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SUMMARY WITH CRITICAL APPRAISAL

Intravitreal Dexamethasone Implants for Non-infectious Uveitis: A Review of Clinical Effectiveness, Cost-effectiveness, and Guidelines

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Abbreviations

BCVA	Best corrected visual acuity
CME	Cystoid macular edema
DMARDs	Disease-modifying antirheumatic drugs
IDI	Intravitreal dexamethasone implant
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
NICE	National institute for health and care excellence
NIU	Noninfectious uveitis
RCT	Randomized controlled trial

Context and Policy Issues

Uveitis is a disease characterized by inflammation of the uvea.[1] Uvea is the middle layer of the eye wall. The anterior uvea segment includes the iris and ciliary body, intermediate uvea includes vitreous humor, and posterior uvea segment is known as the choroid.[2] Based on the location of the Inflammation, uveitis can be classified as anterior uveitis (AU), intermediate uveitis (IU), posterior uveitis (PU) and panuveitis.[2] Panuveitis is defined as uveitis involving all parts of uvea.[1] Based on the etiology, uveitis can be divided into infectious uveitis and non-infectious uveitis (NIU).[2] NIU includes uveitis caused by systemic immune-mediated disease, immune-related drug reactions, or some syndromes resulting in uveitis.[2] The common complications of uveitis include cystoid macular edema (CME), cataract, intraocular pressure elevation, and glaucoma; the risk of specific complications of uveitis depends on the underlying illness.[2,3]

Treatment of NIU is still clinically challenging.[4] There is very limited information from controlled trials.[3] The treatment choice for NIU depends upon the location of the uveitis (such as AU/IU/PU). In the literature, it has been indicated that the initial treatment for non-infectious posterior uveitis is corticosteroids administered locally or systemically.[1] Non-infectious anterior uveitis is commonly treated with topical glucocorticoids. However, posterior uveitis is generally not responsive to topical medication.[3]

Intravitreal dexamethasone implant (IDI, 0.7 mg, Ozurdex) is usually used for patients with uveitis, when underlying systemic disease is well controlled or is not present.[1] Following corticosteroids, immunosuppressive drugs including methotrexate and azathioprine are commonly used. Long-term use of systemic corticosteroids above 7.5 mg per day is not recommended due to potential adverse effects such as cataract, glaucoma, etc.[1]

In Canada, intravitreal dexamethasone implants (IDI) are indicated for the treatment of NIU affecting the posterior segment of the eye.[5] The pivotal trial used to support the Health Canada's indication was a single, multicenter, masked RCT for the treatment of NIU affecting the intermediate and posterior segment of the eye.[5,6] In the treatment of NIU, the Health Canada recommended dose regimen of IDI is one dose. The product monograph notes that for uveitis, there is no experience with reinjection and it is therefore not recommended (p. 4) but also notes that the need for IDI reinjection is determined by physician based on patient's clinical need.[5] For other indications (e.g. diabetic macular edema), reinjection at an interval of six months between two injections has been recommended.[5] IDI is not recommended by Health Canada for pediatric use.[5]

The purpose of this report is to review the clinical effectiveness, safety, cost-effectiveness of IDI in the treatment of NIU. Of particular interest is evidence on different dose regimens

of IDI (e.g., a single implant or two implants with approximately six months between doses, or continual treatment (i.e., three or more implants) or implants at intervals of less than every six months). In addition, this report also reviews the evidence-based guidelines on the treatment of NIU.

Research Questions

1. What is the clinical effectiveness of intravitreal dexamethasone implants for patients with uveitis?
2. What is the clinical evidence regarding the safety of intravitreal dexamethasone implants for patients with uveitis?
3. What is the cost-effectiveness of intravitreal dexamethasone implants for patients with uveitis?
4. What are the evidence-based guidelines regarding the treatment of patients with uveitis?

Key Findings

Three randomized controlled trials (RCTs), one economic evaluation report and two guideline documents are included in this review. The findings observed in two RCTs indicated that one intravitreal dexamethasone implant (IDI) dose appeared to be a safe and effective option in preventing the complications of uveitic cataract surgery. One RCT suggested that IDI was superior to periocular triamcinolone injection for treating uveitic macular edema with minimal risk of intraocular pressure elevation. However, the findings reported in the three RCTs should be interpreted with caution due to various limitations of the study design. The UK economic report indicated that IDI was cost-effective compared with the limited current practice in the treatment of non-infectious uveitis (NIU). Nevertheless, uncertainty remains due to scarcity of evidence. American Academy of Ophthalmology (AAO) guidance provided the recommendations on the use of non-corticosteroid systemic immunomodulatory treatment in NIU. NICE guideline recommended adalimumab and IDI be options for the treatment of NIU. No recommendation on the IDI dose regimen (i.e., the number of implants and frequency of reinjections) was specified in NICE guideline. Further research needed to address uncertainty on the clinical efficacy and safety, cost-effective as well as the clinical guidelines regarding the use of different dose regimens of IDI in the treatment of NIU.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Ozurdex (dexamethasone) and uveitis. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited

to English language documents published between January 01, 2015 and February 25, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1-4: Adults with non-infectious uveitis
Intervention	Q1-4: Intravitreal Dexamethasone 0.7 mg implant (Ozurdex); any number of implants (e.g., a single implant or two implants with approximately 6 months between doses, or continual treatment [i.e., 3 or more implants] or implants at intervals of less than every 6 months)
Comparator	Q1, 2, 3, 4: -systemic agents, such as antimetabolites (e.g., methotrexate, azathioprine), biologics (e.g., adalimumab) - systemic or local steroids (e.g., prednisone) -Placebo or sham treatment -Dexamethasone 0.7 mg intravitreal implant with a different number of implants Q2: -no comparator
Outcomes	Q1. Clinical effectiveness (e.g., vision related function, health-related quality of life, incidence of uveitis) Q2. Safety (e.g., glaucoma, eye inflammation, eye infections) Q3. Cost-effectiveness (e.g., cost per benefit gained, cost per QALY) Q4. Recommendations regarding the treatment of patients with non-infectious uveitis
Study Designs	Health technology assessments, Systematic Reviews/Meta-Analyses, Randomized Controlled Trials, Non-Randomized Studies, Economic Evaluations, Evidence- based Guidelines.

QALY = quality-adjusted life year

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications or were published prior to 2015. Studies on mixed populations that did not present results separately (i.e. subgroup) for patients with NIU were excluded. Studies on mixed interventions that did not present results separately (i.e. subgroup) for patients with IDI were excluded. Guidelines with unclear methodology or not providing recommendations specifically for treatment of patients with NIU were also excluded.

Critical Appraisal of Individual Studies

The included RCTs were assessed with SIGN 50 Methodology Check list 2,[7] economic evaluation studies were assessed using the Drummond checklist,[8] and guidelines were assessed with the AGREE II instrument.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 333 citations were identified in the literature search. Following screening of titles and abstracts, 290 citations were excluded and 43 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 40 publications were excluded for various reasons, and seven publications met the inclusion criteria and were included in this report. These comprised three RCTs,[10-12] and two publications representing one economic analysis,[1,13] and two relevant evidence-based guideline was identified.[14,15] Appendix 1 presents the PRISMA[16] flowchart of the study selection.

Summary of Study Characteristics

The details regarding the characteristics of included studies are provided in Table 2, Table 3, and Table 4 in Appendix 2.

Study Design

Three randomized controlled trials (all published in 2019),[10-12] were relevant for this report.

One economic evaluation report presented in two publications (published in 2017 and 2019 respectively)[1,13] were included in this report. It used the perspective of the UK National Health Service and a lifetime time horizon. A Markov model was used. Efficacy data were obtained from one RCT.[6] Data of costs were calculated based on standard UK sources.

Two evidence-based guidelines[14,15] were identified. In the American Academy of Ophthalmology (AAO) guideline[14] the evidence used for generating the recommendations were based on a systematic review. The recommendations were developed based on the consensus of international experts using a modified Delphi technique. In NICE guideline[15] the evidence used for the recommendations was submitted by AbbVie and Allergan. The recommendations were developed by NICE appraisal committee. The recommendation on the use of IDI was based on one RCT.[6] The strength of recommendations was graded in the AAO guideline,[14] but not in the NICE guideline.[15]

Country of Origin

Countries indicated for the first authors of the primary studies were India for two RCTs[10,11] and USA for one RCT.[12] The country indicated for the first author of the economic analysis report[1,13] was UK and the AAO guideline[14] was developed by a group of international experts from the UK, USA, France, Japan, Brazil, Singapore and Saudi Arabia. No author was indicated in the NICE guidance.[15] The guideline was meant to apply in the UK.

Patient Population

Of the three RCTs,[10-12] the study by Gupta[10] was conducted in patients with anterior, intermediate, or posterior uveitis with cataract who were undergoing cataract surgery (N = 30 patients, Age: ≥ 15 years). The RCT by Sudhalkar[11] was conducted in patients with intermediate uveitis (IU)/posterior uveitis (PU) associated cataract undergoing cataract surgery (N=43 patients, age: ≥ 18 years); The RCT by Thorne[12] was conducted in patients with uveitic macular edema. (N=192 patients, 235 eyes, Age: ≥ 18 years).

In the economic analysis[1,13] the base case was an adult patient with non-infectious intermediate uveitis, posterior uveitis or panuveitis under the assumption that the efficacy of the fluocinolone implant is the same as that of intravitreal dexamethasone implant.

The target populations in AAO guideline[14] and NICE guideline[15] were on adult patients with NIU.

Interventions and Comparators

The RCT by Gupta,[10] compared IDI plus standard of care (SOC) with SOC. The RCT by Sudhalkar,[11] compared IDI with systemic steroids; The RCT by Thorne[12] compared IDI with intravitreal triamcinolone acetonide injection (ITA) or periocular triamcinolone acetonide injection (PTA). In addition, in the RCT by Thorne,[12] patients were permitted to have reinjections at different time points (such as reinjection of IDI at 12 weeks and, ITA or PTA at 8 weeks). Changes of treatment from PTA to ITA, and from ITA to IDI were also permitted. The number of implants ranged from 1 to 3 for IDI, 1 to 5 for ITA, and 1 to 4 for PTA.

The economic evaluation[1,13] compared IDI with limited current practice (LCP, defined in the RCT data source as intravitreal dexamethasone 0.35 mg implant or sham procedure).

The AAO guideline provided recommendations on the use of noncorticosteroid systemic immunomodulatory agents for the treatment of NIU. The NICE guideline provided recommendations on the use of IDI and adalimumab for the treatment of NIU.

Outcomes

In the RCT by Gupta,[10] outcomes included mean central macular thickness (CMT), logMAR best corrected visual acuity (logMAR BCVA), laser flare photometry (LFP), and adverse events. In the RCT by Sudhalkar,[11] outcomes included incidence of postoperative cystoid macular edema (CME), the change in BCVA, central subfield thickness (CST) and complications. In the RCT by Thorne[12] outcomes included CST at various time-points over 24 weeks (the primary outcome was CST reduction at 8 weeks), ≥20% improvement and resolution of macular edema, BCVA, and intraocular pressure (IOP) events over 24 weeks.

The economic evaluation[1,13] reported incremental cost-effectiveness ratios (ICER).

The recommendations in the AAO guideline[14] were on the use of non-corticosteroid systemic immunomodulatory agents. The NICE guideline[15] was on the use of IDI and adalimumab.

Summary of Critical Appraisal

The critical appraisal of the included RCTs, economic evaluation report and guidelines are briefly presented below. The detailed information on critical appraisal are available in Table 5, Table 6, and Table 7 in Appendix 3.

RCTs

The research objectives were clearly reported in all three RCTs.[10-12] The outcome measurements in all three RCTs were standard and reliable. No dropouts were reported in two RCTs[10,11] and dropouts was <5% in one RCT.[12] Intention to treat analysis was used in all three RCTs. Two RCTs[10,11] declared no conflict of interest; and one RCT[12] reported potential conflicts. Several key limitations of the RCTs include: the randomization method and allocation concealment was not described in two trials.[10,11] Whether the RCT by

Gupta[10] had an open-label design or included some form of blinding was not described. The RCT by Sudhalkar was an open-label design and the RCT by Thorne[12] was partially blinded (i.e., the patients and treating clinicians were not blinded, but the primary outcome [Central subfield thickness] assessors were). Sample sizes in two RCTs[10,11] were relatively small (< 50 patients). No power calculation was included. In one RCT by Thorne[12] the underlying condition of uveitis and the type of uveitis were not well balanced among treatment groups. In the RCT by Thorne,[12] it was permitted to have reinjections at different time points; and after 8 weeks, it was also changes of treatment from PTA to ITA, and from ITA to IDI were permitted. The number of implants in each treatment group varied. In the RCT by Gupta,[10] the between group treatment difference of the changes from baseline for the BCVA, CMT reduction and LFP were not reported. Finally, two RCTs[10,11] were conducted in India, where the clinical standard practice may differ from Canadian clinical settings. (See Table 5 for more information on the appraisal of the RCTs)

Economic evaluation

In the economic evaluation[1,13] the objective, strategies, time horizon, perspective, and sources of clinical and cost data were stated. Incremental analysis and sensitivity analysis were conducted. The conclusions were consistent with the results reported. The key limitations included time frame of the included studies appeared to be too short and lack of direct or indirect comparison between IDI and adalimumab in the treatment of patients with NIU. (See Table 6 for more detail on the appraisal of the economic evaluation)

Guidelines

In the two guidelines[14,15] the scope, purpose, intended users and the target population were indicated. The guideline development group was composed of relevant expertise. Potential conflicts were declared in both guidelines. The key limitations included the health questions was not specified in NICE guideline and whether the views and preferences of the target population (patients, public, etc.) have been sought was not described in AAO guidelines.[14] The NICE guideline was not based on a systematic review. And no strengths and limitations of the body of evidence are clearly reported in NICE guideline.[15] (See Table 7 for more detail on the appraisal of the guidelines)

Summary of Findings

Findings are briefly summarized below. The details are available in Appendix 4: Table 8, Table 9 and Table 10

Clinical effectiveness and safety of IDI in the treatment of patients with non-infectious uveitis

Efficacy outcomes

In the RCT by Gupta,[10] it was found that at 6 months after uveitic cataract surgery, patients in the IDI group achieved a statistically significant better logMAR BCVA compared with standard of care alone group (IDI vs. SOC: 0.036 vs.0.181, P = 0.024). Central macular thickness (CMT) was also reported to be significantly lower in the IDI group compared to the SOC group at 6 months post-surgery. It was also indicated that patients in the IDI group had statistically significantly less postoperative laser flare photometry (LFP) (P<0.05) compared to SOC group at 6 months post-surgery. No statistically significant difference between treatment group were observed in terms of mean IOP at 6 months.

In the RCT by Sudhalkar,[11] the authors reported that the BCVA improved significantly in both groups in terms of change from baselines (BCVA logMAR: IDI: 0.08, P = 0.012; systemic steroids:0.04, P = 0.013). However, there was no statistically significant between group difference in change from baseline (P = 0.42); The central subfield thickness (CST) change from baseline was not statistically significant in either groups. There was no statistically significant treatment group difference in terms of CST change from baseline (P = 0.47).

In the RCT by Thorne,[12] at 24 weeks follow up, it was reported that patients in the IDI group achieved a statistically significant greater improvement in BCVA than in the PTA group (between group difference of 5 letters, P < 0.019). However, no statistically significant treatment group difference in terms of BCVA improvement were observed between the IDI and ITA groups (P = 0.84). At 24 weeks, CST reduction was 39%, 36%, and 32%, in IDI, ITA and PTA group respectively. No statistically significant difference of change from baseline was observed between IDI and PTA (P = 0.07). The P-value was not reported for comparing IDI with ITA group in terms of treatment group difference in changes from baseline.

Adverse events

In the RCT by Gupta,[10] at 6 months after cataract surgery, one patient in the IDI group had vitreous hemorrhage; no patient had any CME. In the SOC group, six patients (37.5%) developed CME, one patient (6.25%) developed postoperative hypotony (IOP< 10mm Hg).

In the RCT by Sudhalkar,[11] one patient (5%) in IDI group and two patients (8%) in the systemic steroids group developed CME.

In the RCT by Thorne[12] the events of IOP change from baseline (> 10 mmHg) was statistically significant higher in IDI group than PTA group (P = 0.009). No statistically significant difference was reported comparing IDI with the ITA group (P = 0.30). No statistically significant difference was reported comparing IDI with the ITA group or PTA group in terms of vision acuity decrease (≥ 15 standard letters). (See Table 8 for detailed findings from the RCTs)

Cost-Effectiveness of IDI comparing with current practice

The cost-effectiveness analysis[1,13] demonstrated that, for the treatment of NIU, the estimated incremental cost-effectiveness ratio (ICER) of one IDI intravitreal implant compared with limited current practice (LCP) was £19,509 per quality-adjusted life year (QALY) gained. IDI may be associated with an ICER of £56,329 per QALY gained compared with LCP when using plausible alternative assumptions. The authors concluded that IDI was estimated to be cost-effective using generally accepted UK thresholds.[1] (See Table 9 for detailed findings from the economic evaluation)

Guidelines regarding the treatment of patients with uveitis

The AAO guideline,[14] provided recommendations on the use of non-corticosteroid systemic immunomodulatory therapy in patients with NIU. The guideline suggested the use of adalimumab, infliximab, for the treatment of NIU. It indicated that there was no evidence to support the use of etanercept in NIU. It also suggested that subcutaneous secukinumab in nonanterior NIU is not supported. No recommendation on how to use of IDI was developed.

The NICE guideline[15] recommended adalimumab as an option in the treatment of adult patients with posterior NIU who had inadequate response to corticosteroids. IDI was also

recommended as an option in the treatment of adult patients with posterior NIU. No recommendations on the dosing regimen of IDI (# of implants or the frequency of the implants) were provided. (See Table 10 for detailed recommendations from the guidelines)

Limitations

The RCT by Sudhalkar[11] was an open-label design. The RCT by Gupta[10] was not clearly defined whether it is a blinded or open-label design. Therefore, treatment bias may exist in the two RCTs. In the two RCTs[10,11] the sample size was relatively small and may lack sufficient power to detect treatment group differences. In addition, in the RCT by Gupta,[10] the comparative improvement of the BCVA, CMT reduction and LFP improvement between IDI and SOC should be interpreted with caution since the between group difference for changes from baseline were not reported and the baseline BCVA, CMT and LFP were numerically better in IDI group than SCO group. The key limitation of the RCT by Thorne[12] included lack of a double blinded study design and the underlying condition of uveitis and the type of uveitis were not well balanced. Furthermore, the RCT allowed reinjections at different time points for each of the three treatments (such as reinjection of IDI at 12 weeks, but reinjection of ITA or PTA at 8 weeks), and after 8 weeks permitted changes of treatment from PTA to ITA, and from ITA to IDI, hence, Interpretation of the comparative results beyond the 8-week timepoint was more challenging. In the RCT by Thorne,[12] although the number of injections ranged from 1 to 3 for IDI, 1 to 5 for ITA, and 1 to 4 for PTA, there were no subgroup analyses based on the number of injections.[12] Overall, the findings of the three RCTs should be interpreted with caution due to the limitations discussed above. In addition, the duration of the RCTs were at 6 months for two RCTs.[10,11] The primary outcome was assessed at week 8 in one RCT.[12] Therefore, the long-term efficacy and safety outcomes of using IDI in the treatment of NIU remains unclear. Finally, two RCTs[10,11] were conducted in India. Whether the findings can be generalized to the Canadian setting is uncertain.

In the economic evaluation report,[1,13] the perspective used in economic evaluation was that of UK, hence generalizability to the Canadian setting is unclear. In addition, no direct or indirect comparison between IDI and adalimumab in the treatment of patients with NIU was provided.

Among the two included guidelines,[14,15] the AAO guidelines[14] were for the use of non-corticosteroid systemic immunomodulatory therapy in non-infectious uveitis, and no IDI us recommendations was made. The NICE guideline provided recommendations on the use of IDI, however, recommendation on the dosing regimen (i.e., maximum number of injection or frequency of the reinjection) was not provided.

Conclusions and Implications for Decision or Policy Making

Three randomized controlled trials, one economic evaluation report and two guideline documents are included in this review. The findings observed in two RCTs indicated that one dose of IDI appeared to be a safe and effective option in preventing the complications of uveitic cataract surgery. One RCT suggested that IDI was superior to periocular triamcinolone injection for treating uveitic macular edema with minimal risk of intraocular pressure elevation. However, the findings reported in the three RCTs should be interpreted with caution due to various limitations of the study design. The UK economic report indicated that IDI was cost-effective compared with the limited current practice in the treatment of NIU. Nevertheless, uncertainty remains due to scarcity of evidence. AAO

guidance provided recommendations on the use of non-corticosteroid systemic immunomodulatory treatment in NIU but did not provide a recommendation on IDI. The NICE guideline recommended adalimumab and IDI be options for the treatment of NIU. No recommendations on the IDI dose regimen (i.e., the number of injections and frequency of reinjections) was specified in NICE guideline. Further research needed to address uncertainty on the clinical efficacy and safety, cost-effectiveness as well as the clinical guidelines regarding the use of different dose regimen of IDI in the treatment of NIU.

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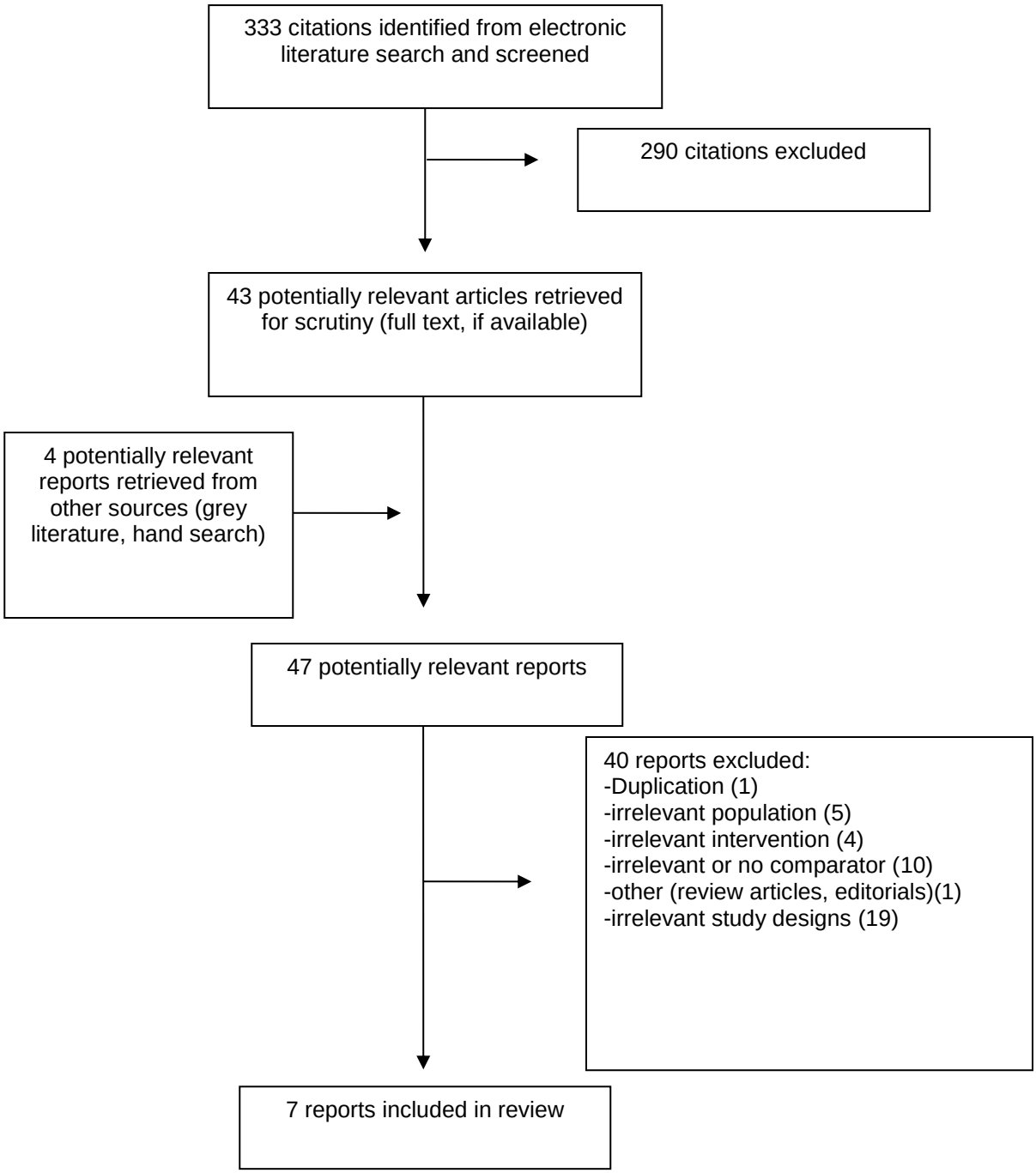
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Gupta G,[10] 2019, India	RCT Setting: Eye surgery Clinic; Objective: to assess postoperative inflammation using LFP, following phacoemulsification with or without single IDI in addition to SOC in patients undergoing uveitic cataract surgery	Patients with anterior, intermediate, or posterior uveitis with visually significant cataract undergoing cataract surgery Age: ≥ 15 years N= 30 patients IDI+SOC group: N = 14; SOC group: N= 16)	Intervention: IDI +SOC Comparator: SOC	LFP (the primary outcome) CME CMT BCVA Length of follow-up: ≥24 weeks
Sudhalkar A,[11] 2019, India	RCT Setting: eye hospital Objective: To determine the utility of the IDI as an alternative to systemic steroids as prophylaxis against CME in patients with chronic, recurrent CME associated IU/PU undergoing uveitic cataract surgery.	Patients with IU/PU and uveitic cataract undergoing cataract surgery; Age: ≥ 18 years N = 43 patients IDI: N=20 Systemic steroids: N=23	Intervention: IDI Comparator: Systemic steroids	CME (the primary outcome) BCVA CST Complications Length of follow-up: 6 months
Thorne JE,[12] 2019, USA	RCT; Setting: Multiple-nation, 26 clinic centers including 23 centers in USA and 1 in Canada, I in Australia and 1 in UK Objective: To evaluate the comparative effectiveness of	Patients with uveitic macular edema Age: ≥ 18 years N= 192 patients (235 eyes) IDI: N = 64 patients (79 eyes) ITA: N = 63 (82 eyes) PTA : N = 65 (74 eyes)	Intervention: **IDI** (one IDI used for 78 eyes; 2nd IDI for 44 eyes and 3rd IDI for 3 eyes) Comparator: -**ITA** (one ITA used for 79 eyes; 2nd for 38 eyes; 3rd for 8 eyes and 4th for 2 eyes)	CST (the primary outcome) ≥20% improvement and resolution of macular edema, BCVA, IOP Length of follow-up: ≥ 24 weeks, however, the primary outcome (i.e., CST) was assessed at 8 weeks

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	three regional corticosteroid injections for uveitic macular edema: PTA, ITA, and IDI		-**PTA** (one for 73 eyes; 2nd for 36 eyes, 3rd for 4 eyes and 4th for 1 eyes)	

BCVA: best corrected visual acuity; CME: cystoid macular edema; CMT: central macular thickness; CST = Central subfield thickness; IU = intermediate uveitis; IDI = intravitreal dexamethasone implant; IOP = intraocular pressure; LFP = LFP Laser flare photometry; PU = posterior uveitis; RCT = randomized controlled trial; SOC = standard of care; PTA = periocular triamcinolone acetonide; ITA = intravitreal triamcinolone acetonide.

Table 3: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
Squires H,[13] 2017, UK Squires H,[1] 2019, UK	Cost-effectiveness of SC adalimumab and IDI, each compared with current practice, based on Markov model. Over a lifetime horizon, NHS and PSS perspective	To evaluate the clinical effectiveness and cost-effectiveness of SC adalimumab and IDI in adults with non-infectious intermediate uveitis, posterior uveitis or panuveitis.	Adult patient with non-infectious intermediate posterior uveitis or panuveitis	Intervention: ●adalimumab ●IDI Comparator: limited current practice	A Markov model; sensitivity analyses	Clinical data: from 1 RCT[6] Cost data: based on standard UK Sources.	The efficacy of the fluocinolone implant is the same as that of IDI.

IDI = intravitreal dexamethasone implant; PSS = Personal Social Services; RCT = randomized controlled trial; SC = subcutaneous

Table 4: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Dick AD,[14], 2017, USA (AAO guideline)						
Intended users: Clinicians **Target population:**	Non-corticosteroid systemic immunomodulatory therapy in NIU	Clinical efficacy and safety outcomes based on systematic	SR/MA expert opinion, and practical experience to support	Using the Oxford Centre for Evidence-Based Medicine	Consensus using a modified Delphi technique and assigned	Whether the guideline was externally reviewed by experts was not described

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Patients with NIU		review (but not clearly described)	the treatment of patients with NIU with non-corticosteroid immunomodulatory agents.	levels of evidence[17]	Oxford levels of evidence.	
NICE, [15], 2017, UK						
Intended users: Clinicians **Target population:** Patients with NIU	Adalimumab IDI	Clinical efficacy and safety outcomes based on the RCT [6]	Evidence submitted by AbbVie and Allergan and a review of these submissions by the assessment group For IDI, based on one RCT[6]	Not described	The appraisal committee reviewed the data available on the clinical and cost effectiveness of adalimumab and IDI, evidence on the nature of NIU and the value placed on the benefits of adalimumab and IDI patients and clinical experts, and effective use of NHS resources	Whether the guideline was externally reviewed by experts was not described

AAO = American Academy of Ophthalmology; ACRAF = American College of Rheumatology/Arthritis Foundation; DMARDs = disease-modifying antirheumatic drugs; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; MA = Meta-Analyses; NICE = national institute for health and care excellence; NIU = noninfectious uveitis; RCT = randomized controlled trial; SR = systematic review.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Clinical Studies using SIGN 50 Check list[7]

Strengths	Limitations
Gupta G, 2019,[10]	
• Research question clearly defined • Randomization method clearly described • Only difference between groups was treatment under investigation • Outcome was standard, valid and reliable • No dropouts • Intention to treat analysis used • Declared no conflict of interest	• Randomization allocation not described • Blindness/Open-label design not described • Key characteristics in the two treatment arms were not well comparable. Type of uveitis were not balanced well. preoperative CME was not documented • Whether the SOC are balanced between two treatment arms were not reported • Small sample size and conducted in one research site, not conducted in Canada or North America.
Sudhalkar A, 2019,[11]	
• Research question was clearly defined • Randomization method was clearly described • Only difference between groups is treatment under investigation • Outcome was standard, valid and reliable • No dropout • Intention to treat analysis applied • Declared no conflict of interest	• Randomization allocation not described • Open-label design • Key characteristics in the two treatment arms were not well reported. Baseline vision acuity and the type of uveitis were not well balanced. • Small sample size and conducted in one research site, not conducted in Canada or North America.
Thorne JE, 2019,[12]	
• Research question clearly defined • Randomization method clearly described • Randomized allocation described. • Visual acuity examiners and members of the Reading Center that graded the OCT images were masked to study treatment • The characteristics were distributed similarly across the three treatment groups except for the presence of active uveitis and baseline BCVA. • Outcome was standard, valid and reliable • Dropout (<5%) • Intention to treat analysis applied. • Multicenter RCT • Conflicts of Interest declared	• Participants, treating clinicians, and coordinators were not masked • Underlying condition of uveitis and the type of uveitis were not well balanced • Number of injections of each treatment varied • Changing of the treatment were allowed after 8 weeks

BCVA = best corrected vision acuity; CME = cystoid macular edema; OCT = optical coherence tomography; RCT = randomized controlled trial; SOC = standard of care;

Table 6: Strengths and Limitations of Economic Studies using the Drummond Checklist[8]

Strengths	Limitations
Squires H,[13] 2017, UK ; Squires H,[1] 2019, UK	
●Objectives were stated. ●The strategies compared were stated ●Time horizon and perspective were stated ●Clinical data sources were stated. ●Cost data sources were stated ●Discounting was considered ●Incremental analysis was reported. ●Sensitivity analyses, threshold analyses and probabilistic sensitivity analysis were conducted. ●Conclusions were consistent with the results reported, but it was indicated that there was insufficient evidence to make robust conclusions. ●Conflicts of interest was declared .	●Time frame used in included studies appeared to be too short ● Lack of direct or Indirect comparison between IDI and adalimumab in the treatment of patients with NIU

Table 7: Strengths and Limitations of Guidelines using AGREE II[9]

Item	Guideline	
	AAO guideline (Dick AD,[14], 2017, USA)	NICE,[15], 2017, UK
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	y	y
2. The health question(s) covered by the guideline is (are) specifically described.	y	Not stated
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	y	y
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	y	y
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Not stated	y
6. The target users of the guideline are clearly defined.	yes	yes
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	yes	Not stated
8. The criteria for selecting the evidence are clearly described.	yes	yes
9. The strengths and limitations of the body of evidence are clearly described.	yes	Not stated
10. The methods for formulating the recommendations are clearly described.	yes	yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	yes	yes
12. There is an explicit link between the recommendations and the supporting evidence.	yes	yes
13. The guideline has been externally reviewed by experts prior to its publication.	yes	yes

Item	Guideline	
	AAO guideline (Dick AD,[14], 2017, USA)	NICE,[15], 2017, UK
14. A procedure for updating the guideline is provided.	yes	Not stated
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	yes	yes
16. The different options for management of the condition or health issue are clearly presented.	yes	yes
17. Key recommendations are easily identifiable.	yes	yes
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	Not stated	yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Not stated	yes
20. The potential resource implications of applying the recommendations have been considered.	Not stated	yes
21. The guideline presents monitoring and/or auditing criteria.	Not stated	Not stated
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	Not stated	Not stated
23. Competing interests of guideline development group members have been recorded and addressed.	yes	yes

AAO = American Academy of Ophthalmology; NICE = national institute for health and care excellence.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Gupta G, 2019,[10]	
IDI +SOC: N = 14 patients (14 eyes) SOC: N= 16 patients (16 eyes) *At 6 months post-surgery* *Efficacy outcomes* **Mean logMAR BCVA** ± SD: IDI+SOC: 0.036 ± 0.063, SOC: 0.181 ± 0.225; p = 0.024[a] **Mean IOP** ± SD (mmHg): IDI + SOC: 13.86 ± 1.95 SOC: 15.06 ± 3.31; p = 0.244[a] **Mean LFP** ± SD (photon units/ms) IDI + SOC: 12.29 ± 11.78 SOC group: 24.30 ± 17.62; p = 0.035[a] **Mean CMT** (µm) ± SD IDI + SOC: 267.81 ± 34.26 SOC: 306.50 ± 53.55; p = 0.03[a] *Adverse events* IDI + SOC: one patient had vitreous hemorrhage. No patient had any CME, hypotony during follow up; SOC: 6 patients (37.5%) developed CME during follow-up visits, 1 (6.25%) patient developed postoperative hypotony (IOP< 10mm Hg).	On page 1337: "… dexamethasone implant is a safe and effective option for preventing and managing the postoperative inflammation in uveitic cataract cases and is also useful in preventing the complications of cataract surgery in uveitic cases."
Sudhalkar A, 2019,[11]	
IDI: N=20 patients (20 eyes) Systemic steroids: N= 23 patients (23 eyes) *Efficacy outcomes* **Visual acuity (CDVA)** Change from baseline at 6 months post-surgery **(logMAR)** IDI: 0.08 ± 0.05; p = 0.012[b] Systemic steroids: 0.04 ± 0.06, p = 0.13[b]	On page 491: "*IVD is a good alternative as prophylaxis in IU/PU and cataract in preventing postoperative CME*"

Main Study Findings	Authors' Conclusion
(The between group difference of the changes from baseline value was not reported in the original article, only p value was reported) IDI versus Systemic steroids: p =0.42[c] **CST** change from baseline at 6 months post-surgery (µM), (Change from baseline value was not reported in the original article, only p value was reported) IDI: p = 0.33[b] Systemic steroids: p = 0.45[b] **CST at 6 months: (µM)** IDI: 206.5 ± 16.4 (165–250) Systemic steroids: 198 ± 14; p = 0.47[a] *Adverse events* **IOP required medications.** IVD group: 4 Systemic steroids group: 3 **CME developed:** IDI: 1 patient Systemic steroids: 2 patients	
Thorne JE,[12] 2019, USA	
IDI: N=64 patients (79 eyes), maximum # of injection: 3 PTA: N=65 patients (74 eyes), maximum # of injection: 4 ITA: N=63 (74 eyes), maximum # of injection: 5 *Efficacy outcomes* **BCVA** Change from baseline (based on standard letters**)** at **6 months,** mean (95%CI) IDI: 9.21 (6.62, 11.80), p<0.0001[b] ITA: 9.60(6.87, 12.34), p<0.0001[b] PTA: 4.07 (0.64, 7.51); p <0.0001[b] **BCVA** between group difference of change from baseline at 6 months **(**Mean) IDI vs IVT: mean, 3.37; P =0.84[c] IDI vs. PTA: mean: 5.14; P value: = 0.019[c] **CST reduction at 8 weeks: (%)** IDI: 46% ITA: 39%, (IDI vs. ITA) p value not reported PTA: 23%, (IDI vs. PTA) p < 0.0001[d] **CST reduction at 24 weeks: (%)**	On page 2: "…*the IDI were superior to PTA for treating uveitic macular edema with modest increases in the risk of IOP elevation. This risk did not differ significantly between intravitreal treatments.*"

Main Study Findings	Authors' Conclusion
IDI: 39% ITA: 36%, IDI vs. ITA, p not reported **PTA: 32%, IDI vs. PTA, p < 0.07[a]** **20% Improvement of macular edema at week 8** (%, 95% CI **)** IDI: 84% (74, 94) ITA:79% (70, 88) ; difference (IDI vs. ITA), 5%, p = 0.45 PTA: 41% (29, 52); difference (IDI vs. PTA), 44%, *p < 0.0001* **20% Improvement of macular edema at 6 months** (%, 95% CI) IDI : 74% (61, 85) **ITA : 73% (63, 83); difference (IVI vs. ITA) 0.2%, p = 0.98** PTA : 61% (50, 72), difference (IVI vs. PTA), 12%, p = 0.11 **Resolution of macular edema at week 8** (%, 95% CI) IDI: 61%(48, 73) ITA:47%(34, 60); difference (IDI vs. ITA) 13%, p = 0.12 PTA: 20% (12, 30); difference (IDI vs. PTA), 40%, *p =0.001* **Resolution of macular edema at 6 months (%, 95% CI)** **IDI : 41% (28, 54)** **ITA : 36% (24, 48); difference (IVI vs. ITA), 5%, p = 0.54** PTA : 35% (24, 47); difference (IVI vs. ITA) 6%, p =0.51 Ocular *Adverse events* **≥ 10 mmHg increase in IOP from baseline at 6 months**: IDI: 24 events ITA: 18 events; IDI vs. ITA HR (95% CI): 1.43 (0.72, 2.81): p = 0.30 PTA: 9 events; IDI vs. PTA HR (95% CI): 2.85 (1.30,6.28): p = 0.009 **Visual acuity decrease ≥ 15 or more standard letters at 6 months** IDI: 4 events ITA: 3 events; IDI vs ITA HR (95% CI): 1.45 (0.34, 6.26): p = 0.62 PTA: 8 events; IDI vs. PTA HR (95% CI): 0.46 (0.14,1.50): p = 0.20	

BCVA = best-corrected visual acuity; CDVA = corrected distance visual acuity; CI = Confidence Interval; CME = cystoid macular edema ; CMT: central macular thickness; CST = Central Subfield thickness (CST); HR = Hazard ratio; IDI = intravitreal dexamethasone implant; IOP = intraocular pressure; ITA = intravitreal triamcinolone acetonide; LFP = laser flare photometry; PTA = periocular triamcinolone acetonide. SOC = standard of care;

[a] p value for between group difference at 6 months;

[b] p value for intragroup comparison (i.e., change from baseline);

[c] p value for between group difference of changes from baseline at 6 months.

[d] p value for between group difference at week 8

Table 9: Summary of Findings of Included Economic Evaluations

Main Study Findings	Authors' Conclusion
Squires H,[13] 2017, UK ; Squires H,[1] 2019, UK	
Base-case analysis comparing "IDI + LCP" with LCP	On Page 2 in Squires 2019:[1] *"Dexamethasone is estimated to be cost-effective using generally accepted UK thresholds. However there is substantial uncertainty around these results due to scarcity of evidence. Future research on the following would help provide more reliable estimates: effectiveness of dexamethasone versus current practice (instead of LCP), with subgroup analyses for unilateral and bilateral uveitis; incidence of long term blindness; and effectiveness of dexamethasone in avoiding blindness."*

Probabilistic model							
Treatment	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)	Probability of CE at WTP threshold of	
						£20,000	£30,000
IDI + LCP	14.629	40,565	0.029	573	19,509	0.47	0.72
LCP	14.599	39,992				0.53	0.28
Deterministic model							
IDI + LCP	14.641	40,235	0.029	580	20,058		
LCP	14.613	39,655					

CE = cost-effectiveness; ICER = incremental cost-effectiveness ratio; IDI = intravitreal dexamethasone implant; LCP = Limited current practice; QALY = quality-adjusted life year; WTP = willingness to pay.

Note: LCP as provided in the RCT[6]

Table 10: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations[a]
Dick AD,[14], 2017, USA	
On page 5 – 7: "Question 7. Which Biologic Should Be Used for the Treatment of Noninfectious Uveitis?	
"Statement 1: The use of adalimumab for the treatment of NIU is supported"	1B/Grade A
"Statement 2: The use of infliximab for the treatment of NIU is supported"	2B /Grade B/C
"Statement 3: There is no evidence to support the use of etanercept in NIU"	2B/ Grade B
"Statement 4: The use of subcutaneous secukinumab in nonanterior NIU is not supported"	2B/ Grade B
"Statement 5: The use of interferon alfa-2a in nonanterior NIU is supported"	2B/ not reported
"There is limited evidence to support the use of pegylated interferon alfa in nonanterior NIU in patients with Behçet's disease"	2B/ not reported

Recommendations	Strength of Evidence and Recommendations[a]
"Interferon b demonstrated efficacy in the treatment of pars planitis in a small pilot randomized controlled trial"	2B/Grade B
NICE, [15], 2017, UK	
On page 4 "1 Recommendations 1.1 Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids, only if there is: ●active disease (that is, current inflammation in the eye) and ●inadequate response or intolerance to immunosuppressants and ●systemic disease or both eyes are affected (or 1 eye is affected if the second eye has poor visual acuity) and ● worsening vision with a high risk of blindness (for example, risk of blindness that is similar to that seen in people with macular edema). 1.2 Stop adalimumab for non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is 1 of the following: ● new active inflammatory chorioretinal or inflammatory retinal vascular lesions, or both or ● a 2-step increase in vitreous haze or anterior chamber cell grade or worsening of best corrected visual acuity by 3 or more lines or 15 letters. 1.3 Dexamethasone intravitreal implant is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults, only if there is: ●active disease (that is, current inflammation in the eye) and ●worsening vision with a risk of blindness. 1.4 These recommendations are not intended to affect treatment with adalimumab and dexamethasone that was started in the NHS before this guidance was published. Adults having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop."	Not reported

NIU = noninfectious uveitis;

[a]Level of evidence: 1B indicating individual RCT (with narrow Confidence Interval); 2B indicating Individual cohort study (including low quality RCT; e.g., <80% follow-up)

Strength of recommendation: GRADE A: based on level 1 evidence; GRADE B: based on level 2 or 3 studies or extrapolations from level 1; GRADE C: based on level 4 studies or extrapolations from level 2 or 3 studies.[17]