
<td>*CMO resolution and macula leakage (FFA)/BCVA (Snellen chart)</td>
</tr>
<tr>
<td>Sangwan 2015 [27]</td>
<td>RCT</td>
<td>Uveitis/UMO</td>
<td>Fluocinolone Acetonide implant 0.59mg</td>
<td>Fluocinolone Acetonide implant 2.1mg</td>
<td>*Change in uveitis occurrence rate pre-implantation and 3 years' post implantation. Evaluating the non-implanted eye anterior chamber activity, vitreous activity BCVA (LogMAR) and rate to post implantation reoccurrence of uveitis, change in BCVA and area of macular oedema on FFA. Proportion of eyes requiring systemic therapy or pericocular injection. Safety measures (IOP, lens opacity, visual field, ocular adverse events (any IOP&lt;6 mmHg, any loss of ≥3 lines visual acuity from baseline or in the last visit, and retinal tears.</td>
</tr>
<tr>
<td>Callanan 2008 [28]</td>
<td>RCT</td>
<td>Uveitis/UMO</td>
<td>Fluocinolone Acetonide implant 0.59mg</td>
<td>Fluocinolone Acetonide implant 2.1mg</td>
<td>*Recurrence rate in the implanted eye from the 34 weeks before implantation to the 34 weeks after implantation. BCVA (LogMAR), need for adjunctive therapy, and safety measures.</td>
</tr>
<tr>
<td>Jaffe 2006 [53]</td>
<td>RCT</td>
<td>Uveitis/UMO</td>
<td>Fluocinolone Acetonide implant 0.59mg</td>
<td>Fluocinolone Acetonide implant 2.1mg</td>
<td>*BCVA (LogMAR), anatomical macular changes (OCT), adverse events and raised IOP</td>
</tr>
<tr>
<td>Venkatesh 2008 [13]</td>
<td>RCT</td>
<td>UMO</td>
<td>Triamcinolone Acetonide 20mg (0.5ml) cannula method</td>
<td>Triamcinolone 20mg (0.5ml) Smith &amp; Nozik method and orbital floor method</td>
<td>*BCVA (LogMAR), anatomical macular changes (OCT), adverse events including IOP</td>
</tr>
<tr>
<td>Chen and Liang 2016 [49]</td>
<td>RCT</td>
<td>UMO</td>
<td>Triamcinolone Acetonide (0.1ml) subconjunctival</td>
<td>Triamcinolone (0.1ml) intravitreal</td>
<td>*BCVA (LogMAR), anatomical macular changes (OCT), adverse events including IOP</td>
</tr>
</tbody>
</table>

Table 1: Study characteristics, presented by comparison, and outcomes measured
### 4. Corticosteroids vs other drugs (UMO subgroup no details)

**c. Corticosteroids vs anti VEGF**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Uveitis/UMO</th>
<th>Intervention</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahimi 2012</td>
<td>RCT</td>
<td>UMO</td>
<td>Bevacizumab 1.25mg intravitreal</td>
<td>BCVA (LogMAR) / CMT (OCT), AC activity, vitreous activity/ adverse events, raised IOP and cataract progression</td>
</tr>
<tr>
<td>Soheilian 2010</td>
<td>RCT</td>
<td>UMO</td>
<td>Bevacizumab 1.25mg Intravitreal</td>
<td>BCVA (LogMAR), CMT (OCT), macular leakage (FFA), adverse events, IOP and lens opacity</td>
</tr>
<tr>
<td>Lasave 2009</td>
<td>Retrospective Cohort</td>
<td>UMO</td>
<td>Bevacizumab 2.5mg intravitreal</td>
<td>BCVA (LogMAR)/ CMT (OCT)/ adverse events, IOP and lens opacity</td>
</tr>
<tr>
<td>Bae 2011</td>
<td>Retrospective Cohort</td>
<td>UMO</td>
<td>Bevacizumab 1.25mg intravitreal</td>
<td>BCVA (LogMAR), IOP, CMT, adverse events, IOP and lens opacity</td>
</tr>
</tbody>
</table>

**d. Corticosteroids vs NSAID**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Uveitis/UMO</th>
<th>Intervention</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soheilian 2013</td>
<td>RCT</td>
<td>UMO</td>
<td>Diclofenac 500mcg/0.1ml Intravitreal</td>
<td>BCVA (Snellen chart) and (LogMAR), CMT, adverse events, IOP and lens opacity</td>
</tr>
<tr>
<td>Radwan 2013</td>
<td>Retrospective Cohort</td>
<td>UMO</td>
<td>Bromfenac (drops)</td>
<td>BCVA (LogMAR) and CMT</td>
</tr>
</tbody>
</table>

**e. Corticosteroids vs anti TNF**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Uveits/UMO</th>
<th>Intervention</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markomichela kis 2010</td>
<td>Prospective cohort</td>
<td>Uveits/UMO</td>
<td>Infliximab intravenous infusion 5mg/kg/</td>
<td>BCVA (LogMAR), anterior chamber cell activity, vitreous cell activity, degree of inflammation to the posterior segment (retinal vasculitis, retinitis, macular oedema and papillitis)</td>
</tr>
</tbody>
</table>

**f. Corticosteroids vs T cell inhibitor**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Uveitis/UMO</th>
<th>Intervention</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nussenblatt 1991</td>
<td>RCT</td>
<td>Uveitis/UMO</td>
<td>Cyclosporine 10mg/Kg oral</td>
<td>BCVA ≥ 15 letters (ETDRS), Vitreous haze ≥2 increments and anterior chamber activity</td>
</tr>
</tbody>
</table>

**Immunomodulatory vs placebo**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Uveitis/UMO</th>
<th>Intervention</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nguyen 2016a</td>
<td>RCT</td>
<td>Uveitis/UMO</td>
<td>Adalimumab (loading dose 80mg followed by fortnightly 40mg) subcutaneous</td>
<td>(LogMAR), proportion of CMT change, change in AC activity, vitreous haze score, BCVA</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Condition</td>
<td>Interventions</td>
<td>Comparator</td>
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<tr>
<td>-----------------------</td>
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<tr>
<td><strong>Immunomodulatory vs Immunomodulatory</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Jaffe 2016 [47]</td>
<td>RCT</td>
<td>Uveitis/UMO</td>
<td>Adalimumab (loading dose 80mg followed by fortnightly 40mg) subcutaneous</td>
<td>Placebo</td>
</tr>
<tr>
<td>Nguyen 2016b [46]</td>
<td>RCT</td>
<td>Uveitis/UMO</td>
<td>Sirolimus 44µg intravitreal</td>
<td>Sirolimus 440µg or 880µg intravitreal</td>
</tr>
<tr>
<td>Nguyen 2016c [44]</td>
<td>RCT</td>
<td>Uveitis/UMO</td>
<td>Sirolimus 440µg, intravitreal</td>
<td>Sirolimus880µg intravitreal</td>
</tr>
<tr>
<td>Mackensen 2013 [34]</td>
<td>RCT</td>
<td>UMO</td>
<td>Interferon beta 44µg subcutaneous three times a day</td>
<td>Methotrexate 20mg subcutaneous once a week</td>
</tr>
<tr>
<td>Rathinam 2014 [48]</td>
<td>RCT</td>
<td>Uveitis/UMO</td>
<td>Methotrexate 25mg weekly (oral)</td>
<td>Mycophenolate 1g twice daily (oral)</td>
</tr>
<tr>
<td><strong>NSAID</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allgeri 2014 [33]</td>
<td>RCT</td>
<td>UMO</td>
<td>Indomethacin 0.5% drops four times a day</td>
<td>Artificial tears of methyl-hydroxy-propyl-cellulose four times a day</td>
</tr>
<tr>
<td><strong>NSAID vs anti VEGF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radwan 2013 [39]</td>
<td>Retrospective</td>
<td>UMO</td>
<td>Bromfenac (drops)</td>
<td>Bromfenac with either intravitreal Triamcinolone 4mg or Bevacizumab intravitreal **</td>
</tr>
<tr>
<td><strong>Acetazolamide vs Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lashay 2003 [36]</td>
<td>Randomised</td>
<td>UMO</td>
<td>Acetazolamide 250mg orally twice daily</td>
<td>Placebo (multivitamin) PO</td>
</tr>
<tr>
<td>Whitcup 1996 [35]</td>
<td>Randomised</td>
<td>UMO</td>
<td>Acetazolamide 500mg orally twice daily</td>
<td>Placebo (multivitamin)</td>
</tr>
<tr>
<td>Farber 1994 [55]</td>
<td>Randomised</td>
<td>UMO</td>
<td>Acetazolamide 250mg orally slow release twice daily</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Vitamin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nussenblatt 2006 [52]</td>
<td>RCT</td>
<td>UMO</td>
<td>Vitamin E 1600IU daily (oral)</td>
<td>Placebo (oral)</td>
</tr>
</tbody>
</table>

* The primary reported outcome in the included study. Absence of the star indicates unspecified outcomes in terms of primary or secondary. **Dosage of Bevacizumab was not reported.
Quality assessment revealed concerns over allocation concealment for RCTs, and masking for both participants and outcome assessors in observational studies. Summary for Cochrane risk of bias are shown in Figure 2, Figure 3, Supplementary Table 3 (RCTs), Supplementary Table 4 (crossover RCTs) and Supplementary Table 5 (observational studies).

**Figure 2: Risk of bias summary for RCTs**

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Intention-to-treat analysis (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alleghi et al 2014</td>
<td>✗</td>
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<td>✗</td>
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</tr>
<tr>
<td>Callinan et al 2006</td>
<td>✗</td>
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<td>✗</td>
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<tr>
<td>Chen et al 2001</td>
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<td>✗</td>
<td>✗</td>
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<td>✗</td>
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<td>Jaffe et al 2006</td>
<td>✗</td>
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<td>Jaffe et al 2016</td>
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<td>Kuppermann et al 2007</td>
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</table>
Types of studies and reported outcomes

The efficacy of intervention for the outcomes of importance for this review (BCVA, CMT, macular leakage) is provided in Table 2 and safety data in Table 3. In addition any comparisons between interventions (where reported) are highlighted in the text below, and any comparison for each intervention vs baseline (where reported) is provided in the Supplementary Documents.

1. Corticosteroid

1.1 Corticosteroid versus no pharmacological agent

Three RCTs [25,26,42,43] compared intravitreal corticosteroid injections to sham, two of which did not report specifically on a UMO subgroup. The remaining RCT, by Shin et al, reported no significant difference between corticosteroid and sham for BCVA, CMT or area of macular leakage at any time point [43].

1.2 Corticosteroid versus different corticosteroid
Two RCTs compared fluocinolone implant to systemic prednisolone [29,50]. Tomkins et al, reported no significant difference between interventions for BCVA and CMT [29]. In the one study by Pavesio et al that reported macular leakage, there was a significantly greater improvement in intravitreal fluocinolone compared to systemic prednisolone [50].

1.3 Corticosteroids versus same corticosteroids (Same route but different doses)

Three RCTs compared two different doses of fluocinolone implant with limited UMO-specific subgroup data given [27,28,53]. All studies reported no significant difference between implants for macular leakage at all time points [27,28,53].

1.4 Same dose and different routes of administration (Corticosteroids versus same Corticosteroids)

Two RCTs compared triamcinolone in different routes of administration including subtenon, orbital floor, intravitreal and subconjunctival routes. Venkatesh reported no significant difference between subtenon and orbital floor method for BCVA and CMT at any time point [13]. However, Chen and Liang, reported a significant difference between interventions, for BCVA and CMT favouring subconjunctival group compared to intravitreal triamcinolone [49].

1.5 Corticosteroids versus same corticosteroids (Different route and different dose)

Two studies compared triamcinolone administered via intravitreal route to either subtenon route or orbital floor injection at different doses. In comparison between interventions, there was no significant difference at any time point for BCVA in either trial [37,41]. In the one study that reported macular leakage, there was a significantly greater improvement in intravitreal triamcinolone compared to the orbital floor [41].

1.6 Corticosteroids vs anti VEGF

Four studies compared intravitreal triamcinolone to bevacizumab: in the two RCTs, there was no significant difference at any time point for BCVA in either trial [31,54]. Similar findings were noted in the two retrospective cohort studies of the same comparison [40,51]. For CMT, only one study showed a significant difference between interventions, favouring intravitreal triamcinolone. There was reduction in CMT vs baseline in all interventions in all studies, with a potential trend favouring greater benefit with intravitreal triamcinolone compared to anti-VEGF [54]. In the one study by
Soheilian et al. that reported macular leakage, there was no significant difference between interventions [31].

1.7 Corticosteroids versus NSAID
A single RCT compared intravitreal corticosteroid to intravitreal NSAID. In comparison between interventions, there was no significant difference at any time point for BCVA and CMT [30].

1.8 Corticosteroids vs immunomodulatory
Two studies compared corticosteroid to immunomodulatory agents [32,38], one of which did not report specifically on a UMO subgroup. The remaining RCT with UMO subgroup, by Nussenblatt et al, did not report any data on the difference between interventions, however, a complete resolution of macular leakage was reported in both interventions [32].

2. Immunomodulatory

2.1 Biological agent (Anti-TNF) versus placebo
Two RCTs (VISUAL I) and (VISUAL II) compared anti TNF to placebo. UMO was a subgroup of the study population, with no UMO-specific subgroup data given, and no further evaluation was possible [45,47].

2.2 Antimetabolites versus antimetabolites
A single RCT compared methotrexate to mycophenolate. In comparison between interventions, there was no significant difference for UMO resolution at any time point [48].

2.3 T-cell inhibitor versus T-cell inhibitor
Two RCTs by Nguyen et al. compared three different doses of intravitreal sirolimus [44,46]. Limited UMO subgroup data was provided, with no reported statistical comparisons either to baseline or between interventions for CMT or BCVA and macular leakage.

2.4 Biological agent versus antimetabolites
A single RCT compared Interferon beta to methotrexate, with a significant difference between interventions favouring interferon beta for BCVA and CMT [34].

3. Anti VEGF
Anti-VEGF agents were compared to corticosteroids and are addressed earlier in section 1.6.

4. NSAID

4.1 NSAID versus placebo
A single RCT compared indomethacin 0.5% to methyl-hydroxy-propyl-cellulose. In comparison between interventions, there was no significant difference for BCVA and CMT [33].

4.2 NSAID vs (NSAID and corticosteroid (triamcinolone) or NSAID) and anti VEGF

A retrospective cohort study compared a NSAID to a combination of the same NSAID with either intravitreal anti VEGF or intravitreal corticosteroid. There was no significant difference between interventions for BCVA and CMT, despite the statistical significance from baseline in dual therapy groups [39].

5. Carbonic anhydrase inhibitor

5.1 Carbonic Anhydrase inhibitor (Acetazolamide) versus placebo

Three randomised crossover studies compared carbonic anhydrase inhibitor (acetazolamide) to placebo. All studies reported no significant benefit of acetazolamide on BCVA [35,36,55]. In the one study by Whitcup et al, acetazolamide was associated with significantly greater reduction in macular leakage compared to placebo [35].

6. Vitamins

6.1 Vitamin E vs placebo

A single RCT compared vitamin E to placebo. The study reported no significant difference between groups for BCVA,CMT and macular leakage [52].

Adverse events (AEs)

1. Corticosteroids

Raised intra-ocular pressure (IOP) and cataract progression were the most commonly reported adverse events in studies using corticosteroid, especially after local administration. Elevated IOP (from baseline) was reported in 8 studies, the proportion of participants with raised IOP being 10-40% occurring over 4-12 weeks follow-up including different routes of administration (6 intravitreal, 1 subtenon, 1 subconjunctival and 1 orbital floor). Only four of these studies reported additional use of medical IOP-lowering treatment for IOP>22mmHg (range of 10-16%) [37,41,43,51] and one study reported one patient requiring glaucoma surgery (representing 5% of those who had had intravitreal triamcinolone in that study) [40].
Cataract progression was reported in five studies after local injection of triamcinolone, the proportion of participants was ranging from 5-68% (intravitreal 14-68%, orbital floor 27%, subconjunctival 15%) between 6-12 months of follow-up [30,31,40,41,43]. There were no studies which provided UMO-subgroup-specific data for AE in systemic vs local corticosteroid therapy. Other reported ocular adverse events occurred predominantly after local therapies of corticosteroid injections comprised subconjunctival haemorrhage (5%-10%) [49], vitreous opacity, requirement for vitrectomy and vitreous haemorrhage that resolved spontaneously [54]. Blepharoptosis was also reported in one patient following subtenon corticosteroid injection which resolved spontaneously [51].

2. **Immunomodulatory**

Flu-like symptoms (46%) were the most common AEs in interferon beta; with one further serious AE (hypertensive crisis in a patient with known systemic hypertension) (11%) was reported [34]. However, nausea (19%) and headache (20%) were the most common AEs in methotrexate and mycophenolate [34,48].

3. **Non-steroidal anti-inflammatory drugs (NSAID)**

Posterior subcapsular cataract was the only reported AE following intravitreal injection of diclofenac sodium (13%) [30].

4. **Anti VEGF**

Hypopyon (a visible layer of inflammatory cells in the anterior chamber) was the only reported AE following bevacizumab injection (7%) [31].

5. **Carbonic Anhydrase inhibitor (Acetazolamide)**

In the two studies that reported AEs with acetazolamide, non-serious AEs include paraesthesia, nausea, drowsiness, weight loss, fatigue, and allergic reaction, mild nausea, pins and needles [35,55]. In the one study by Farber et al, severe AEs were reported including severe allergic reaction, severe diuresis and haematuria [55].

6. **Vitamins**

No AEs were reported [32].
Table 2: Mean BCVA, CMT and area of macular leakage

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>BCVA (Baseline)</th>
<th>BCVA ≤3 months</th>
<th>BCVA &gt;3 and ≤6 months</th>
<th>BCVA &gt;6 months</th>
<th>CMT (Baseline)</th>
<th>CMT ≤3 months</th>
<th>CMT &gt;3 and ≤6 months</th>
<th>CMT &gt;6 months</th>
<th>Mean area of UMO at baseline</th>
<th>Mean area of macular leakage/Proportion of resolved leakage</th>
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<tbody>
<tr>
<td>I. Corticosteroids vs Placebo</td>
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<td>Shin 2015 [43]</td>
<td>IVTA</td>
<td>69±9.6 (EDTRS)</td>
<td>70(EDTRS)</td>
<td>74(EDTRS)</td>
<td>337±83μm</td>
<td>270μm (P=0.014)</td>
<td>245μm</td>
<td>2.3±1.91</td>
<td>0.95 (P=0.025) -3month 0.85 (S) 6 months</td>
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<td>Sham</td>
<td>70±9.0 (EDTRS)</td>
<td>73(EDTRS)</td>
<td>69 (EDTRS)</td>
<td>312±59μm</td>
<td>280μm (P=0.02)</td>
<td>270μm</td>
<td>3.6±4.99</td>
<td>3.6 (NS) 0.75 (S) -6 months</td>
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<td>Pavesio (2010) [50]</td>
<td>0.59mg fluocinolone implant</td>
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<td>Tomkins-Netzer 2015 [29]</td>
<td>0.59mg fluocinolone implant</td>
<td>62 (EDTRS) median</td>
<td>68 (EDTRS) median (NR) 2yrs</td>
<td>68% (NR)2yrs. Resolution 77% (NR) 2yrs. Improvement</td>
<td>58% (NR) -2yrs</td>
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<td>systemic prednisolone</td>
<td>63 (EDTRS) median</td>
<td>67 (EDTRS) median (NR) 2yrs</td>
<td>52% (NR) 2yrs Resolution 65% (NR) 2yrs. Improvement</td>
<td>31% (NR) -2yrs</td>
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<td>BCVA &gt;3 and ≤6 months</td>
<td>BCVA &gt;6 months</td>
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<td>CMT &gt;6 months</td>
<td>Mean area of UMO at baseline</td>
<td>Mean area of macular leakage/ Proportion of resolved leakage</td>
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<td>33mm²</td>
<td>7mm² (P&lt;0.01) - 1yr. 6mm² (P&lt;0.01) - 3yrs.</td>
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<td>25mm²</td>
<td>26mm² (P=0.91) - 1yr. 25mm² (P=0.80) 3yrs 5 favouring 0.59mg fluocinolone implant</td>
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<td>30mm²</td>
<td>5mm² (P&lt;0.01) 1yr. 23mm² (P=0.44) 3yrs.</td>
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<td>Intergroup comparison</td>
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<td>18 mm²</td>
<td>S favouring 2.1mg fluocinolone implant at 1year only NR between implants</td>
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<td>Jaffe 2006 [53]</td>
<td>0.59mg fluocinolone implant and 2.1mg i fluocinolone implant (combind)</td>
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<td>25% achieved 3 or more line of BCVA on LogMAR</td>
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<td>36mm²</td>
<td>7mm² (P&lt;0.05) 34wks</td>
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<td>5.3% achieved 3 or more line of BCVA on LogMAR</td>
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<td>42mm²</td>
<td>29mm² (NS) 34wks</td>
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<td>NR</td>
<td>P&lt;0.0001 favouring implanted eyes</td>
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<td>Venkatesh 13</td>
<td>PSTA (Cannula method)</td>
<td>0.65 LogMAR</td>
<td>0.15 LogMAR (P=00)</td>
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<td>382±174µm</td>
<td>214± 35µm (P=0)</td>
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<td>PSTA (Smith &amp; Nozik)</td>
<td>0.60 LogMAR</td>
<td>0.14 LogMAR (P=00)</td>
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<td>310± 85µm</td>
<td>208± 29µm (P=0)</td>
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<td>OFTA</td>
<td>0.65 LogMAR</td>
<td>0.19 LogMAR (P=00)</td>
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<td>373±101µm</td>
<td>262 ± 74µm (P=003)</td>
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<td>Intergroup comparison</td>
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<tr>
<td>Chen &amp; Liang 2016 [49]</td>
<td>IVTA</td>
<td>2.9±1.1 (SWR)</td>
<td>4±1.4 (NR)</td>
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<td>493±99µm</td>
<td>256±85µm (NR)</td>
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<td>BCVA (Baseline)</td>
<td>BCVA ≤3months</td>
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<tr>
<td>Sub conj (TA)</td>
<td>3.0±1.2 (SWR)</td>
<td>4.8±1.3(NR)</td>
<td></td>
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<td></td>
<td>485±101µm</td>
<td>214±66µm (NR)</td>
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<tr>
<td>Intergroup comparison</td>
<td>P&lt;0.05</td>
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<td>P&lt;0.05</td>
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<tr>
<td>Choudhury &amp; Ghosh 2007 [37]</td>
<td>IVTA</td>
<td>0.67±0.10 LogMAR</td>
<td>0.22±0.15 LogMAR (NR)</td>
<td>0.22±0.10 LogMAR (NR)</td>
<td>485±101µm</td>
<td>214±66µm (NR)</td>
<td>78% (NR)-3 months</td>
<td>89% (NR)-6 months</td>
<td></td>
<td>78% (NR)-6 months</td>
<td>100% (S)-1 and 3 months</td>
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<tr>
<td>Intergroup comparison</td>
<td>P=0.74</td>
<td>P=0.99</td>
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<td>P=0.32</td>
<td>P=0.53</td>
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<tr>
<td>Roessel 2009 [41]</td>
<td>IVTA</td>
<td>0.61±0.35 LogMAR</td>
<td>0.47±0.31 LogMAR (P=0.02)</td>
<td>0.62±0.33 LogMAR (NR)</td>
<td>485±101µm</td>
<td>214±66µm (NR)</td>
<td>76% (NR)-1month</td>
<td>20% (N)-3, 6 and 9months</td>
<td></td>
<td>76% (NR)-12 months</td>
<td>100% (S)-1 and 3 months</td>
</tr>
<tr>
<td>Intergroup comparison</td>
<td>P=0.86</td>
<td>0.10</td>
<td>0.018</td>
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<td>III. Corticosteroids vs other drugs</td>
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<td>a. Corticosteroids vs anti VEGF</td>
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<tr>
<td>Rahimi 2012 [54]</td>
<td>IVTA</td>
<td>0.48±0.22 LogMAR</td>
<td>0.07 ± 0.06 LogMAR (P&lt;0.001)</td>
<td>0.03 ± 0.04 LogMAR (P&lt;0.001)</td>
<td>485±101µm</td>
<td>214±66µm (NR)</td>
<td>76% (NR)-12 months</td>
<td>76% (NR)-12 months</td>
<td></td>
<td>76% (NR)-12 months</td>
<td>100% (S)-1 and 3 months</td>
</tr>
<tr>
<td>Intergroup comparison</td>
<td>P=0.772</td>
<td>P=0.326</td>
<td></td>
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<td></td>
<td>P=0.010</td>
<td>P&lt;0.001</td>
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<tr>
<td>Soheilian 2010 [31]</td>
<td>IVTA</td>
<td>0.85±0.34 LogMAR</td>
<td>△ -0.14±0.30 LogMAR (P=0.95)</td>
<td>△ -0.29±0.32 LogMAR (P=0.004)</td>
<td>485±101µm</td>
<td>△ -56±76µm (P=0.016)</td>
<td>60% (P=0.005) 12 weeks</td>
<td>68.8% (P=0.002) 24week</td>
<td></td>
<td>38.5% (P=0.206) 12 weeks</td>
<td>57.1% (P=0.089) 24weeks</td>
</tr>
<tr>
<td>Intergroup comparison</td>
<td>△ -0.19±0.21</td>
<td>△ -0.29±0.28</td>
<td>△ -0.35±0.45</td>
<td></td>
<td></td>
<td>△ -75±108 µm (P=0.03)</td>
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<tr>
<td>Study</td>
<td>Interventions</td>
<td>BCVA (Baseline)</td>
<td>BCVA ≤3 months</td>
<td>BCVA &gt;3 and ≤6 months</td>
<td>BCVA &gt;6 months</td>
<td>CMT (Baseline)</td>
<td>CMT ≤3 months</td>
<td>CMT &gt;3 and ≤6 months</td>
<td>CMT &gt;6 months</td>
<td>Mean area of UMO at baseline</td>
<td>Mean area of macular leakage/Proportion of resolved leakage</td>
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<td></td>
<td>LogMAR</td>
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<td>LogMAR</td>
<td>LogMAR</td>
<td>(P=0.005)</td>
<td>(P=0.004)</td>
<td>(P=0.016)</td>
<td>(P=0.091)</td>
<td>(P=0.985)</td>
<td>(μm (P=0.483))</td>
</tr>
<tr>
<td>Intergroup comparison</td>
<td>P=0.775</td>
<td>P=0.770</td>
<td>P=0.936</td>
<td>P=0.894</td>
<td>P=0.777</td>
<td>P=0.338</td>
<td>P=0.098</td>
<td>P=0.176</td>
<td>P=0.359</td>
<td>P=0.376</td>
<td>(69.2% P=0.031) -36weeks</td>
</tr>
<tr>
<td>Lasave 2009</td>
<td>IVTA</td>
<td>1.1 ± 0.2 LogMAR</td>
<td>0.7 ± 0.4 LogMAR</td>
<td>0.7 ± 0.3 LogMAR</td>
<td>455±239µm</td>
<td>289±141µm</td>
<td>296±134µm</td>
<td>296±134µm</td>
<td>345±135µm</td>
<td>345±135µm</td>
<td>(69.2% P=0.031) -36weeks</td>
</tr>
<tr>
<td></td>
<td>IVB</td>
<td>1.2 ± 0.4 LogMAR</td>
<td>1 ± 0.3 LogMAR</td>
<td>0.8 ± 0.4 LogMAR</td>
<td>401±142µm</td>
<td>323±108µm</td>
<td>345±135µm</td>
<td>345±135µm</td>
<td>345±135µm</td>
<td>345±135µm</td>
<td>(69.2% P=0.031) -36weeks</td>
</tr>
<tr>
<td>Intergroup comparison</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Bae 2011</td>
<td>IVTA</td>
<td>0.73±0.33 LogMAR</td>
<td>0.43 LogMAR</td>
<td>0.58 LogMAR (P &lt; 0.001)</td>
<td>594±151µm</td>
<td>△</td>
<td>328±233µm</td>
<td>△</td>
<td>166±227µm</td>
<td>167±154µm</td>
<td>(P &lt; 0.001)</td>
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<tr>
<td></td>
<td>PSTA</td>
<td>0.71±0.23 LogMAR</td>
<td>0.56 LogMAR</td>
<td>0.58 LogMAR (P &lt; 0.001)</td>
<td>582±146µm</td>
<td>△</td>
<td>166±227µm</td>
<td>△</td>
<td>167±154µm</td>
<td>167±154µm</td>
<td>(P &lt; 0.001)</td>
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<tr>
<td></td>
<td>IVB</td>
<td>0.73±0.41 LogMAR</td>
<td>0.56 LogMAR</td>
<td>0.56 LogMAR (P&lt;0.011)</td>
<td>537±214µm</td>
<td>△</td>
<td>167±154µm</td>
<td>△</td>
<td>167±154µm</td>
<td>167±154µm</td>
<td>(P &lt; 0.001)</td>
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<tr>
<td>Intergroup comparison</td>
<td>P=0.869</td>
<td>NR</td>
<td>NR</td>
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<td>b. Corticosteroids vs NSAID</td>
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<tr>
<td>Soheilian 2013</td>
<td>IVTA</td>
<td>0.75±0.49 LogMAR</td>
<td>0.63±0.48 LogMAR</td>
<td>0.48±0.49 LogMAR</td>
<td>0.58±0.39 LogMAR</td>
<td>642±289µm</td>
<td>335±109µm</td>
<td>407±92µm</td>
<td>510±194µm</td>
<td>510±194µm</td>
<td>(P=0.398)</td>
</tr>
<tr>
<td></td>
<td>IVDS</td>
<td>0.67±0.22 LogMAR</td>
<td>0.69±0.39 LogMAR</td>
<td>0.70±0.37 LogMAR</td>
<td>0.64±0.35 LogMAR</td>
<td>488±104µm</td>
<td>439±161µm</td>
<td>404±196µm</td>
<td>403±132µm</td>
<td>403±132µm</td>
<td>(P=0.123)</td>
</tr>
<tr>
<td>Intergroup comparison</td>
<td>P=0.779</td>
<td>P=0.281</td>
<td>P=0.463</td>
<td>P=0.281</td>
<td>P=0.955</td>
<td>P=0.613</td>
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<td>c. Corticosteroids vs T cell inhibitor</td>
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<tr>
<td>Nussenblatt 1991</td>
<td>Cyclosporine</td>
<td>0.75±0.49 LogMAR</td>
<td>0.63±0.48 LogMAR</td>
<td>0.48±0.49 LogMAR</td>
<td>0.58±0.39 LogMAR</td>
<td>642±289µm</td>
<td>335±109µm</td>
<td>407±92µm</td>
<td>510±194µm</td>
<td>510±194µm</td>
<td>(P=0.398)</td>
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<td></td>
<td>Prednisolone</td>
<td>0.67±0.22 LogMAR</td>
<td>0.69±0.39 LogMAR</td>
<td>0.70±0.37 LogMAR</td>
<td>0.64±0.35 LogMAR</td>
<td>488±104µm</td>
<td>439±161µm</td>
<td>404±196µm</td>
<td>403±132µm</td>
<td>403±132µm</td>
<td>(P=0.123)</td>
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<tr>
<td>Intergroup comparison</td>
<td>P=0.779</td>
<td>P=0.281</td>
<td>P=0.463</td>
<td>P=0.281</td>
<td>P=0.955</td>
<td>P=0.613</td>
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<tr>
<td>Study</td>
<td>Interventions</td>
<td>BCVA (Baseline)</td>
<td>BCVA ≤3 months</td>
<td>BCVA &gt;3 and ≤6 months</td>
<td>BCVA &gt;6 months</td>
<td>CMT (Baseline)</td>
<td>CMT ≤ 3 months</td>
<td>CMT &gt;3 and ≤6 months</td>
<td>CMT &gt;6 months</td>
<td>Mean area of UMO at baseline</td>
<td>Mean area of macular leakage/ Proportion of resolved leakage</td>
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<td>2. Immunomodulatory Agents</td>
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<td>1. Immunomodulatory vs immunomodulatory</td>
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<tr>
<td>Nguyen 2016c [44]</td>
<td>Sirolimus 44μg implant</td>
<td>46% (NR)</td>
<td>5months</td>
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<tr>
<td></td>
<td>Sirolimus 440μg implant</td>
<td>55% (NR)</td>
<td>5months</td>
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<td></td>
<td>Sirolimus 880μg implant</td>
<td>49% (NR)</td>
<td>5months</td>
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<tr>
<td>Nguyen 2016b [46]</td>
<td>Sirolimus440μg implant</td>
<td>461±139μm (NS)</td>
<td>403±148μm (NS)</td>
<td>419±160μm (NS)</td>
<td></td>
<td>57% (NS)-3months</td>
<td>28% (NS)-6months</td>
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<tr>
<td></td>
<td>Sirolimus880μg implant</td>
<td>375 ±89μm (NS)</td>
<td>313±66μm (NS)</td>
<td>457±204μm (NS)</td>
<td></td>
<td>83% (NS)-3months</td>
<td>67% (NS)-6months</td>
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<td></td>
<td>Intergroup comparison</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Mackensen 2013 [34]</td>
<td>Interferon beta</td>
<td>0.48 LogMAR</td>
<td>0.16 LogMAR (P=0.0039)</td>
<td>430μm</td>
<td>228μm (P=0.0039)</td>
<td>409μm (P=0.781)</td>
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<td></td>
<td>Methotrexate</td>
<td>0.34 LogMAR</td>
<td>0.25 LogMAR (P=0.1309)</td>
<td>371μm</td>
<td>409μm (P=0.781)</td>
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<tr>
<td></td>
<td>Intergroup comparison</td>
<td>P=0.0435 favouring interferon</td>
<td>P&lt;0.0001 favouring interferon</td>
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<tr>
<td>Rathinam 2014 [48]</td>
<td>Methotrexate</td>
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<td></td>
<td>Mycophenolate mofetil</td>
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<td>Intergroup comparison</td>
<td>P=0.31</td>
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<td>3. Anti VEGF</td>
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<tr>
<td>Anti-VEGF agents were compared to corticosteroids and are addressed above</td>
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<td>4. NSAID</td>
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<td>1. NSAID vs Placebo</td>
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<tr>
<td>Allgeri 2014 [33]</td>
<td>Indomethacin 0.5%</td>
<td>0.47 average in decimal (P&lt;0.001)</td>
<td>0.56 average in decimal (P&lt;0.0001)</td>
<td>446±149μm (P&lt;0.0001)</td>
<td>360μm (P&lt;0.001)</td>
<td>280μm (P&lt;0.001)</td>
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<tr>
<td>Study</td>
<td>Interventions</td>
<td>BCVA (Baseline)</td>
<td>BCVA ≤3 months</td>
<td>BCVA &gt;3 and ≤6 months</td>
<td>BCVA &gt;6 months</td>
<td>CMT (Baseline)</td>
<td>CMT ≤ 3 months</td>
<td>CMT &gt;3 and ≤6 months</td>
<td>CMT &gt;6 months</td>
<td>Mean area of UMO at baseline</td>
<td>Mean area of macular leakage/ Proportion of resolved leakage</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>0.52 average in decimal</td>
<td>0.5 average in decimal NS</td>
<td>0.55 average in decimal NS</td>
<td>390±162μm</td>
<td>405μm (NS)</td>
<td>410μm (NS)</td>
<td></td>
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<tr>
<td></td>
<td>Intergroup comparison</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
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<td>II.</td>
<td>NSAID vs anti VEGF</td>
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<td></td>
<td>Radwan 2013 [39]</td>
<td>Bromfenac</td>
<td>0.39±0.28 LogMAR</td>
<td>0.31± 0.27 LogMAR (P=0.911)</td>
<td>354±97μm</td>
<td>302±63μm (P=0.145)</td>
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<td></td>
<td>IVB+ Bromfenac</td>
<td>0.55±0.24 LogMAR</td>
<td>0.35± 0.23 LogMAR (P=0.001)</td>
<td>459±155μm</td>
<td>288±81μm (P=0.002)</td>
<td></td>
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<tr>
<td></td>
<td>IVTA + Bromfenac</td>
<td>0.52±0.50 LogMAR</td>
<td>0.33± 0.55 LogMAR (P=0.017)</td>
<td>423±175μm</td>
<td>260±46μm (P=0.009)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Intergroup comparison</td>
<td>P= 0.928</td>
<td>P=0.279</td>
<td></td>
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<td>5.</td>
<td>Carbonic Anhydrase inhibitor (Acetazolamide)</td>
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</tr>
<tr>
<td>I.</td>
<td>Acetazolamide vs placebo</td>
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<tr>
<td></td>
<td>Whitcup 1996 [35]</td>
<td>Acetazolamide</td>
<td>48(EDTRS)</td>
<td>48[EDTRS]</td>
<td>48(EDTRS)</td>
<td>2.1</td>
<td>Range 0.0-20.0</td>
<td>1.5</td>
<td>Range 0.0-5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>49(EDTRS)20/1</td>
<td>51 [EDTRS]</td>
<td>51 [EDTRS]</td>
<td>51 [EDTRS]</td>
<td>Range8-76</td>
<td>Range8-76</td>
<td>Range15-78</td>
<td>Range15-78</td>
<td>Range 0.2-20.0</td>
<td>Range 0.2-20.0</td>
</tr>
<tr>
<td></td>
<td>Intergroup comparison</td>
<td>NS</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Lashay 2003 [36]</td>
<td>Acetazolamide</td>
<td>0.537 LogMAR</td>
<td>Range 0.1-1.5</td>
<td>0.448 LogMAR</td>
<td>Range 0.1-1.5</td>
<td>1.892</td>
<td>Range 0-4</td>
<td>1.678</td>
<td>Range 0-4 (P=0.99)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0.430 LogMAR</td>
<td>Range 0.1-1.5</td>
<td>0.430 LogMAR</td>
<td>Range 0.1-1.5</td>
<td>Range 0-4</td>
<td>1.643</td>
<td>Range 0-4</td>
<td>1.714</td>
<td>Range 0-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intergroup comparison</td>
<td>NS</td>
<td></td>
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</table>

22
<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>BCVA (Baseline)</th>
<th>BCVA ≤3months</th>
<th>BCVA &gt;3 and ≤6 months</th>
<th>BCVA &gt;6 months</th>
<th>CMT (Baseline)</th>
<th>CMT ≤ 3 months</th>
<th>CMT &gt;3 and ≤6 months</th>
<th>CMT &gt;6 months</th>
<th>Mean area of UMO at baseline</th>
<th>Mean area of macular leakage/ Proportion of resolved leakage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farber 1994</td>
<td>Acetazolamide 0.57LogMAR</td>
<td>0.49 LogMAR</td>
<td>P= 0.01</td>
<td></td>
<td></td>
<td>DNA</td>
<td>DNA</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Placebo 0.51 LogMAR</td>
<td>0.50 LogMAR</td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
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<tr>
<td></td>
<td>Intergroup comparison</td>
<td>NS</td>
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<td>NS</td>
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<td>6. Vitamin E</td>
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<td>NS</td>
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<tr>
<td>Vitamin E</td>
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<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Nussenblatt 2006</td>
<td>Vitamin E 59±5(EDTRS)</td>
<td>54±5 (EDTRS)</td>
<td>232±47µm</td>
<td></td>
<td>367±59µm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Placebo 57±6(EDTRS)</td>
<td>56±6 (EDTRS)</td>
<td>467±124µm</td>
<td></td>
<td>392±119µm</td>
<td></td>
<td></td>
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<td></td>
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<td>NS</td>
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<tr>
<td></td>
<td>Intergroup comparison</td>
<td>NS</td>
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<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

PSIU: Posterior Segment Involving Uveitis,
IVTA: Intravitreal triamcinolone acetonide,
PSTA: Posterior subtenon triamcinolone acetonide,
OFTA: Orbital floor triamcinolone acetonide,
VB: Intravitreal bevacizumab, IVDS: Intravitreal diclofenac sodium,
NS: Non-significant change from baseline with no reported P value.
P value in brackets represents the comparison to the baseline
S: Reported as significant from baseline but no P value
NR: Not reported as significant or non-significant and no P value
SWR: Scale was not reported.
AP value without brackets represents the group comparison
Δ Represent the mean change from baseline CMT values were rounded to the nearest value
NB: Data in the above table represent the latest available data within the follow-up in the given time points (e.g. ≤3months would include 3months data).
<table>
<thead>
<tr>
<th>Study</th>
<th>Raised IOP from baseline</th>
<th>Cataract progression</th>
<th>Other Ocular AEs</th>
<th>Systemic AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Corticosteroids vs corticosteroids</strong></td>
<td></td>
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<tr>
<td>Shin 2015 [43]</td>
<td>A higher mean change from baseline in IVTA group vs sham at 1, 2 &amp; 3 months. <em>No further data reported.</em></td>
<td>25% (IVTA) and 15% (sham) at 6 months (IVTA) phakic patients are 64% (Placebo) phakic patients are 55%</td>
<td>No other ocular adverse event related to the study groups</td>
<td>No systemic AEs</td>
</tr>
<tr>
<td>Chen 2016 [49]</td>
<td>41% (IVTA) 29% (SConjTA) Time point and definition of raised IOP was not reported</td>
<td>Not reported</td>
<td>Subconjunctival haemorrhage: 5% (IVTA) and 5% (SConjTA) Inflammation: 10% (IVTA) and 2% (SConjTA) Recurrence of UMO: 22% (IVTA) and 5% (SConjTA) Retinal detachment 2% (IVTA) and 0% (SConjTA)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Venkatesh 2008 [13]</td>
<td>30% (Cannula PSTA) 40% (Smith and Nozik PSTA) 10% (OFTA). At 1 week</td>
<td>Not reported</td>
<td>Other adverse events such as ptosis, fat prolapse and fat necrosis were not noted in the study</td>
<td>No systemic AEs</td>
</tr>
<tr>
<td>Choudhry &amp; Ghosh 2007 [37]</td>
<td>10% IVTA (at 1 week); contralateral eye was therefore not given the intended PSTA</td>
<td>No corticosteroid related cataract progression</td>
<td>No other ocular AEs</td>
<td>No systemic AEs</td>
</tr>
<tr>
<td><strong>II. Corticosteroids vs anti-VEGF</strong></td>
<td></td>
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<tr>
<td>Roesel 2008 [41]</td>
<td>20% (IVTA) and 0% (OFTA) at 1 month</td>
<td>68% (IVTA) 27% (OFTA) At 12 months</td>
<td>No other AEs related</td>
<td>No systemic AEs</td>
</tr>
<tr>
<td>Rahimi 2012 [54]</td>
<td>Higher from baseline to 20.0 mmHg (IVTA) vs 17.8 mmHg (IVB). Time point not reported and no data on baseline IOP</td>
<td>No cataract progression</td>
<td>No other ocular AEs</td>
<td>No systemic AEs</td>
</tr>
<tr>
<td>Soheilian 2010 [31]</td>
<td>No cases of raised IOP</td>
<td>31% (IVTA), cataract surgery was performed in one</td>
<td>Hypopyon 7% (IVB) and 0% (IVTA)</td>
<td>No systemic AEs</td>
</tr>
</tbody>
</table>
### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Raised IOP from baseline</th>
<th>Cataract progression</th>
<th>Other Ocular AEs</th>
<th>Systemic AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasave 2009 [40]</td>
<td><em>Baseline to 3 months:</em> 15.1mmHg to 21.5mmHg (IVTA) 15.4mmHg to 16.6mmHg (IVB)*</td>
<td>No cataract progression in IVB</td>
<td>Vitreous opacity 7% (IVB) and 0% (IVTA) Vitreous haemorrhage 6% (IVTA) and 0% (IVB)</td>
<td>No systemic AEs</td>
</tr>
<tr>
<td></td>
<td><em>Surgical glaucoma treatment:</em> 5% (IVTA) and 0% (IVB)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bae 2011 [51]</td>
<td><em>Baseline to follow-up (time point not reported):</em> 12.4mmHg to 19.6mmHg (IVTA) 11.6mmHg to 13.4mmHg (IVB) 12.1mmHg to 17.3mmHg (PSTA)*</td>
<td>No cataract progression in any of the study group</td>
<td>Blepharoptosis 10% (PSTA) 0% (IVTA and IVB)</td>
<td>No systemic AEs</td>
</tr>
<tr>
<td></td>
<td><em>Surgical glaucoma treatment:</em> 9% (IVTA), 0% (PSTA) and 0% (IVB)*</td>
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<tr>
<td></td>
<td><em>Percentage of eyes with increased IOP&gt;5mmHg (Time point not reported)</em> 45.5% (IVTA, 40% (PSTA) and 10% (IVB)*</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Soheilian 2013 [30]</td>
<td>No episodes of increased IOP</td>
<td>No other ocular AEs</td>
<td>No systemic AEs</td>
<td></td>
</tr>
<tr>
<td>Mackensen 2013 [34]</td>
<td>No reported episodes of increased IOP</td>
<td>No reported cataract progression in the study groups</td>
<td>No reported ocular AEs e</td>
<td>SAE: Hypertensive crisis (INF) in 11% required hospitalisation. Most common AEs 46% in INF was flu-like symptoms and most common AEs 19% in MTX were nausea and infections (pharyngitis, urinary tract infection) Infection site injection (INF 17%, MTX 15%) Tiredness (INF 2%, MTX 11%) Thrombophlebitis (INF 2%, MTX 0%) Muscle cramps (INF 21%, MTX 19%) Nausea (INF 4%, MTX 19%)</td>
</tr>
<tr>
<td>Rathinam [48]</td>
<td>10% (MXT) 5% (MM)</td>
<td>Vitreous haemorrhage 2% (MXT) 0% (MM)</td>
<td>Non-serious adverse events were reported in 80% of the MXT and 82% of the MM. Headache was the most common AE 20% in</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Raised IOP from baseline</td>
<td>Cataract progression</td>
<td>Other Ocular AEs</td>
<td>Systemic AEs</td>
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<tr>
<td>Soheilian 2013 [30]</td>
<td>No reported episode of increased IOP</td>
<td>PCO (12.5%) (diclofenac sodium)</td>
<td>No other ocular AEs</td>
<td>No systemic AEs</td>
</tr>
<tr>
<td>3. NSAIDs</td>
<td></td>
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<tr>
<td>4. Anti VEGF</td>
<td></td>
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<tr>
<td>Anti-VEGF agents are addressed earlier</td>
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<tr>
<td>5. Carbonic Anhydrase inhibitor (Acetazolamide)</td>
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<tr>
<td>Farber 1994 [55]</td>
<td>No reported episodes of increased IOP</td>
<td>No reported cataract progression in the study groups</td>
<td>No reported ocular AEs</td>
<td>Acetazolamide: Severe allergic reaction, severe diuresis, haematuria, severe fatigue, muscle cramps, body rash, excessive paraesthesia in extremities, nausea, drowsiness, weight loss and chronic fatigue</td>
</tr>
<tr>
<td>Lashay 2003 [36]</td>
<td>No reported episodes of increase IOP</td>
<td>No reported cataract progression in the study groups</td>
<td>No reported ocular AEs</td>
<td>Acetazolamide: six non-compliant patients to acetazolamide. No further details reported</td>
</tr>
<tr>
<td>Whitcup 1996 [35]</td>
<td>No reported episodes of increase IOP</td>
<td>No reported cataract progression in the study groups</td>
<td>No reported ocular AEs</td>
<td>92% (acetazolamide), 14% (placebo). Instances of paraesthesia, nausea, drowsiness, weight loss, chronic fatigue, cutaneous allergic reaction, mild nausea, pins and needles.</td>
</tr>
<tr>
<td>6. Vitamin</td>
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<tr>
<td>No reported adverse events</td>
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</table>

**Notes:**
- **PSIU:** Posterior Segment Involving Uveitis
- **IVTA:** Intravitreal triamcinolone acetonide
- **PSTA:** Posterior subtenon triamcinolone acetonide
- **OFTA:** Orbital floor triamcinolone acetonide
- **IVB:** Intravitreal bevacizumab
- **IVDS:** Intravitreal diclofenac sodium
- **TA:** Triamcinolone acetonide
- **MXT:** Methotrexate
- **MM:** Mycophenolate Mofetil
- **PCO:** Posterior Capsular Opacification
Discussion

This systematic review provides a comprehensive overview of the pharmacological agents used to treat UMO. Of the 31 included studies, most were RCTs (70%), the remainder being randomised crossover trials (10%), prospective cohort studies (6%) and retrospective cohort studies (13%). A critical distinction was between those which enrolled UMO patients (65%) and those studies that enrolled UMO as a subgroup of all enrolled patients (35%). There were, therefore, relatively few studies that met the ideal scenario of being a well-designed RCT specifically enrolling UMO patients (35%). Our study, therefore, highlights that, for many of these pharmacological agents, there is little evidence for them being effective and safe in UMO.

The relative scarcity of RCT data for these agents in UMO is highlighted by the fact that there were no agents for which there were sufficient homogenous trials for a meta-analysis. It is worth noting that a previous systematic review by Karim et al [21] did undertake a meta-analysis of acetazolamide, based on the three trials which we also identified [35,36,55]. In our opinion, the different doses and formulations of acetazolamide used across these three studies precluded a meta-analysis, so we have simply presented this data in narrative format.

Of the agents considered within this review, the most commonly used are corticosteroids. Increasingly these are being given locally, including via intravitreal slow-release implants. Our review highlights the potential value of these being effective in reducing UMO and avoiding systemic side-effects. It also underlines the significant rates of ocular adverse events, notably secondary intraocular pressure elevation (leading on to glaucoma) and cataract of all local corticosteroid therapies, regardless the route of administration. Another drug of current interest is the anti-TNF agent, adalimumab. The high-profile VISUAL studies have led to its licensing for the treatment of posterior segment involving non-infectious uveitis [45], but the lack of UMO-specific subgroup data means that we cannot yet evaluate its potential role in the treatment of UMO. A significant number of other immunomodulatory agents have been trialled in UMO, but relatively few in a study design
that allows firm conclusions as to relative benefit. It is perhaps worth highlighting that the study by Mackensen’s et al found methotrexate to be significantly less effective in the treatment of UMO than interferon beta [34]. In most uveitis centres in the USA and the UK, it is more common to use methotrexate (or in recent years’ mycophenolate mo fetil) whereas interferon beta is rarely used. Mackensen argues that interferon should be the treatment of choice for UMO [34]. There are however two caveats: first, the drug-related morbidity is significantly higher with interferon (particularly low mood) [34]; and second, this is only a single study.

The major strengths of this review are that it provides the most comprehensive literature review of the treatment of UMO to date. Studies were selected, assessed and extracted following the pre-specified published protocol [22] and according to PRISMA guidelines [23]. The index and free text terms for the condition (MO) and the disease context (uveitis) were used to broaden the search and capture all the available records. All measures were taken to avoid missing records including: checking the reference lists of the included reviews/studies; seeking opinions of experts of existing knowledge in the field of uveitis and UMO and contacting authors to provide missing or unclear data; and avoiding language or date restrictions.

An additional strength of this systematic review was that it included non-randomised as well as randomised studies. Whilst we acknowledge the potential allocation bias in not randomising, the inclusion of such studies can provide useful additional evidence; particularly as such studies often have longer follow-up periods and may identify adverse events that would not be identified through RCTs which may comprise far fewer patient-years of follow-up.

The major limitation lies in the reporting of the primary studies and the likely gap between the volume of UMO-specific data assessed here, and the much larger volume of data that will have been collected patients with UMO as part of studies on posterior segment involving uveitis (PSIU). The primary reason for this gap is that studies with broad PSIU inclusion criteria (for example the VISUAL studies) often include a significant proportion of patients with UMO, and yet many do not report the data relating to these patients as a separate subgroup. It is interesting to note that in some of these
studies CMT is reported for the whole group even without specific discussion of the diagnosis of UMO. In this context, a reduction in CMO, often accompanied by an improvement in visual acuity, does provide indirect evidence that an intervention is effective in UMO. Our pre-specified protocol, however, excluded such data since such studies do not specifically report the UMO group (or subgroup), and thus no firm conclusion can be drawn as to an intervention’s effect in this group.

In terms of evaluating the comprehensiveness of the searches, as with any systematic review, there is always the concern as to whether searches retrieved all appropriate literature. This is more likely where the population of interest is a subgroup of a study. It is possible that some relevant articles may have been missed due to indexing such as where UMO was a subgroup and was not specified in the title or abstract.

Overall, the greatest challenges here are the paucity of evidence on which to base an assessment of the effectiveness of the pharmacological agents in the treatment of UMO, and the variable methods of reporting including time points. Our review highlights priority areas for future RCTs, for example, the need for head-to-head studies for many of the major immunomodulatory drugs, and the need to conduct studies which are either exclusive to UMO or are designed to include stratification according to presence or absence of UMO and report the UMO-subgroup data. This is needed if we are to define the relative efficacy and safety of these agents and define their place in treatment pathways. For example, the VISUAL studies have resulted in the licensing of adalimumab for PSIU in the USA and Europe, but it is not clear the extent to which adalimumab would be of value for those patients where UMO would be the primary sign of uveitis activity.

We have discussed elsewhere the challenges of designing and delivering clinical trials in uveitis [56], but UMO itself should be relatively amenable to clinical trial evaluation, having the advantage of a sensitive objective instrument-based measure [57]. Furthermore, of all the indicators of disease activity in uveitis, UMO is the sign most closely associated with an effect on visual function [58]. In light of this, it is surprising that there are so few high quality RCTs evaluating the major interventions
in UMO. This may in part be due to the desire of the major pharmaceutical companies to secure as broad a license as possible e.g. ‘posterior segment involving uveitis rather than the narrower ‘UMO’. Our review highlights the need for more well-designed, adequately powered UMO-specific RCTs.

In summary, this systematic review provides a comprehensive overview of the pharmacological agents used to treat UMO. It is the largest systematic review in the field to date and is particularly relevant in the context of the changing landscape of uveitis treatment in which new therapies, such as the dexamethasone implant (Ozurdex) and adalimumab now being licensed for the treatment of posterior segment-involving uveitis. Whilst this review presents the available evidence to support pharmacological intervention in UMO for a range of drugs and routes of administration, it also highlights areas where the evidence base is still lacking, and where appropriately focused trials are needed to guide best practice for treating this sight-threatening condition.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>Anti-Tumour Necrosis Factor</td>
</tr>
<tr>
<td>Anti-VEGF</td>
<td>Anti Vascular Endothelia Growth Factor</td>
</tr>
<tr>
<td>BCVA</td>
<td>Best Corrected Visual Acuity</td>
</tr>
<tr>
<td>CMT</td>
<td>Central Macular Thickness</td>
</tr>
<tr>
<td>CENTRAL</td>
<td>Cochrane Central Register of Controlled Trials</td>
</tr>
<tr>
<td>CINAHL</td>
<td>Cumulative Index to Nursing and Allied Health Literature.</td>
</tr>
<tr>
<td>ETDRS</td>
<td>Early Treatment Diabetic Retinopathy Study</td>
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<tr>
<td>FFA</td>
<td>Fluorescein Fundus Angiogram</td>
</tr>
<tr>
<td>IVB</td>
<td>Intravitreal Bevacizumab</td>
</tr>
<tr>
<td>IVDS</td>
<td>Intravitreal Diclofenac Sodium</td>
</tr>
<tr>
<td>IVTA</td>
<td>Intravitreal Triamcinolone Acetonide</td>
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<tr>
<td>MEDLINE</td>
<td>Medical Literature analysis and Retrieval System Online</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drugs</td>
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<tr>
<td>OCT</td>
<td>Optical Coherence Topography</td>
</tr>
<tr>
<td>OFTA</td>
<td>Orbital Floor triamcinolone Acetonide</td>
</tr>
<tr>
<td>PSIU</td>
<td>Posterior Segment-Involving Uveitis</td>
</tr>
<tr>
<td>PSTA</td>
<td>Posterior Subtenon Triamcinolone Acetonide</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</td>
</tr>
<tr>
<td>UMO</td>
<td>Uveitic Macular Oedema</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumour Necrosis Factor</td>
</tr>
</tbody>
</table>
Declarations

Conflict of interest
The authors declare that they have no competing interests.

Authors’ contributions
MT is an NIHR clinical research fellow and he is involved in all stages of the systematic review including identifying, selecting, extracting and appraising data. MT drafted the manuscript. MT, DM and AD, led the development and structuring of systematic review. AD and PM provided clinical input; MC made substantial contributions to the systematic review version. RB was involved in screening, extracting and appraising the collected data. MC, JM, AD, DM and PM provided supervisory support, inputted to the design of the study, commented on the draft manuscript. All authors have read and approved the final manuscript.

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