Long Term Follow-up and Optimization of Infliximab in Refractory Uveitis Due to Behçet's Disease. National Study of 103 Caucasian Patients

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Running Title: *IFX in Behçet-uveitis.*

ABSTRACT

Objective: In a large series of Caucasian patients with refractory uveitis due to Behçet disease (BD) treated with infliximab (IFX) we assessed: a) long-term efficacy and safety and b) IFX optimization when ocular remission was achieved.

Methods: Multicenter study of IFX-treated patients with BD uveitis refractory to conventional immunosuppressant agents.103 patients/185 affected eyes were treated with IFX as first biologic therapy as follows: 3-5 mg/kg i.v. at 0, 2, 6 and then every 4-8 weeks. a) The main outcome variables were analyzed at baseline, 1st week, 1st and 6th months and 1st and 2nd years of IFX therapy. b) After remission, based on a shared decision between patient and clinician, IFX optimization was performed. Efficacy, safety, and cost of IFX therapy were evaluated.

Results: In whole series (n=103), main outcome variables showed a rapid and maintained improvement, reaching remission in 78 patients after a mean IFX duration of 31.5 months. Serious adverse events were observed in 9 patients: infusional reactions (n=4), tuberculosis (n=1), Mycobacterium avium pneumonia (n=1), severe oral ulcers (n=1), palmoplantar psoriasis (n=1) and colon carcinoma (n=1).

In the optimization subanalysis, the comparative study between optimized and non-optimized groups showed: a) no differences in clinical characteristics at baseline; b) similar maintained improvement in most ocular outcomes; and c) lower severe adverse events, and d) lower mean IFX costs in optimized group (4,826.52 vs. 9,854.13 euros/patient/year).

Conclusions: IFX seems to be effective and relatively safe in Caucasian patients with refractory BD uveitis. IFX optimization is effective, safe, and cost-effective.

INTRODUCTION

Ocular involvement is one of the most severe manifestations of Behçet`s Disease (BD) and occurs in 35-90% of patients, leading to visual loss in a range between 13% and 74% of them [1-5]. Nevertheless, biologic therapy has improved the ocular prognosis of these patients. Anti-TNFα drugs, especially adalimumab (ADA) and infliximab (IFX), have been the most studied group [6]. ADA has been approved by the EMA and the FDA for non-infectious non-anterior uveitis, based on two Phase III trials (VISUAL I and VISUAL II) [7, 8]. However, the number of patients with BD included in these studies was scarce, 12 patients [11%] in the VISUAL I and 10 [9%] in the VISUAL II study.

Although IFX has not been approved in the USA or Europe for non-infectious uveitis, it has been successfully used for treating uveitis refractory to conventional immunosuppressive therapy [9-21]. Therefore, according to Expert Panel Recommendations, IFX has a good-quality evidence and should be considered in the early management of BD patients with vision-threatening ocular manifestations [22]. Moreover, in Japan, IFX has been approved for uveoretinitis due to BD, at the dose of 5 mg/kg (0, 2, 6, and then every 8 weeks) [23, 24]. In recent years, several retrospective observational studies with a relatively large sample of patients with BD uveitis and treated with IFX were performed [25-29].

On the other hand, an increased risk of relapses when IFX treatment is withdrawn, even in patients with sustained remission, has been reported [29]. Furthermore, biologic therapy optimization in systemic diseases has shown a reduction in the number and severity of adverse events and in the cost of treatment [30, 31]. Thus, a study on the efficacy and safety of ADA optimization in patients with refractory uveitis secondary to BD has been recently published [30]. However, to the best of our knowledge, there is no information on IFX therapy optimization in BD patients with refractory uveitis [30, 31].

Taking into account these considerations, our aims were to evaluate, in a large series of Caucasian BD patients with refractory uveitis, **a)** the long-term efficacy and safety of

IFX therapy and, **b)** if optimization therapy can be successfully performed when ocular remission is achieved.

PATIENTS AND METHODS

Design, Enrolment Criteria and Definitions

This study is part of a broader open-label multicenter study that included 177 Caucasian patients with refractory uveitis due to BD treated with IFX and ADA as first-line biologic therapy [32]. IFX was used in 103 patients and ADA in 74. The objectives of this study were **a)** to evaluate the long term efficacy and safety of IFX and **b)** to establish whether the IFX optimization is equally effective, safe and cost-effective.

Patients were followed-up at 35 Uveitis Units from different Spanish hospitals.

BD was diagnosed according to the Classification Criteria for BD proposed by the International Study Group in 1990 [33]. Anatomical classification of uveitis was performed according to the Standardization of Uveitis Nomenclature (SUN) Working Group [34].

All the patients had uveitis refractory to corticosteroids and had previously received at least one conventional synthetic immunosuppressive drug [32].

Malignancy or systemic infectious diseases were excluded before anti-TNF onset, as previously described [9, 10, 20, 35-40].

The conventional immunosuppressive drugs and dosages used before IFX onset were as follows: cyclosporine A (CsA) (3-6 mg/kg/p.o./day), methotrexate (MTX) (7.5-25 mg/s.c. or p.o./week) azathioprine (AZA) (100-150 mg/p.o./day) and mycophenolate mofetil (2-3 g/p.o./day). The therapeutic schedule included three consecutive pulses of methylprednisolone (MP) 500-1000 mg/day in cases of severe uveitis.

IFX was administered as follows: a loading intravenous (i.v.) dose of 3-5 mg/kg at weeks 0, 2 and 6, and then a maintenance dose every 4-8 weeks until remission was achieved.

Remission was established if there were no signs of intraocular inflammation for at least 3 months.

Relapses were defined as the occurrence of a new flare of uveitis in a patient who had reached remission [41].

Based on a shared decision between the patient and the physician, IFX was optimized once ocular remission was achieved. Only those patients with an initial standard maintenance dose of 5 mg/kg every 8 weeks have been selected for the subanalysis of IFX optimization. Optimization was performed by prolonging IFX dosing interval and/or reducing IFX dose. The non-optimized group included those patients with BD uveitis who reached remission after IFX therapy and the dose and interval were maintained unchanged.

Before IFX onset, all patients signed written informed consent, since prescription of IFX was an *off-label* indication by the EMA for the treatment of non-infectious and non-anterior uveitis. In addition, the approval of the corresponding Ethics committee was obtained (2018.081).

Outcome variables

To determine efficacy, the intraocular inflammation, macular thickness, visual acuity and the sparing effect of glucocorticoids and total immunosuppression load were assessed. These variables were recorded at baseline (IFX onset), 1st week, 2nd week, 1st month, 3rd month, 6th month and 1st and 2nd years consecutively. Intraocular inflammation included the following features: anterior or posterior chamber inflammation, vitritis, retinal vasculitis, papillitis, and macular thickness. The degree of intraocular inflammation was evaluated according to the SUN Working Group [34]. Vitritis was assessed by the Nussenblatt scale [41].

Fluorescein angiography (FA) was performed to assess the presence of retinal vasculitis. Retinal vasculitis was defined as retinal angiographic leakage, staining and/or occlusion on FA [5].

To assess the macular thickness, High-Definition Optical Coherence Tomography (OCT), using a Cirrus HD-OCT (Carl Zeiss, Dublin, CA, USA), was performed. Scans were obtained using the 512x128 scan pattern. Macular thickening was defined as a macular thickness >250 μm.

The best-corrected visual acuity (BCVA) was estimated using the Snellen chart. Immunosuppression degree was calculated according to the semi-quantitative scale proposed by Nussenblatt et al [42]. The grading scheme provides a combined, single numeric score for the total immunosuppression load per unit of body weight and per day. Grades for each agent (prednisone, cyclosporine, azathioprine, methotrexate, and chlorambucil) ranged on a scale from 0 to 9, whereas mycophenolate mofetil ranged from 0 to 7. For patients receiving multiple medications, the sum of the grading score for each drug was used to calculate the total immunosuppression score on a scale from 0 to 15.

Statistical analysis

Results were expressed as mean ± standard deviation (SD) or as median and interquartile range [IQR] [25th, 75th] as appropriate. Normality of data was assessed by the Kolmogorov-Smirnov test. Continuous variables were compared with the two-tailed Student's t-test or the Mann-Whitney U test. Chi-square test or Fisher exact test and McNemar's tests were used to compare dichotomous variables and Wilcoxon signed-rank test was used to compare continuous variables before and after IFX therapy. Variables assessed and compared with baseline (IFX onset), evaluated at 1st week, 1st month, 3rd month, 6th month and 1st and 2nd years, were the following: BCVA, anterior chamber (AC) cell count, vitritis, vasculitis, OCT and glucocorticoid sparing effect. Additionally, the same variables were analyzed and compared at baseline, at the time of optimization and at the last visit separately in each group (optimized and non-optimized patients). The probability of improvement of ocular variables and the occurrence of adverse events during the study period were compared using unadjusted Kaplan-Meier survival analysis and log-rank tests. To adjust for the possible within and

between-eye correlation we used a repeated measured general linear model (variables were log-transformed before analysis), and Bonferroni procedure was carried out to test for multiple comparisons. Statistical significance was considered as a two-tailed p-value <0.05 in all the calculations. Statistica software (StatSoft) was used for data processing.

RESULTS

Demographic and clinical features at baseline

From a series of 177 Caucasian patients with refractory uveitis due to BD, IFX was used as the first biologic agent in 103 (55 men/48 women) patients. The mean age was 40.4±10.1 years. The median duration of uveitis before IFX onset was 36 [12-72] months. In most cases, uveitis was bilateral (79.6%). The main demographic and clinical data of the whole series have been previously published [32] and are summarized in **Table 1**.

Besides oral glucocorticoids (mean maximum prednisone daily dosage 54.4±15.8 mg/day) and before the onset of biologic therapy, patients had received the following immunosuppressive agents: i.v. pulses of MP in 30 patients, CsA in 77 patients (mean dose 4.9±0.8 mg/kg/day), AZA in 58 patients (mean dose 137.2±32.3 mg/day), MTX in 45 patients (mean dose 16.7±3.6 mg/week). The immunosuppression load score was 9.1±4.1.

Efficacy of Infliximab therapy

The main outcome variables assessed in the study (intraocular inflammation, macular thickness, and BCVA) showed a rapid and maintained improvement throughout the study (**Figure 1**).

A statistically significant improvement was observed in all the variables analyzed since the first week. The mean BCVA increased from a mean value of 0.44±0.28 before the

onset of biologic therapy to 0.63±0.28 at 2nd year (p<0.0001). At the same time, all patients had a progressive improvement in intraocular inflammation. The percentage of eyes with improvement of AC cell count according to SUN criteria was increased to 80.4% at 2nd year. With respect to eyes with vitritis, an improvement was seen in 84.4% at 2nd year. In addition, a significant decrease in the percentage of eyes with retinal vasculitis (58% at the beginning compared to 2% at 2nd year) was also observed. In addition, OCT mean value (μ) decreased from 337.7±121.8 at the onset of IFX therapy to 267.8±52.9 at 2nd year (p=0.006) (**Figure 1**).

The immunosuppression load score was also reduced by almost half (from 9.1±4.1 to 4.8±3.5 at 2-years follow-up) one year after starting IFX. Furthermore, the daily median dose of prednisone was reduced from 30 [20-45] mg/day at baseline to 1.25 [0-5] mg/day at 2nd year (**Figure 1**).

Follow-up and safety of Infliximab therapy

After a mean follow-up of 31.5±23.5 months, 78 patients (76.5%) achieved ocular remission. IFX was withdrawn in 57 (55.3%) patients, in 20 of them due to maintained remission and in the remaining 37 because of inefficacy (n=18), preference of change to subcutaneous administration (n=9), toxicity/side effects (n=9) and pregnancy wishes (n=1). In 34 of these 37 patients in which IFX was withdrawn, switching was done from IFX to ADA in 32 cases (18 because of treatment failure, preference of subcutaneous administration in nine patients and in the remaining five because of toxicity/side effects), to rituximab (RTX), in one case due to side effects and to etanercept (ETN), in another patient due to side effects. Additionally, further switching to golimumab (n=1) and RTX (n=1) was necessary for two patients due to ADA inefficacy.

Severe complications leading to discontinuation of IFX therapy were observed in 9 patients: infusional reactions (n=4), tuberculosis (n=1), *Mycobacterium avium* pneumonia (n=1), severe oral ulcers (n=1), palmoplantar psoriasis (n=1) and colon carcinoma (n=1).

IFX optimization: subanalysis of efficacy, side effects, and cost

Ocular remission was achieved in 78 of the 103 IFX-treated patients (76.5%) after a mean of 31.5±23.5 months of therapy. A subanalysis was performed in a group of 60 patients who achieved ocular remission with the standard dose of 5 mg/kg at weeks 0, 2, 6 and then every 8 weeks (standard dose). The dose was optimized in 18 patients (optimized group) while in the remaining 42, the dose of 5 mg/kg every 8 weeks was maintained until the end of the follow-up period (non-optimized group).

Optimized patients did not show significant demographic or clinical differences at IFX onset when compared with the non-optimized group (**Table 2**). Ocular features at IFX onset were similar in both groups, as well as the previous use of conventional immunosuppressants, the number of patients receiving oral glucocorticoids or MP pulses and the mean dose of prednisone (**Table 2**).

Following IFX onset, the intraocular inflammation, macular thickness, visual acuity and, the sparing effect of glucocorticoids was assessed in both groups. In the optimized group, the BCVA increased progressively from baseline to the time of IFX optimization (0.33±0.21 vs. 0.68±0.28; p <0.0001). This improvement was maintained at the last visit when compared with baseline values (0.70±0.29; p <0.0001) (**Figure 2A**). Also, in the optimized group, mean OCT (μm) decreased from 303.5±23.3 (IFX onset) to 276.5±34.6 (last visit; p=0.18).

Improvement of intraocular inflammation also persisted with optimization. Thus, the percentage of eyes with an improvement of AC cells/vitritis (SUN criteria) increased from 50/45.5% (IFX onset) to 100/100% at the time of optimization and at the last follow-up visit, respectively. A significant decrease in the percentage of patients with retinal vasculitis (44.4% at the baseline vs. 0% at the time of optimization and 0% at the final visit) was also observed. Improvement of all ocular parameters was also observed in the non-optimized group. Because of that, most ocular outcomes were

similar in the optimized and non-optimized groups after a mean follow-up of 46.6±18.4 and 27.9±24.8 months since the onset of IFX therapy in optimized and non-optimized patients, respectively. Using the data for the last observation carried forward (LOCF) in the follow-up period, in both groups (optimized vs. non-optimized patients), the percentages were as follows: AC cells improvement: 18/18 vs. 39/42 patients (100% vs. 96.3%) (p=0.99); Vitritis improvement: 18/18 vs. 31/42 patients (100% vs. 74.1%) (p=0.07); Retinal vasculitis (absence): 18/18 vs. 42/42 patients (100% vs. 100%). Kaplan-Meier curves for both groups regarding the probability of improvement of AC cells and vitritis, and the corresponding results of the log-rank tests are shown in the **Figures 3A and 3B.**

Regarding the optimized group, the dose schedule and maintenance intervals of IFX were as follows: 3 mg/kg every 8 weeks (n=2), 3 mg/kg every 10 weeks (n=4), 5 mg/kg every 10 weeks (n=6) and 5 mg/kg every 12 weeks (n=6). In 6 patients, IFX was finally successfully withdrawn. The immunosuppressive load in optimized vs. non-optimized patients at LOCF in the follow-up was 11.0 (8.0-14.0) vs. 8.0 (5.8-12.3); p=0.06.

We also observed a sparing glucocorticoid effect in both groups. Dosage at LOCF in optimized vs. non-optimized patients was 5.0 (0.0-8.8) vs. 2.5 (0.0-5.0) mg/d (p=0.57) (**Figure 2B**).

We have found no statistically significant differences considering the outcome variables (baseline vs. final values), between optimized and non-optimized patients, when repeated measures general linear models were built and adjusted by age, sex, duration of Behçet disease, previous use of azathioprine and presence of vitritis at baseline. Concerning BCVA p-value was 0.36 (p for the interaction: 0.20). The corresponding figure for prednisone dosage was p= 0.17 (p for the interaction: 0.63).

Moreover, when we analyzed the number of relapses, we observed that both groups had very similar medians (0 [0-1] in optimized and 0 [0-2] in non-optimized patients), without statistically significant differences between them (p=0.85) (**Table 2**).

No serious adverse events were observed in the optimized group, but they were found in 3 patients (7.1%) from the non-optimized group (p=0.55), all infusional skin reactions (**Table 2**). For this reason, IFX was permanently withdrawn in these patients. **Figure 3 C** shows the Kaplan-Meier analysis concerning the cumulative probability free from serious adverse events in optimized and non-optimized patients.

Finally, the mean IFX treatment costs were much lower in the optimized group than in the non-optimized group (4826.52 vs. 9854.13 euros/patient/year), achieving an overall annual cost reduction of 51%.

DISCUSSION

To the best of our knowledge, this multicenter study represents the largest series of Caucasian patients with refractory uveitis due to BD undergoing IFX therapy. This therapy seems to be effective and relatively safe in short and long-term. After remission, IFX optimization was successfully performed in 18 (30%) out of 60 patients, being a therapeutic scheme of similar efficacy but safer and less expensive.

Although the incidence of ocular sequelae due to uveitis in patients with BD has decreased, it still remains inappropriately high [3, 5, 43]. Therefore, different targeted therapies have been studied. Thus, high serum TNF-α in aqueous humor of patients with uveitis, including those with BD-related uveitis, have been reported [44, 45].

IFX is a human/mouse chimeric monoclonal IgG1 anti-TNF-α antibody widely used in immune-mediated diseases, including uveitis. However, randomized phase III studies with IFX in uveitis have not been published yet. Nevertheless, in patients with severe uveitis related to BD, IFX has demonstrated efficacy in observational studies [9, 11, 25-28, 46].

In the present study, we describe one of the largest series of patients with uveitis due to BD, refractory to conventional immunosuppressive drugs undergoing IFX therapy in a real-world setting, and the largest series in a Caucasian population. All patients had received high doses of glucocorticoids and, at least, one conventional synthetic immunosuppressive agent before biologic therapy was started. In all patients, IFX was prescribed because of poor control of ocular inflammation with conventional therapy. IFX was effective in most cases, with a statistically significant rapid and maintained improvement of all ocular parameters during a 2-year follow-up. In addition, we have observed a glucocorticoid-sparing effect, showing a significant decrease in the median oral prednisone dose from 30 mg/day at IFX onset to 5 mg/day after 2 year of therapy. In the last three years, several studies reported by *Fabiani C et al* support our results, with high drug retention rates, remarkable sparing glucocorticoid effect and very similar long-term efficacy and safety data [25-28].

Furthermore, IFX therapy was discontinued in 20 patients after reaching a sustained remission, similarly to data published by several authors [47, 48]. However, IFX was withdrawn in 18 (17.5%) patients due to inefficacy. Whether this fact could be related to the development of long-term anti-drug antibodies remains speculative, since we did not perform such tests.

In the present study, the number of patients on IFX who experienced serious adverse events at 2 years was lower than in other series [11] and most of them were mild infusional reactions. Nevertheless, serious adverse events leading to discontinuation of the biologic treatment were observed in one patient who had a reactivation of latent tuberculosis, as described in several studies with other anti-TNFα drugs [49]. The incidence of neoplasms in patients with biological treatment still remains a controversial issue. Nevertheless, a recent meta-analysis did not demonstrate an increased risk of cancer in rheumatoid arthritis patients treated with anti-TNFα agents compared with

placebo [50]. In our series, one patient developed a colon carcinoma, but we cannot establish that the tumor was related to IFX therapy.

Optimization of long-term biologic therapy in patients who achieve remission is of great relevance in terms of efficacy, side-effect reduction and costs. Several studies have shown that intensive outpatient strategies involving tight control and frequent monitoring of disease activity as well as treatment adjustments to meet therapeutic goals can produce better outcomes than traditional strategies. In this regard, we previously reported the successful optimization of adalimumab treatment in 23 patients who had achieved clinical remission in patients with refractory uveitis secondary to BD, reducing costs and also adverse events [30].

In the present study, both optimized and non-optimized patients presented a maintained improvement of ocular parameters analyzed. Moreover, a lower frequency of severe side effects without an increase in the number of relapses was observed in optimized group. In Spain, IFX cost (Remicade® 100 mg/20 ml vial) for a standard weight of 70 kg is around 1,408 euros. Therefore, optimization after remission yielded a significant reduction of the mean cost of IFX per patient and year.

Up to 50% of patients with uveitis due to BD may have relapses when abruptly discontinuing biologic treatment [27], once remission is achieved. Therefore, IFX optimization has been performed slowly by progressive prolongation of dosing interval and decreasing the dose sequentially.

Based on our experience, we propose a protocol for the IFX optimization in refractory uveitis secondary to BD who achieves remission. In this regard, after 12 months of treatment with IFX and once remission was reached and sustained for at least 3-6 months, we recommend any of the following two alternatives: **a)** extending very slowly, but progressively, the dosing intervals with regular monitoring of ocular inflammation parameters; **b)** reducing the dose to 3 mg/kg every 8 weeks and then increase progressively the dosing interval with thigh ocular control. Once the dosing interval has

been increased up to every 12 weeks, and there is no ocular inflammation data, we recommend discontinuing treatment but keeping close monitoring. If relapse occurs, the patient should be restarted with the standard dose of 5 mg/kg every 8 weeks (**Figure 4**).

Our study has several limitations due to its observational nature and the relatively low number of optimized patients. Because of that, further randomized controlled trials comparing conventional immunosuppressive drugs and other anti-TNFα agents are required. However, it is really difficult nowadays to carry out such a clinical trial in these specific diseases, and even less since the entry of biosimilars into the market. Therefore, future information will be probably obtained from observational multicenter studies, such as ours.

In conclusion, our results suggest that IFX seems to be effective and relatively safe, at short and long-term, in Caucasian patients with refractory BD uveitis. IFX optimization could be feasible, safer, and more cost-effective than conventional IFX therapy.

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FIGURE LEGENDS

FIGURE 1. Rapid and maintained improvement following the onset of TNF-α infliximab (IFX). **A**. Best-corrected visual acuity (BCVA); **B**. Macular thickness (OCT); **C**. Retinal vasculitis (% affected eyes); **D**. Percentage of patients with improvement on anterior chamber cells and vitritis according to Standardization of Uveitis Nomenclature (SUN) Working Group criteria; **E.** Glucocorticoid-sparing effect following IFX therapy (mg/day).

FIGURE 2. Rapid and maintained improvement following the onset of infliximab (IFX) regardless of further optimization. No significant differences between optimized and non-optimized patients were seen. **A**. Mean best-corrected visual acuity (BCVA); **B**. Successful glucocorticoid-sparing effect following the onset of IFX therapy. p values for panels A and B show the differences between baseline findings and those observed at each period of time, including the time of optimization and the last visit. The assessment was performed in optimized and non-optimized patients.

FIGURE 3. Kaplan-Meier curves showing the probability of AC cells improvement (panel **A**); the probability of vitritis improvement (panel **B**); and the cumulative probability free from serious adverse events (panel **C**) in optimized (black lines) and non-optimized (grey lines) patients.

FIGURE 4. A proposed protocol for optimization of infliximab (IFX) dose up to withdrawal by **A)** extending the dosing interval progressively (upper panel), or **B)** reducing the dose and prolonging the dosing interval (lower panel).

TABLE 1. Main general features and long-term follow-up of a series of 103 patients with refractory uveitis due to Behçet's disease treated with infliximab (IFX).

Number of patients/eyes affected, n/n	103/185
Age, mean (SD), years	40.4 (10.1)
Sex, men/women, n/n (%)	55/48 (53.4/46.6)
HLA-B51 positive (%)	69.4
Duration of Behçet Disease before IFX, median [IQR] months	40 [17-87]
Duration of uveitis before IFX, median [IQR] months	36 [12-72]
Ocular features at the time of IFX onset	
- AC cells count, median [IQR]	1 [0-2]
- Vitritis, median [IQR]	1 [0-2]
- BCVA, mean (SD)	0.44 (0.28)
- OCT, mean (SD)	337.7 (121.8)
- Retinal vasculitis, % affected eyes	58
Pattern of uveitis, n (%)	
- Bilateral/unilateral	82/21 (79.6/20.4)
- Anterior	11 (10.7)
- Posterior	28 (27.2)
- Panuveitis	64 (62.1)
Previous treatment to anti-TNF onset, n (%)	
- CsA	77 (74.8)
- AZA	58 (56.3)
- MTX	45 (43.7)
- Pulses of i.v. MP	30 (29.1)
- Oral glucocorticoids	100 (100)
- Other treatments	34 (33.0)
Prednisone dose at IFX onset, median [IQR], mg/d	30 [20-45]

Regimen of IFX therapy	
Monotherapy/combined treatment, n (%)	25/78 (24.2/75.8)
- AZA	17 (16.5)
- CsA	32 (31.1)
- MTX	26 (25.2)
- MMF	1 (1)
- Tacrolimus	1 (1)
- CFX	1 (1)
IFX dosage, n (%)	
- 3 mg/kg i.v. (0, 2, 6 weeks) and then every 4-8 weeks	8 (7.8)
- 4 mg/kg i.v. (0, 2, 6 weeks) and then every 4 weeks	1 (1)
- 5 mg/kg i.v. (0, 2, 6 weeks) and then every 4-8 weeks	94 (91.2)
Follow-up on IFX therapy, mean (SD), months	31.5 (23.5)
- **Remission, n (%)**	78 (76.5)
- **Discontinuation treatment, n (%)**	57 (55.3)
○ Remission	20 (19.4)
○ Inefficacy	18 (17.5)
○ Side effects/toxicity	9 (8.7)
○ Other	10 (9.7)
- **Severe side-effects, n (per 100 patients/year)**	9 (8.7)

Abbreviations: AC: anterior chamber; ADA: adalimumab; AZA: azathioprine; BCVA: best-corrected visual acuity; CFX: cyclophosphamide; CsA: cyclosporine A; IFX: infliximab; MMF: mycophenolate mofetil; MTX: methotrexate; MP: methylprednisolone; OCT: optical coherence tomography; TNF: tumor necrosis factor.

TABLE 2. Main General features and follow-up of a subgroup of patients (n= 60) with Refractory Uveitis Due to BD who Achieved Remission after the standard dose of IFX therapy (5 mg/kg at 0, 2, 6 and then every 8 weeks). Differences between Optimized and Non-optimized patients

	Patients with Optimized dose N=18	**Patients without Optimized dose N=42**	**P**
Number of patients/eyes affected, n/n	18/34	42/77	
Age, mean (SD), years	39.5 (9.8)	38.8 (10.5)	0.82
Sex, men/women, n/n (%)	10/8 (55.6/44.4)	25/17 (59.5/40.5)	0.78
Duration of Behçet Disease before IFX, median [IQR] months	52 [36-119]	36 [12-48]	0.07
Duration of uveitis before IFX, median [IQR] months	38 [18-119]	35 [10-48]	0.11
Ocular features at the time of IFX onset			
- AC cells count, median [IQR]	2 [1-4]	2 [1-2]	0.29
- Vitritis, median [IQR]	2 [1.5-3]	2 [1-2]	0.02
- BCVA, mean (SD)	0.32 (0.21)	0.37 (0.26)	0.51
- OCT, mean (SD)	303.5 (23.3)	397.7 (155.77)	0.12
- Retinal vasculitis, affected eyes, N (%)	48 (9 50%)	58 (26 66.7%)	0.23
Pattern of uveitis, n (%)			
- Bilateral/unilateral	16/2 (88.9/11.1)	35/7 (83.3/16.7)	0.71
- Anterior	0 (0)	6 (14.3)	0.17
- Posterior	5 (27.8)	8 (19.0)	0.50
- Panuveitis	13 (72.2)	28 (66.7)	0.67
Previous treatment to anti-TNF onset, n (%)			
- Oral corticosteroids	17 (94.4)	40 (97.6)	0.52
- CsA	12 (66.7)	28 (66.7)	0.99
- AZA	14 (77.8)	21 (50.0)	0.05

- MTX	8 (44.4)	20 (47.6)	0.82
- Pulses of i.v. MP	3 (18.8)	15 (38.5)	0.16
- Other treatments	7 (38.9)	15 (35.7)	0.82
Prednisone dose at IFX onset, mean (SD), mg/d	40.3 (20.6)	41.4 (15.5)	0.81
Regimen of IFX therapy			
Monotherapy/combined treatment, n (%)	15 (83.3)	30 (71.4)	0.33
- AZA	5 (27.8)	4 (9.5)	0.11
- CsA	9 (33.3)	8 (19.0)	0.32
- MTX	4 (22.2)	15 (35.7)	0.30
- MMF	0 (0)	1 (2.4)	0.99
- Tacrolimus	0 (0)	1 (2.4)	0.99
- CFX	0 (0)	1 (2.4)	0.99
Follow-up on IFX therapy, median [IQR], months	48 [33-60]	24 [6-60]	0.007
- **Relapses, median (IQR)**	0 [0-1]	0 [0-2]	0.46
- **End follow-up remission, %**	100	75.6	0.024
- **Severe side effects, n (per 100 patients/year)**	0 (0)	3 (0.78)	0.55
- **Cost (mean), euros per year**	4,826.52	9,854.13	**-**

Abbreviations: AC: anterior chamber; ADA: adalimumab; AZA: azathioprine; BCVA: best-corrected visual acuity; BD: Behçet disease; CFX: cyclophosphamide; CsA: cyclosporine A; IFX: infliximab; MMF: mycophenolate mofetil; MTX: methotrexate; MP: methylprednisolone; OCT: optical coherence tomography; TNF: tumor necrosis factor.

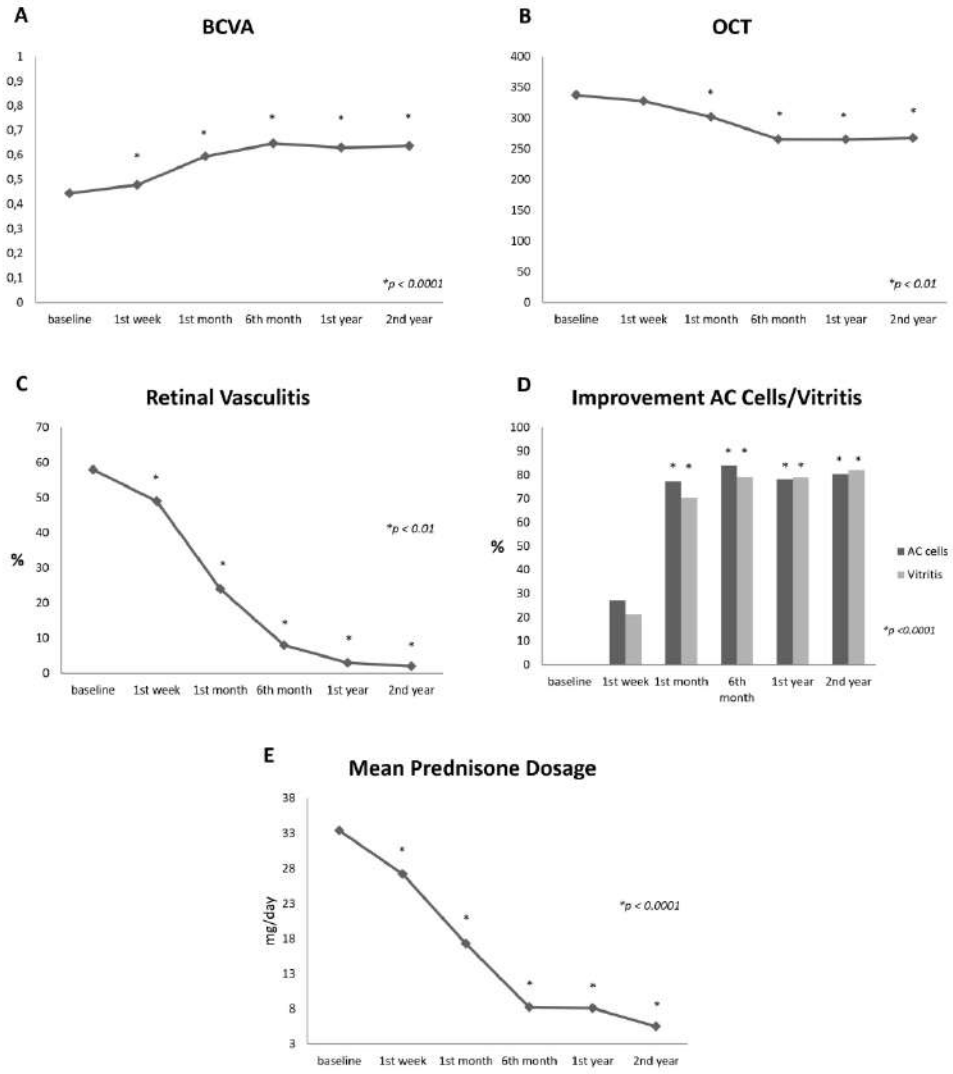

FIGURE 1. Rapid and maintained improvement following the onset of TNF-α infliximab (IFX). A. Best-corrected visual acuity (BCVA); B. Macular thickness (OCT); C. Retinal vasculitis (% affected eyes); D. Percentage of patients with improvement on anterior chamber cells and vitritis according to Standardization of Uveitis Nomenclature (SUN) Working Group criteria; E. Glucocorticoid-sparing effect following IFX therapy (mg/day).

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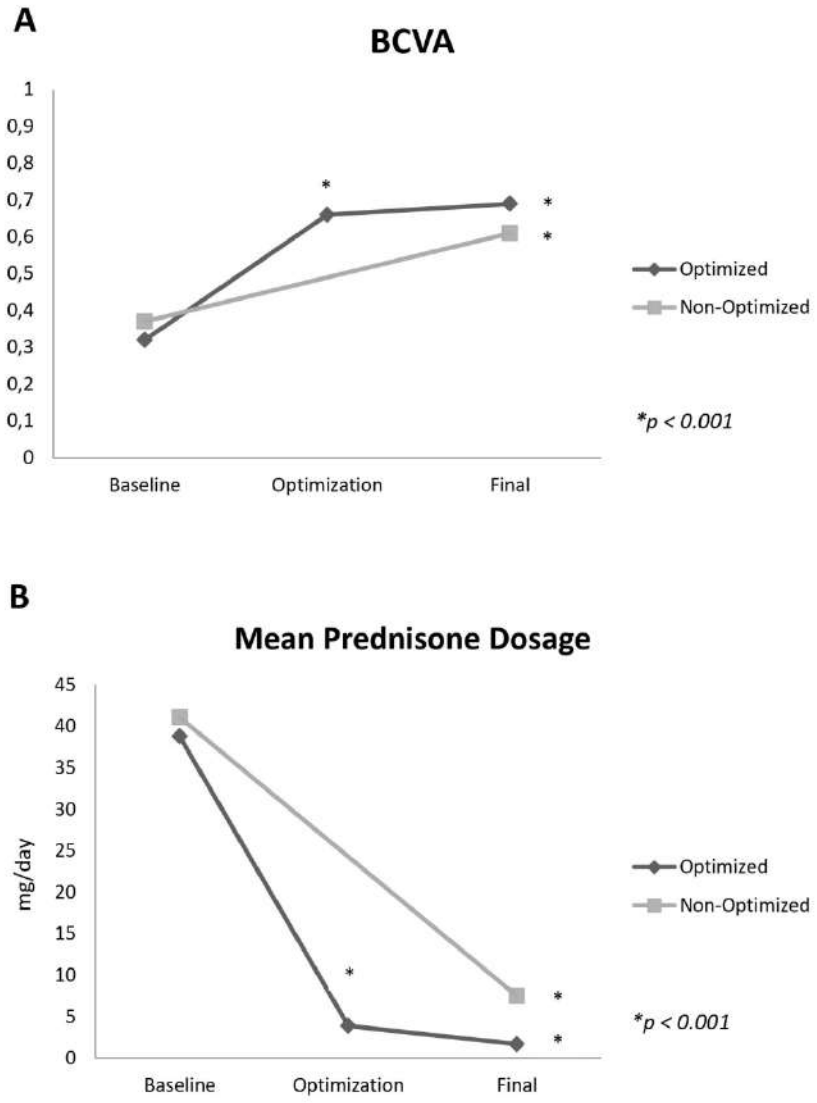

FIGURE 2. Rapid and maintained improvement following the onset of infliximab (IFX) regardless of further optimization. No significant differences between optimized and non-optimized patients were seen. A. Mean best-corrected visual acuity (BCVA); B. Successful glucocorticoid-sparing effect following the onset of IFX therapy. p values for panels A and B show the differences between baseline findings and those observed at each period of time, including the time of optimization and the last visit. The assessment was performed in optimized and non-optimized patients.

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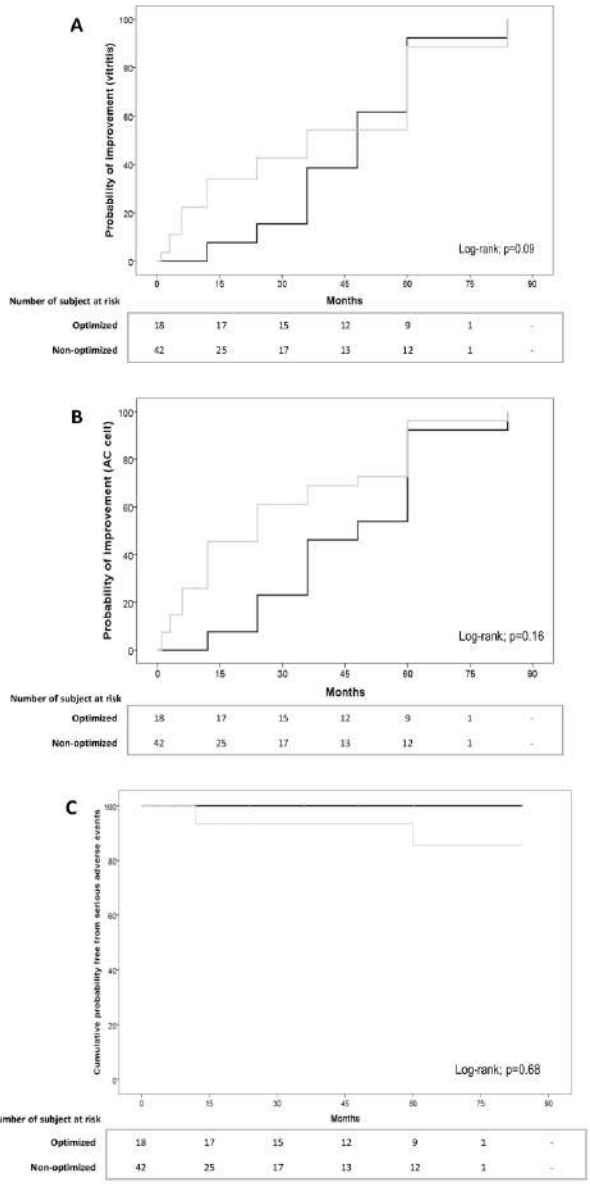

FIGURE 3. Kaplan-Meier curves showing the probability of AC cells improvement (panel A); the probability of vitritis improvement (panel B); and the cumulative probability free from serious adverse events (panel C) in optimized (black lines) and non-optimized (grey lines) patients.

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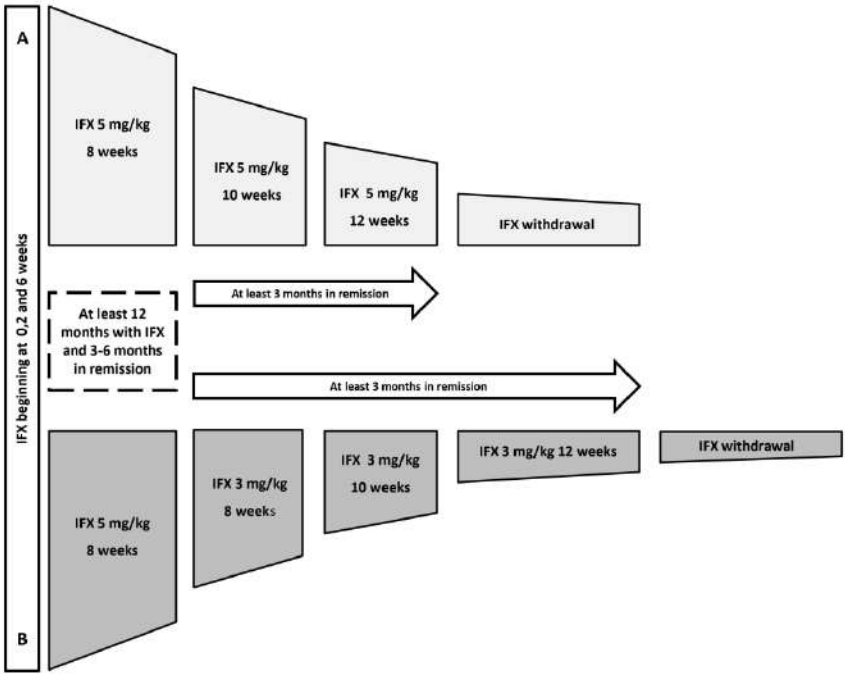

FIGURE 4. A proposed protocol for optimization of infliximab (IFX) dose up to withdrawal by A) extending the dosing interval progressively (upper panel), or B) reducing the dose and prolonging the dosing interval (lower panel).

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