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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

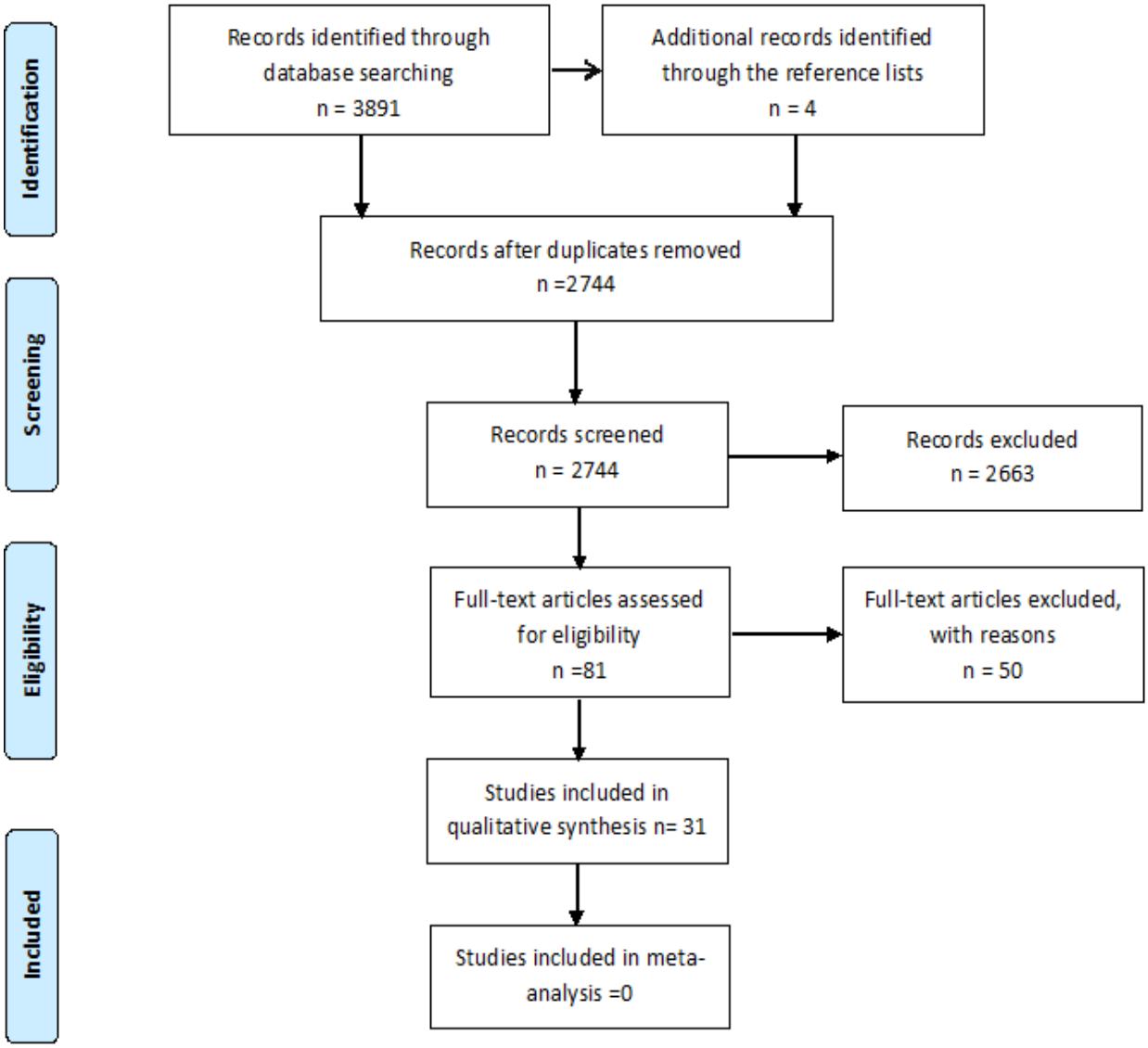
Data were grouped together from the same study design and by each intervention and comparison, with data tabulated and a narrative synthesis of evidence conducted for each outcome of relevance to the review.

Multiple time point data were available within the same study and between studies and considerd 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.

Figure 1: PRISMA Flow Diagram



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 1: Study characterisitics, presented by comparison, and outcomes measured

	Author/year	Design	Population	Intervention	Comparator	Outcomes
Corticosteroids	**1. Corticosteroids vs Placebo (UMO subgroup no details)**					
	Kuppermann 2007 Williams 2009 [25,26]	RCT	CRVO, Irvine-Gass syndrome and DMO	Dexamethasone 350 µg or 700µg implant (DDS)	Observation	*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
	Lowder 2011 [42]	RCT	Uveitis/UMO	Dexamethasone 350 µg or 700µg implant (DDS)	Sham	*BCVA (Snellen chart), CMT, Safety measures, IOP and cataract progression
	Shin 2015 [43]	RCT	UMO	Intravitreal Triamcinolone a Acetonide 4mg	Sham	*BCVA (ETDRS), CMT, IOP and cataract progression
	2. Corticosteroids vs Corticosteroids					
	Pavesio 2010 [50]	RCT	Uveitis/UMO	Fluocinolone Acetonide implant 0.59	Standard of Care	*Uveitis recurrence rate, BCVA (LogMAR), macular leakage Safety outcomes (IOP, Lens opacity and adverse events)
	Tomkins-Netzer 2015 [29]	RCT	UMO	Systemic prednisolone (1mg/kg/day up to 60mg/day)	Fluocinolone Acetonide implant 0.59mg	*CMO resolution and macula leakage (FFA)/BCVA (Snellen chart)
	3. Corticosteroids vs same Corticosteroids different dosing or routes (UMO subgroup no details					
	Sangwan 2015 [27]	RCT	Uveitis/UMO	Fluocinolone Acetonide implant 0.59mg	Fluocinolone Acetonide implant 2.1mg	*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 periocular injection. Safety measures (IOP, lens opacity, visual field, ocular adverse events (any IOP<6 mmHg, any loss of ≥3 lines visual acuity from baseline or in the last visit, and retinal tears.
	Callanan 2008 [28]	RCT	Uveitis/UMO	Fluocinolone Acetonide implant 0.59mg	Fluocinolone Acetonide implant 2.1mg	
	Jaffe 2006 [53]	RCT	Uveitis/UMO	Fluocinolone Acetonide implant 0.59mg	Fluocinolone Acetonide implant 2.1mg	*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.
	Venkatesh 2008 [13]	RCT	UMO	Triamcinolone Acetonide 20mg (0.5ml) cannula method	Triamcinolone 20mg (0.5ml) Smith & Nozik method and orbital floor method	*BCVA (LogMAR), anatomical macular changes (OCT), adverse events and raised IOP
	Chen and Liang 2016 [49]	RCT	UMO	Triamcinolone Acetonide (0.1ml) subconjunctival	Triamcinolone (0.1ml) intravitreal	*BCVA (LogMAR), anatomical macular changes (OCT), adverse events including IOP

	Choudhry and Ghosh 2007 [37]	RCT (internally randomised within the individual)	UMO	Triamcinolone Acetonide intravitreal 4mg	Triamcinolone Acetonide subtenon 20mg	*BCVA (LogMAR), anatomical macular changes (FFA), adverse events including cataract progression and raised IOP
	Roesel 2008 [41]	Retrospective cohort	UMO	Triamcinolone Acetonide 4mg intravitreal	Triamcinolone Acetonide 40mg orbital floor	*BCVA (LogMAR), macular leakage (FFA), adverse events including cataract progression and raised IOP
	4. Corticosteroids vs other drugs (UMO subgroup no details)					
	c. Corticosteroids vs anti VEGF					
	Rahimi 2012 [54]	RCT	UMO	Bevacizumab1.25mg intravitreal	Triamcinolone Acetonide 4mg intravitreal	BCVA (LogMAR) /CMT (OCT), AC activity, vitreous activity/ adverse events ,raised IOPI and cataract progression
	Soheilian 2010 [31]	RCT	UMO	Bevacizumab 1.25mg Intravitreal	Triamcinolone Acetonide 2mg intravitreal	BCVA (LogMAR), CMT (OCT), macular leakage (FFA), adverse events, IOP and lens opacity
	Lasave 2009 [40]	Retrospective Cohort	UMO	Bevacizumab 2.5mg intravitreal	Triamcinolone Acetonide 4mg intravitreal	BCVA (LogMAR)/ CMT (OCT)/ adverse events, IOP and lens opacity
	Bae 2011 [51]	Retrospective cohort	UMO	Bevacizumab 1.25mg intravitreal	Triamcinolone Acetonide 4mg intravitreal or Triamcinolone Acetonide 40mg subtenon	BCVA (LogMAR), IOP, CMT, adverse events, IOP and lens opacity
	d. Corticosteroids vs NSAID					
	Soheilian 2013 [30]	RCT	UMO	Diclofenac 500mcg/0.1ml Intravitreal	Triamcinolone 2mg/0.05m Intravitreal	BCVA (Snellen chat) and (LogMAR), CMT, adverse events, IOP and lens opacity
	Radwan 2013 [39]	Retrospective cohort	UMO	Bromfenac (drops)	Bromfenac with either intravitreal Triamcinolone 4mg or Bevacizumab intravitreal 25mg/ml	BCVA (LogMAR) and CMT
	e. Corticosteroids vs anti TNF					
	Markomichelakis 2010 [38]	Prospective cohort	Uveitis/UMO	Infliximab intravenous infusion 5mg/kg/	Methylprednisolone 1g/day or intravitreal Triamcinolone 4mg	BCVA (LogMAR), anterior chamber cell activity, vitreous cell activity, degree of inflammation to the posterior segment (retinal vasculitis, retinitis, macular oedema and papilitis)
	f. Corticosteroids vs T cell inhibitor					
	Nussenbalatt 1991 [32]	RCT	Uveitis/UMO	Cyclosporine 10mg/Kg oral	Prednisolone 64mg or 42mg oral	BCVA ≥ 15 letters (ETDRS), Vitreous haze ≥2 increments and anterior chamber activity
immunomodulatory	**Imunnomodulatory vs placebo**					
	Nguyen 2016a [45]	RCT	Uveitis/UMO	Adalimumab (loading dose 80mg followed by fortnightly 40mg) subcutaneous	Placebo	(LogMAR), proportion of CMT change, change in AC activity, vitreous haze score, BCVA

	Jaffe 2016 [47]	RCT	Uveitis/UMO	Adalimumab (loading dose 80mg followed by fortnightly 40mg) subcutaneous	Placebo	BCVA (LogMAR), time to evidence of UMO on OCT, efficacy and time treatment failure and safety
	Immunomodulatory vs immunomodulatory					
	Nguyen 2016b [46]	RCT	Uveitis/UMO	Sirolimus 44µg intravitreal	Sirolimus 440µg or 880µg intravitreal	BVCA, *the proportion of eyes with vitreous haze score of 0.5 at 5 months without the use of rescue therapy, the proportion of eyes with vitreous haze score of 0 at 5 months, and adverse events
	Nguyen 2016c [44]	RCT	Uveitis/UMO	Sirolimus 440µg, intravitreal	Sirolimus880µg intravitreal	*BCVA (EDTRS), CMT, vitreous cells and AC cells safety parameters (adverse events, serious adverse events)
	Mackensen 2013 [34]	RCT	UMO	Interferon beta 44µg subcutaneous three times a day	Methotrexate 20mg subcutaneous once a week	*BCVA (LogMAR), CMT (OCT), QoL (NEI VFQ-25). Vitreous haze, Ac activity and adverse events
	Rathinam 2014 [48]	RCT	Uveitis/UMO	Methotrexate 25mg weekly (oral)	Mycophenolate 1g twice daily (oral)	Change in BCVA, adverse events and resolution of UMO, *treatment success
NSAID	**1. NSAID vs Placebo**					
	Allgeri 2014 [33]	RCT	UMO	Indomethacin 0.5% drops four times a day	Artificial tears of methyl-hydroxy-propyl-cellulose four times a day	*BCVA (LogMAR) and CFT (central foveal thickness (OCT)
	2. NSAID vs anti VEGF					
	Radwan 2013 [39]	Retrospective cohort	UMO	Bromfenac (drops)	Bromfenac with either intravitreal Triamcinolone 4mg or Bevacizumab intravitreal **	(LogMAR) and CMT (OCT)
Carbonic Anhydrase Inhibitor	**Acetazolamide vs Placebo**					
	Lashay 2003 [36]	Randomised crossover	UMO	Acetazolamide 250mg orally twice daily	Placebo (multivitamin) PO	(LogMAR), CMO changes (FFA)
	Whitcup 1996 [35]	Randomised crossover	UMO	Acetazolamide 500mg orally twice daily	Placebo (multivitamin)	grading (FFA), BCVA (Snellen chart) number of letters read and adverse reaction
	Farber 1994 [55]	Randomised crossover	UMO	Acetazolamide 250mg orally slow release twice daily	Placebo	(LogMAR), posterior vitreous penetration ratio, (PVP, mid vitreous penetration ratio (MVPR) and clinical chemistry
Vitamin	**Vitamin E**					
	Nussenblatt 2006 [52]	RCT	UMO	Vitamin E 1600IU daily (oral)	Placebo (oral)	BCVA (ETDRS) and CMT (OCT)

* 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

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

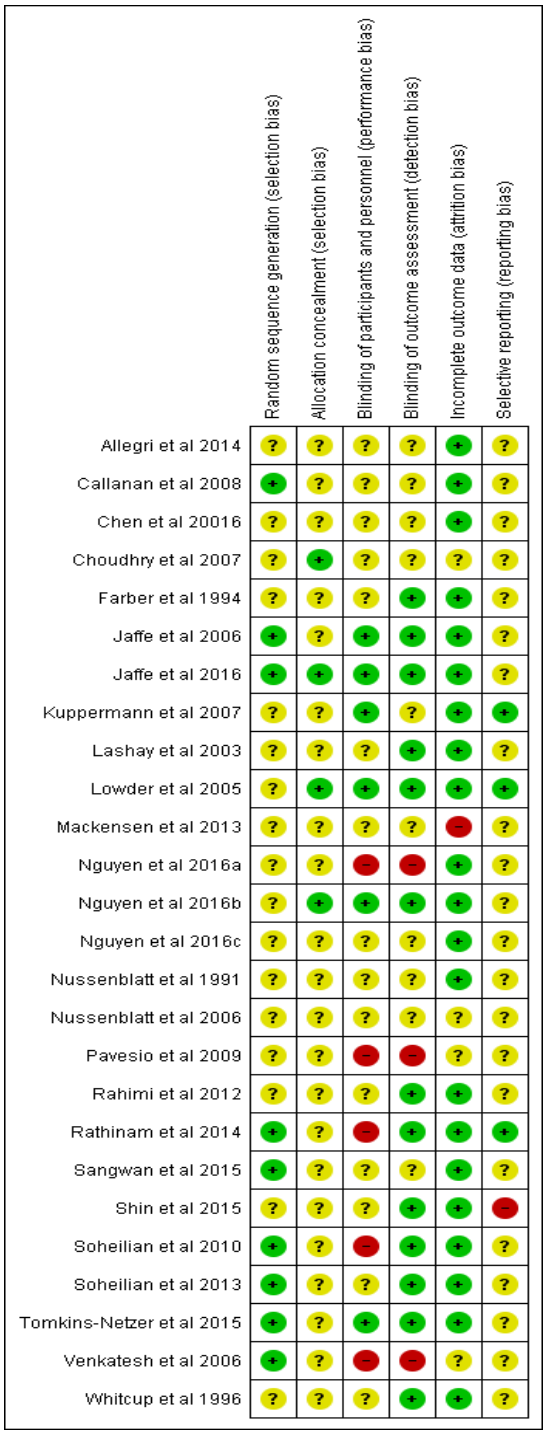
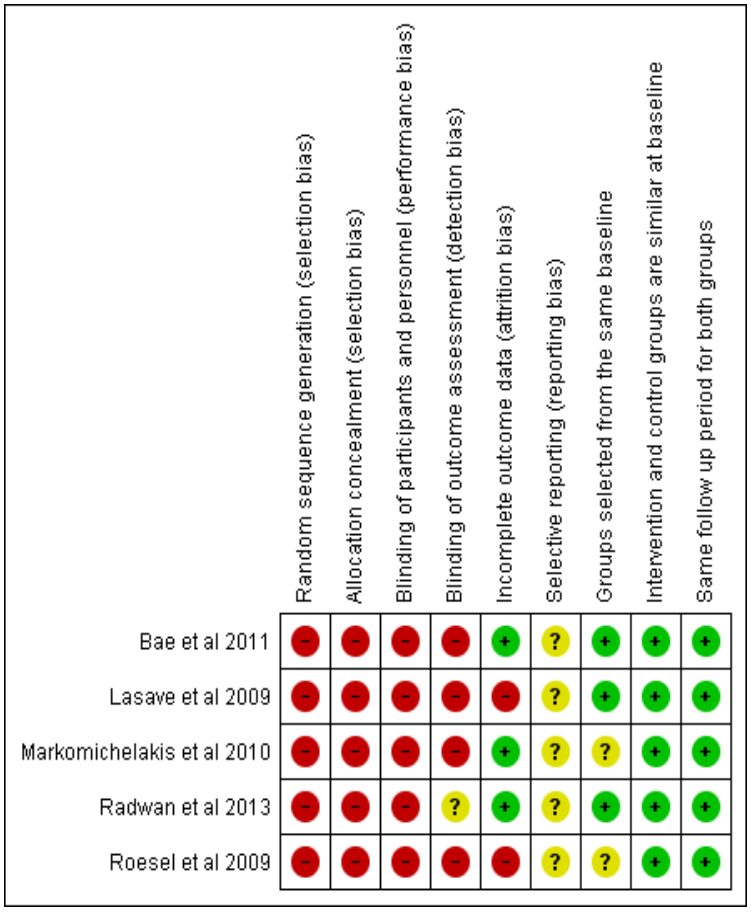


Figure 3: Risk of bias summary for observational studies



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 sytemic 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 el 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].

132 **Table 2: Mean BCVA, CMT and area of macular leakage**

Study	Interventions	BCVA (Baseline)	BCVA ≤3months	BCVA >3 and ≤6 months	BCVA >6 months	CMT (Baseline)	CMT ≤ 3 months	CMT >3 and ≤6 months	CMT >6 months	Mean area of UMO at baseline	Mean area of macular leakage/ Proportion of resolved leakage
1. Corticosteroids											
I. Corticosteroids vs Placebo											
Shin 2015 [43]	IVTA	69±9.6 (EDTRS)	70(EDTRS)	74(EDTRS)		337±83mμ	270μm P=0.014	245μm		2.3±1.91	0.95 (P=0.025) -3month 0.85 (S) 6 months
	Sham	70±9.0 (EDTRS)	73(EDTRS)	69 (EDTRS)		312±59μm	280μm (P=0.02)	270μm		3.6±4.99	3.6 (NS) 0.75 (S) -6 months
	Intergroup comparison		NS	NS			NS	NS			NS from month 4 onward
II. Corticosteroids vs Corticosteroids											
Pavesio (2010) [50]	0.59mg fluocinolone implant										87% 2yrs. (NR)
	Standard of care										74% 2yrs. (NR)
	Intergroup comparison										P=0.003 favouring implanted eyes
Tomkins-Netzer 2015 [29]	0.59mg fluocinolone implant	62 (EDTRS) median			68 (EDTRS) median (NR) 2yrs				68% (NR)2yrs. Resolution 77% (NR) 2yrs. Improvement		58%. (NR) -2yrs
	systemic prednisolone	63 (EDTRS) median			67 (EDTRS) median (NR) 2rys				52% (NR) 2yrs Resolution 65% (NR) 2yrs. Improvement		31%. (NR) -2yrs
	Intergroup comparison				P=0.86				P=0.28 P=0.20		P=0.12.- 2yrs.
Sangwan 2015 [27]	0.59mg fluocinolone implant									38.0mm^2	9mm^2 (NR) -34wks 6mm^2 (NR) 3yrs
	2.1mg fluocinolone implant									46mm^2	5mm^2 (NR) -34wks 15mm^2 (NR) -3yrs
	Intergroup comparison										P<0.0001 favouring implanted eyes at both visits

Study	Interventions	BCVA (Baseline)	BCVA ≤3months	BCVA >3 and ≤6 months	BCVA >6 months	CMT (Baseline)	CMT ≤ 3 months	CMT >3 and ≤6 months	CMT >6 months	Mean area of UMO at baseline	Mean area of macular leakage/ Proportion of resolved leakage
Callanan 2008 [28]	0.59mg fluocinolone implant									33mm^2	7mm^2 (P<0.01)-1yr. 6mm^2 (P<0.01)- 3yrs.
	Non-implanted eyes of 0.59mg									25mm^2	26 mm^2) (P=0.91) -1yr. 25 mm^2 (P=0.80) 3yrs S favouring 0.59mg fluocinolone implant
	2.1mg fluocinolone implant									30mm^2	5mm^2 P<0.01) 1yr. 23mm^2 (P=0.44) (3yrs.
	Non-implanted eyes of 2.1mg									18 mm^2	15mm^2 (P=0.23) 1yr. 19 mm^2 (P=0.39) 3yrs.
	Intergroup comparison										S favouring 2.1mg fluocinolone implant at 1year only NR between implants
Jaffe 2006 [53]	0.59mg fluocinolone implant and 2.1mg i fluocinolone mplant (combind)				25% achieved 3 or more line of BCVA on LogMAR					36mm^2	7mm^2 (P<0.05) 34wks
	Non implanted eyes				5.3% achieved 3 or more line of BCVA on LogMAR					42mm^2	29mm^2 (NS) 34wks
	Intergroup comparison				NR						P<0.0001 favouring implanted eyes
Venkatesh [13]	PSTA (Cannula method)	0.65 LogMAR	0.15 LogMAR (P=00)			382±174µm	214± 35µm (P=00)				
	PSTA (Smith & Nozik)	0.60 LogMAR	0.14 LogMAR (P=00)			310± 85µm	208± 29µm (P=00)				
	OFTA	0.65 LogMAR	0.19 LogMAR (P=00)			373±101µm	262 ± 74µm (P=003)				
	Intergroup comparison		P=0.759				P=0.83				
Chen & Liang 2016 [49]	IVTA	2.9±1.1 (SWR)	4±1.4 (NR)			493±99µm	256±85µm (NR)				

Study	Interventions	BCVA (Baseline)	BCVA ≤3months	BCVA >3 and ≤6 months	BCVA >6 months	CMT (Baseline)	CMT ≤ 3 months	CMT >3 and ≤6 months	CMT >6 months	Mean area of UMO at baseline	Mean area of macular leakage/ Proportion of resolved leakage
	Sub conj (TA)	3.0±1.2 (SWR)	4.8±1.3(NR)			485±101µm	214±66µm (NR)				
	Intergroup comparison		P<0.05 favouring Sub conj (TA)				P<0.05 favouring Sub conj (TA)				
Choudhury & Ghosh 2007 [37]	IVTA	0.67±0.10 LogMAR	0.22±0.15 LogMAR (NR)	0.22±0.10 LogMAR (NR)							78% (NR) -3 months 89% (NR) -6 months
	PSTA	0.69±0.14 LogMAR	0.28±0.21 LogMAR (NR)	0.22±0.15 (NR)							56% (NR) -3 months 78% (NR) -6 months
	Intergroup comparison		P=0.74	P=0.99							P=0.32 -3 months P=0.53 -6 months
Roesel 2009 [41]	IVTA	0.61±0.35 LogMAR	0.47±0.31 LogMAR (P=0.02)	0.62±0.33 LogMAR (NR)	0.67±0.33 LogMAR (NR)	NA					100% -(S)-1 and 3 months 75% -(NR)6 months 42% (NR)-12months
	OFTA	0.58±0.39 LogMAR	0.46±0.38 LogMAR (P=0.03)	0.47±0.38 LogMAR (NR)	0.44±0.31 LogMAR (NR)	NA					76%(NR)-1month 20% (NR)-3, 6 and 9months
	Intergroup comparison		P=0.86	0.10	0.018						P=0.36 (1 months) P<0.05 (3 months) P=0.1 (6 months) P= 0.56 (12 months)
III. Corticosteroids vs other drugs											
a. Corticosteroids vs anti VEGF											
Rahimi 2012 [54]	IVTA	0.48±0.22 LogMAR	0.07 ± 0.06 LogMAR (P<0.001)	0.03 ± 0.04 LogMAR (P<0.001)	NA	296±33µm	218±29.0µm (P<0.001)	199 ± 28µm (P<0.001)	NA		
	IVB	0.47±18 LogMAR	0.06 ± 0.06 LogMAR (P<0.001)	0.03 ± 0.04 LogMAR (P<0.001)	NA	310±52mµm	234±13µm (P<0.001)	221±12µm (P<0.001)	NA		
	Intergroup comparison		P=0.772	P=0.326			P=0.010 favouring IVTA	P<0.001 favouring IVTA			
Soheilian 2010 [31]	IVTA	0.85±0.34 LogMAR	Δ −0.14±0.30 LogMAR (P=0.95)	Δ −0.29±0.32 LogMAR (P=0.004)	Δ −0.32±0.32 LogMAR (P=0.001)	361±138µm	Δ −56±76µm (P=0.016)	Δ −69±86µm (P=0.010)	Δ −75±108 µm (P=0.03)		60% (P=0.005) 12 weeks 68.8% (P=0.002) 24week 78.6%(P=0.003) 36weeks
	IVB	0.95±0.38	Δ −0.19±0.21	Δ −0.29±0.28	Δ −0.35±0.45	387±184µm	Δ −57±111µm	Δ 1±143µm	Δ −42±171		38.5%(P=0.206)- 12 weeks 57.1% (P=0.089) -24weeks

Study	Interventions	BCVA (Baseline)	BCVA ≤3months	BCVA >3 and ≤6 months	BCVA >6 months	CMT (Baseline)	CMT ≤ 3 months	CMT >3 and ≤6 months	CMT >6 months	Mean area of UMO at baseline	Mean area of macular leakage/ Proportion of resolved leakage
		LogMAR	LogMAR (P=0.005)	LogMAR (P=0.004)	LogMAR P=0.016		(P=0.091)	(P=0.985)	µm (P=0.483)		(69.2% P=0.031) -36weeks
	Intergroup comparison		P=0.775	P=0.770	P=0.936		P=0.894	P=0.077	P=0.338		P=0.098 -12 weeks P=0.176 -24week P=0.359 -36weeks
Lasave 2009 [40]	IVTA	1.1 ± 0.2 LogMAR	0.7 ± 0.4 (P<0.001)	0.7 ± 0.3 (P<0.001)		455±239µm	289±141µm (P<0.0001)	296 ± 134µm (P=0.001)			
	IVB	1.2 ± 0.4 LogMAR	1 ± 0.3 LogMAR (P=0.006)	0.8 ± 0.4 LogMAR (P=0.031)		401±142µm	323± 108µm (P=0.012)	345±135µm (P 0.056)			
	Intergroup comparison		NR	NR			NR	NR			
Bae 2011 [51]	IVTA	0.73±0.33 LogMAR	0.43 LogMAR (P < 0.001)			594±151µm	Δ −328±233µm (P < 0.001)				
	PSTA	0.71±0.23 LogMAR	0.58 LogMAR (P < 0.001)			582±146µm	Δ −166±227µm (P < 0.001)				
	IVB	0.73±0.41 LogMAR	0.56 LogMAR (P<0.011)			537±214µm	Δ −167±154µm (P < 0.001)				
	Intergroup comparison		P=0.869				P=0.636				
b. Corticosteroids vs NSAID											
Soheilian 2013 [30]	IVTA	0.75±0.49 LogMAR	0.63±0.48 LogMAR (P=0.043)	0.48±0.49 LogMAR (P=0.043)	0.58±0.39 LogMAR (P=0.50)	642±289µm	335±109µm (P=0.018)	407±92µm (P=0.028)	510±194µm (P=0.398)		
	IVDS	0.67±0.22 LogMAR	0.69±0.39 LogMAR (P>0.99)	0.70±0.37 LogMAR (0.786)	0.64±0.35 LogMAR (0.779)	488±104µm	439±161µm (P=0.123)	404±196µm (P=0.161)	403±132µM (P=0.123)		
	Intergroup comparison		P=0.779	P=0.281	P=0.463		P=0.281	P=0.955	P=0.613		
c. Corticosteroids vs T cell inhibitor											
Nussenblatt 1991 [32]	Cyclosporine										47%
	Prednisolone										63%
	Intergroup comparison										P=0.376

Study	Interventions	BCVA (Baseline)	BCVA ≤3months	BCVA >3 and ≤6 months	BCVA >6 months	CMT (Baseline)	CMT ≤ 3 months	CMT >3 and ≤6 months	CMT >6 months	Mean area of UMO at baseline	Mean area of macular leakage/ Proportion of resolved leakage
2. Immunomodulatory Agents											
I. Immunomodulatory vs immunomodulatory											
Nguyen 2016c [44]	Sirolimus 44µg implant							46% (NR) 5months			
	Sirolimus 440µg implant							55% (NR) 5months			
	Sirolimus 880µg implant									49%(NR) 5months	
Nguyen 2016b [46]	Sirolimus440µg implant					461±139µm	403±148µm (NS)	419±160µm (NS)			57% (NS) -3months 28% (NS)-6months
	Sirolimus880µg implant					375 ±89µm	313±66µm (NS)	457±204µm (NS)			83% (NS)-3months. 67% (NS)-6months
	Intergroup comparison						NS	NS			NS
Mackensen 2013 [34]	Interferon beta	0.48 LogMAR	0.16 LogMAR (P=0.0039)			430µm	228µm (P=0.0039)				
	Methotrexate	0.34 LogMAR	0.25 LogMAR (P=0.1309)			371µm	409µm (P=0.781)				
	Intergroup comparison		P=0.0435 favouring interferon			P<0.0001 favouring interferon					
Rathinam 2014 [48]	Methotrexate										77% (NR)-5 months
	Mycophenolate mofetil										54% (NR)- 5 months
	Intergroup comparison										P=0.31
3. Anti VEGF											
Anti-VEGF agents were compared to corticosteroids and are addressed above											
4. NSAID											
I. NSAID vs Placebo											
Allgeri 2014 [33]	Indomethacin 0.5%	0.4 average in decimal	0.47 average in decimal (P<0.001)	0.56 average in decimal (P<0.0001)		446±149µm	360µm (P<0.001)	280µm (P<0.001)			

Study	Interventions	BCVA (Baseline)	BCVA ≤3months	BCVA >3 and ≤6 months	BCVA >6 months	CMT (Baseline)	CMT ≤ 3 months	CMT >3 and ≤6 months	CMT >6 months	Mean area of UMO at baseline	Mean area of macular leakage/ Proportion of resolved leakage
	Placebo	0.52 average in decimal	0.5 average in decimal NS	0.55 average in decimal NS		390 ±162µm	405µm (NS)	410µm (NS)			
	Intergroup comparison		P<0.001	P<0.001			P<0.001	P<0.001			
II. NSAID vs anti VEGF											
Radwan 2013 [39]	Bromfenac	0.39± 0.28 LogMAR	0.31± 0.27 LogMAR (P=0.911)			354±97µm	302±63µm (P=0.145)				
	IVB+ Bromfenac	0.55±0.24 LogMAR	0.35± 0.23 LogMAR (P=0.001)			459±155µm	288±81µm (P=0.002)				
	IVTA + Bromfenac	0.52±0.50 LogMAR	0.33± 0.55 LogMAR (P=0.017)			423±175µm	260±46µm (P=0.009)				
	Intergroup comparison		P= 0.928				P=0.279				
5. Carbonic Anhydrase inhibitor (Acetazolamide)											
I. **Acetazolamide vs placebo**											
Whitcup 1996 [35]	Acetazolamide	48(EDTRS) (20/100-2 Range 15-70	48(EDTRS) (20/100-2) Range 8-72							2.1 Range 0.0-20.0	1.5 Range 0.0-5.0
	Placebo	49(EDTRS)20/100-1) Range8-76	51 (EDTRS) (20/100+1) Range15-78							2 Range 0.2-20.0 2.1	2.0 Range 0.0-20.0
	Intergroup comparison		NS								P=0.01
Lashay 2003 [36]	Acetazolamide	0.537 LogMAR Range 0.1-1.5	0.448 LogMAR Range 0.1-1.5							1.892 Range 0-4	1.678 Range 0-4 (P=0.99)
	Placebo	0.430 LogMAR Range 0.1-1.5	0.430 LogMAR Range 0.1-1.5					Range 0-4		1.643 Range 0-4	1.714 Range 0-4
	Intergroup comparison		NS								NS

Study	Interventions	BCVA (Baseline)	BCVA ≤3months	BCVA >3 and ≤6 months	BCVA >6 months	CMT (Baseline)	CMT ≤ 3 months	CMT >3 and ≤6 months	CMT >6 months	Mean area of UMO at baseline	Mean area of macular leakage/ Proportion of resolved leakage
Farber 1994 [55]	Acetazolamide	0.57LogMAR	0.49 LogMAR P= 0.01							DNA	DNA
	Placebo	0.51 LogMAR	0.50 LogMAR							NR	NR
	Intergroup comparison		NS							NR	NR
6. Vitamin											
Vitamin E vs placebo											
Nussenblatt 2006 [52]	Vitamin E	59 ±5(EDTRS) SWR		54±5 (EDTRS) 4 months		232±47µm		367±59µm 4 months			
	Placebo	57± 6(EDTRS) SWR		56 ±6 (EDTRS) (NS) 4 months		467±124µm		392±119µm (NS) 4 months			
	Intergroup comparison			NS				NS			

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
△ 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).**

149 **Table 3: List of adverse events**

Study	Raised IOP from baseline	Cataract progression	Other Ocular AEs	Systemic AEs
1. Corticosteroids				
I. Corticosteroids vs corticosteroids				
Shin 2015 [43]	A higher mean change from baseline in IVTA group vs sham at 1,2 & 3 months. *No further data reported.*	25% (IVTA) and 15% (sham) at 6months (IVTA) phakic patients are 64% (Placebo) phakic patients are 55%	No other ocular adverse event related to the study groups	No systemic AEs
Chen 2016 [49]	41% (IVTA) 29% (SConjTA) Time point and definition of raised IOP was not reported	Not reported	*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)	Not reported
Venkatesh 2008 [13]	30% (Cannula PSTA) 40% (Smith and Nozik PSTA) 10% (OFTA). At 1 week	Not reported	Other adverse events such as ptosis, fat prolapse and fat necrosis were not noted in the study	No systemic AEs
Choudhry& Ghosh 2007 [37]	10% IVTA (at 1 week); contralateral eye was therefore not given the intended PSTA	No corticosteroid related cataract progression	No other ocular AEs	No systemic AEs
II. Corticosteroids vs anti-VEGF				
Roesel 2008 [41]	20% (IVTA) and 0% (OFTA) at 1 month	68% (IVTA) 27% (OFTA) At 12months	No other AEs related	No systemic AEs
Rahimi 2012 [54]	Higher from baseline to 20.0mmHg (IVTA)) vs 17.8mmHg (IVB). Time point not reported and no data on baseline IOP	No cataract progression	No other ocular AEs	No systemic AEs
Soheilian 2010 [31]	No cases of raised IOP	31% (IVTA), cataract surgery was performed in one	*Hypopyon* 7% (IVB) and 0% (IVTA)	No systemic AEs

Study	Raised IOP from baseline	Cataract progression	Other Ocular AEs	Systemic AEs
		patient (20%) No cataract progression in IVB	*Vitreous opacity* 7% (IVB) and 0% (IVTA) *Vitreous haemorrhage* 6% (IVTA) and 0% (IVB)	
Lasave 2009 [40]	*Baseline to 3 months:* 15.1mmHg to 21.5mmHg (IVTA) 15.4mmHg to 16.6mmHg (IVB) *Surgical glaucoma treatment:* 5% (IVTA) and 0% (IVB)	5% (IVTA) 0% (IVB) At 12months	No other ocular AEs	No systemic AEs
Bae 2011 [51]	*Baseline to follow-up (time point not reported):* 12.4mmHg to 19.6mmHg(IVTA) 11.6mmHg to 13.4mmHg (IVB) 12.1 mmHg to17.3mmHg(PSTA) *Surgical glaucoma treatment:* *9% (IVTA), 0% (PSTA) and 0% (IVB)* *Percentage of eyes with increased IOP>5mmHg (Time point not reported)* *45.5% (IVTA, 40% (PSTA) and10% (IVB)*	No cataract progression in any of the study group	*Blepharoptosis* 10% (PSTA) 0% (IVTA and IVB)	No systemic AEs
Soheilian 2013 [30]	No episodes of increased IOP	14% (IVTA)	No other ocular AEs	No systemic AEs
2. Immunomodulatory agents				
Mackensen 2013 [34]	No reported episodes of increased IOP	No reported cataract progression in the study groups	No reported ocular AEs e	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%, MXT 15%)* *Tiredness (INF 2%, MXT 11%)* *Thrombophlebitis (INF 2%, MXT 0%)* *Muscle cramps (INF 21%, MXT 19%)* *Nausea (INF 4%, MXT 19%*)
Rathinam [48]	10% (MXT) 5% (MM)	12%(MXT) 8% (MM)	*Vitreous haemorrhage* 2% (MXT) 0% (MM)	Non-serious adverse events were reported in 80% of the MXT and 82% of the MM. *Headache was the most common AE 20% in*

Study	Raised IOP from baseline	Cataract progression	Other Ocular AEs	Systemic AEs
			Hypotony 0% (MXT) 2% (MM) *Acute catarrhal* 2% (MXT) 0% (MM)	*MXTand 31% in* MM *Fever for 12 hours (MXT 5%,* MM *23%)* *Nausea (MXT 15%,* MM *5%)* *Systemic infection (MXT 10%,* MM *7%)* *Vomiting (MXT 7%, MM 5%)* *Diarrhoea and fatigue (MXT 10%,* MM *10%)* *Dyspnoea, mood changes and cardiac dysfunction was reported in 3% of the* MM *and non-in MXT group*
3. NSAIDs				
Soheilian 2013 [30]	No reported episode of increased IOP	PCO (12.5%) (diclofenac sodium)	No other ocular AEs	No systemic AEs
4. Anti VEGF				
Anti-VEGF agents are addressed earlier				
5. Carbonic Anhydrase inhibitor (Acetazolamide)				
Farber 1994 [55]	No reported episodes of increased IOP	No reported cataract progression in the study groups	No reported ocular AEs	Acetazolamide: Severe allergic reaction, severe diuresis, haematuria, severe fatigue, muscle cramps, body rash, excessive paraesthesia in extremities, nausea, drowsiness, weight loss and chronic fatigue
Lashay 2003 [36]	No reported episodes of increase IOP	No reported cataract progression in the study groups	No reported ocular AEs	Acetazolamide: six non-compliant patients to acetazolamide. No further details reported
Whitcup 1996 [35]	No reported episodes of increase IOP	No reported cataract progression in the study groups	No reported ocular AEs	92% (acetazolamide), 14% (placebo). Instances of paraesthesia, nausea, drowsiness, weight loss, chronic fatigue, cutaneous allergic reaction, mild nausea, pins and needles.
6. Vitamin				
No reported adverse events				

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 mofetil) 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

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

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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