Non-infectious non-anterior uveitis: Pharmacological management

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Abstract

Non-infectious non-anterior uveitis (NINA-U) includes a heterogeneous group of sight-threatening conditions. NINA-U can be incapacitating and associated with a profound impact in the quality of life and well-being of the patients. To prevent this catastrophic course, a quick, complete, and maintained suppression of the inflammatory manifestations is required. To achieve this objective, we count with several drugs, including corticosteroids and immunomodulatory drugs (IMDs). Corticosteroids are the cornerstone of NINA-U treatment due to their rapid effect in suppressing inflammation. They can be administered using different routes (periocular, intravitreal, or systemic) depending on the characteristics and location of the disease. Local corticosteroids are able to achieve a high bioavailability within the eye, with minimal systemic dissemination. They are associated with a higher risk of local adverse events (mostly cataracts and elevation of the intraocular pressure). Systemic corticosteroids are usually administered orally, although under certain circumstances, they can be administered intravenously. When corticosteroids alone are not able to control the disease; or when they are associated with serious adverse events; or when the disease is severe, IMDs can be combined with systemic and/or local corticosteroids. Several are used in clinical practice (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, tacrolimus, cyclophosphamide, and biological agents), based on evidence on their efficacy/effectiveness and safety generated in randomized controlled trials and observational studies, respectively. These drugs are usually used in monotherapy, although several studies have shown that a varying percentage of patients will require changing the IMD or adding a second drug in combination to successfully control the disease.

Key words: Uveitis. Corticosteroids. Immunomodulatory drugs. Clinical management.

Epidemiology and burden of the uveitis

Uveitis comprises a heterogeneous group of rare diseases characterized by inflammation of the middle layer of the eye wall and adjacent tissues, such as the vitreous and the retina. These conditions can be classified according to the primary anatomical location of the inflammation (anterior, intermediate, posterior, or panuveitis)¹, which will determine the prognosis and recommended therapy for the disease. In addition, uveitis can also be classified based on their etiology: infectious, the most frequent in the developing world, and non-infectious uveitis (NIU), comprising most of the causes in the EU and the US².

Regarding the etiology of NIU, in recent years, there have been substantial advances in the understanding of their pathogenic mechanisms, pointing to the interplay between a complex genetic background³ and environmental factors, triggering a deregulated innate and adaptive immune response^{4,5}, able to overcome the ocular immune privilege.

Uveitis are potentially sight-threatening diseases. The World Health Organization estimated that, worldwide, uveitis represented up to 10% of causes of blindness (almost 4 million people)⁶. In the EU and US, and after diabetic retinopathy, uveitis represents the second major treatable cause of blindness in those 20-65 years of age⁷, accounting for up to 10% of cases of blind

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registrations⁸. In addition, more than 50% of the subjects affected with these conditions will develop complications related to the uveitis, and more than 30% will suffer visual impairment⁹. Furthermore, uveitis is associated with a negative impact in the subject's quality of life¹⁰. Because of the profound impact on patient's health and their higher prevalence in young- to middle-aged adults¹¹, these conditions are associated with an important economic, social, and personal burden, resulting in work disability, reduced productivity, and work loss¹².

Among NIU, those affecting more posterior segments of the eye (intermediate, posterior, or panuveitis) are associated with worse prognosis, greater risk of vision loss, ocular complications, and a greater impact in the subject's quality of life¹³, as they can affect structures that are essential for vision, such as the macula or the optic nerve. Because of this greater deleterious impact of non-infectious non-anterior uveitis (NINA-U), in this article, we will discuss the different medical treatments and strategies used to manage these conditions.

Management of the NINA-U

As pointed out, considering the potential negative impact of NINA-U on patients' health and well-being, their correct management is essential for preserving visual function and avoiding ocular and extraocular morbidity¹⁴. Patients are usually treated based on the presence and location of signs of inflammatory activity using a stepwise protocol to fully control the inflammation as soon as possible. Furthermore, it is fundamental to realize that most NINA-U are relapsing or chronic diseases that will require long-term treatment (sometimes for many years) to maintain a complete abrogation of the ocular inflammatory manifestations, since the presence of even low levels of residual inflammation or the occurrence of inflammatory relapses have been associated with worse visual prognosis¹⁵⁻¹⁷. At the same time, during the often prolonged treatment, local and systemic safety issues have to be considered, and, depending on the drugs prescribed, different measures and periodic assessments have to be carried out to prevent and early detect adverse events¹⁸.

Corticosteroids

These medications remain the gold standard agents in the management of NINA-U due to their immediate efficacy. Location and severity of the inflammation will influence their route of administration¹⁹⁻²¹. Although

corticosteroids are able to carry out a rapid and complete suppression of the ocular inflammatory process, they are also associated with local and systemic adverse events, most of them related to a prolonged treatment with high dosages²².

To increase the bioavailability of corticosteroids at the inflamed tissue and decrease the systemic exposure (and therefore reducing the risk of systemic adverse events), alternative routes of drug delivery were developed, including periocular and intravitreal.

Periocular

Experimental studies have clearly demonstrated that posterior periocular corticosteroid injections produce high concentrations of active agent within the posterior segment of the eye, higher than systemic corticosteroids, particularly when the eye is inflamed^{23,24}. This therapeutic option is useful in the management of posterior segment inflammation in NINA-U: several studies have shown an improvement in visual acuity and a reduction in inflammatory manifestations, including macular edema, when corticosteroids are administered locally^{25,26}. They are particularly applicable to patients with active disease in one eye only; when there are specific contraindications to systemic corticosteroid therapy or combined with systemic therapy in case of persistent or refractory macular edema²⁷. However, a major issue to long-term management of NINA-U with periocular corticosteroid injections is the limited duration of action (mean duration being 9 weeks²³) that would require repeated injections, increasing the risk of local adverse events, typically elevation of intraocular pressure/glaucoma and cataract onset and progression²⁶.

Intravitreal

This route of administration is able to achieve the highest intraocular corticosteroids bioavailability, as it bypasses the blood–retinal barrier and inoculates the drug directly in the eye. However, although this route has been successful in reducing macular edema and improving visual acuity, its duration of action is typically short term and associated with higher risk of corticosteroids related adverse events (even compared with periocular corticosteroids), such as ocular hypertension and cataracts. In addition, this route is associated with injection-related adverse events, including retinal detachment, vitreous and intraocular hemorrhage, and endophthalmitis²⁸.

To overcome the need for repeated and frequent injections to abrogate the inflammatory process, sustained release intravitreal corticosteroid implants have been developed, able to administer corticosteroids locally over an extended period overtime (months/years). These implants are available in short-acting (dexamethasone implants) and long-acting forms (fluocinolone acetonide implants).

Dexamethasone implants are able to release corticosteroids for up to 6 months, and they have shown a reduction in inflammation and increase in visual acuity, when compared with sham injections in a randomized controlled trial²⁹. It also showed improved effectivity when compared with pericocular corticosteroids injections, measured as reduction of uveitis macular edema and increase of visual acuity³⁰. However, no differences were observed when compared with intravitreal corticosteroids injections.

Regarding fluocinolone acetonide implants, they are able to release corticosteroids for up to 3 years with minimal systemic absorption. They have shown efficacy in reducing recurrences and improving visual acuity, when compared with the previous uveitis history of the patient³¹. In addition, when compared with systemic corticosteroid therapy combined with immunomodulatory drugs (IMDs), they showed a similar control of inflammation³², although in the long term (up to 7 years follow-up), systemic therapy achieved better outcomes. The major caveat of this treatment are the local adverse events: almost all treated eyes required cataract surgery, three-fourths required intraocular pressure lowering medications, and almost half required glaucoma surgery³¹.

Recently, a fluocinolone acetonide insert has been developed, releasing corticosteroids at a lower dosage and for up to 3 years. It has shown efficacy in reducing the recurrence when compared with sham injections³³, with lower risk of intraocular pressured hypertension and similar risk of cataract development and progression. No comparison with the fluocinolone acetonide implants has been performed so far.

Systemic corticosteroids

Systemic corticosteroids are used to treat severe inflammatory manifestations in the posterior parts of the eye. Initial recommended dosage is 1 mg/kg/day of oral prednisone or equivalent (up to 60 mg/day). However, lower initial dosages could be used depending on the intensity and characteristics of the inflammatory manifestations³⁴. After 2-4 weeks, the initial dosage

is progressively tapered with the objective of maintaining a complete control of the inflammatory process at a prednisone dose of ≤ 7.5 mg/day, a dosage that is associated with low risk of systemic and local adverse events³⁵.

In case of vision-threatening diseases, with severe ocular inflammation, high dosages of intravenous corticosteroids can be administered in pulses (the traditional dose suggested is 1000 mg of methylprednisolone per day for 3 consecutive days³⁶). Several observational studies have shown that this strategy results in substantial improvement for most subjects treated and it was associated with low risk of ocular and systemic adverse events^{37,38}. However, it is important to point out that in a comparative retrospective study in subjects with acute Vogt-Koyanagi-Harada disease, the route of administration (oral vs. intravenous) was not significantly associated with visual outcomes or the development of sight-threatening ocular complications³⁹.

IMDs

In addition to corticosteroids, IMDs may be required to control the inflammatory manifestations of the NINA-U or to prevent the onset of ocular structural complications. The most frequent causes of IMD indication are related to the arise of issues with the local and/or systemic corticosteroid treatment: when they are not able to control the disease, when these medication are associated with intolerable adverse events (local or systemic), or when high dosages of systemic corticosteroids are needed to control inflammation ($> 7.5/10$ mg/day of prednisone or equivalent)¹⁴. Furthermore, the presence of severe disease is also considered an indication for IMDs, such as bilateral uveitis; NINA-U with posterior, optic nerve or macular involvement; or a disease that severely impairs daily activities^{14,40}.

Several IMDs are currently prescribed as part of the standard of care of NINA-U patients, such as cyclosporine (CSA), methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), tacrolimus, cyclophosphamide, and biological agents (adalimumab, infliximab, rituximab, IFN- β , and IFN- $\alpha 2a$)^{14,40-42}. Their use is supported by evidence generated in several randomized controlled trials^{14,43}, attesting their effectivity and safety in NINA-U. It bears mentioning that, with the exception of CSA in few European countries, infliximab in Japan, and adalimumab in US and the EU, no other IMDs have regulatory approval for their prescription in NINA-U.

Furthermore, several observational retrospective studies have outlined, in daily clinical practice, the effectiveness of several IMDs used in monotherapy⁴⁴⁻⁴⁷. These studies have shown different rates of clinical outcomes, such as achievement of inactivity, corticosteroid sparing, and remission, for the different drugs. However, these and others studies have underlined that in a percentage of patients, the use of IMDs in monotherapy was unable to achieve a sustained control of the inflammatory process: Joshi et al.⁴⁸ reported that a large proportion of uveitis patients initially prescribed with IMDs in monotherapy underwent several changes in their immunosuppressive treatment overtime (40-75% of patients had to discontinue their first IMD due to ineffectiveness or serious adverse events). In addition, 55% required a change in their initial treatment. Menezo et al.⁴⁹ showed that 32% of patients in IMD monotherapy required the addition of a second drug. Goldberg et al.⁵⁰ reported in patients with multifocal choroidopathies initially treated with MMF that at 24 months follow-up, 21% required the addition of a second IMD to control inflammation. Data from Abasolo et al.⁵¹ showed that among patients initially receiving IMDs in monotherapy, 46.2% required a modification in their initial treatment (27.4% of patients added a second IMD due to inefficacy and 18.9% switched to a new IMD).

Despite the brief discussion in the latest international consensus document regarding NIU management¹⁴, the combination of two or more IMDs could offer advantages over monotherapy, increasing effectiveness by addressing different therapeutic pathways and decreasing the incidence of adverse events, as the combinations could allow the prescription of a lower dose of the drugs combined⁵². In fact, the effectiveness and tolerability of combination therapy with IMDs for the treatment of NINA-U⁵³⁻⁵⁵, as well as other immune-mediated inflammatory diseases, such as rheumatoid arthritis⁵⁶, have been evaluated in several observational retrospective case reports/series or open label studies including several conditions: Pascalis et al.⁵⁷ analyzed intermediate and posterior uveitis patients resistant to IMD monotherapy and high corticosteroids dosage, who were treated with CSA and MTX in combination, observing a good response in most patients, both in control of the inflammation and visual acuity improvement. In Birdshot retinochoroidopathy, Cervantes-Castañeda et al.⁵³ reported that the combination of CSA and MMF was able to induce inactivity in 63% of patients during the first 12 months of follow-up, all being able

to discontinue the systemic corticosteroid treatment. In addition, the probability of no vitreous inflammation was 81% at 12 months. In serpiginous choroiditis, Hooper et al.⁵⁵ reported five patients successfully treated with a combination of CSA, AZA, and systemic corticosteroids, with a rapid and maintained induction of inactivity. In addition, Akpek et al.⁵⁴ reported six patients with the same condition, treated with a combination of CSA, AZA, and cyclophosphamide, who achieve control of inflammation. In Vogt-Koyanagi-Harada syndrome, five patients treated with systemic corticosteroids, AZA and CSA showed a rapid control of the inflammatory process, and decreased the frequency of recurrences during follow-up⁵⁸. Arcinue et al.⁵⁹ also reported the successful use of this combination and of CSA and MMF in these patients. In ocular Behçet's disease, combination of cyclophosphamide and AZA showed efficacy in 295 patients⁶⁰. The combination of CSA and infliximab was also proven successful⁶¹. Despite the evidence from observational studies, a direct comparison between combination and monotherapy has not been published yet, although some groups have adopted the use of combination therapy as the initial IMD treatment for particular conditions⁶², and a randomized clinical trial is being carried out to assess the efficacy and safety of this therapeutic approach⁶³.

Conclusions

NINA-U are a heterogeneous group of mostly chronic or relapsing diseases that can lead to vision loss and produce high levels of disability and a reduction in the quality of life. To prevent these negative outcomes, careful pharmacological management is needed, with the objective of a complete and maintained suppression of the inflammatory process. Corticosteroids, administered using different routes based on the clinical manifestation and diagnosis, are the cornerstone of treatment, due to their almost immediate effect. Furthermore, IMDs in monotherapy or in combination can, and in several instances should, be combined with corticosteroids to ensure a maintained control of the inflammatory manifestations and prevent the arise of permanent ocular structural damage leading to irreversible vision loss.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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