Lower Relapses Rate With Infliximab Versus Adalimumab in Sight-Threatening Uveitis: A Multicenter Study of 330 Patients

Georgina Maalouf, Anaïs Andrillon, Mathilde Leclercq, Pascal Sève, Philip Bielefeld, Julie Gueudry, Thomas Sené, Cherif Titah, Thomas Moulinet, Bénédicte Rouvière, et al.

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Running title :

Lower relapse with infliximab versus adalimumab in uveitis.

Georgina Maalouf [1*], Anaïs Andrillon [2*], Mathilde Leclercq [1,3*], Pascal Sève [4], Philip Bielefeld [5], Julie Gueudry [6], Thomas Sené [7], Cherif Titah [8] Thomas Moulinet [9], Bénédicte Rouvière [10], Damien Sène [11], Anne-Claire Desbois [1], Fanny Domont [1], Sara Touhami [12], Thomas Thibault[1], Carolla El Chamieh [2], Patrice Cacoub [1], Laurent Kodjikian [13], Lucie Biard [2] Bahram Bodaghi [12], and David Saadoun [1].

1 Sorbonne Universités, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology,F-75013, Paris, France, Centre national de références Maladies Autoimmunes et systémiques rares, Centre national de références Maladies Autoinflammatoires rares et Amylose inflammatoire; INSERM, UMR S 959, Immunology-Immunopathology- Immunotherapy (I3); F-75005, Paris, France;

2 Department of Biostatistics and Medical Information, CRESS UMR 1153, INSERM, ECSTRRA Team, Saint-Louis University Hospital, AP-HP, University of Paris, Paris, France;

3 CHU Rouen, Internal Medicine Department, F-76000 Rouen, France ;

4 Internal Medicine Department, Hôpital de la Croix- Rousse, Hospices Civils de Lyon, Lyon Cedex 04, France; Faculté de Médecine Lyon-Sud, Université Claude Bernard-Lyon 1, Lyon, France ;

5 Internal Medicine and systemic diseases department (Medicine Interne 2), Dijon University hospital, Dijon, France;

6 Ophthalmology Department, Hospital Charles Nicolle, CHU Rouen, F-76000 Rouen, France; EA7510, UFR Santé, Rouen University, F-76000 Rouen, France ;

7 Internal Medicine Department, Fondation Rothschild, F-75000 Paris, France;

8 Ophtalmology Department , Fondation Rothschild, F-75000 Paris, France

9 Department of Internal Medicine, CHRU de Nancy, F-54000 Nancy, France; Université de Lorraine, Inserm UMR_S 1116, F-54000 Nancy, France;

10 Internal Medicine and pneumology Department, CHU de Brest, Hôpital La Cavale Blanche, Brest Cedex, France ;

11 Internal Medicine Department, Lariboisière Hospital, Paris, France; INSERM UMR, Paris Diderot University, Paris, France ;

12 Ophthalmology Department, DHU View Restore, Pitié Salpêtrière Hospital, Paris, France;

13 Ophthalmology Department, Hôpital de la Croix- Rousse, Hospices Civils de Lyon, Lyon Cedex 04, France; Faculté de Médecine Lyon-Sud, Université Claude Bernard-Lyon 1, Lyon, France ;

* Equal contribution

Address correspondence to: Professor David Saadoun, MD, PhD

Département de Médecine Interne et d'Immunologie Clinique, INSERM, UMR_S 959, Hôpital Pitié-Salpêtrière, 83 boulevard de l'hôpital, 75013 Paris, France.

E-mail: david.saadoun@aphp.fr, Phone: +33(0)142178042, Fax: +33(0)142178080.

Word count: 3058 words ; Tables 3, Figures 1, 30 References.

Abstract

Objective: To compare relapse rate of sight threatening non infectious uveitis (NIU) in patients treated with infliximab (IFX) or adalimumab (ADA).

Design: Observational retrospective multicenter study.

Subjects: 330 patients (median age of 36 years (IQR 27-54), with 45.2% of men) with sight threatening NIU (i.e. retinal vasculitis and/or macular edema) treated with anti TNF alpha agents [IFX intravenously at 5 mg/kg at week 0, 2, 6 and every 4-6 weeks or ADA subcutaneously at 80 mg then 40 mg every 2 weeks].

Methods: Data were obtained retrospectively from patient's medical records.

Main Outcome Measures: Relapse rate, complete response of NIU, corticosteroid sparing effect, safety.

Results: Main etiologies of uveitis included Behçet's disease (27%), idiopathic juvenile arthritis (5.8%) and sarcoidosis (5.5%). The estimated relapse rate at 6 months after introduction of biological agents was 13% (95% CI 0.009-0.16). IFX was associated with less relapse risk than ADA (HR 0.52 [95% CI 0.36- 0.77], p= 0.001). ADA and IFX were comparable in terms of complete response rate of NIU, and corticosteroid-sparing effect. Behçet's disease was associated with higher odds of complete response (HR: 2.04 [95% CI 1.16 -3.60] p: 0.01] and less relapse rate (HR: 0.53 [95% CI 0.33 -0.85] p: 0.009) than other causes of NIU with anti TNF alpha agents.

Conclusions: In sight threatening NIU IFX seem to have lower relapse rate than ADA.

Introduction

Non infectious uveitis (NIU) is a heterogeneous group of diseases, characterized by inflammation of intra-ocular structure. With an incidence of 52/100 000 person-years, inflammatory uveitis are responsible of 10-20% of blindness cases in western nations.[1] Sight threatening uveitis are those presenting with retinal vasculitis (RV), and/or cystoid macular edema (CME).[2] RV can vary from mild venous sheathing to severe obstructive vasculitis. Vascular damage can result in loss of vessel wall integrity, leakage of blood constitutes into the retinal extracellular space, and development of CME, a significant factor contributing to vision loss.[3] Moreover, prognosis of uveitis also depends on the relapse rate, which ranges from 30 % to 50 % according to treatment strategies.[4,5]

TNFα is a cytokine that has a major role in regulating the functions of cells involved in the inflammatory process and seems to play a key role in ocular inflammatory diseases. [6] In mice models, high level of tumor necrosis factor alpha (TNF-α) was found in aqueous humor of uveitis and was responsible for T lymphocytes and macrophages ocular infiltration. Blockage of TNF-α and its receptor is effective in the control of intra-ocular inflammation in mice models of experimental autoimmune uveitis.[6]

There is an unmet need for additional effective therapies in patients with sight threatening NIU beyond corticosteroids which remain the mainstream treatment despite their well-known adverse effects.[7] The antimetabolites are commonly used as initial corticosteroid-sparing treatments for uveitis before progressing to biologic therapies. The use of mycophenolate mofetil compared with methotrexate as first-line corticosteroid-sparing treatment did not result in superior control of inflammation in NIU.[8]

The VISUAL studies provided significant support for the role of biologic agents in treating noninfectious uveitis. The trials showed that ADA offers an advantage in disease control for patients with NIU, reducing the risk of relapse and allowing for the reduction in corticosteroids usage.[9,10,11] ADA has been approved by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for the treatment of patients suffering from non-infectious non-anterior uveitis in case of steroid-dependency or contraindication to corticosteroids.[12]ADA and IFX currently represent the most frequently employed monoclonal anti-TNF-α biologic agents [13,14] the efficacy of both ADA and IFX in the resolution of sight threatening NIU, has been suggested in few retrospective studies. [9,15,16] Al-Janabi et al focused in their retrospective cohort on the long-term outcome of ADA and IFX in refractory NIU. Their results suggest the efficacy of these treatments with a satisfactory disease control (87.2%), a reduced use of systemic immunosuppression, a stable visual acuity, and a 23.7% risk of disease relapse in patients treated with biologic agents after failure of treatment with corticosteroids and a second-line immunosuppression.[17] Nevertheless, large studies comparing the efficacy of anti-TNF-α antibodies (i.e. ADA and IFX) in sight threatening uveitis presenting with either RV or CME are still lacking.

The aim of the nationwide BIOVAS (BIOtherapy in uveitis with retinal VASculitis and /or cystoid Macular edema) study was to compare relapse rate and efficacy of ADA and IFX in sight threatening NIU, presenting with either RV or CME.

Patients and methods

In this multicenter retrospective observational study conducted by the French Uveitis Network we included all adult patients treated for uveitis with either RV or CME with anti-TNFα agents (ADA and IFX) between 2001 and 2019 in French tertiary centers. Adults patients with NIU and RV or CME cortico-dependent and/or refractory to disease modifying anti-rheumatic drugs (DMARDs, i.e., mycophenolate mofetil, methotrexate, azathioprine…) and treated with anti-TNF-α agents (ADA and IFX) were included. CME was defined by a central foveal thickness (CFT) > 300 µm measured with spectral domain optical coherence tomography (OCT) and presence of intraretinal cystic spaces or subretinal fluid in the absence of choroidal neovascularization. Retinal vasculitis was diagnosed with a fluorescein angiography. Patients were excluded if they presented non-infectious uveitis without CME or CME unrelated to uveitis. Patients previously treated with intravitreal implants of dexamethasone within 6 months have been excluded. Patients were excluded if they presented NIU without RV or CME. The study was approved by the local ethic committee of Pitié-Salpêtrière Hospital (Number: 1867484) and adhered to the tenets of the declaration of Helsinki. Informed consent was not required as per French regulation for research on Humans due to the retrospective strictly observational nature of the study.

Study treatment

IFX was administrated intravenously at 5 mg/kg at week 0, 2, 6 and every 4-6 weeks. ADA was administrated subcutaneously at 80 mg then 40 mg every 2 weeks.

Data collection

Data was obtained retrospectively from patient's medical records. Collected data included demographic characteristics (age, sex, geographic ancestry), age at diagnosis,

aetiology of uveitis, previous treatments (corticosteroids and immunosuppressive agents), date of biotherapy treatment initiation, characteristics of uveitis at the time of treatment initiation, indication for ADA or IFX, type and dosage of anti-TNF used (first and second anti-TNF if applicable), corticosteroid dosage at biotherapy treatment initiation, at 6-month and last follow-up, and at relapses if applicable, and outcome at last visit. All patients underwent a complete ophthalmological examination including visual acuity in logMAR (using an Early Treatment Diabetic Retinopathy Study [ETDRS] chart), slit lamp and fundus examination, fluorescein angiography to diagnose retinal vasculitis, and OCT to diagnose CME. Uveitis classification followed the Standardization of Uveitis Nomenclature Working Group criteria [18] and clinical characteristics included anatomic localization, course (acute or chronic), presence of granuloma, retinal vasculitis and macular edema.

Study endpoints:

The primary objective was the relapse rate of sight threatening uveitis in patients treated with ADA and IFX. Relapse was defined as a new ocular inflammation and/or worsening of a preexisting manifestation (RV and/or CME) requiring treatment intensification.

Secondary endpoints included complete response rate of CME and/or RV to ADA and IFX, factors associated with the complete response, and safety of ADA and IFX.

The response to treatment was evaluated according to the SUN Workgroup criteria.[18] Complete response was defined as a decrease to grade 0 in level of inflammation (e.g. anterior chamber cells, vitreous haze) associated with regression of retinal vasculitis and a complete resolution of macular edema 6 months after treatment initiation. Partial response was defined as an improvement of at least 50% of inflammation and/or a significant regression of retinal vasculitis and of macular edema at 6 months. All other situations were

considered as non -response. Corticosteroid sparing was assessed by comparing corticosteroid daily dose between the day of anti-TNFα introduction and after 6 months of treatment. Safety was assessed by analysing the rate and type of side effects. Serious adverse events were defined as those that justified anti-TNFα treatment interruption and/or an hospitalization and/or lead to death.

Statistical analysis:

Categorical variables were summarized with counts and percent and compared using Fisher's exact test. Continuous variables were summarized with the median and interquartile range (IQR) and were compared using Wilcoxon test or Kruskal-Wallis test. For the evaluation of primary and secondary endpoints, each treatment line was considered per patient for univariate and multivariate analysis. Cumulative incidences of first relapse were estimated using Kaplan-Meier method. Factors associated with first relapse were assessed using Cox proportional hazard models and factors associated with complete response were assessed using logistic regression. For both endpoints, an adjusted multivariate model was selected backward variable selection based on Akaike's Information Criterion. Statistical analyses were performed using R Studio Version 3.6.1 and p values < 0.05 were considered to be statistically significant. For the evaluation of primary and secondary end points, each treatment line was considered per patient for univariate and multivariate analysis.

RESULTS

Description of the study population

Table 1 presents baseline characteristics of included patients.

A total of 330 patients with sight threatening NIU were included in our study with 181 females (54.8%). Median age was 36 years (IQR 27-54) and 224 patients were Caucasian (70.9%). Idiopathic uveitis accounted for 125 patients (37.9%), Behçet's disease for 89 patients (27%), idiopathic juvenile arthritis for 19 patients (5.8%) and sarcoidosis for 18 patients (5.5%). Most patients presented with panuveitis and posterior uveitis (55.5% and 32% respectively). CME was present in 114 patients (34.5%), retinal vasculitis in 138 patients (41.8%) and the remaining patients had both visual manifestations. Retinal vasculitis was mainly venous (155 patients 54.8%). Sixty-one patients (23.9%) presented a diffuse vasculitis, while 69 (27%) presented a segmental vasculitis. Sixty-two patients (24%) presented an occlusive vasculitis and 69 (30.5%) a non-occlusive one. Median CFT was 350 µm (IQR 297.5-498.0).

Two hundred eighty-nine patients (87.6%) received a DMARD before the anti TNF alpha agent. At the time of anti-TNF initiation, the median visual acuity was 0.4logMAR (IQR 0.1–1.0). Anti-TNFα was prescribed with concomitant corticosteroid therapy in 295 patients (89.4%), and with concomitant conventional immunosuppressor in 116 patients (37.2%). (Table 1) Median dose of corticosteroid at the start of biotherapy was 20 mg per day (IQR 11.4-40.0). **(Table 1)** Median time of follow-up was 74.50 months [IQR 37-137].

Complete response of sight threatening NIU at 6 months

A total of 381 lines of treatment have been studied (190 ADA/191 IFX). Complete response at 6 months was observed in 37.5% of cases. ADA and IFX had similar complete response rate 36.8% and 38.2 % respectively.

In univariable analysis **(Table 2),** factors associated with complete response to anti TNF alpha agents included the underlying aetiology (p = 0.01), and male gender (p=0.02). There was no statistical difference in complete response rate in patients treated with IFX compared to those treated with ADA, (OR: 0.95 [95% CI 0.62- 1.42], p: 0.84).

In multivariable analysis, Behçet's disease was independently associated with complete response to anti-TNF compared to idiopathic disease [OR:2.04 [95% CI 1.16- 3.58], p=0.014]. **(Figure 1)**

Relapse rate

Relapse occurred in 116 out of 283 lines (40.9% of cases). Specifically, 64 (46%) out of 138 lines for ADA and 52 (35%) out of 145 lines for IFX relapsed. Median time to relapse was of 76 months after the beginning of the biological agents. The estimated relapse rate at 6 months after introduction of biological agents was 13% (95% CI 0.009-0.16).

In univariable analysis **(Table 2)**, factors associated with relapses to anti TNF alpha agents included the underlying aetiology, posterior uveitis and treatment with IFX .

In multivariable analysis (**Figure 1**), the risk of NIU relapse was lower with IFX compared to ADA (HR 0.52 [95% CI 0.36- 0.77], p= 0.001) and in Behçet's disease (compared to the reference idiopathic uveitis) (HR: 0.53 [95% CI 0.33 -0.85] p: 0.009). Patients presenting with posterior uveitis had an increased risk of NIU relapse (HR: 2.24 [95% CI 1.04-4.82), p = 0.04).

Corticosteroid sparing

Both ADA and IFX had a significant corticosteroid-sparing effect. At baseline, 146 patients (87.4%) treated with ADA and 149 patients (91.4%) treated with IFX received oral corticosteroids. The median daily dose of prednisolone was 20 mg (IQR 10.0 to 30.0) at the time of initiation of ADA, and 10 mg (IQR 5.0 to 15.0) at 6 months ($p < 0.0001$). The median daily dose of prednisolone was 20 mg (IQR 15.0 to 45.0) at the time of initiation of IFX and 10 mg (IQR 5.5 to 16.5) at 6 months ($p < 0.0004$).

Safety

Safety-related data are summarized in **Table 3**. Fourty patients (24.5%) experienced at least one side effect during treatment with IFX and 30 (17.9%) patients during treatment with ADA. Patient treated with IFX had slightly more serious adverse events than those treated with ADA (14.7% and 9.5% respectively). The most frequent side effects were infection and hypersensitivity reactions.

DISCUSSION

This multicenter study is to our knowledge the largest cohort of patients treated with anti-TNF-alpha agents for sight-threatening NIU. The main conclusions drawn by this study are 1) patients treated with IFX have two times lower relapse rate of NIU compared to those treated with ADA 2) Behçet's uveitis more likely respond to anti-TNF alpha agents and relapse less frequently than other causes of NIU.

Sight threatening uveitis usually present with retinal vasculitis and/or CME.[2] However, these two elements have just recently been included as endpoints in clinical trials by researchers.[19,20,21] In our study, overall improvement of RV and CME at 6 months of treatment was obtained in 74.4% with ADA and 83.3% with IFX. Complete and partial responses were observed in 36.8 % and 37.6% of cases with ADA and 38.2 % and 45.1% with IFX, respectively. BIOVAS study defined complete response as the resolution of intraocular inflammation associated with regression of RV and or/ CME and complete response at 6 months was achieved in 37.5% of cases. Fabiani et al found in their retrospective study of 48 patients presenting a refractory retinal vasculitis treated with anti TNF alpha agents, a complete remission at 3 and 12 months of 54 and 86%, respectively. Their results imply that a considerable proportion of nonresponsive patients at the 3-month assessment may likely undergo a resolution of RV at a later time.[20] The high proportion of CME in our study may account for the lower response rate. Most of previous studies focused on resolution of intra-ocular inflammation (anterior chamber and/or vitreous haze) without the complete resolution of RV or CME and found better outcomes, ranging from 70% [5,22] to 90% [23] of complete response at 6 months. These results highlight the severity of RV and CME and the difficulty of managing these patients.

Long term outcomes and the maintenance of remission without relapse are essentials that define the control of the disease and the efficacy of any treatment. Relapse occurred in 40.9% of the patients in our cohort. Median time to relapse was 76 months after the beginning of the biological agents. The estimated relapse rate at 6 months after introduction of biological agents was 13%. The rate of relapse found in our cohort is consistent with the scarce literature found on this subject. [4,5] A relapse rate of 23.7%, and a median time to first flare of 5.4 years were reported by al Janabi et al in their retrospective study of 82 patients treated with IFX and ADA for refractory NIU. [17] Diaz-llopiz et al [5] reported a relapse of CME in 18 out of 33 eyes (54%). Relapse occurred in 51% of the patients included in a prospective cohort study that compared IFX and ADA efficacy in the treatment of NIU. [4] Our data suggest a 2 times lower relapse rate of RV and/or CME with IFX in comparison to ADA. To our knowledge, this is the first time such results are shown. There were no reported difference in the relapse rate between patients treated with IFX and those treated with ADA in the cohorts published by Sharma et al [4] and Fabiani et al [20,24] but their work did not intend to evaluate this endpoint.

As previously reported by other groups, IFX and ADA appear comparable in terms of efficacy with a similar rate of complete resolution of RV and CME in our study.[16,20] However, Atienza Mateo et al in a retrospective multicenter study of IFX versus ADA for BD-related uveitis refractory to conventional nonbiologic treatment suggest that ADA was associated with better outcomes than IFX after 1 year of follow-up. [25] In their cohort they found greater improvement of the anterior chamber inflammation, vitritis, and visual acuity with ADA. However, when they compared the response of CME and RV between the two groups, the difference between treatment groups was not significant.

In line with previous studies, [5,16,26] a significant corticosteroid sparing effect was obtained at 6 months in ADA and IFX groups.

Furthermore, we found that Behçet's patients treated with anti TNF alpha agents for sight threatening NIU had two times higher probability of complete response than those presenting an idiopathic uveitis. Behçet's disease presents usually with severe NIU.[27] Efficacy of TNF alpha inhibitors in uveitis of BD has been previously reported.[28,29] In addition, our study highlighted that Behçet's patients tend to relapse less than those with idiopathic uveitis.

The safety profile for ADA and IFX in this study was consistent with the known safety profile of these biologics, and no new safety concerns were identified during long-term exposure. Serious side effects were observed in 9.5% and 14.7% with ADA and IFX, respectively. These results are similar to the VISUAL studies where 11.7% [11], 9.6% [10] and 19% [9] of serious sides effects were reported with ADA. Our study suggest a trend toward higher serious side effects with IFX, consistent with what was already reported by Vallet et al. [16]

We acknowledge some limitations in this study. Our analysis was performed as a retrospective review. We were unable to collect complete longitudinal data on patients who were seen only on an intermittent basis. Prospective enrollment and data collection from the time of diagnosis would have been ideal but is more difficult to achieve with rare diseases. Although the present study only compared ADA and IFX based on observational non-randomized observations, we used a logistic regression approach to minimize potential confusion bias. [30]

In conclusion, IFX was associated with less relapse risk than ADA in sight threatening NIU. Behçet's uveitis more likely respond to anti-TNF alpha agents and relapse less frequently than other causes of NIU.

Acknowledgments

GM, AA, ML, LB and DS developed the concept and designed the study. GM, AA, ML, PS, PB, JG, TS, TM, BR, DS, ACD, FD, ST, TT, PC, BB and DS provided study material or participants. LB , AA and CC did the data analyses. GM, AA, ML, LB and DS wrote the initial draft of the manuscript, and provided critical comments and editing.

All authors contributed to the data interpretation, reviewed the analyses of this manuscript, and approved its final version.

Declaration of interests

GM, AA, ML, PS, PB, JG, TS, TM, BR, DS, ACD, FD, ST, TT, PC, BB, LB and DS have nothing to disclose.

Permissions Information:

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Funding

No funding was received.

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Legends of Tables and Figures:

Table 1: **Table 1**: Demographic and clinical characteristics of the 330 patients.
Data are median [25-75 interquantile range], or number (percentage)
(LogMAR : Logarithm of the Minimum Angle of Resolution , RE : Right Eye , LE : Left Eye, IQR : interquantile range , RV :retinal vasculitis , CME : Cystoid macular edema).
* There were missing data for retinal vasculitis : venous vasculitis (n=47), diffuse vasculitis (n=75), segmental vasculitis (n=74), occlusive vasculitis (n=72), and non occlusive vasculitis (n=104).

Table 2: Univariate analysis of factors associated with complete response, and relapse. OR: odds-ratio, HR: hazard-ratio, IQR: interquartile range. Factors associated with complete response were assessed using logistic regression. Factors associated with first relapse were assessed using Cox proportional hazard models.

Table 3 : Adverse events occurring during anti-TNF-alpha therapies.
N : number of patients with at least one side effect as described
CIDP : Chronic inflammatory demyelinating polyradiculoneuropathy.

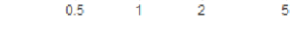
Figure 1 : Forest Plots of multivariable analysis of relapse and complete response (CR) with anti-TNF-alpha agents.

CR to anti-TNF-alpha agents

Variable		N	Odds ratio		p
Disease	Idiopathic	132		Reference	
	Behcet	103		2.04 (1.16, 3.60)	0.01
	Others	135		1.70 (1.02, 2.85)	0.04
Gender	Female	203		Reference	
	Male	167		1.51 (0.98, 2.35)	0.06
Posterior uveitis	0	259		Reference	
	1	111		0.65 (0.40, 1.05)	0.08
Biotherapy	ADA	181		Reference	
	IFX	189		0.91 (0.59, 1.42)	0.69

Relapse with anti-TNF-alpha agents

Variable		N	Hazard ratio		p
Disease	Idiopathic	94		Reference	
	Behcet	83		0.53 (0.33, 0.85)	0.009
	Others	99		0.61 (0.39, 0.93)	0.023
Panuveitis	0	123		Reference	
	1	153		2.07 (0.98, 4.36)	0.057
Posterior uveitis	0	185		Reference	
	1	91		2.24 (1.04, 4.82)	0.040
Biotherapy	ADA	133		Reference	
	IFX	143		0.52 (0.36, 0.77)	<0.001



Variables	All patients Median	Adalimumab	Infliximab
Total	330	167	163
Gender			
Female	181 (54.8)	94 (56.3)	87 (53.4)
Male	149 (45.2)	73 (43.7)	76 (46.6)
Age (years)	36 (27;54)	40 (29;59)	34 (25;49)
Geographic ancestry			
North Africa	54 (17.1)	19 (11.9)	35 (22.4)
Sub-Saharan Africa	28 (8.9)	9 (5.6)	19 (12.2)
Asia	10 (3.2)	5 (3.1)	5 (3.2)
Europe	224 (70.9)	127 (79.4)	97 (62.2)
NA, no.	14	7	7
Underlying disease			
Juvenile idiopathic arthritis	19 (5.8)	11 (6.6)	8 (4.9)
Behçet's disease	89 (27.0)	25 (15.0)	64 (39.3)
Birdshot chorioretinopathy	38 (11.5)	29 (17.4)	9 (5.5)
Idiopathic	125 (37.9)	74 (44.3)	51 (31.3)
Sarcoïdosis	18 (5.5)	13 (7.8)	8 (4.9)
pondylo-arthritis	11 (3.3)	8 (4.8)	10 (6.1)
Vogt-Koyanagi-Harada	9 (2.7)	5 (3.0)	6 (3.7)
Others	21 (6.4)	2 (1.2)	7 (4.3)
Uveitis characteristics			
Bilateral	263 (80.9)	132 (81.5)	131 (80.4)
Panuveitis	183 (55.5)	82 (49.1)	101 (62.0)
Posterior	103 (32.0)	54 (33.5)	49 (30.4)
Median visual acuity (LogMAR) RE (IQR)	0.4 (0.1 to 1.0)	0.4 (0.1 to 0.7)	0.6 (0.2 to 1.0)
Median visual acuity (LogMAR) LE (IQR)	0.4 (0.1 to 0.8)	0.3 (0.1 to 0.7)	0.4 (0.1 to 1.0)
CME and RV	78 (23.7)	44 (26.3)	34 (20.9)
Retinal vasculitis (RV)	138 (41.8)	63 (37.7)	75 (46.0)
Venous vasculitis*	155 (54.8)	79 (54.5)	76 (55.1)
Diffuse vasculitis*	61 (23.9)	34 (25.0)	27 (22.7)
Segmental vasculitis*	69 (27.0)	40 (29.2)	29 (24.4)
Occlusive vasculitis*	62 (24.0)	28 (20.6)	34 (27.9)
Non-occlusive vasculitis*	69 (30.5)	43 (33.6)	26 (26.5)
Cystoid macular edema (CME)	114 (34.5)	60 (35.9)	54 (33.1)
Central Foveal Thickness	350.0 (297.5 to 498.0)	350.0 (295.0 to 491.0)	348.0 (300.0 to 560.0)
Treatment			
Concomitant corticosteroid treatment	295 (89.4)	146 (87.4)	149 (91.4)
Initial corticosteroid dose (mg/d)	20.0 (11.4 to 40.0)	20.0 (10.0 to 30.0)	20.0 (15.0 to 45.0)
Concomitant treatment with immunosuppressive drugs	116 (37.2)	56 (35.4)	60 (39.0)
Previous treatment by immunosuppressive drugs	289 (87.6)	145 (86.8)	144 (88.3)

Parameter	Complete response		Relapse	
	OR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Male gender value	**1.66 (1.08-2.5)**	**0.02**	0.83 (0.57-1.2)	0.31
Age (years)	1,5 (0.8-1.7)	0.29	1.00 (0.99-1.01)	0.56
Etiologies		**0.01**		
Idiopathic uveitis	1		**1**	
Behcet's disease	**1.44 (1.06-2.6)**		**0.48 (0.31-0.76)**	**0.002**
Others	1.54 (0.77-1.8)		0.56 (0.36-0.86)	**0.007**
Concomitant immunosuppressive drugs	1.16 (0.88-1.3)	0.32	0.92 (0.62-1.35)	0.67
Bilateral uveitis	0.89 (0.62-1.29)	0.55	1.03 (0.55 to 1.91)	0.93
Anterior uveitis	1.38 (0.39-4)	0.63	0.78 (0.29-2.11)	0.62
Intermediary uveitis	1.87 (0.39-2.5)	1	1.00 (0.51-1.98)	1
Posterior uveitis	0.69 (0.43-1.52)	0.063	**1.27 (0.86-1.87)**	**0.023**
Pan-uveitis	0.91 (0.41-1.7)	0.16	0.98 (0.67-1.42)	0.91
Biotherapy		0.84		
Adalimumab	1		**1**	
Infliximab	0.95 (0.62-1.42)		**0.51 (0.35-0.74)**	**0.0004**

	Infliximab	Adalimumab
Any adverse events (N, %)	**40 (24.5%)**	**30 (17.9%)**
Infections (N)	**30**	**14**
Pneumonia	4	2
Bronchitis	6	2
Pyelonephritis	2	2
Furonculosis	2	1
Viral symptoms	3	3
Tuberculosis	1	0
Meningitis	1	0
Septic arthritis	1	0
Septicemia	2	0
Hepatitis	1	0
Cholecystitis	1	0
Anal abscess	4	0
Herpes infection	1	0
Mycotic esophagitis	1	0
Pityriasis versicolor	0	1
Cutaneous infection	0	3
Hypersensitivity reaction	**2**	**1**
Injection-site reaction	**1**	**2**
Autoimmune disease	**3**	**4**
Systemic lupus erythematosus	0	2
Psoriasis	1	0
Graves	1	0
CIDP	1	0
Sarcoidosis	0	1
Retrobulbar neuritis	0	1
Neoplasia	**2**	**0**
Cervical dysplasia	1	0
Lymphoma	1	0
Others	**2**	9
Paresthesia	1	0
Arthralgia	1	1
Fatigue	0	3
Migraine	0	2
Hallucinations	0	1
Cytopenia	0	1
Stomatitis	0	1
Serious adverse effects (N, %)	**24 (14.7%)**	**16 (9.5%)**

Death	0	0