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ORIGINAL RESEARCH

Therapeutic Response After Immunosuppressive Drug Prescription in Non-infectious Uveitis: A Survival Analysis

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ABSTRACT

Introduction: To identify factors affecting the response rate to immunosuppressive drugs (ISDs) in patients with non-infectious uveitis (NIU).

Methods: This longitudinal retrospective cohort study included patients from the Hospital Clinico San Carlos Uveitis Clinic diagnosed with NIU from 1992 to 2016. Subjects were followed up from ISD prescription until the achievement of good therapeutic response (GTR), ISD treatment change, or up to 12 months. GTR was defined as the complete resolution of the eye inflammatory manifestations with a corticosteroid dose $\leq$ 10 or $\leq$ 5 mg per day of prednisone or equivalent (GTR10 and GTR5, respectively) maintained for at least 28 days. Kaplan–Meier curves were estimated for GTR. Demographic, clinical, and treatment-related factors were analyzed using Cox robust regression.

Results: A total of 73 patients (100 episodes of ISD prescription) were analyzed. In 44 and 41 episodes, GTR10 and GTR5 were achieved, respectively. A lower hazard for both GTRs was associated with uveitic macular edema at prescription and with a higher "highest oral corticosteroid dose prescribed in the year before ISD prescription". GTR10 was higher if cyclosporine was prescribed (compared to other ISDs), and if

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a higher number of ISDs had been previously prescribed. GTR5 hazard was lower for patients with posterior uveitis or if the ISDs were prescribed before 2008, and higher if periocular corticosteroids had been administered before ISD prescription, or if the duration of the posterior segment activity was shorter.
Conclusions: Factors associated with GTR to ISDs may help to identify patients with NIUs who could benefit from a thorough follow-up.

Keywords: Uveitis; Immunosuppressive drugs; Response to therapy

Key Summary Points

Why carry out this study?

Factors associated with good therapeutic response to immunosuppressive treatments are crucial to prevent permanent ocular damage and visual loss in patients with uveitis.

This study was specifically designed to identify whether different factors may affect the response rate to immunosuppressive drugs in patients with non-infectious uveitis in real clinical practice.

What was learned from the study?

Good therapeutic response was positively associated with the use of cyclosporine, the higher number of ISDs previously prescribed, and the use of periocular corticosteroids, and negatively associated with the higher corticosteroid dose used and with the presence of posterior uveitis and macular edema.

The identification of these associations may help to identify patients with NIUs who could benefit from a thorough follow-up in real clinical practice.

INTRODUCTION

Non-infectious uveitides (NIUs) encompass a varied group of immune-mediated diseases affecting the uvea and adjacent tissues [1]. These conditions, especially those affecting the posterior segment of the eye, may lead to visual impairment and even blindness, thus severely impacting patients' quality of life [2] and entailing a high economic burden [3–5]. They can occur as isolated conditions or as manifestations of an underlying systemic disease including rheumatic conditions in a significant number of patients [6]. Corticosteroids are still the cornerstone of treatment for patients with these types of uveitides mainly in the acute phase of the disease [7]. Corticosteroids for patients with NIU can be administered orally but also topically, as peribulbar or intravitreal injections or as sustained-release implants [7]. However, some patients may be corticosteroid resistant and/or develop well-known ocular and systemic side effects caused by the prolonged use of these medications, mainly when prescribed orally [8, 9]. In those cases, patients will require long-term immunosuppressant drugs (ISDs) for the control of the ongoing immune dysregulation and for the prevention of complications, as well as for their steroid-sparing effect [10] when safe long-term doses of oral corticosteroids are not sufficient to control inflammatory activity. Furthermore, in some conditions, oral corticosteroids at these safe long-term doses are most likely to be ineffective and will require the use of ISDs as part of the initial treatment [11, 12].

Currently, adalimumab and cyclosporine are the only ISDs with regulatory approval for their prescription in NIUs in the European Union, the former supported by high-quality clinical trials [13]. Nevertheless, different ISDs have proven to be effective for the treatment and control of inflammatory ocular activity [14–17]. Furthermore, the treatment options for patients with NIU have been increasing in the last few years [18, 19]. As an example, monoclonal anti-tumor necrosis factor alpha (TNFα) inhibitors such adalimumab or infliximab have proven their effectiveness over the long term in severe

and refractory cases with an excellent drug retention rate [20, 21].

Nevertheless, the analysis of factors associated with therapeutic response is scarce. Therefore, once the decision to prescribe an ISD to a patient with NIU is taken, the evidence to identify which patients are more likely to achieve inactivity is scarce [3]. For this purpose, identifying factors associated with therapeutic response in subjects with NIUs is an essential step and the objective of the present study [22].

METHODS

Design and Setting

We carried out a longitudinal retrospective cohort study, with subjects collected from the Hospital Clínico San Carlos (HCSC) Uveitis Clinic (Madrid; tertiary care center). HCSC Ethics Review Board approval was obtained (internal code 19/338-E) as a retrospective study and a waiver of informed consent was obtained for use of de-identified clinical records. Furthermore, the study was conducted in accordance with the Declaration of Helsinki.

Patients

Patients were included in the study from January 1992 (the establishment of the uveitis clinic) until December 2016 and followed up until December 2017. We used the following inclusion criteria to select the patients: (a) attending or having attended the HCSC uveitis clinic; (b) clinically diagnosed with any NIU, based on an expert ophthalmological examination; (c) treated with at least one ISD [cyclosporine A (CYA), methotrexate (MTX), azathioprine (AZA), and biological therapies] as a result of the NIU activity; (d) with an ocular exploration registered in the clinical records at the ISD prescription; (e) with active ocular inflammatory manifestations at ISD prescription; (f) with a follow-up in our clinic of at least 12 months and at least two follow-up visits after the ISD prescription.

We excluded from the study those patients (a) diagnosed with scleritis, episcleritis, pemphigoid, or optic neuritis; or (b) diagnosed with a neoplastic or active infectious disease (e.g., tuberculosis, histoplasmosis) at any time during follow-up. In addition, we also excluded treatment episodes (a) when the ISD was prescribed at another uveitis clinic; (b) when the ISD was prescribed because of extraocular manifestations of a systemic disease associated with the NIU; and (c) when the ISD was prescribed in the setting of a clinical trial or a specific treatment protocol.

Clinical records for the patients that were selected following the aforementioned inclusion and exclusion criteria were reviewed, and demographic and clinical data of relevance for the analyses were extracted.

Variables

There were two main outcomes of our study. Firstly, the achievement of a good therapeutic response with $\leq$ 10 mg/day of oral prednisone or equivalent (GTR10), which was defined as (a) a complete suppression of the ocular inflammatory manifestations (all of the following: $\leq$ 0.5+ cells in the anterior chamber, $\leq$ 0.5+ vitreous haze, no active chorioretinal lesions, no active retinal vascular lesions, and no uveitic macular edema); AND (b) treatment with $\leq$ 10 mg/day of oral prednisone or equivalent, and $\leq$ 2 drops/day of prednisolone acetate or equivalent; AND (c) no ISD withdrawal related to an adverse event, patient or physician decision; AND (d) the absence of ocular inflammation and the prednisone dose had been documented in at least two consecutive visits to the clinic, at least 28 days apart.

Secondly, the achievement of a good therapeutic response with $\leq$ 5 mg/day of oral prednisone or equivalent (GTR5), which was defined in the same way as GTR10, except for requirement (b), defined instead as treatment with $\leq$ 5 mg/day of oral prednisone or equivalent.

Several independent variables were analyzed as potential risk factors for the main outcomes, including demographic and clinical variables,

and treatment-related factors (see Supplementary Text, Appendix: Variables).

Statistical Analysis

Dichotomous and categorical variables were summarized using proportions. Continuous variables were summarized using the median and the first and third quartiles (Q1–Q3). Crude incidence rates and 95% confidence intervals (CI) of GTR10 and GTR5 were presented as the number of events per 100 patient-years and were estimated by dividing the number of events that occurred during follow-up by the number of person-years of exposure.

Kaplan–Meier cumulative incidence curves were estimated to account for the achievement of good therapeutic responses. Bivariable and multivariable Cox robust regression models were fitted to estimate the influence of demographic and disease-related variables on the hazard of achievement of a GTR10 and GTR5 [23–25]. Results from the Cox models were expressed as hazard ratios (HR) with corresponding 95% CIs. To verify if the proportional hazards assumption (PH) held for a variable of interest, the Schoenfeld residuals and the scaled Schoenfeld residuals were used [24]. If a variable or certain category of a categorical variable was non-proportional, an additional extended Cox model (including a time-varying interaction covariate factor-by-time, with time as a continuous variable) was estimated [26].

To handle the presence of missing data, the classification and regression trees algorithm from the mice R package was used, with the default setting and five imputations [27].

Analyses were performed using STATA v13 software (Stata Corp), and R statistical software version 3.3.2 [28]. Further details can be found in the Supplementary Text, Appendix: Methods.

RESULTS

Patients' Characteristics

Clinical records from 174 patients diagnosed with uveitis and prescribed with ISDs were reviewed. After the inclusion and exclusion criteria were applied, 100 treatment episodes belonging to 73 patients were selected and analyzed (Fig. 1). Table 1 shows the demographic and disease-related characteristics of the patients analyzed in this study. Table 2 shows the main baseline treatment-related and clinical characteristics of the worst affected eye at the time of ISD prescription included in the analysis. Baseline characteristics were those at the beginning of the follow-up of each treatment episode, which is the time at ISD prescription. A complete description of the treatment-related and clinical characteristics at baseline is presented in Supplementary Table S1.

After each ISD prescription (treatment episode) and based on the time of follow-up

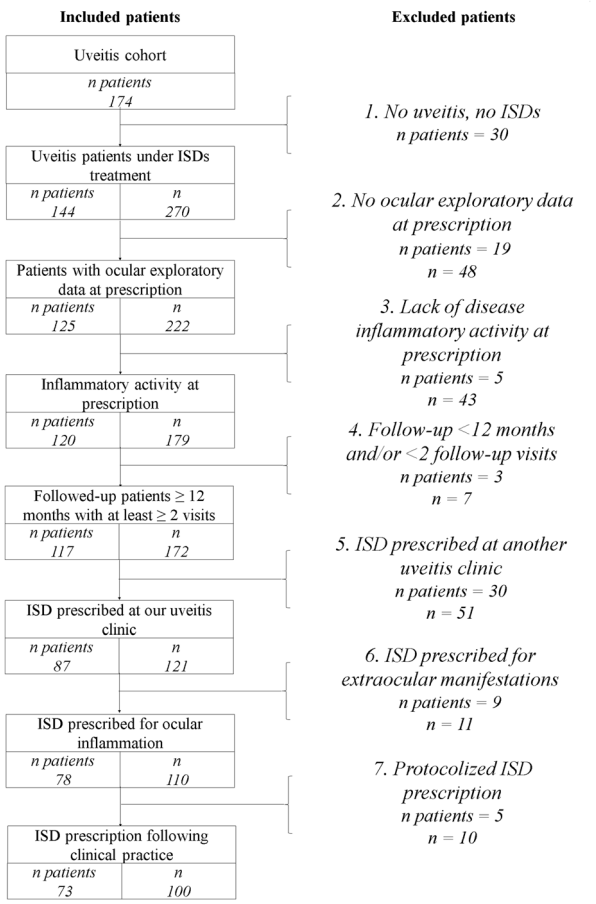

Fig. 1 Flowchart of patients included in a study to assess clinical response to immunosuppressive drugs in patients with noninfectious uveitis

Table 1 Demographic and disease-related characteristics of patients with uveitis and at least one immunosuppressive drug prescription analyzed in this study

Variable	*n* = 73
Women, *n* (%)	42 (57.53)
Age at first visit, median (IQR)	33.76 (24.83–47.08)
Year of first visit, *n* (%)	
> 2008	33 (45.21)
> 2000 & < 2008	23 (31.51)
< 2000	17 (23.29)
Spaniard, *n* (%)	65 (89.04)
Transferred from another uveitis clinic, *n* (%)	26 (35.62)
Unilateral, *n* (%)	9 (12.33)
Location, *n* (%)	
Anterior	4 (5.48)
Intermediate	15 (20.55)
Posterior	22 (30.14)
Panuveitis	32 (43.84)
Uveitis pattern, *n* (%)	
Acute bilateral anterior uveitis	2 (2.74)
Anterior chronic uveitis	2 (2.74)
Bilateral chorioretinitis	12 (16.44)
Retinal vasculitis	12 (16.44)
Intermediate uveitis	15 (20.55)
Panuveitis with chorioretinitis	11 (15.07)
Panuveitis with retinal vasculitis	16 (21.92)
Panuveitis with exudative retinal detachment	3 (4.11)
Diagnosis, *n* (%)	
Chorioretinitis	14 (19.18)
Behçet's disease	8 (10.96)
Multiple sclerosis	3 (4.11)
Idiopathic panuveitis	16 (21.92)
Idiopathic intermediate uveitis	11 (15.07)
Idiopathic retinal vasculitis	9 (12.33)
Sarcoidosis	2 (2.74)
Others	10 (13.70)
Systemic disease, *n* (%)	
No associated disease	56 (76.71)
Spondyloarthropathy	1 (1.37)
Multiple sclerosis	3 (4.11)
Beçhet's disease	8 (10.96)
Sarcoidosis	2 (2.74)
Psoriasis	1 (1.37)
Crohn's disease	1 (1.37)
Whipple disease	1 (1.37)
Age when the first ISD was prescribed, median (IQR)	36.77 (25.83–48.84)
Year when the first ISD was prescribed, *n* (%)	
> 2008	38 (52.05)
> 2000 & < 2008	22 (30.14)
< 2000	13 (17.81)
Elapsed time from first visit to first ISDs, *n* (%)	
> 1 year	25 (34.25)
2–12 months	27 (36.99)
First month	9 (12.33)
Before first visit in our clinic and/or first visit	12 (16.44)

IQR interquartile range, *ISD* immunosuppressive drug

definition and the main outcome variable analyzed, the median (Q1–Q3) follow-up time was 0.32 years (0.13–0.75), ranging from 0.03 to 1.00 for GTR10, and 0.36 years (0.17–0.90), ranging from 0.03 to 1.00 for GTR5. During this period, in 44 (44%) and 41 (41%) of these 100 episodes, the GTR10 and GTR5 were achieved after a median (Q1–Q3) follow-up time of 0.19 years (0.11–0.36) and 0.25 years

Table 2 Main baseline treatment-related and clinical characteristics of the worst affected eye of patients with uveitis at the time of the immunosuppressive drug prescriptions analyzed in this study

Variable	*n* = 100
Age at ISD prescription, median (IQR)	34.92 (24.80–47.54)
Year at ISD prescription, *n* (%)	
> 2008	61 (61.00)
> 2000 & < 2008	28 (28.00)
< 2000	11 (11.00)
Time from first visit to ISD prescription (in years), median (IQR)	1.03 (0.23–2.65)
Prescribed ISD, *n* (%)	
Adalimumab	9 (9.00)
Azathioprine	16 (16.00)
Azathioprine + cyclosporine	1 (1.00)
Cyclosporine	43 (43.00)
Cyclosporine + infliximab	1 (1.00)
Golimumab	1 (1.00)
Infliximab	1 (1.00)
Methotrexate + infliximab	2 (2.00)
Methotrexate	22 (22.00)
Tocilizumab	4 (4.00)
Number of previously prescribed ISDs, *n* (%)	
0	59 (59.00)
1	22 (22.00)
2	11 (11.00)
≥ 3	8 (8.00)
ISD prescribed in combination with other(s), *n* (%)	32 (32.00)
ISD use in the previous year before prescription, *n* (%)	39 (39.00)
Periocular corticosteroids use during last 3 months, *n* (%)	23 (23.00)
Oral corticosteroids dosage at prescription, median (IQR)	20.00 (7.50–40.00)
Highest oral corticosteroid dose prescribed in the previous year, median (IQR)	22.50 (0.00–50.00)
Best corrected visual acuity, median (IQR)	0.90 (0.60–1.00)
Cells in anterior chamber, *n* (%)	
No	52 (52.00)
0.5+	11 (11.00)
1+	18 (18.00)
2+	9 (9.00)
≥ 3+	10 (10.00)
Ocular hypertension, *n* (%)[a]	9 (10.34)
Cataracts, *n* (%)[b]	
No	62 (63.92)
Yes/intraocular lense	17 (17.53)/18 (18.56)
Vitreous haze, *n* (%)[c]	
No	52 (52.53)
0.5+	6 (6.06)
1+	13 (13.13)
2+	19 (19.19)
≥ 3+	8 (9.09)
Snowballs, *n* (%)[c]	8 (8.08)
Snowbanks, *n* (%)[d]	6 (6.12)
Vasculitis, *n* (%)[c]	
No	62 (62.63)
Posterior pole	7 (7.07)
Peripheral	30 (30.30)
Cystoid macular edema, *n* (%)[c]	47 (47.47)
Chorioretinal lesions, *n* (%)[c]	
No	51 (51.52)
Non-active chronic lesions	30 (30.30)

Table 2 continued

Variable	*n* = 100
Active lesions	18 (18.18)
Papillitis, *n* (%)[c]	8 (8.08)
Exudative retinal detachment, *n* (%)[d]	2 (2.04)

IQR interquartile range, *ISDs* immunosuppressive drugs
[a]Missing data from 13 episodes of immunosuppressive drug prescription
[b]Missing data from 3 episodes of immunosuppressive drug prescription
[c]Missing data from 1 episode of immunosuppressive drug prescription
[d]Missing data from 2 episodes of immunosuppressive drug prescription. All corticosteroid doses are expressed in equivalent mg of prednisone

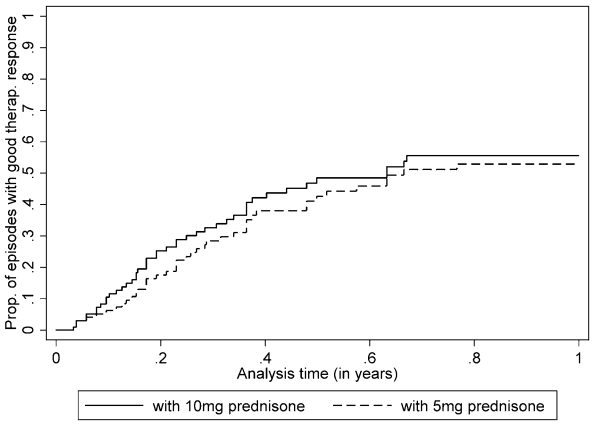

Fig. 2 Kaplan–Meier failure curves representing good therapeutic response with 10 or 5 mg/day of oral prednisone or equivalent, following immunosuppressive drug prescription in patients with noninfectious uveitis

(0.15–0.38), respectively. The crude incident rates [95% CI] per 100 patient-years of GTR10 and GTR5 were 102.02 [75.92–137.09] episodes and 87.93 [64.75–119.42] episodes, respectively (Fig. 2), with a median [95% CI] survival time of 0.67 (0.36–1.03) years and 0.77 [0.48–1.15] years, respectively.

Influence of Demographic, Clinical, and Disease-Related Variables in Good Therapeutic Responses to ISDs

Clinical characteristics of the worst affected eye at the time of ISD prescription after imputing missing data are presented in Supplementary Table S2. As a result of their low prevalence, some dichotomous variables were excluded from the analysis, while other categorical variables had their categories restructured. Supplementary Table S3 presents the demographic, disease-related, and clinical-related characteristics of the worst affected eye at the time of the ISD prescription that was finally analyzed.

Results from the bivariate Cox PH regression models are shown in Supplementary Table S4. Several variables showed an association with the hazard of achieving both GTR10 and GTR5 ($p < 0.2$) while fulfilling the PH assumption. In addition, a few variables that violated the PH assumption showed a significant factor-by-time interaction (Supplementary Table S5).

For the multivariable analysis of GTR10 and GTR5, we first assessed the independence of effects of those clinically related variables (further details can be found in the Supplementary Text, Appendix: Multivariable models generation; Supplementary Tables S6 and S7; and Supplementary Figs. S1 and S2). Different models were fitted for demographic variables, clinical-related variables, ISD-related variables, other treatment-related variables, and clinical characteristics of the worst affected eye-related variables. The variables that remained statistically significant were included in a multivariable model. Different combinations of these variables were tested and the final multivariable models used for GTR10 and GTR5 with the lowest Akaike information criterion (AIC) are shown in Table 3. Two variables (highest oral corticosteroid dosage in the previous year and presence of macular edema) were associated with a lower hazard of achieving both outcomes, with very similar effect sizes. In addition, other variables showed an independent association with either GTR10 or GTR5. For the former, CYA prescription and a higher number of ISDs prescribed before the episode analyzed were associated with a higher hazard of GTR10. Furthermore, for the second ISD prescribed, there was a negative (HR < 1) and significant

Table 3 Final multivariable Cox robust regression to analyze the independent association between variables and the achievement of a good therapeutic response with 10 mg/day or 5 mg/day of oral prednisone or equivalent after immunosuppressive drug prescription, in subjects with non-infectious uveitis

Variable	GTR10			GTR5		
	HR (95% CI)	*p* value	*p* value[a]	HR (95% CI)	*p* value	*p* value[a]
Year at ISD prescription (< 2008)	NA	NA	NA	0.47 (0.23–0.96)	0.039	0.017
Year at ISD prescription × time	NA	NA	NA	5.13 (0.46–57.47)	0.19	–
Posterior uveitis	NA	NA	NA	0.25 (0.09–0.76)	0.014	0.021
Posterior uveitis × time	NA	NA	NA	245.91 (17.15–3526.60)	5.10×10^{-5}	–
Cyclosporine prescription	2.04 (1.14–3.67)	0.017	0.56	NA	NA	NA
Number of previous ISDs						
0	Ref	–	–			
1	12.61 (2.07–76.73)	5.9×10^{-3}	0.001	NA	NA	NA
≥ 2	3.54 (1.55–8.05)	2.6×10^{-3}	0.56	NA	NA	NA
1 previous ISD × time	0.01 (0.001–1.00)	0.005	–	NA	NA	NA
Periocular corticosteroids use during last 3 months	NA	NA	NA	4.58 (1.27–16.55)	0.020	2.00×10^{-4}
Periocular corticosteroids × time	NA	NA	NA	0.02 (1.80×10^{-3}–0.21)	1.30×10^{-3}	–
Highest oral corticosteroids dosage (mg) in the previous year	0.98 (0.97–0.99)	0.013	0.83	0.99 (0.97–0.99)	0.046	0.60
Macular edema	0.14 (0.04–0.45)	9.3×10^{-3}	0.001	0.15 (0.06–0.42)	2.70×10^{-4}	0.024
Macular edema × time	14.20 (1.55–103.10)	0.019	–	3.86 (0.19–77.15)	0.38	–
Posterior activity duration, *n* (%)						

Table 3 continued

Variable	GTR10			GTR5		
	HR (95% CI)	*p* value	*p* value[a]	HR (95% CI)	*p* value	*p* value[a]
No activity				Ref	–	–
1–6 months	NA	NA	NA	15.79 (3.53–70.62)	3.10×10^{-4}	7.00×10^{-4}
6–12 months	NA	NA	NA	2.92 (0.57–14.90)	0.20	0.067
No follow-up	NA	NA	NA	6.89 (1.80–26.38)	4.80×10^{-3}	7.10×10^{-3}
1–6 months × time	NA	NA	NA	4.39×10^{-3} (1.78×10^{-4}–0.11)	9.10×10^{-4}	–
No follow-up × time	NA	NA	NA	3.88 (9.67×10^{-3}–1558.22)	0.66	–

CI confidence interval, *GTR5* good therapeutic response with 5 mg/day of prednisone, *GTR10* good therapeutic response with 10 mg/day of prednisone, *HR* hazard ratio, *Ref* reference category
[a]Schoenfeld test *p* value

interaction with time, meaning that its higher hazard diminished during follow-up. The opposite interaction (HR > 1) was observed for the presence of macular edema, and therefore its lower hazard increased with time.

For GTR5, those treatment episodes initiated before 2008 were associated with a lower hazard of GTR5. Posterior uveitis was also associated with a lower hazard of response, although this hazard greatly increased with time (significant interaction with time, HR > 1). The opposite effect was observed for the use of periocular corticosteroids during the 3 months before ISD prescription: they increased the hazard of GTR5, but it decreased with time (significant interaction with time, HR < 1). Finally, the duration of the activity in the posterior pole was also independently associated with GTR5: compared to those without activity in the previous year, those patients with a shorter duration of posterior pole activity (< 6 months of registered activity) had a higher hazard of GTR5, although it diminished with time (significant interaction with time, HR < 1). On the other hand, those with no follow-up duration before the ISD prescription also showed a higher hazard of good response.

DISCUSSION

In this longitudinal retrospective cohort study, we have reported, in patients with NIUs, the incidence rates of achieving ocular inactivity in response to ISDs with two doses of oral corticosteroids. Furthermore, we have identified several demographic, clinical, and disease-related variables independently associated with these outcomes. Although several studies have described the rates of ISD response in adults [14–17, 29–45] and pediatric patients with uveitis [46–52], the effect of different variables on the response rate has not been studied in the majority of them. Among those evaluating this topic, the variables associated with treatment response were studied mostly for patients with Behçet disease (BD)-related uveitis [53, 54]. In one study, duration of uveitis was found to be associated with a poor visual prognosis and with long-term structural complications, the latter also related to the presence of HLA-B51 and panuveitis. Another study found that disease activity levels at the start of treatment predicted the duration of response to monoclonal TNF antagonists. Two studies evaluated also the retention rate of anti-TNF for the treatment of BD-related uveitis. Adalimumab [20] and infliximab [21] showed excellent retention rates

up to 4 years (63.5%) and 10 years (47.11%), respectively, and these rates were not affected by the concomitant use of ISDs. In addition, negative prognostic factors for BD uveitis did not have any effect on ADA efficacy.

In our study, for the definition of good therapeutic response, we used two different oral corticosteroid dosage thresholds (GTR5 and GTR10), already used in other studies [31, 32]. Tapering corticosteroids until discontinuation, although desirable, is not always possible, and low doses are often required to prevent relapses [55]. However, our knowledge about long-term adverse effects of corticosteroids has improved and, consequently, doses that in the past were deemed safe (5–10 mg/day of prednisone or equivalent) are now known to be related to long-term undesirable adverse events [56], and therefore avoided in favor of even lower doses. Considering that our cohort has included patients since the early 1990s, the use of both thresholds reflects better the evolution of the real clinical practice. Nevertheless, the number of patients achieving GTR10 and GTR5 was similar, as only three patients achieved GTR10 but not GTR5 during the follow-up time.

The reported rates of clinical response to ISDs are widely variable among published studies, ranging from 24.9% for anterior uveitis [31] to 84.6% for NIUs, regardless of the locations [37] at 12 months. We must bear in mind the significant heterogeneity of clinical response definitions and populations of patients studied. As an example, some studies used composite scores to evaluate responses [29, 30] while others used the equivalent terms of inactivity recorded in the clinical records [31, 35, 36]. Therefore, although our response rate is consistent with those reported, comparisons must be interpreted cautiously.

In addition, we have identified several factors independently associated with GTR, two of them being associated with the two definitions used: highest systemic corticosteroid dose prescribed during the year before ISD prescription, and presence of macular edema. Regarding the former, higher corticosteroid doses are usually prescribed for patients with severe and even sight-threatening uveitis for the fastest control of inflammation [55]. The higher dose prescribed could also be related to a delay in the onset of ISD therapy. According to the literature, an early introduction of an aggressive ISD treatment, using proper doses and combination therapies when needed, is recommended for the reduction of relapses and ocular complications due to inflammation and to corticosteroids use, owing to its significant steroid-sparing effect [12, 57, 58]. Therefore, although the partial efficacy of the ISD or the delay of its indication may seem more related to the corticosteroid-accumulated dose (that showed a lack of association in our study with both outcomes) than to the highest corticosteroid dose prescribed the year before the ISD prescription, a possible association must be considered when interpreting our results. Furthermore, locoregional steroid injections or implants have also shown a corticosteroid-sparing effect [7]. Twelve dexamethasone implants were administered to five patients during the ISD treatment episodes. Among those, one of them had received one more ocular injection of dexamethasone implant the year before the beginning of their follow-up. In three other patients, a dexamethasone intravitreal implant was administered during the year before the follow-up, but not during the follow-up. No intravitreal corticosteroid injections were recorded among the patients included. While periocular corticosteroids use during last 3 months was positively related to GTR5, sustained release corticosteroid implants could not be included for the analysis because of their low number among the patients included, and therefore no effect on GTR could be evaluated. Nevertheless, a potential role in GTR should not be disregarded.

Regarding macular edema, its association with a lower hazard of ISD response in our study is consistent with previous reports, and it might require more time than other ocular inflammatory manifestations to be controlled, therefore hampering the achievement of GTR. Supporting this observation, we found that the hazard of GTR increased during follow-up. After reviewing previous studies, its association with ISD response was not assessed.

Among other variables associated with response, the previous use of other ISDs also showed an independent association: the higher

the number of ISDs previously prescribed, the higher hazard of achieving GTR10. This variable might be also related to more recalcitrant uveitis. This matter has been analyzed in other studies, with conflicting results. One study observed that the previous use of T cell inhibitors (such as CYA), but not other categories of ISDs, in patients treated with MTX (64.1% uveitis) was associated with a higher likelihood of therapeutic response [35]. In other studies, the previous use of other antimetabolites in patients treated with AZA (63% uveitis) [31] and the previous use of alkylating agents in patients treated with (mycophenolate mofetil) MMF (72% uveitis) [36] were associated with a lower likelihood of treatment success. However, the previous use of alkylating agents before AZA or the previous use of antimetabolites before MMF did not affect the therapeutic response to AZA or MMF, respectively. Finally, in another study of patients treated with MMF [38], the corticosteroid-sparing success was less likely if they had previously used other ISDs, regardless of the category. On the basis of these heterogeneous reports, we could hypothesize that each particular patient is prone to different degrees of response to the different ISDs available, probably depending on the subject's intrinsic characteristics. However, the use of other drugs that do not result in a satisfactory therapeutic response, in addition to delaying the achievement of a GTR, may also modulate the effect of the next prescribed drug, increasing or decreasing its chances of inducing a good response. Nevertheless, structural and irreversible ocular damage may develop until inflammatory control is achieved, and therefore an early control of inflammation should be still a mandatory objective.

There are some limitations in our study, some of them already pointed out. We have performed a retrospective study in which data was retrieved from patients who attended a single center for 27 years. This study design allows us to evaluate a time length otherwise very difficult to reach for a prospective study, but, as a well-known limitation of retrospective studies, indications for ISD treatment prescription and overall patient management were conducted in real-life clinical practice by ophthalmologists and rheumatologists not following a standardized protocol. In addition, as a result of this follow-up extension, some of the data may reflect a clinical practice that has changed with time as more therapeutic options have arisen. As an example, we related the presence of macular edema with a lower GTR, but we have to take into account that we included a few patients treated with tocilizumab, whose efficacy in this condition has been previously described [59]. All these facts may cause heterogeneity, but we want to point out that clinical care was provided by physicians with an extensive experience in the management of intraocular inflammation.

In addition, although other studies, such as the Systemic Immunosuppressive Therapy for Eye Diseases study [31, 33, 35], have produced high-quality evidence regarding the effectiveness of ISDs in real-life clinical practice, they did not carry out a thorough analysis of factors that may affect the clinical response to these drugs. Furthermore, these studies were often designed to analyze the effect of particular therapies given alone. In our study, we have systematically analyzed the effect of several variables related to demographic, disease, and treatment characteristics on the therapeutic response to ISDs, not only prescribed in monotherapy but also in combination. To our knowledge, no other study has followed this approach.

Another potential limitation for the generalization of our findings may be the characteristics of our cohort, which was composed of adults and Caucasian patients, and thus our observations should be interpreted with caution when applied to pediatric patients or non-Caucasian patients. As the number of patients achieving GTR10 but not achieving GTR5 is small, it is not possible to extract strong conclusions after comparing the factors differently associated with one or other GTR definition. Nevertheless, they seem to point in a similar direction and no contradictory results have been found. Finally, as different ISDs were analyzed, comparisons between doses and routes of administration could not be performed. Few studies have evaluated this topic. For cyclophosphamide, high dosages (100–-150 mg/day) were associated with significantly

greater success in controlling inflammation than lower doses (≤ 75 mg), with no differences between routes of administration [32].

We also want to point out that in our study most of the treatment episodes were prescribed in monotherapy (71%), although a considerable number of patients were reported as non-anterior uveitis and thus could be considered severe cases (94.5%). The number of combinations between synthetic ISDs such as methotrexate or azathioprine, or their combination with biologic ISDs such as anti-TNFα might seem proportionally low (32% of treatment courses). We consider that this observation could be related to the fact that combined therapy is not often used as the initial treatment of patients with NIU in clinical practice (in our cohort, only three patients were initially prescribed with two ISDs in combination). Most episodes of combined therapy are related to the addition of a second ISD, usually when only an incomplete therapeutic response is achieved. Thus, the majority of the combined treatment episodes included in our study were preceded by a monotherapy course. In addition, as commented before, we included cases treated several years ago, before the introduction of anti-TNFs in the therapeutic arsenal of these conditions. Grouping the episodes by the year of treatment onset in quartiles, we observed that the more recent the episode, the higher likelihood of being combination therapy (1991–2004, 20%; 2004–2009, 24%; 2009–2013, 36%; and 2013–2016, 48%). Furthermore, the percentage of episodes of combined therapy using biologics increased from 0% in the first quartile, to 66% in the second and third, to 92% in the fourth quartile. Considering that the last episodes analyzed in this work started in 2016, this could explain the low percentage of episodes in combination therapy.

CONCLUSION

Several variables associated with therapeutic response to ISDs in patients with NIU have been identified. This approach may lead to better timing and accuracy in ISD prescription, therefore achieving a faster and complete suppression of inflammation and minimizing potential complications derived from the necessity of dose adjustments or treatment modification [22]. Further studies are required to demonstrate if those patients with risk factors for a more difficult inflammatory control may require a more intensive immunosuppressive therapy early in the disease course to prevent the development of chronic and irreversible ocular damage.

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Compliance with Ethics Guidelines. Hospital Clínico San Carlos Ethics Review Board approval was obtained (internal code 19/338-E) as a retrospective study and a waiver of informed consent was obtained for use of de-identified clinical records. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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