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ORIGINAL ARTICLE

Comparative efficacy between adalimumab and infliximab in the treatment of non-infectious intermediate uveitis, posterior uveitis, and panuveitis: a retrospective observational study of 107 patients

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Abstract

To compare the efficacy of adalimumab (ADA) and infliximab (IFX) in patients with non-infectious intermediate uveitis, posterior uveitis, and panuveitis. Demographic, clinical, instrumental, and therapeutic data from patients enrolled were collected at the start of treatment, at 12-month follow-up, and at the last follow-up assessment. One hundred seven patients (46 females, 187 eyes) were enrolled, 66 (61.7%) treated with ADA and 41 (38.3%) with IFX. Bilateral involvement was observed in 80 cases. The mean follow-up was 26.45 ± 21.71 months for ADA patients and 56.60 ± 56.04 months for IFX patients. The overall decrease of uveitis frequency during the first 12 months of treatment was 66.7% in the IFX group and 84.2% in the ADA group, compared to the previous 12 months ($p = 0.09$). A significantly higher corticosteroid dosage was found among patients treated with ADA at the last follow-up visit ($p = 0.008$). The percentage of patients co-administered with corticosteroids was significantly higher among ADA patients both at the 12-month visit ($p = 0.03$) and at the last visit ($p = 0.0004$). The frequency of uveitic macular edema (UME) was significantly higher among patients treated with ADA compared to those treated with IFX at the 12-month assessment ($p = 0.015$) and at the last follow-up visit ($p = 0.011$); central macular thickness was significantly higher in ADA group compared to the IFX group at the last follow-up assessment ($p = 0.04$). ADA and IFX have shown a similar efficacy in controlling uveitis relapses, but IFX showed a more pronounced corticosteroid sparing effect and a significantly higher capacity in resolving UME compared to ADA.

Keywords Behçet's disease · Macular edema · Retinal vasculitis · TNF-blocking antibodies · Uveitis

Introduction

Non-infectious intermediate uveitis, posterior uveitis, and panuveitis represent a heterogeneous group of inflammatory conditions involving the uvea and adjacent ocular tissues. Eyes may be affected by uveitis as a consequence of systemic inflammatory diseases including Behçet's disease (BD), Vogt-Koyanagi-Harada disease, sarcoidosis, and seronegative

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spondyloarthritis. However, isolated and idiopathic uveitis are encountered in a not-negligible number of patients [1, 2].

Uveitis may represent a challenging condition capable of inducing visual loss and even complete blindness. Consequently, it may severely affect patients' quality of life in most of the areas of everyday life, especially physical domains, general health, and social functioning [3]. For these reasons, optimal management of noninfectious uveitis represents an essential step in order to prevent ocular complications leading to irreversible visual impairment. In this regard, systemic corticosteroids (CS) represent the cornerstone of therapy in acute phases, while conventional disease-modifying anti-rheumatic drugs (cDMARDs) and/or biologic therapy with monoclonal tumor necrosis factor (TNF)-α inhibitors are indicated to control persistent or severe inflammation in the long term, in order to prevent ocular structural complications and to allow a rapid CS tapering [4, 5].

Adalimumab (ADA) and infliximab (IFX) currently represent the most frequently employed monoclonal anti-TNF-α biologic agents. However, based on two randomized control trials (RCTs) [6, 7], to date, ADA is the only biologic approved by the Food and Drug Administration and the European Medicines Agency for treatment of adult patients with non-infectious intermediate uveitis, posterior uveitis, and panuveitis [8, 9]. Conversely, although IFX is supported by a wide international literature, no RCTs have been performed to establish the efficacy of this agent in patients with uveitis. Nevertheless, current evidences based on retrospective and prospective open-label trials support the use of IFX for non-infectious uveitis, especially in patients affected by BD [10–14].

In spite of the increasing number of studies on the effective role of ADA and IFX in patients with uveitis, to date, only a few studies have looked for differences in the effectiveness of the two monoclonal anti-TNF-α agents in the context of non-infectious intermediate uveitis, posterior uveitis, and panuveitis [15–17]. On this basis, the present study has been carried out in order to identify any difference between ADA and IFX in controlling eye inflammation, preserving visual function, prevent ocular complications, and tapering systemic CS.

Materials and methods

Patients with non-infectious intermediate uveitis, posterior uveitis, and panuveitis treated with TNF-α inhibitors, either ADA or IFX, were retrospectively enrolled in the study.

The choice of the TNF-α antagonist had been left to the discretion of the patient's physician. Before starting ADA or IFX, patients had undergone chest radiograph, Mantoux and/or QuantiFERON tests, liver markers for HBV and HCV infections, and HIV, syphilis, and *Toxoplasma gondii* serologies in order to rule out active or latent infections. Similarly, cardiac and malignant conditions were excluded. The following demographic, clinical, and therapeutic data related to the start of ADA or IFX treatment (baseline), the 12-month evaluation, and the last follow-up visit were retrospectively collected: gender, anatomical classification of uveitis according to the Standardization of Uveitis Nomenclature (SUN) Working Group criteria [18], unilaterality or bilaterality of uveitis, age at uveitis onset, age at the start of biologic therapy, any systemic disease associated with uveitis, the age at onset of systemic diseases (when identified), the number of ocular relapses reported during the 12 months preceding the start of ADA or IFX and during the 12 months following the start of treatment, the occurrence of retinal vasculitis identified at fluorescein angiography (FA), previous and concomitant treatments, daily CS dosage, best corrected visual acuity (BCVA) assessed at Snellen chart in decimal fractions, central macular thickness (CMT) assessed at optical coherence tomography (OCT), treatment adjustments, and any ocular complications during follow-up. Patients showing a CMT > 300 μm at OCT were classified as having uveitis macular edema (UME).

An *ocular inflammatory relapse* was defined as a worsening of ocular inflammation according to the SUN criteria [18]. The frequency of ocular inflammatory relapses was expressed as cumulative number of events/100 patients/year.

In order to concomitantly assess the overall systemic disease activity, BD current activity form and ankylosing spondylitis disease activity score were respectively used as clinimetric tools in patients with BD and spondyloarthritides [19, 20].

The aim of this study was to compare the efficacy of ADA and IFX in patients with non-infectious intermediate uveitis, posterior uveitis and panuveitis in terms of decrease in the frequency of uveitis relapses, corticosteroid sparing effect, impact on BCVA, improvement and/or resolution of UME, control of retinal vasculitis, cDMARDs withdrawal, biologic treatment discontinuation related to primary or secondary inefficacy or safety concerns during follow-up, frequency of uveitis-related ocular complications during treatment.

The endpoints of the study were represented by (i) a statistically significant difference in the decrease of uveitis relapses during the first 12 months of treatment compared to the 12 months preceding the start of anti-TNF-α therapies among patients treated with ADA (ADA group) and subjects treated with IFX (IFX group) and (ii) a statistically significant difference between ADA and IFX groups in the mean daily corticosteroid dosage (prednisone or equivalent) administered at baseline, at the 12-month visit, and at the last follow-up evaluation. Additional endpoints were represented by a statistically significant difference between ADA and IFX groups in the following clinical variables recorded at baseline, at 12-month visit, and at the last follow-up evaluation: BCVA at Snellen

chart, mean CMT values obtained at OCT, frequency of patients showing a CMT > 300 μm, frequency of patients with retinal vasculitis, frequency of patients concomitantly treated with cDMARDs, percentage of patients discontinuing the study treatments because of primary or secondary inefficacy or safety concerns, and number of eventual ocular complications. The number of eyes affected by ocular complications was standardized as events/100 patients/year in order to overcome any bias related to the different length of follow-up between the two groups.

Descriptive statistics included sample size, percentages, means, and standard deviations. After having assessed normality distribution with Shapiro-Wilk test, pair wise comparisons of quantitative data were performed by using unpaired two-tailed *t* test or Mann-Whitney two-tailed U test, as appropriate; Fisher exact test was performed for categorical variables. Two tailed *p* values < 0.05 were considered statistically significant.

Results

One-hundred and seven patients (46 females, 187 eyes) with intermediate uveitis, posterior uveitis, or panuveitis were enrolled. Unilateral and bilateral eye involvement was observed in 27 and 80 patients, respectively. Seventy-one patients (66.4%) had suffered from retinal vasculitis during their ocular history, and 37 presented with retinal vasculitis at baseline (34.6%). Sixty-six (61.7%) patients were treated with ADA (114 eyes) and 41 (38.3%) with IFX (73 eyes). Table 1 summarizes demographic, clinical, and treatment data obtained from the two groups of patients. Table 2 summarizes ocular parameters recorded at baseline and at the following study time-points as well as the treatment adjustments and withdrawals occurred during follow-up.

Anti-TNF-α treatment was started because of severe and refractory sight-threatening uveitis in 87 cases (81.3%) showing active or recently active (within 60 days) ocular inflammation. The other 20 patients required biologic treatment due to overall systemic disease activity (including also other active organ involvement). The mean follow-up of patients treated with ADA was 26.45 ± 21.71 months; the mean follow-up of patients administered with IFX was 56.60 ± 56.04 months.

During the 12 months preceding the study treatments, the number of ocular relapses was 128.6 events/100 patients/year for patients undergoing IFX and 168.9 episodes/100 patients/year for patients undergoing ADA. During the first 12 months of treatment, the number of ocular relapses was 42.86 episodes/100 patients/year for patients administered with IFX and 26 episodes/100 patients/year for patients treated with ADA. The overall decrease of uveitis frequency was 66.7% in the IFX group and 84.2% in the ADA group ($p = 0.09$).

No differences were found in the mean daily CS dosage between the two groups of patients at baseline ($p = 0.66$) and at the 12-month assessment ($p = 0.27$), while a significantly higher dosage was identified among patients treated with ADA at the last follow-up visit ($p = 0.008$). The mean CS tapering showed no statistically significant differences among groups between baseline and the 12-month visit ($p = 0.39$), between the 12-month assessment and the last follow-up visit ($p = 0.29$), and between baseline and the last follow-up visit ($p = 0.22$). No differences were identified in the number of patients receiving CS between the two groups of patients at baseline ($p = 0.29$). Conversely, the percentage of patients concomitantly treated with CS was significantly higher among patients treated with ADA compared with those treated with IFX both at the 12-month assessment ($p = 0.03$) and at the last follow-up visit ($p = 0.0004$). Data concerning treatment with CS are illustrated in Fig. 1.

No statistically significant differences were identified in the BCVA values between ADA and IFX groups at baseline ($p = 0.28$), at 12-month assessment ($p = 0.28$), and at the last follow-up evaluation ($p = 0.13$). Changes in mean BCVA values during follow-up are summarized in Table 2.

No differences were identified in the number of patients showing UME at OCT between the two groups at baseline ($p = 0.29$). Conversely, the frequency of UME was significantly higher among patients treated with ADA compared to those treated with IFX at the 12-month assessment ($p = 0.015$) and at the last follow-up visit ($p = 0.011$). No differences were found in the mean CMT between ADA and IFX groups at baseline ($p = 0.47$) and at the 12-month visit ($p = 0.10$); conversely, CMT values were significantly higher in the ADA group compared to IFX group at the last follow-up assessment ($p = 0.04$). In the subgroup of patients with UME at baseline, the mean decrease in the CMT did not show any statistically significant difference between ADA and IFX during the first 12 months of treatment ($p = 0.51$), between the 12-month assessment and the last follow-up visit ($p = 0.07$) as well as between baseline and the last visit ($p = 0.39$). The frequency of UME and mean CMT values at baseline and at the following study time-points is represented in Fig. 2.

No differences were identified in the frequency of retinal vasculitis between the two groups of patients at baseline ($p = 0.11$), at the 12-month evaluation ($p = 0.70$), and at the last follow-up visit ($p = 0.30$). No differences were found in the number of patients concomitantly administered with cDMARDs at baseline ($p > 0.99$) and at the last follow-up assessment ($p = 0.16$). No differences were disclosed between the two groups of patients in the number of treatment discontinuations and treatment adjustments at the 12-month assessment ($p = 0.42$ and $p = 0.14$, respectively) and at the last follow-up evaluation ($p = 0.29$ and $p = 0.10$, respectively). The frequency of retinal vasculitis identified at FA during the study period is reported in Table 2 and Fig. 3.

Table 1 Demographic, clinical, and therapeutic data from patients treated with adalimumab and infliximab. Data are referred to baseline assessment

	Adalimumab group	Infliximab group	*p* value
Age, years (mean ± SD)	39.52 ± 12.08	42.15 ± 12.14	0.17
Age at uveitis onset (mean ± SD)	29.97 ± 12.1	30.07 ± 12.26	0.94
Uveitis duration (mean ± SD)	9.10 ± 7.37	11.59 ± 8.63	0.05
Age at systemic disease onset (mean ± SD)	24.11 ± 15.42	23.78 ± 16.1	0.99
Systemic disease duration (mean ± SD)	8.74 ± 9.17	12.00 ± 12.14	0.16
Ocular diagnosis			
Intermediate uveitis, *n* (%)	5 (7.6)	1 (2.4)	0.40
Posterior uveitis, *n* (%)	24 (36.4)	22 (52.4)	0.11
Panuveitis, *n* (%)	37 (56.1)	19 (45.3)	0.43
Retinal vasculitis, *n* (%)	46 (69.7)	25 (61.0)	0.40
Systemic diagnosis, *n* (%)			
Behçet's disease	43 (65.2)	31 (76.2)	0.29
Spondyloarthritis	4 (6.1)	1 (2.4)	> 0.99
Inflammatory bowel disease	3 (4.5)	0 (0.0)	–
Juvenile idiopathic arthritis	1 (1.5)	0 (0.0)	–
Sarcoidosis	1 (1.5)	0 (0.0)	–
Vogt-Koyanagi-Harada disease	1 (1.5)	1 (2.4)	> 0.99
Idiopathic uveitis	13 (19.7)	9 (21.4)	0.81
Previous treatments			
Corticosteroids	100	100	> 0.99
cDMARDs, *n* (%)	51 (77.3)	31 (75.6)	> 0.99
Cyclosporine	27	23	0.52
Methotrexate	20	12	> 0.99
Azathioprine	17	8	0.62
Mycophenolate mofetil	3	6	0.08
Sulphasalazine	2	1	> 0.99
Cyclophosphamide	2	2	0.63
Biologic agents, *n* (%)	19 (28.8)	9 (22.0)	0.54
Infliximab	13	–	–
Adalimumab	–	8	–
Etanercept	1	0	–
Certolizumab pegol	0	2	–
Golimumab	0	1	–
Anakinra	5	0	–
Rituximab	1	0	–
Abatacept	1	0	–
Treatment at baseline			
Corticosteroids, *n* (%)	62 (93.9)	41 (100)	0.29
cDMARDs, *n* (%)	31 (46.7)	20 (48.8)	> 0.99
Cyclosporine	7	8	0.22
Methotrexate	11	6	0.77
Azathioprine	9	3	0.32
Mycophenolate mofetil	1	4	0.07
Sulphasalazine	2	0	–

cDMARDs conventional disease modifying anti-rheumatic drugs, *SD* standard deviation

During follow-up, ocular complications occurred in 10 patients (14 eyes) treated with ADA and in 9 patients (15 eyes) treated with IFX. No significant differences were found between groups in the frequency of patients with ocular complications at the 12-month evaluation ($p > 0.99$) and at the end of follow-up ($p = 0.44$). When the number of eyes presenting

Table 2 Ocular parameters and treatment changes recorded at baseline, at 12-month assessment and at the last follow-up visit

Items	Biologic agents	Baseline	*p* value	12-month	*p* value	Last follow-up	*p* value
BCVA, mean ± SD	ADA	7.0 ± 3.66	0.28	7.4 ± 3.5	0.28	7.3 ± 3.6	0.13
	IFX	6.4 ± 3.4		6.8 ± 3.4		6.9 ± 3.4	
Retinal vasculitis	ADA	35	0.11	13.6	0.70	7.1	0.27
	IFX	55.2		8.3		0.0	
Treatment discontinuation	ADA	–	–	21.2	0.42	31.8	0.29
	IFX			12.2		41.5	
Ocular complications	ADA	–	–	15.2	> 0.99	15.2	0.44
	IFX			12.0		22.0	
Treatment adjustments	ADA	–	–	17.4	0.14	20.8	0.10
	IFX			3.7		4.5	

Except for BCVA values, ocular parameters are described as percentage compared to the total number of patients treated with ADA or IFX

ADA adalimumab, *BCVA* best corrected visual acuity (provided in decimals), *IFX* infliximab, *SD* standard deviation

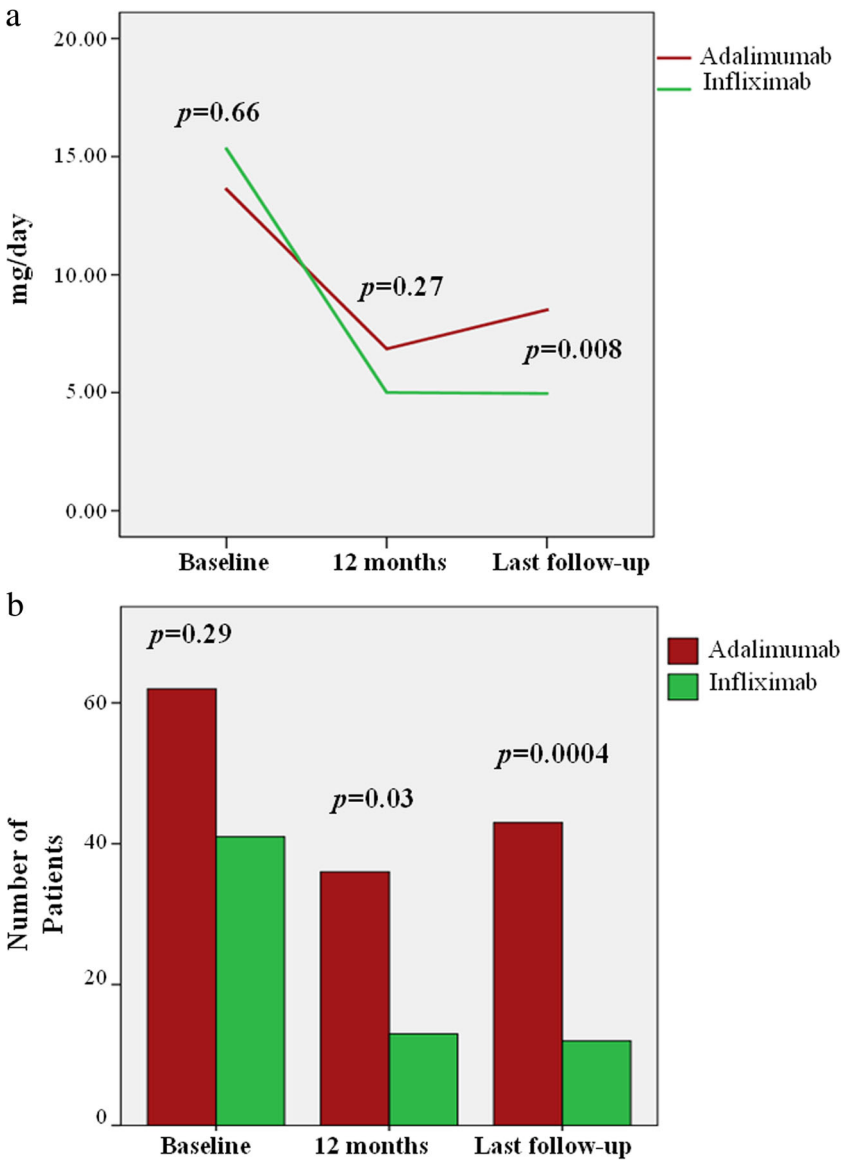

Fig. 1 Graphical representation of the mean systemic corticosteroid dosage (mg/day of prednisone or equivalent) (**a**) and the cumulative number of patients taking corticosteroids (**b**) at baseline, at the 12-month visit and at the last assessment. The relatively low corticosteroid dosage at baseline is related to the inclusion criteria of the study (see the "Method" section), which permits the enrollment of patients with a recent (within 60 days) active uveitis in addition to those experiencing active ocular disease at the start of the study

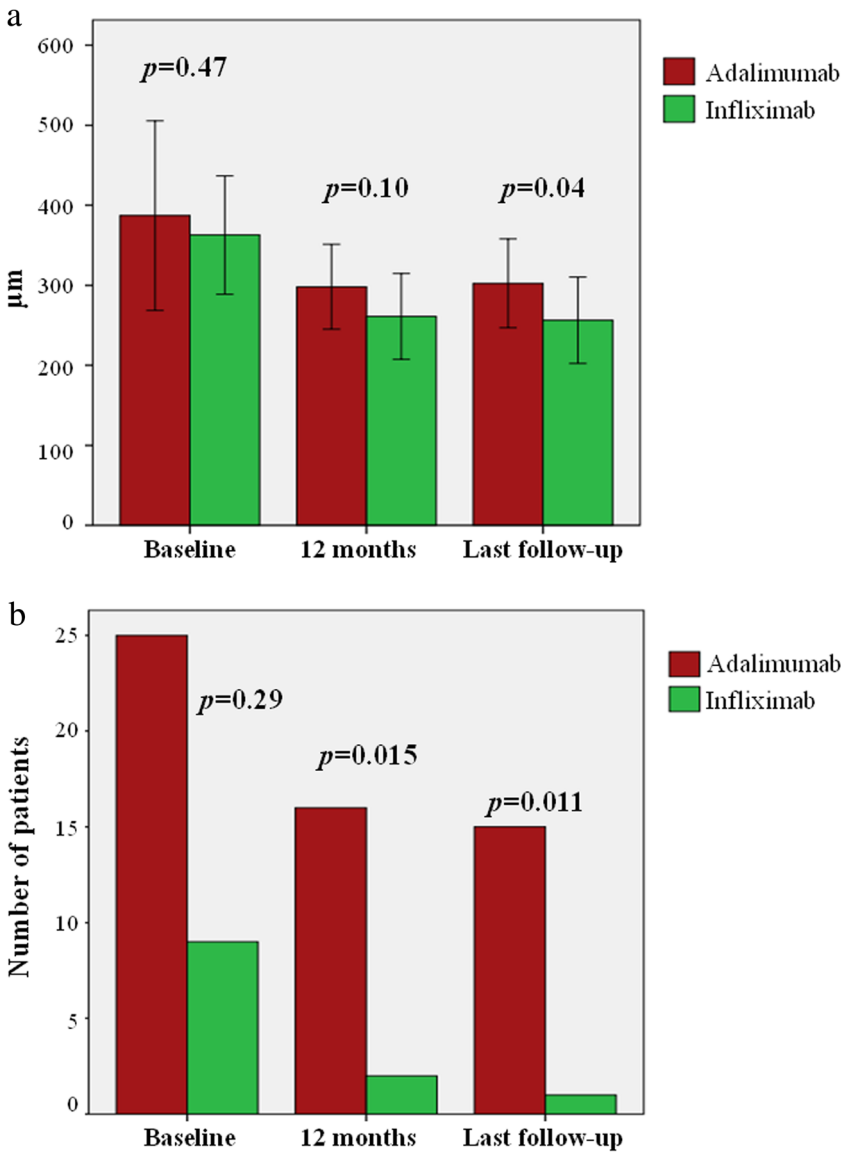

Fig. 2 Histograms show the mean value of the central macular thickness (CMT) assessed at the optical computed tomography during follow-up among patients with uveitic macular edema (UME) at baseline (**a**); the cumulative number of patients with UME (CMT > 300 μm) at baseline and at the following study time-points (**b**). The error bars in the upper histogram represent one standard deviation from the mean

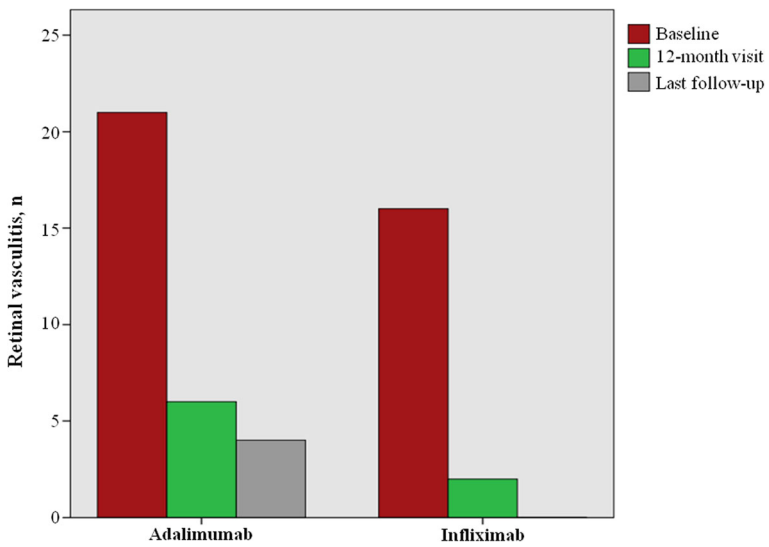

Fig. 3 Number of patients undergoing adalimumab or infliximab and presenting with retinal vasculitis identified at the fluorescein angiography performed at the start of the study (baseline), at the 12-month assessment and at the last follow-up visit

uveitis-related complications was standardized for the length of follow-up, the number of eyes involved/100 patients/year was 9.64 in the ADA group and 9.8 in IFX group. Ocular complications are detailed in Fig. 4.

Discussion

During the last decade, an increasing number of papers have highlighted the effectiveness of monoclonal TNF-α blockers in patients with uveitis, pointing out their role in controlling ocular inflammation, decreasing the number of relapses, preventing retinal vasculitis, and contrasting UME as a challenging sight-threatening complication [6, 7, 10–17, 21–24]. In particular, most of the international literature focuses on the role of ADA and IFX that currently represent the most frequently employed biologic agents in patients with uveitis. Nevertheless, comparative studies between the two TNF-α inhibitors are currently lacking and understanding which of the two may have a higher role in counteracting any single manifestation of uveitis is an unmet need. In this context, the present study has been conducted with the aim to determine any difference between ADA and IFX in terms of efficacy, by assessing their ability in controlling uveitis relapses and allowing CS tapering in patients with intermediate uveitis, posterior uveitis, and panuveitis. Clinical efficacy has been also investigated by assessing any difference in preserving visual function, controlling retinal vasculitis, resolving UME, preventing structural complications, and inducing withdrawal of concomitant use of cDMARDs.

Our data confirm that both monoclonal TNF-α inhibitors are highly effective in the treatment of non-infectious intermediate uveitis, posterior uveitis, and panuveitis. In particular, both ADA and IFX were able to induce a remarkable decrease in the frequency of uveitis relapses compared to the 12 months preceding TNF-α inhibition. Although the decrease of uveitis recurrences appeared higher among patients treated with ADA, no statistically significant differences were highlighted between the two study groups. Conversely, the number of patients treated with CS was significantly lower in the IFX group since the 12-month assessment and then at the last follow-up visit. Among those patients remaining on CS treatment, no significant differences were found between ADA and IFX in the mean daily CS intake after 1 year of treatment, while the significantly lower CS dosage identified among patients treated with IFX at the last visit should be considered in the view of the different length of follow-up. Overall, our data suggest no differences between the two biologics in the mean systemic CS dosages when a concomitant low-dose steroid treatment is given; on the other hand, IFX appears to allow more frequent CS withdrawals with no statistically significant impact on the frequency of uveitis relapses.

No differences were identified between the two anti-TNF-α biologic agents at the different time points in terms of stabilization of visual acuity, frequency of retinal vasculitis identified at FA, number of patients concomitantly administered with cDMARDs, frequency of treatment discontinuations and adjustments. These data highlight a similar efficacy of ADA and IFX in preventing visual loss in patients with uveitis and avoiding retinal vasculitis as one of the most fearsome sight-threatening manifestations in such patients. Likewise, the two biologic agents showed a similar cDMARDs sparing effect as well as an overlap probability of undergoing treatment adjustments to reestablish systemic response and treatment discontinuation because of primary or secondary inefficacy or safety concerns.

Of note, the number of patients showing UME was significantly lower among subjects treated with IFX than those

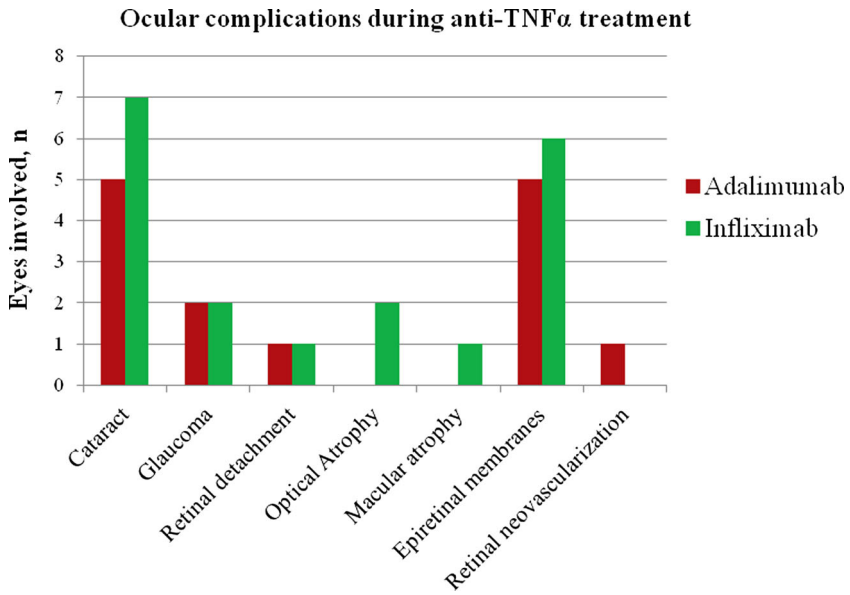

Fig. 4 Number of eyes involved by specific uveitis-related ocular complications. As also reported in the "Result" section, uveitic complications were identified in 10 patients (14 eyes) treated with adalimumab and 9 patients (15 eyes) treated with infliximab. Four eyes treated with infliximab developed two complications during follow-up

treated with ADA both at the 12-month assessment and at the last visit. Conversely, no differences were identified in the number of patients with UME at the start of TNF-α inhibition. Furthermore, CMT was found significantly higher in the ADA group compared to IFX group at the last follow-up assessment. As a whole, these results seem to suggest a higher efficacy of IFX in controlling UME when compared to ADA. Although these results await for a confirmation by prospective RCTs, they represent intriguing elements to pay attention to when dealing with UME, that is the most common cause of visual impairment in patients with uveitis and requires an early treatment even in patients with full visual acuity [25–27].

No significant differences were identified in the number of patients with uveitis-related complications during the follow-up. Similarly, the number of eyes affected by uveitis-related complications was similar between the two TNF-α inhibitors when standardized as eyes involved/100 patients/year. Therefore, our data suggest that the incidence of uveitis-related ocular complications is similar disregarding the type of the TNF-α inhibitor used.

To the best of our knowledge, only one previous study conducted by Vallet et al. has been performed with the aim to identify differences in the efficacy and safety of ADA and IFX in patients with intermediate uveitis, posterior uveitis, and panuveitis [15]. However, the authors also enrolled patients suffering from anterior uveitis and identified different endpoints related to different aims. In particular, Vallet et al. compared ADA and IFX in terms of clinical response according to the SUN working group criteria, event-free survival, and serious side effects [15]. On the other hand, the endpoints identified in the present study are aimed at assessing any difference in the decrease of uveitis relapses along with the evaluation of other indicators of efficacy, including CS sparing effect, control of retinal vasculitis, resolution of UME, and prevention of ocular complications, which are the main causes of vision loss [4, 28, 29].

Limitations of this study include the retrospective design and the different length of follow-up among ADA and IFX patients. However, while the longer follow-up could have favored IFX in meeting the endpoints over time, a longer employment could have worked against IFX owing to a greatest chance to experience a loss of efficacy or a reduction of performance during a longer period of observation. This could be the case of the mean daily CS intake, which showed to increase from the 12-month assessment to the last follow-up visit only among ADA patients despite the shorter follow-up period.

In conclusion, ADA and IFX have shown a similar efficacy in controlling ocular relapses, preserving visual function, uveitis-related ocular complications, and controlling retinal vasculitis. Conversely, IFX showed a more pronounced CS sparing effect and a significantly higher capacity in resolving UME if compared with ADA. Although these findings require to be confirmed by prospective RCTs, they represent intriguing clues to take into account for the optimal management of non-infectious intermediate uveitis, posterior uveitis, and panuveitis along with uveitis-related sight-threatening complications.

Compliance with ethical standards

The study has been approved by the Ethics Committee of Azienda Ospedaliera Universitaria Senese, Siena, Italy. The study protocol was conformed to the tenets of the Declaration of Helsinki and informed consent was obtained from all patients enrolled.

Disclosures None.

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