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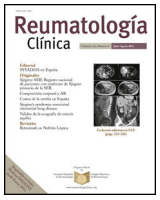

Special Article

SER recommendations for the treatment of uveitis

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ABSTRACT

Objective: To develop evidence-based expert-consensus recommendations for the management of non-infectious, non-neoplastic, non-demyelinating disease associated uveitis.
Methods: Clinical research questions relevant to the objective of the document were identified, and reformulated into PICO format (patient, intervention, comparison, outcome) by a panel of experts selected based on their experience in the field. A systematic review of the available evidence was conducted, and evidence was graded according to GRADE (*Grading of Recommendations Assessment, Development, and Evaluation*) criteria. Subsequently, recommendations were developed.
Results: Three PICO questions were constructed referring to uveitis anterior, non-anterior and complicated with macular edema. A total of 19 recommendations were formulated, based on the evidence found and/or expert consensus.
Conclusions: Here we present the first official recommendations of the Spanish Society of Rheumatology for the treatment of non-infectious and non-demyelinating disease associated uveitis. They can be directly applied to the Spanish healthcare system as a tool for assistance and therapeutic homogenisation.

Recomendaciones SER sobre el tratamiento de la uveítis

Palabras clave:
Uveítis
Panuveítis
Uveítis intermedia
Edema macular
GRADE

RESUMEN

Objetivo: Elaborar recomendaciones basadas en la evidencia disponible y el consenso de expertos para el manejo terapéutico de los pacientes con uveítis no infecciosas, no neoplásicas y no asociadas a enfermedad desmielinizante.
Métodos: Se identificaron preguntas clínicas de investigación relevantes para el objetivo del documento, reformuladas en formato PICO (paciente, intervención, comparación, *outcome* o desenlace) por un panel

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de expertos seleccionados en base a su experiencia en el área. Se realizó una revisión sistemática de la evidencia, graduándose de acuerdo a los criterios *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE). Subsecuentemente, se formularon las recomendaciones.
Resultados: Se seleccionaron 3 preguntas PICO, referentes a uveítis anteriores, no anteriores y complicadas con edema macular. Se formularon un total de 19 recomendaciones con base en la evidencia encontrada y/o consenso de expertos.
Conclusiones: Se presenta el primer documento oficial de la Sociedad Española de Reumatología de recomendaciones para el tratamiento de las uveítis. Pueden aplicarse directamente al sistema sanitario español como herramienta de ayuda y homogenización terapéutica.

Introduction

Uveitis is a form of intraocular inflammation that affects the middle layer of tissue of the eyeball called the uvea. In uveitis, the inflammatory process typically begins in the uveal tract; however, adjacent structures such as the vitreous, papilla, or retina may also be affected. In half of all cases, its origin is unknown or unclassified, and it is estimated that one third of all cases are due to a rheumatic disease, including juvenile idiopathic arthritis, the group of spondyloarthritis, Behçet's disease, certain systemic types of vasculitis and sarcoidosis, among others. The incidence of uveitis is 52 cases per 100,000 inhabitants/year and prevalence is 70 cases per 100,000 inhabitants/year in developed countries,[1–3] where it is currently the third leading cause of blindness among people of working age; yet, at the same time, it remains a largely unknown condition in the general population.

The most commonly used classification is based on the anatomical location where the inflammation predominates. It was established by the International Uveitis Study Group in 1987,[4] and divides them into anterior (AU), when the iris or the anterior portion of the ciliary body is affected (iritis or iridocyclitis); intermediate (IU), in which the pars plana (pars planitis) is involved, and posterior (PU), affecting the choroid or the retina (choroiditis, chorioretinitis, retinal vasculitis). Furthermore, we refer to panuveitis when they affect the entire uvea. Another classification of endogenous uveitis is based on aetiology; in this regard, we can distinguish four major categories of uveitis: infectious uveitis; purely ophthalmological, non-infectious uveitis (idiopathic uveitis and specific ophthalmological syndromes); uveitis linked to immune-mediated diseases, and masking syndromes (non-inflammatory processes, generally neoplastic diseases, which can simulate uveitis).

The Spanish Society of Rheumatology (SER) has drawn up a series of recommendations based on the available evidence and expert consensus concerning treatment for the management of patients with non-infectious, non-neoplastic uveitis, not associated with demyelinating disease, to enhance our understanding of the problem and thereby decrease the unjustified variability of all the specialists involved.

Methods

These recommendations have been prepared using a synthesis of the scientific evidence and consensus techniques that reflect expert agreement on the basis of the available evidence and their clinical experience. These recommendations were drawn up following the procedure set out below:

Creation of the working group. An interdisciplinary working group was assembled consisting of five rheumatologists chosen by an open call from among the members of the SER and two ophthalmologists with ample experience in this disease. Clinical and methodological aspects were coordinated by two rheumatologists as principal investigators (PI) and a methodology specialist from the SER Research Unit, respectively. Together, they comprised the recommendations development group (RDG).

Identification of key areas. The contents and key aspects of the document were defined and the clinical research questions were posed that have the greatest impact on clinical practice. The questions were reformulated in patient, intervention, comparison, or outcome (PICO) format.

Bibliographic search. A literature search for randomised clinical trials (RCTs) was carried out in PubMed (MEDLINE), EMBASE (Elsevier), and Cochrane Library (Wiley Online) databases until January 2021. The process was then completed by a manual search of the references of the studies identified, as well as other references that the reviewers and experts felt to be of interest. Full articles published in indexed scientific journals were considered.

Analysis and synthesis of the scientific evidence. Systematic reviews were performed of the scientific evidence available. The quality of the evidence was assessed according to the methodology of the international working group *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE).[5] The GRADE system calls for the importance of the outcome measures for a given clinical question to be ranked on the basis of how relevant they are for decision making. Outcomes are classified as critical; important, but not critical, or not important for decision making. In this case, outcomes were classified by consensus by the panel of experts responsible for drafting this document. Considering a combination of components (study design, risk of bias, inconsistency, directionality, imprecision, and likelihood of publication bias), the quality of evidence for each critical or important outcome was classified and defined as high (very unlikely that new studies will change the estimate), moderate (likely that new studies will change our confidence in the outcome), low (very likely that new studies will impact our confidence in the outcome and may change it), and very low (any estimated outcome is highly doubtful). The outcomes covered in each question and their importance can be found in Appendix A Annex II (section f for each drug group in each question).

Recommendation formulation. After critical reading and synthesis, the RDG proceeded to formulate specific recommendations in the light of the scientific evidence. This formulation was based on "formal evaluation" or "reasoned judgement", having previously summarised the evidence for each of the clinical questions and taking into account the quality or certainty of the scientific evidence identified, patients' values and preferences, the balance between desirable and undesirable effects of the interventions, and aspects such as the equity, acceptability, and feasibility of their implementation, following the GRADE5 methodology. Frameworks were used to aid in the process of moving from evidence to recommendations (Evidence to Decision), which are available in Appendix A Annex II. At the end of this process, the strength (weak or strong) and direction (for or against) of the recommendations were determined, with varying implications for different users of the recommendations (Table 1).

In addition, the RDG felt that there were certain important aspects that needed to be highlighted, but for which there was a

Table 1
Implications of the strength of recommendation under the GRADE system.

Recommendation	Patients	Clinicians	Managers/Planners
Strong	Most people would agree with the recommended action and only a small number would not.	Most patients should receive the recommended intervention.	The recommendation can be adopted as health policy in most situations.
Weak or conditional	Most people would agree with the recommended action, but a significant number would not.	Recognises that different options will be appropriate for different patients and that the physician must help each patient arrive at the decision most consistent with his or her values and preferences.	There is a need for substantial debate and stakeholder involvement.

Source: Atkins et al.[5]

lack of sound scientific evidence to support them. These cases are often related to aspects of treatment that are considered good clinical practice and would not normally be questioned. These aspects were assessed as Good Clinical Practice (GCP) points or recommendations.

External review and public exposure. The draft document was sent to professionals selected for their expertise in uveitis to conduct an independent external review with the aim of increasing the external validity of the document and to ensure the accuracy of the recommendations. The document was then made available to SER members and other potentially interested groups (scientific societies, industry, etc.) for public review, so as to collect their feedback and scientific argumentation of the recommendations.

Clinical research questions

The recommendations address three clinical issues:

1. In patients with non-infectious, non-neoplastic anterior uveitis not associated with demyelinating disease, how efficacious and safe are the drug treatments?
2. In patients with non-anterior, non-infectious, non-neoplastic uveitis, not associated with demyelinating disease, how efficacious and safe are the drug treatments?
3. In patients with non-infectious uveitic macular oedema, how efficacious and safe are the drug treatments?

General preliminary considerations

The present recommendations are intended for rheumatologists and other specialists involved in treating patients with non-infectious, non-neoplastic, and non-associated demyelinating disease, as well as non-infectious uveitic macular oedema (UME). Management in these cases varies widely and depends on the clinical pattern, aetiology, severity, and prognostic factors of the condition. Diagnosis and treatment of uveitis and its associated pathology, when present, is generally undertaken by a multidisciplinary team, with several specialists involved in the process. Therapy of uveitis ranges from topical treatment and peri- or intraocular injections to systemic treatment with corticosteroids and conventional synthetic, targeted synthetic, and biological immunomodulatory drugs. The current existence of guidelines, expert recommendations, or specific treatment position papers for such heterogeneous pathologies is scarce and not widely consistent.[6–8] All of the above makes it necessary that the available evidence in this field be reviewed and synthesised and a recommendation document based on this evidence be drawn up in order to minimise variability and improve patient management and prognosis in cases of non-infectious, non-neoplastic uveitis, uveitis not associated with demyelinating disease, and non-infectious UMO.

Markers of severity

In this document, markers of disease severity include the presence of worsening visual function, bilateral disease, vitreous opacity, macular or optic nerve disease, retinal vascular inflammation, MS, exudative detachment or vision-threatening structural complications, recurrent or chronic disease, and, in some cases, associated systemic disease.[9]

Considerations regarding certain therapeutic groups

Elevated reactive aldehyde species (RASP) bolsters a series of proinflammatory reactions involved in different ocular inflammatory processes, including AU.[10] This group of drugs includes reproxalap, a novel RASP inhibitor for treating a range of eye conditions such as non-infectious AU, allergic conjunctivitis, and dry eye; nevertheless, there is no experience using it in Spain and there is no supporting evidence of quality. It has therefore not been considered for inclusion in these recommendations.

Results

A total of 19 recommendations have been formulated (Table 2), divided into three areas corresponding to three clinical questions. Additional information concerning the sections described below can be found in the Supplementary material (Appendix A Annex II).

Anterior uveitis

What is the efficacy and safety of drug treatments available for patients with non-infectious, non-neoplastic anterior uveitis not associated with demyelinating disease?

AU is defined as an intraocular inflammatory process in which the inflammatory reaction is predominantly located in the anterior chamber (AC) of the eye.[4] It is the most common anatomical subtype of uveitis in clinical practice. It has been estimated to account for 60% of all cases of uveitis in tertiary referral centres and up to 90% of all cases seen in primary centres.[11] Different studies have reported prevalence figures for AU ranging from 54.5 to 81.7 per 100,000 people.[12,13] By age group, UA is calculated to comprise 81% of all cases of uveitis in adults and 75% of all paediatric patients.[13]

Corticoids

Recommendation 1. Topical corticosteroids are recommended as the first treatment option in anterior uveitis, with prednisolone as first line treatment (strong recommendation in favour).

□ In patients with AU with concomitant ocular surface damage, the use of preservative-free and phosphate-free topical corticosteroids is recommended (GCP recommendation).

Table 2
SER recommendations concerning the treatment of uveitis.

	Strength of recommendation
Anterior Uveitis Recommendations	
Recommendation 1. In anterior uveitis, topical corticosteroids are recommended as the first treatment option, with prednisolone as the first line of treatment.	Strongly in favour
• In patients with AU in whom there is concomitant damage to the ocular surface, the use of preservative-free and phosphate-free topical corticosteroids could be considered.	Good clinical practice
* In our setting, topical prednisolone or topical dexamethasone is used interchangeably as first-line treatment in cases of UA.	
**While there are other corticosteroids, such as difluprednate and loteprednol, which have demonstrated efficacy and could be an alternative to prednisolone in certain cases, they are not available for use in our context.	
Recommendation 2. Although with the evidence available it is not possible to make a recommendation in favour or against generalised treatment with non-steroidal anti-inflammatory drugs for anterior uveitis, the drafting group suggests the topical use of these drugs as corticosteroid-sparing treatment and/ or to prevent recurrence in selected cases of chronic anterior uveitis, such as heterochromic Fuchs' uveitis, and as an adjunctive measure in the treatment of uveitic macular oedema.	Good clinical practice
Recommendation 3. In patients with recurrent anterior uveitis, especially if associated with spondyloarthritis, the use of sulfasalazine is suggested.	Weak in favour
Recommendation 4. The drafting group suggests that in patients with chronic or recurrent anterior uveitis (idiopathic, associated with spondyloarthritis or other systemic diseases) methotrexate should be used as an alternative to sulfasalazine.	Good clinical practice
Recommendation 5. In patients with refractory or recurrent anterior uveitis, adalimumab is recommended for patients who have failed conventional therapies.	Weak in favour
Recommendation 6. In patients with refractory or recurrent anterior uveitis, other TNFα-inhibiting monoclonal antibodies, such as certolizumab, golimumab, or infliximab could also be used.	Good clinical practice
Recommendation 7. The drafting group does not recommend the use of etanercept or anti-IL17A drugs as treatment for anterior uveitis.	Good clinical practice
Recommendations for Non-Anterior Uveitis	
Recommendation 8. In non-anterior, non-infectious, non-neoplastic uveitis not associated with demyelinating disease (NANIND), systemic corticosteroids are recommended to control acute inflammation, mainly when there is a risk of vision loss and in cases of bilateral involvement.	Strong in favour
• In cases of severe, bilateral NANIND uveitis, high-dose, intravenous corticosteriods is suggested.	Good clinical practice
• If systemic corticosteroids are started, the lowest effective dose possible to control the inflammation should be assessed and, once achieved, the dose should be gradually titrated down while closely monitoring both the course of the uveitis and possible adverse events from the drug.	Good clinical practice
• As prior therapy, or when initiating synthetic or biological immunomodulators if necessary, the use of systemic corticosteroids can be contemplated given their prompt effect.	Good clinical practice
• In acute episodes of NANIND uveitis, mainly unilateral, periocular injections should be considered, using the injection method the specialist feels most confident about, depending on his or her experience.	Good clinical practice
• In cases of severe NANIND uveitis or refractory to periocular injections, the use of sustained-release corticosteroid implants is recommended, either dexamethasone or fluocinolone acetonide, in particular in cases in which the disease is limited to the eye and affects only one side.	Strongly in favour
• In elderly patients or those with comorbid diseases that make the use of conventional synthetic or biological immunomodulatory drugs inadvisable or contraindicated, the use of corticosteroid sustained-release implants (dexamethasone and fluocinolone acetonide) should be considered.	Good clinical practice
• The use of intravitreal corticosteroid injections other than implants is not suggested, since more effective and safer alternatives exist.	Good clinical practice
Recommendation 9. In moderate to severe chronic course non-anterior, non-infectious, non-neoplastic, non-associated with demyelinating disease (NANIND) uveitis, the use of conventional synthetic immunomodulators is recommended for long-term control of inflammation and/ or as a corticosteroid-sparing agent.	Strongly in favour
• The recommended conventional synthetic immunomodulators are mycophenolate (mycophenolate mofetil and sodium), cyclosporine, methotrexate, tacrolimus, azathioprine, and cyclophosphamide; this last one for patients who are refractory to other treatments or if their indication depends on another type of extraocular involvement.	Weak in favour
• There are no data to support the use of one conventional synthetic immunomodulator over another, so the choice will depend on the patient's characteristics, the underlying systemic disease, tolerance to the drug, and the experience in the use and availability of the drug.	Good clinical practice
The combination of conventional synthetic immunomodulators may be considered in cases in which adequate control is not achieved with monotherapy, as well as their association with biological immunomodulators.	Good clinical practice
Recommendation 10. For the treatment of patients with severe or refractory NANIND uveitis, the use of TNFα-inhibiting monoclonal antibodies is recommended, especially adalimumab.	Strong in favour
• Infliximab, golimumab, certolizumab, tocilizumab, and rituximab may be alternatives to adalimumab if deemed necessary.	Good clinical practice
• Etanercept is not advised for the treatment of NANIND uveitis.	
Recommendation 11. The RDG do not recommend the use of secukinumab to treat NANIND uveitis.	Weak against
Recommendation 12. In view of the lack of evidence, intravitreal route of administration of biologics in patients with NANIND uveitis is not recommended.	Good clinical practice
Recommendations for Uveitic Macular Oedema	
Recommendation 13. In uveitic macular oedema, systemic corticosteroids are suggested and, if administered locally, the periocular route or dexamethasone or fluocinolone implants are recommended.	Strong in favour
• The use of intravitreal triamcinolone is not proposed, given that it is off-label and there are effective alternatives, such as dexamethasone and fluocinolone implants.	Weak against
• As for the methods of periocular injection, use the one that the specialist feels most confident about, depending on their experience, as no difference in efficacy and safety has been seen.	Good clinical practice
Recommendation 14. In subjects with mild uveitic macular oedema, acetazolamide is recommended as a therapeutic option for initial and short-term treatment.	Good clinical practice
Recommendation 15. There is insufficient evidence to recommend methotrexate, mycophenolate, or cyclosporin A, tacrolimus, or azathioprine for the treatment of uveitic macular oedema; however, they are suggested as therapeutic options in treatment-refractory cases or as a corticosteroid-sparing alternative.	Good clinical practice

Table 2 (*Continued*)

	Strength of recommendation
Recommendation 16. In patients with mild uveitic macular oedema, non-steroidal anti-inflammatory drugs are proposed as one possible adjuvant treatment option.	Good clinical practice
* While the evidence concerning the efficacy of topical indomethacin suggests that it may be of limited benefit to the resolution of uveitic macular oedema, it is not available for use in our setting.	Good clinical practice
Recommendation 17. Intravitreal anti-VEGF agents are suggested for uveitic macular oedema when there is a contraindication to corticosteroids.	Good clinical practice
Recommendation 18. In subjects with uveitic macular oedema, the use of TNFα-inhibiting monoclonal antibodies, and more specifically adalimumab, is advised on the basis of the positive results in clinical practice.	Good clinical practice

* In our setting, prednisolone or topical dexamethasone is used interchangeably as first-line treatment in cases of UA (GCP recommendation).

** Even though other corticosteroids, such as difluprednate and loteprednol, have proven to be efficacious and could represent an alternative to prednisolone in certain cases, they are not available for use in our context.

Relevant clinical considerations

□ The formulation of prednisolone acetate makes the use of measures to increase epithelial permeability such as the need for applicators or iontophoresis unnecessary in the treatment of AU.

First-line treatment of an acute outbreak of AU consists of topical administration of glucocorticoids and mydriatics, as advocated by numerous publications, in addition to clinical practice and expert recommendations published by a number of scientific societies.[7,14] Topical corticosteroids have been the standard of care for AU since 1950, despite the paucity of published evidence that attests to their efficacy. Their adverse effects (AEs) are widely known and include local irritation, hyperemia, and blurred vision, and, in the mid to long term, they may contribute to the development of ocular hypertension, cataracts, and favour the corneal collagen lysis, not to mention the growth of micro-organisms such as viruses, fungi, and amoebae. For all of the aforementioned reasons, and regardless of the fact that the evidence for corticosteroids versus placebo comes from old, low-quality RCTs,[15,16] the RDG recommends their use as the first treatment option (and prednisolone as first-line treatment). It is unlikely that new studies conducting such a comparison would be ethically acceptable. Furthermore, from the evidence identified and in view of its low quality, it is not possible to conclude the comparative efficacy of rimexolone versus prednisolone in patients with AU,[17–19] which has led the RDG to refrain from making any recommendation with regard to rimexolone. Other topical corticosteroids, such as difluprednate, which has demonstrated superior efficacy to prednisolone,[20] or loteprednol, with similar or slightly inferior efficacy, albeit with less of an effect on intraocular pressure (IOP),[21] could be used as an alternative to prednisolone; nevertheless, they are not available in Spain. The use of an applicator or techniques such as iontophoresis are measures intended to enhance intraocular penetration of the drug by increasing epithelial permeability;[22,23] however, the presentation of prednisolone in acetate form makes this measure unnecessary. The RDG, on the basis of its own experience, believes that there is unlikely to be a difference in terms of equality in the administration of different corticosteroids; moreover, this is a widely available and commonly used group of drugs and therefore presents no new problems of applicability.

A detailed description of the evidence evaluated and the process that has been followed from evidence to recommendations can be found in the Supplementary material (Appendix A Annex II). Translated with www.DeepL.com/Translator (free version)

Non-steroidal anti-inflammatory drugs

Recommendation 2. Despite the fact that with the evidence currently available it is not possible to make a recommendation for or against generalised treatment with non-steroidal anti-inflammatory drugs for anterior uveitis, the recommendations drafting group suggests that these drugs be used topically to spare corticosteroids and/ or to prevent flare-ups in specific cases of chronic anterior uveitis, such as Fuchs heterochromic uveitis, and as an adjunctive measure in the treatment of uveitic macular oedema. (GCP recommendation).

Nonsteroidal anti-inflammatory drugs (NSAIDs) have the potential of reducing the concomitant use of topical corticosteroids by decreasing the AEs associated with them. Nevertheless, the quality of the evidence identified in the systematic review (SR) is deemed to be low, consisting of old trials[16,24,25] and no RCTs that assessed recently introduced NSAIDs could be located; consequently, the RDG zx does not conclude that, on the basis of this evidence, neither a strong nor a weak recommendation can be made to indicate the use of topical NSAIDs to treat the manifestations of UA, and that further well-designed, prospective, controlled studies are necessary. That said, clinical experience of use, as well as some very low quality non-RCTs outside the reviewed body of evidence,[26–28] would point to the potential usefulness of the new topical NSAIDs as adjunctive therapy in the treatment of UA manifestations, such as associated MS, and therefore, a GCP recommendation is issued. Based on their own criteria, the RDG zx consider that situations of inequitable access to this group of treatments are unlikely to exist, and that NSAIDs are likely to be accepted by patients, regardless of the potential for more stinging compared to corticosteroids, given that it is a mild, short-lived AE. They do not see any major hurdles to the implementation of topical NSAIDs. In the case of bromfenac and nepafenac, which are not funded by the national health system (NHS), this prescription may not be accepted by some individuals on the basis of price, particularly if given over an intermediate period of time.

A detailed description of the evidence pondered and the process that has led from evidence to recommendations can be found in the Supplementary material (Appendix A Annex II).

Conventional synthetic immunomodulators

Recommendation 3. In patients with recurrent anterior uveitis, especially if associated with spondyloarthritis, sulfasalazine is suggested (weak recommendation in favour).

Recommendation 4. The recommendations drafting group suggests that methotrexate be used as an alternative to sulphasalazine in cases of chronic or recurrent anterior uveitis (idiopathic, associated with spondyloarthritis or other systemic diseases) (GCP recommendation).

On the basis of their clinical experience and low quality evidence identified in the SR that indicates a possible beneficial effect on visual acuity and the risk of relapse, the ERG zx has issued a weak recommendation in favour of the use of sulfasalazine in

patients with recurrent UA, with special emphasis on people with spondyloarthritis.[29] In addition, based on their own criteria, it considers that sulfasalazine is a low-cost drug and that it will probably be well accepted by patients, inasmuch as it is an oral treatment with few, tolerable AEs in their clinical experience. As a result, they consider that there would be more equitable access to this immunomodulator and that there are no issues associated with its use. If an alternative were to be necessary, the RDG zx suggests the use of methotrexate, based on their experience, and has therefore established a GCP recommendation for this purpose.

A detailed description of the evidence examined and the process leading from evidence to recommendations can be found in the Supplementary material (Appendix A Annex II).

Biological immunomodulators

Recommendation 5. In patients with refractory or recurrent anterior uveitis, the use of adalimumab is recommended for those in whom conventional therapies have failed (weak recommendation in favour).

Recommendation 6. Other monoclonal antibodies inhibiting TNFα, such as certolizumab, golimumab, or infliximab, may also be used in cases of refractory or recurrent anterior uveitis (GCP recommendation).

Recommendation 7. The recommendations drafting group zx does not recommend etanercept or anti-IL17A drugs as treatment for anterior uveitis (GCP recommendation).

On this group of drugs, the SR identified only one RCT on adalimumab, which reports a risk-benefit balance that has been considered probably favourable to the intervention and whose quality of evidence on the effects is low.[30] With this evidence in mind and based on their clinical experience, the RDG has issued a weak recommendation in favour of the use of adalimumab for UA. Based on low quality non-RCT studies identified by the RDG outside the reviewed body of evidence,[31–34] and its own judgement and experience, two GCP recommendations have been issued, one in favour of the use of other TNFα inhibitor monoclonal antibodies, such as certolizumab, golimumab or infliximab, in refractory or recurrent UA, and one against the use of etanercept and anti-IL17A drugs for UA in general. The RDG considers that biosimilars are available for adalimumab at an affordable annual cost per patient. Access to the drug is unlikely to be a problem, even though it has no indication for idiopathic UA not associated with systemic disease, so off-label use must be requested. Administration may require access to a uveitis unit, which could affect equity for patients who do not have access to a uveitis unit or qualified specialists in their health centre. The RDG does not consider that there are overall barriers to the implementation of adalimumab therapy for the treatment of UA.

A detailed description of the evidence considered and the process that has led from evidence to recommendations can be found in the Supplementary material (Appendix A Annex II).

Non-anterior uveitis

What are the efficacy and safety of pharmacological treatments in those individuals with non-anterior, non-infectious, non-neoplastic uveitis not accompanied by demyelinating disease?

Non-anterior, non-infectious, non-neoplastic, non-associated with demyelinating disease (NANIND) uveitis are likely to be of autoimmune origin and pose a significant threat to sight.[35] They include IU, PU, and panuveitis. Prognosis is more serious in those that involve the posterior pole and can cause significant visual complications and even blindness, with the obvious loss of patients' quality of life, in addition to the significant costs that this entails.[36–38] They may be limited to the eye or occur as manifestations of underlying systemic diseases.[39] Steroid treatment tends to be the initial approach in these patients[40,41]; however, other immunosuppressive treatments are often required to control the disease.[42]

Corticosteroids

Recommendation 8. In non-anterior, non-infectious, non-neoplastic uveitis not associated with demyelinating disease (NANIND), systemic corticosteroids are recommended to control acute inflammation, notably when there is a risk of vision loss and in cases of bilateral involvement (strong recommendation in favour).

- ☐ The use of high-dose intravenous corticosteroids should be explored for severe, bilateral NANIND uveitis (GCP recommendation).
- ☐ If systemic corticosteroids are initiated, titration to the lowest effective dose possible to control inflammation and, once achieved, a gradual tapering of the dose with close monitoring of both uveitis activity and possible adverse drug events is suggested (GCP recommendation).
- ☐ Systemic corticosteroids can be evaluated as a preliminary therapy, or when commencing synthetic or biological immunomodulators if necessary, thanks to their rapid effect (GCP recommendation).
- ☐ Periocular injections should be contemplated, particularly in acute, unilateral episodes of NANIND uveitis, using the injection method the specialist feels most comfortable with, depending on their experience (GCP recommendation).
- ☐ In severe NANIND uveitis or uveitis refractory to periocular injections, the use of sustained-release corticosteroid implants is recommended, whether dexamethasone or fluocinolone acetonide, most notably in those cases in which the disease is limited to the eye and is unilateral (strong recommendation in favour).
- ☐ In elderly patients or individuals who have other concomitant pathologies that make the use of conventional synthetic or biological immunomodulatory drugs inadvisable or contraindicated, sustained-release corticosteroid implants (dexamethasone and fluocinolone acetonide) should be weighed up (GCP recommendation).
- ☐ Use of intravitreal corticosteroid injections other than implants is not advised, as safer and more effective alternatives are available (GCP recommendation).

Relevant clinical considerations

General considerations

- ☐ In the choice of corticosteroid sustained-release implant will depend on the type of involvement and patient characteristics, given the varying duration of effect, which is up to six months in the case of the dexamethasone implant and up to three years in the case of the FA implant.
- ☐ Once the inflammation has been brought under control, the dose of oral corticosteroids should be gradually tapered, with the aim of discontinuing or reaching the lowest effective dose as soon as possible, for which treatment with a background immunosuppressive drug may be considered.

Implementation considerations

- ☐ Local therapies require consultation with specialised ophthalmology for administration.

Monitoring and evaluation

□ During treatment with local corticosteroids, IOP should be assessed, and, if systemic corticosteroids are being used, HTN and glycaemia should also be monitored, adapting treatment in patients who already present these conditions or initiating it if necessary. If prolonged use of corticoids is anticipated, especially if they are to be prescribed at medium-high doses, local osteoporosis guidelines should be reviewed to assess bone protection with antiresorptive treatment.[43]

Despite the scant evidence identified and its limited quality,[44] a strong recommendation has been issued in favour of the use of systemic corticosteroids in NANIND, either orally or intravenously. This paucity of evidence is likely to be derived from the absence of trials examining a therapy that is already widely used in routine clinical practice,[45] and from the consensus that systemic corticosteroids, whether administered orally or intravenously, are the mainstay of acute treatment of moderate-severe uveitis and may be the only treatment necessary in certain cases. Furthermore, based on its own criteria, the RDG zx has issued three GCP recommendations that complement the previous one as regards severe and bilateral uveitis treated with systemic corticosteroids, the minimum effective dose, as well as the administration of corticosteroids prior to disease-modifying drugs. A strong recommendation has also been made in favour of the use of sustained-release corticosteroid implants for the treatment of NANIND uveitis, substantiated by evidence from three RCTs comparing dexamethasone implant at doses of 0.35 and 0.70 mg and versus placebo[46] and fluocinolone acetonide (FA) implant against placebo or regular care,[47,48] the results of which demonstrate a balance in favour of their use, and the criteria of the RDG zx, based on their experience in clinical practice (two additional RCTs examined the implantation of FA at higher doses than those commercially available, which could pose safety problems for patients, and have therefore not been included).[49,50] They are particularly indicated in cases in which the disease is limited to the eye owing to their local effect, with unilateral involvement and preferably in pseudophakic patients given the possibility of developing cataracts, albeit the latter is based on the panel's experience and could not be extracted from the evidence reviewed. Lastly, two GCP recommendations have also been issued, one in favour of the use of corticosteroid sustained-release implants in elderly patients or those with conditions contraindicating immunomodulators, and the other against the use of intravitreal free corticosteroid injections, in view of the existence of alternatives that are probably more effective and safer. In addition, a number of relevant clinical considerations have been issued to complement the recommendations. The RDG, based on its own discretion, holds the view that the intervention may increase equality given the ready accessibility of systemic corticosteroids across all healthcare settings. Access to local therapies will depend more on access to specialised ophthalmologists, typically associated with uveitis units, the availability of which is neither uniform nor universal. These units typically have operating theatres and devices for the placement of intraocular implants. Likewise, they regard the treatment of NANIND uveitis with systemic corticosteroids as likely to be widely accepted by patients and prescribers given the potential severity of the disorder to be treated. As for intraocular implants, patients' possible reluctance to eye surgery can be countered by a thorough explanation of the procedure and that the effect can be expected to last for a long period of time. Treatment of NANIND uveitis with systemic and local corticosteroids is feasible, as it is now routine clinical practice, albeit the need for dedicated facilities and intravitreal drug delivery equipment may limit its feasibility.

An in-depth description of the evidence considered and the process that has taken the evidence to recommendations can be found in the Supplemental material (Appendix A Annex II).

Conventional synthetic immunomodulators

Recommendation 9. In moderate or severe chronic non-anterior, non-infectious, non-neoplastic, not associated with demyelinating disease (NANIND) uveitis, the use of conventional synthetic immunomodulators is recommended for long-term control of inflammation and/ or as corticosteroid-sparing agents (strong recommendation in favour).

□ The conventional synthetic immunomodulators recommended are mycophenolate (mycophenolate mofetil and sodium), cyclosporine, methotrexate, tacrolimus, azathioprine, and cyclophosphamide, in this last case for individuals refractory to other treatments or if their indication depends on another type of extraocular condition (weak recommendation in favour).
□ There are no data to support the use of one conventional synthetic immunomodulator over another; the choice, therefore, will depend on each subject's characteristics, underlying systemic disease, tolerance to the drug, and on the experience with and availability of the drug (GCP recommendation).
□ The combination of conventional synthetic immunomodulators might be explored in cases in which adequate control is not achieved with monotherapy, as well as in association with biological immunomodulators (GCP recommendation).

Relevant clinical considerations

General considerations

□ Experience in other conditions has revealed that when using methotrexate at doses starting at 15 mg per week, subcutaneous administration is favourable to the oral route, given its greater bioavailability.

The RDG has issued a strong recommendation in favour of the use of conventional synthetic immunomodulators for the treatment of moderate-severe NANIND uveitis requiring long-term control or corticosteroid-sparing therapy, in particular in those cases involving the posterior pole. Based on moderate- or low-quality evidence and/ or its own experience, the RDG has put forth a weak recommendation regarding which conventional synthetic immunomodulators are recommended for the treatment of NANIND uveitis, i.e., mycophenolates (mycophenolate mofetil and sodium),[51–53] cyclosporine,[54–56] methotrexate,[52,53] tacrolimus,[55] and azathioprine. There is little evidence comparing the efficacy of different conventional synthetic immunomodulators in the study population, and given their low quality and the scarce differences detected, the panel considers that there is no data to endorse the use of one drug in this class over another; the choice, therefore, will depend on the specific patient characteristics, experience, and availability of the drug, as well as on the underlying systemic disease, if any. On the other hand, the combination of immunomodulators has yet to be adequately studied and there are no data to substantiate specific combinations or the use of one combination over another. Nonetheless, given that this is common clinical practice in cases not controlled with monotherapy, just as in the association of conventional synthetic immunomodulators with biologic or targeted synthetic immunomodulators, the panel recommends that this therapeutic option be assessed, bearing in mind the underlying disease, the patient's characteristics and the safety profile of the drugs to be combined. The panel suggests that the use of cyclophosphamide for the treatment of NANIND uveitis be con-

templated in cases of severe uveitis that significantly compromise vision, principally in patients with severe uveitis associated with systemic diseases that require this treatment. Given its safety profile and the low quality of the evidence identified,[57] it is suggested mainly in cases refractory to other therapies or if its indication depends on another type of extraocular involvement. Furthermore, while evidence has been identified that reports a possible beneficial effect of locally administered sirolimus,[58–60] it is not possible to recommend its use, given that it is not currently marketed in our context. There are no data to recommend for or against other conventional synthetic immunomodulators such as salazopyrin, chlorambucil, or leflunomide. Finally, a clinical consideration on how methotrexate should be administered depending on the dose has been developed according to the experience and discretion of the RDG. This intervention could increase equality in the opinion of the EG, and while it is true that access to uveitis units is neither uniform nor universal, it is true that access to conventional synthetic immunomodulators is. On the other hand, it believes that NANIND uveitis treatment with these therapies is likely to be widely accepted by both patients and prescribers, as they are drugs with which there is ample experience, that have an adequate safety profile, and that are convenient for patients to use. In addition, the intervention cost is low. The RDG believes that the use of these treatments in NANIND uveitis is feasible, given that it is standard clinical practice; consequently, they do not see any particular barriers to their implementation.

An in-depth description of the evidence considered and the process that has taken the evidence to recommendations can be found in the Supplemental material (Appendix A Annex II).

Biological immunomodulators and JAK inhibitors

Recommendation 10. TNF-α-inhibiting monoclonal antibodies, particularly adalimumab, are recommended for the treatment of severe or treatment-resistant NANIND uveitis (strong recommendation in favour).

- ☐ Infliximab, golimumab, certolizumab, tocilizumab, and rituximab can serve as alternatives to adalimumab, if deemed necessary (GCP recommendation).
- ☐ Etanercept is disadvised for NANIND uveitis management (GCP recommendation).

Recommendation 11. The RDG does not recommend secukinumab to treat NANIND uveitis (weak recommendation against).

Recommendation 12. In light of the lack of evidence regarding the intravitreal delivery route is not recommended in subjects with NANIND uveitis (GCP recommendation).

Relevant clinical considerations

General considerations

- ☐ Rituximab is advised as an alternative treatment in special situations in which other immunomodulating-agents cannot be used or are contraindicated.

The RDG has found that the evidence identified regarding the use of TNF-inhibiting monoclonal antibodies, and in particular adalimumab, enables a strong recommendation to be made in favour, as it is the anti-TNF drug for which the evidence is most robust,[61,62] in addition to the fact that it is available and indicated for use in patients with NANIND uveitis; the RDG is of the opinion that other drugs in this class, such as infliximab, golimumab, certolizumab, tocilizumab, and rituximab, may also have a positive balance; however, the evidence for these drugs displays serious limitations, so it has issued a GCP recommendation in favour of their use. A weak recommendation against the use of secukinumab has been given based on several studies that were terminated prematurely because it demonstrated a lack of desired effects in the study population.[63–65] Furthermore, no compelling evidence was found for intravitreal biologic drugs in patients with NANIND uveitis; hence, the RDG advises against their use until new evidence evaluates this route of administration (GCP). No evidence was found on JAK inhibitors that met the inclusion criteria; thus, it is not possible to make a recommendation with respect to their use in NANIND uveitis, although new efficacy and safety data may support their future use in this patient population. Finally, a relevant clinical consideration is made regarding the use of rituximab as a therapeutic alternative in special situations. The RDG, on the basis of its own judgement, feels that the intervention could affect equality given the need for access to a uveitis unit. While it is true that access to these units is not uniform or universal, access to these treatments is. Likewise, treatment of NANIND uveitis with biological immunomodulators is likely to be widely accepted by patients and prescribers alike, as there is experience with these drugs in other conditions, with an acceptable safety profile, and are typically used in patients with potentially severe involvement who require rapid control of inflammation. The RDG sees the implementation of NINAND uveitis treatment as feasible, inasmuch as it is already conducted in routine clinical practice.

An in-depth description of the evidence considered and the process that has taken the evidence to recommendations can be found in the Supplemental material (Appendix A Annex II).

Uveitic macular oedema

In individuals with uveitic macular oedema, how efficacious and how safe are drug treatments?

MO is an inflammatory process that causes fluid to accumulate in the area of the retina that is responsible for central vision, the macula.[66] It is one of the leading causes of vision loss in uveitis. According to several studies, it accounts for 41% of vision loss and 29% of blindness in uveitis.[67,68] UMO can appear in any type of uveitis, although it is more common in PU and IU than in anterior uveitis. Since the appearance and development of optical coherence tomography (OCT), with which macular oedema is quantified, its treatment has changed radically and is currently a priority to prevent vision loss in uveitis.

Corticosteroids

Recommendation 13. Systemic corticosteroids are advised for uveitic macular oedema and, if administered locally, periocular corticosteroids or dexamethasone or fluocinolone implants (strong recommendation in favour).

- ☐ The use of intravitreal triamcinolone is not advocated, as it is not indicated and there are effective alternatives, such as dexamethasone and fluocinolone implants (weak recommendation against).
- ☐ As for the methods of periocular injection, the method the specialist feels most confident in, depending on his or her own expertise, should be used, as no difference in efficacy and safety has been observed (GCP recommendation).

Relevant clinical considerations

Subgroup considerations

- ☐ In patients with glaucoma in particular, special precautions with the adverse effects of intravitreal corticosteroids must be (cataracts and increased intraocular pressure).

□ In young phakic patients, the risk of cataracts with intravitreal administration of triamcinolone, dexamethasone, and fluocinolone.

The SR of the bibliography identified a total of two RCTs that evaluated systemic corticosteriods against control and interferon alpha[67] and against oral cyclosporine,[54] and sever RCTs that assessed local corticosteriods: intravitreal triamcinolone,[69–73] supracoridal,[74] and periocular injection.[70] Moreover, an RCT that compared three methods of injection of triamcinolone (posterior subtenon cannula, the Smith and Nozik method, and orbital floor injection).[75] In addition, three RCTs that assessed corticosteroid implants were found: FA implant compared to systemic corticosteroids,[49,76] and simulated injection,[77,78] and intravitreal dexamethasone implant versus periocular injection of triamcinolone acetonide and to intravitreal triamcinolone acetonide.[70] As for the MUST study, the RDG indicates that the 0.59-mg dose used in the implant is not currently marketed in Europe; given that this high dose can give rise to relevant ocular AE, such as IOP elevation and the appearance of glaucoma, this study has not been included in the analysis. Taking into account the quality of this evidence and the balance of desirable and undesirable effects, which has been deemed favourable to these interventions (as well as numerous publications outside the body of evidence reviewed), that its used has been endorsed by the experience of the RDG and by the existence of a general consensus with respect to the use of corticosteroids in uveitis as the basis of treatment, a strong recommendation has been made in favour of the use of systemic corticosteroids and dexamethasone and FA implants in individuals with UMO. A weak recommendation has also been issued against the use of intravitreal triamcinolone, due to the existence of alternatives that reveal a better risk-benefit balance in the management of UMO,[70] and other considerations regarding its lack of authorized indication for this condition. The RDG considers that the professional should use the method of drug injection they trust most; as a result, it has issued a GCP recommendation based on low quality evidence and their own criterion. Finally, a series of relevant clinical considerations with patient subgroups based on the RDG's consensus and experience. In general, the RDG deems that it is unlikely to generate inequalities in access to corticosteroid treatments, owing to the fact that both systemic and implant treatment are indicated and the use of other intraocular off-label corticosteriods will not be routinely contemplated (but can be used). Similarly, it does not appear that there will be barriers to implementation in the different routes of corticosteroid administration beyond those associated with the facilities needed to administer injections and implants. The 0.59 mg implant dose of FA is not acceptable for use due to its safety profile and is not commercially available. On the other hand, while the use of intravitreal triamcinolone may be no less acceptable or feasible, it is not recommended given that there are other effective drugs that are indicated for MO on the technical data sheet.

An in-depth description of the evidence considered and the process that has taken the evidence to recommendations can be found in the Supplemental material (Appendix A Annex II).

Carbonic anhydrase inhibitors

Recommendation 14. In patients with mild uveitic macular oedema, the use of acetazolamide is recommended as a therapeutic option for initial and short-term treatment (GCP recommendation).

The RDG has issued a good clinical practice recommendation for the use of acetazolamide in mild UMO based on their experience and the low quality of the evidence about its possible protection against VA impairment.[79–81] Based on their own estimation, the RDG consider that there are unlikely to be concerns about the equality of the intervention, as the drug is widely available to any specialist and to patients. It also does not consider that there are likely to be acceptability issues with acetazolamide treatment, always bearing in mind that the patient must be evaluated comprehensively. Acetazolamide is available in Spain and used in many centres to treat UMO in clinical practice, so no barriers to its implementation are to be expected. Patients treated with acetazolamide should undergo a general work-up and associated pathologies (renal, ion) and the use of concomitant drugs should be considered. If use is prolonged, kidney function and ion parameters should be monitored by laboratory testing.

An in-depth description of the evidence considered and the process that has taken the evidence to recommendations can be found in the Supplemental material (Appendix A Annex II).

Conventional synthetic immunomodulators

Recommendation 15. There is insufficient evidence to recommend methotrexate, mycophenolate, cyclosporin A, tacrolimus, or azathioprine for the treatment of uveitic macular oedema; however, they are indicated as a therapeutic option in treatment-resistant cases or as corticosteroid-sparing agents (GCP recommendation).

The evidence identified for methotrexate, mycophenolate, and cyclosporin A is scarce and of low or very low quality;[52,82,83] nevertheless, based on their own criteria and experience, the RDG resolved to issue a GCP recommendation in favour of their use. Likewise, no evidence was found regarding the use of tacrolimus and azathioprine in cases of UMO; however, and on the basis of the RDG's judgement and expertise, these treatments are included in the recommendation in favour. Two RCTs of the drug sirolimus reported together in the same article58 were identified; nonetheless, inasmuch as it is not available in our setting, it was not judged relevant to issue a recommendation on its use. The RDG consider that some of the drugs reviewed, such as methotrexate, mycophenolate, cyclosporin A, tacrolimus, and azathioprine, which are used in routine clinical practice in cases in which oedema is accompanied by other inflammatory signs, is acceptable and feasible, despite the fact that some of them are not approved in the technical data sheet. Similarly, they also point out that the use of intravitreal sirolimus and cyclosporin G is not feasible at present, given that these medications are not commercially available. If systemic drugs such as methotrexate, mycophenolate, or cyclosporine are used, the RDG deem that an overall examination of the patient should be performed, taking into account concomitant conditions and pharmaceuticals, along with regular monitoring that includes blood tests (complete blood count, complete biochemistry) and urine tests to monitor side effects.

An in-depth description of the evidence considered and the process that has taken the evidence to recommendations can be found in the Supplemental material (Appendix A Annex II).

Non-steroidal anti-inflammatory drugs

Recommendation 16. Non-steroidal anti-inflammatory drugs are suggested as one option for coadjuvant therapy in patients with mild uveitic macular oedema (GCP recommendation).

*While the evidence on the efficacy of topical indomethacin points toward some limited efficacy in resolving uveitic macular oedema, it is not available for use in our setting.

The SR of the literature identified very limited evidence on these drugs in subjects with UMO. Only one RCT evaluated topical indomethacin versus placebo,[84] which is not available in Spain, but has issued a GCP recommendation regarding the use of NSAIDs in mild UMO based on its clinical experience in improving mild oedema. In addition, a study of intravitreal diclofenac was located,

the quality of evidence for which was judged to be very low, and the RDG did not consider issuing a recommendation given that it is not used in routine clinical practice. The RDG, based on their own judgement, consider interventions with NSAIDs to be very accessible. There are unlikely to be acceptability issues with a topical treatment, but some clinicians and patients may be against an intravitreal injection, due to the higher risks involved and the need for a certain degree of experience to administer it. The NSAIDs reviewed in the localised literature are not available/ indicated in Spain. The NSAIDs used in routine clinical practice (nepafenac, bromfenac), although relatively low in cost, may present problems, since patients have to pay for them in full, increasing inequity in patients with lower economic capacity.

An in-depth description of the evidence considered and the process that has taken the evidence to recommendations can be found in the Supplemental material (Appendix A Annex II).

Biological immunomodulating drugs

Recommendation 17. Intravitreal anti-VEGF drugs are advised for uveitic macular oedema when there is a contraindication to corticosteroids (GCP recommendation).

Recommendation 18. In patients with uveitic macular oedema, the use of TNFα-inhibiting monoclonal antibodies, and more specifically adalimumab, is suggested on the basis of good results in clinical practice (GCP recommendation).

Recommendation 19. The recommendations drafting group considers that the poor quality of the evidence available does not justify a recommendation for rituximab, sarilumab, or cytotoxic drugs in individuals with uveitic macular oedema (GCP recommendation).

If the uveitic macular oedema is refractary:

□ Tocilizumab is suggested, or interferon alfa may also be considered depending on the person's experience with the drug, given the increased occurrence of adverse events and the difficulty in accessing the drug (GCP recommendation).

The evidence identified concerning this class of drugs exhibits low certainty. Based on two studies that have assessed intravitreal injection of bevacizumab versus the same route of administration of triamcinolone,[72,73] a GCP recommendation has been issued in favour of the use of anti-VEGF agents to treat UMO, in particular when there is a contraindication to corticosteroids, or those forms of UMO in the context of uveitis whose activity is controlled. Taking into account the poor quality of the evidence and the risk-benefit balance of the comparisons between interventions identified in the SR, the RDG concludes that it is not possible to recommend either in favour or against the use of sarilumab,[85] tocilizumab,[86] rituximab, and combined cytotoxic therapy;[87] but based on their own judgement, they suggest the use of tocilizumab for refractory UMO. The same is true for subcutaneous interferon alfa, which requires experience in its use and, in some cases, is also difficult to access. Moreover, based on the RDG's judgement and expertise, they have issued a GCP recommendation in favour of the use of adalimumab. Biologics may not be accessible to all specialists, depending on the hospital, and may reduce equality, inasmuch as they are not approved for UMO as per the technical specifications, in addition to being expensive. However, there would be no inequality for the patient if the treatment cost is covered by the hospital pharmacy. The RDG consider that there are likely to be no acceptability concerns regarding the treatments. As for the feasibility of implementation, the RDG believe that there may be some difficulty, given that these treatments are not approved on the technical specifications for UMO and, as such, authorisation from hospital management is required for their use. In the particular case of interferon alpha, access is highly restricted to certain hospitals and certain specialists, and could therefore present serious difficulties in its use.

An in-depth description of the evidence considered and the process that has taken the evidence to recommendations can be found in the Supplemental material (Appendix A Annex II).

Discussion

Uveitis and uveitic macular oedema comprise a heterogeneous group of pathologies in which there is still great therapeutic variability in clinical practice. This is partly due both to the condition itself and to the paucity of scientific evidence on the subject and, therefore, to the lack of consensus documents with respect to treatment. This document attempts to unify the therapeutic management of non-infectious, non-neoplastic AU non-associated with demyelinating disease, as well as non-infectious uveitic macular oedema. Management in these cases is widely divergent and depends in turn on the clinical pattern, aetiology, severity, and prognostic factors of uveitis. The creation of multidisciplinary units for the joint management of these conditions, shared continuing education across specialties, and the publication of real-world data on the management of these conditions has narrowed the gap in standardisation of treatment in recent years. The limitations of this recommendations document include the scant quality of the published scientific evidence, as well as the heterogeneity of the inflammatory ocular pathology included. Following the SR of the available scientific evidence and the clinical expertise provided in the management of these patients by a multidisciplinary group of rheumatology and ophthalmology specialists, a series of treatment recommendations are established, all aimed at enhancing knowledge of the issue, minimising unjustified variability, and facilitating early and coordinated action by all possible specialists involved in the subject. Three clinical research questions were posed for the purpose of this document. A qualitative synthesis of the scientific evidence and consensus techniques were used to reach agreement among experts based on the scientific evidence and their clinical experience. The phases of the process include: creation of the multidisciplinary working group, identification of key areas, bibliographic search, analysis, and synthesis of the scientific evidence. The evaluation of the quality of the evidence and the grading of the strength of the recommendations was conducted following the methodology of the international working group *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE).[5]

This document contains a total of 19 treatment recommendations formulated and subdivided into different treatment groups and areas: UA, non-anterior, and uveitic macular oedema. Given the aforementioned limitations of this document, it is important to bear in mind the RDG's criteria and expertise in managing these conditions and their treatment for the formulation and grading of the recommendations. Due to the heterogeneous nature of the pathology in question, the RDG advocate individualised therapy, taking into account the type of ocular inflammation, the association with systemic disease and/ or the need for treatment of such disease, the presence of markers of severity previously described in this document, prognostic factors, and comorbidities that might limit therapeutic options and lines of treatment.

The first official SER recommendations document for the treatment of uveitis and uveitic macular oedema of non-infectious aetiology and not associated with demyelinating disease are presented. They can be directly applied to the Spanish healthcare system as a tool for assistance and therapeutic homogenisation in this heterogeneous group of inflammatory eye diseases associated or not with systemic disease.

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Appendix A. Supplementary data

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