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Efficacy and safety of certolizumab pegol and golimumab in the treatment of non-infectious uveitis

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ABSTRACT

Objective. *The aim of the study was to evaluate the efficacy of golimumab (GOL) and certolizumab pegol (CZP) as additional treatment options for the treatment of uveitis.*

Methods. *Patients with longstanding uveitis receiving either GOL or CZP were retrospectively evaluated in terms of frequency of ocular flares, drug survival, changes in best corrected visual acuity (BCVA) and steroid-sparing effect.*

Results. *Twenty-one patients (30 eyes), 17 of whom being female, were enrolled in the study; 16 out of 21 patients had been previously treated with other tumour necrosis factor (TNF)-α blockers. A significant reduction in ocular flares (from 128.6 bouts for 100 patients-year to 42.9 events for 100 patients-year) was observed between the 12 months prior to the start of GOL or CZP and the 12 months thereafter (p=0.01). The 36-month drug survival was 54.5% for CZP and 50.0% for GOL with no statistically significant differences between the two biologic agents. No differences were detected concerning BCVA values and the mean corticosteroid intake between baseline and the last follow-up. The safety profile was excellent.*

Conclusions. *GOL and CZP represent effective and safe treatment choices for patients with uveitis also when unsuccessfully treated with other anti-TNF-α drugs, permitting a significant reduction in the frequency of ocular flares and preserving visual function with a good long-term retention rate.*

Introduction

Non-infective uveitis may be sustained by a protean group of immune-mediated diseases and is associated with severe ocular complications including macular oedema, epiretinal membranes, cataract, and ocular hypertension which are closely related to a poor visual prognosis and more difficult-to-treat patients (1).

A prompt and effective treatment should be warranted in order to obtain a better visual outcome. In this regard, corticosteroids (CS) remain the cornerstone of treatment, but patients may require persistent high-dose CS resulting in challenging systemic side effects. Other patients may also be non-responsive to CS or necessitate a quick dose escalation. In these cases immunosuppressive agents should be taken into account to prevent potential short- and long-term ocular sequelae associated with a poor visual outcome (2). With the advent of biotechnological drugs, especially anti-tumour necrosis factor (TNF)-α, major advances have been made for the treatment of non-infectious uveitis, particularly in refractory cases. In particular, adalimumab (ADA) and infliximab (IFX) display the highest level of evidence and expert consensus guidelines consider these agents for patients whose disease is inadequately controlled by CS and immunosuppressants (3, 4). In spite of the good results obtained with these agents, a proportion of patients ranging from 25 to 60% may be nonresponsive to IFX or ADA or develop adverse events (AE) (5, 6). Therefore, a wider therapeutic armamentarium could facilitate the management of sight-threatening uveitis.

To date, only a few studies have addressed the effectiveness of alternative TNF-α inhibitors such as certolizumab pegol (CZP) and golimumab (GOL) on refractory uveitis (7-14). Therefore, we herein describe our experience based on a retrospective analysis of patients affected by uveitis and treated with CZP and GOL.

Patients and methods

The present study is a retrospective evaluation of medical charts related to 21 patients treated with GOL or CZP because of different systemic inflammatory disorders associated with uveitis or owing to idiopathic uveitis. In particular, GOL regimen consisted in 50 mg every 4 weeks subcutaneously, while CZP was initially given at a dose of 400 mg for induction and 200 mg fortnightly thereafter. Follow-up was done with periodic medical visits every 3 months or when necessary (disease relapse or safety concerns). The choice of the TNF-α antagonist had been left to the discretion of the patient's physician according to the specific clinical context. Best corrected visual acuity (BCVA) was assessed with Snellen chart in decimal fractions at any visit.

Diagnosis of Behçet's syndrome (BS),

Table I. Demographic and clinical features of patients affected by uveitis treated with golimumab.

Patient number	Gender	HLA-B51	HLA-B27	Age at uveitis onset	Uveitis duration (years)	Anatomic pattern	Laterality	Systemic diagnosis	Previous therapies
1	F	+	-	30	30	PAN	BL	BS	ETN, IFX, ADA, RTX
2	F	-	-	40	6	AU	ML	BS	ADA
3	F	-	-	38	1	AU	BL	BS	MTX, ADA
4	F	-	-	3	30	AU	BL	JIA	MTX, IFX, ADA
5	F	-	-	51	4	AU	ML	SpA	MTX, ETN, IFX, ADA
6	F	-	-	57	5	AU	ML	BS	MTX, IFX, ADA
7	F	+	-	50	2	IU	ML	BS	MTX, ADA
8	M	+	-	29	18	AU	ML	BS	IFX, ADA
9	M	+	-	18	20	PAN	ML	BS	AZA, ADA
10	F	-	+	26	8	AU	BL	SpA	MTX, IFX, ADA

AU: anterior uveitis; ADA: adalimumab; AZA: azathioprine; BL: bilateral; BS: Behçet's syndrome; ETN: etanercept; HLA: human leukocyte antigen; F: female; IFX: infliximab; IU: intermediate uveitis; JIA: juvenile idiopathic arthritis; M: male; ML: monolateral; MTX: methotrexate; PAN: panuveitis; RTX: rituximab; SpA: spondyloarthritis.

Table II. Demographic and clinical features of patients affected by uveitis treated with certolizumab pegol.

Patient number	Gender	Age at uveitis onset	HLA-B51	HLA-B27	Uveitis (years)	Anatomic pattern	Laterality	Systemic diagnosis	Previous therapies
1	F	56	+	-	12	AU	ML	SpA	-
2	F	45	-	-	10	AU	BL	SpA	CsA
3	F	30	+	-	6	AU	BL	BS	AZA, ETN, IFX, ADA
4	M	33	-	-	14	PAN	BL	-	ADA
5	F	40	-	-	6	AU	ML	BS	ETN, ADA,
6	F	38	-	-	1	AU	BL	BS and sacroileitis	-
7	F	58	-	+	3	AU	ML	SA	-
8	F	6	-	-	28	AU	ML	JIA	ETN, ADA
9	F	51	-	-	4	AU	ML	SpA	MTX, ETN, IFX, ADA
10	F	39	-	-	3	PU	BL	BS and sacroileitis	-
11	M	18	+	-	19	PAN	ML	BS	AZA, ADA

AU: anterior uveitis; ADA: adalimumab; AZA: azathioprine; BL: bilateral; BS: Behçet's syndrome; CsA: cyclosporine; ETN: etanercept; HLA: human leukocyte antigen; F: female; IFX: infliximab; JIA: juvenile idiopathic arthritis; M: male; ML: monolateral; MTX: methotrexate; PAN: panuveitis; PU: posterior uveitis; AS: ankylosing spondylitis; SpA: spondyloarthritis.

axial or peripheral spondyloarthritis (SpA) and juvenile idiopathic arthritis had been made basing on the internationally accepted criteria. Standardization of the Uveitis Nomenclature (SUN) Working Group criteria were adopted to classify the anatomic pattern of intraocular inflammation (15).

The primary aim of this study was to evaluate the efficacy of GOL and CZP in patients with uveitis either idiopathic or related to systemic inflammatory disorders. Secondary aims addressed the following issues: i) to evaluate patients' persistence on therapy with GOL and CZP; ii) to examine the consequences of drugs on visual acuity; iii) estimating CS-sparing effect; iv) evaluating the safety profile and ocular complications during GOL and CZP treatment.

The study protocol conformed to the tenets of the Declaration of Helsinki and was approved by the local Ethics Committee of the Azienda Ospedaliera Universitaria Senese. Informed consent was obtained from each patient.

Statistics

The data were computed using IBM SPSS Statistics for Windows, v. 24 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics was used to calculate percentage, mean and standard deviation or median and interquartile range, as appropriate. Normality distribution was assessed with the Shapiro-Wilk test. Analysis of repeated categorical measures was performed with McNemar test. Cumulative survival rates were studied via Kaplan-Meier plot with time 0 representing therapy initiation and the event being the drug discontinuation. Breslow test was used to compare survival curves in the early follow-up stage, while Log-rank (Mantel-Cox) test was used to compare survival curves in the final follow-up phase. Mann-Whitney U-test and Friedman test were used for the analysis of samples, as required. The threshold for statistical significance was set to $p<0.05$ and all p-values were two-sided.

Results

Twenty-one patients (30 eyes, 17 females) were enrolled. Eleven patients were treated with CZP and 10 with GOL. The mean treatment duration was 16.45±7.93 months for patients treated with CZP and 30.00±29.47 months for patients treated with GOL. Ocular involvement was unilateral and bilateral in 12 and 9 cases, respectively. The localisation of uveitis was anterior in 22 eyes, intermediate in 1 eye, posterior in 2 eyes; panuveitis was identified in 5 eyes. Seven (33.3%) patients started biologic treatment because of active or recently active (within 60 days) ocular

involvement, 14 (66.7%) patients due to active or recently active (within 60 days) ocular and systemic inflammatory involvement. There was no evidence of active retinal vasculitis at baseline in any of the enrolled patients. Coadjuvant immunosuppressive therapy was used in 10 patients, including methotrexate (n=6), azathioprine (n=3) and cyclosporine A (n=1). Main demographic and therapeutic characteristics of this series of patients are summarised in Table I for subjects treated with GOL and Table II for patients managed with CZP.

The number of ocular flares decreased from 128.6 events for 100 patients-year during the 12 months preceding the start of the study to 42.9 events for 100 patients-year during the first 12 months of GOL and CZP administration (p=0.01). At the last follow-up visit, uveitis was inactive in 18 out of 21 patients.

Although GOL retention rate was slightly higher than that identified among patients treated with CZP during a 36-month follow-up (54.5% and 50.0%, respectively), cumulative retention rates did not show any statistically significant difference between the two TNF-α inhibitors (p=0.736 with Log-rank test and p=0.676 for Breslow test). Figure 1 illustrates the cumulative survival of GOL and CZP evaluated separately.

BCVA improved in 3 eyes, worsened in 6 eyes and did not change in 21 eyes. The overall BCVA collected at baseline (8.71±2.22) and at last follow-up (8.14±2.04) did not show significant differences (p=0.557). Similarly, no statistically significant differences were observed in the daily prednisone (or equivalent) intake between the different time points (p=0.249).

Looking at the safety profile, one skin ulcerative lesion on the left hand occurred in 1 patient treated with GOL determining treatment discontinuation. No serious AE were observed. Ocular complications were recorded in 6 (20%) eyes: posterior synechiae in 2 eyes treated with CZP, glaucoma and cataract in 2 eyes treated with GOL and macular oedema in the last 2 eyes (one treated with CZP and the other with GOL).

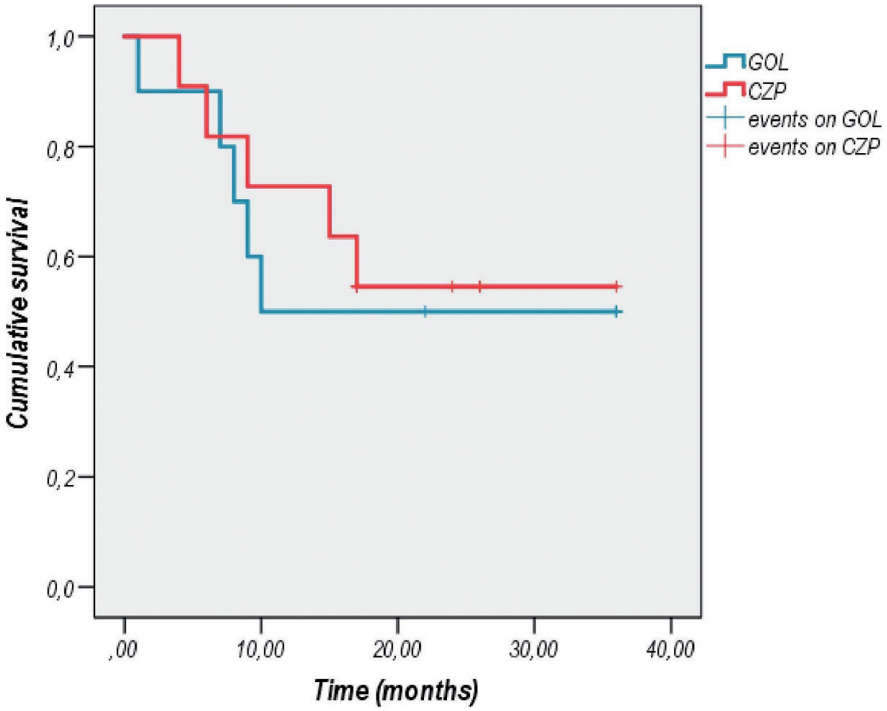

Fig. 1. Kaplan-Meier survival curves obtained from patients treated with golimumab (GOL) and certolizumab pegol (CZP) during the study period. Time zero represents the start of treatments with the event being GOL or CZP discontinuation.

Discussion

Inhibition of TNF-α with ADA or IFX is highly effective for the treatment of refractory uveitis, showing remarkable rates of complete response over time (16). Nevertheless, a considerable amount of patients may be non-responsive or exhibit safety issues to these TNF-α blockers and switching to another anti-TNF-α could be a feasible option in such cases (5, 6). Despite the few data currently available, CZP and GOL may be of high interest in the therapeutic decision-making process for chronic or relapsing refractory uveitis, especially for multidrug resistant cases. Moreover, while GOL shows advantages in terms of routes and frequency of administration, CZP may display interesting pharmacokinetic perspectives due to its PEGylated structure. Furthermore, both agents have shown a decreased immunogenicity compared with other anti-TNF-α agents (9, 13).

According to the few literature data currently available and mostly based on BS patients, GOL has proven an effective role in inducing control of uveitis flares, resolution of eye inflammation, improvement of the BCVA and reduction of the central macular thickness also in multiresistant cases (7-12). Regarding CZP, to date no firm conclusions may be drawn in BS patients with multiorgan involvement including ocular manifestations (17). However, encouraging results have been described by Llorenç *et al*. in patients with refractory chronic-relapsing uveitis treated with CZP, since ocular quiescence was obtained in 5/7 patients, 3 patients withdrew corticosteroids and the overall BCVA significantly improved within one month of treatment (13). Similarly, Rudwaleit *et al*. observed a more than 3 time-decrease in the number of ocular flares in comparison with the control group in a sample of SpA patients treated with CZP during a 24-week period (14).

Our results display a notable efficacy of GOL and CZP for the management of uveitis in terms of flare prevention and long-term retention rate, which was comparable to those referenced in the literature about IFX and ADA (18). In addition, although no statistical significance was identified in BCVA changes, GOL and CZP have proven a tangible role in preserving visual function.

No significant differences emerged when comparing the mean daily prednisone (or equivalent) intake at baseline with that administered at the last

follow-up visit. This last finding differs from what previously reported in the literature (7, 9), and could be at least explained partially by the relatively low CS dosages at baseline. This was related to the inclusion of patients already undergone to CS tapering at treatment initiation.

Limitations of this study include its retrospective design, the lack of a control group and the limited number of patients (many of our endpoints were investigated on patients treated with GOL and CZP all together in order to increase sample size for statistical purposes).

In conclusion, GOL and CZP appear effective and safe treatment options capable of inducing a significant reduction of ocular flares, preservation of visual function and a good long-term retention rate in patients with uveitis also if previously treated with other anti-TNF-α drugs.

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