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INFLIXIMAB VERSUS ADALIMUMAB IN THE TREATMENT OF REFRACTORY INFLAMMATORY UVEITIS: MULTICENTER STUDY FROM THE FRENCH UVEITIS NETWORK.

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ABSTRACT

Objectives: To analyze the factors associated with response to anti-TNFα and to compare the efficacy and safety of infliximab (IFX) and adalimumab (ADA) in patients with refractory non infectious uveitis.

Methods: Observational multicenter study including 160 patients [median age of 31 [21-42] years with 39% of men] with refractory uveitis treated with anti-TNFα [IFX 5mg/kg at weeks 0, 2, 6 and every 5-6 weeks (n=98) and ADA 40mg/14days (n=62)]. Factors associated to complete response were assessed in multivariate analysis. Comparison between efficacy and safety of IFX and ADA was performed using a propensity score approach accounting for baseline characteristics.

Results: Main etiologies of uveitis included Behçet's disease (36%), juvenile idiopathic arthritis (22%), spondylarthropathies (10%) and sarcoidosis (6%). The overall response rate at 6 and 12 months was of 87% (**26% of complete response**) and 93% (**28% of complete response**), respectively. The median time to complete response was 2 (0-12) months. In multivariate analysis, Behçet's disease (SHR= 2.52 [1.35-7.71], p=0.004) and a number of uveitis flares before anti-TNFα greater than 5 (HR=1.97 [1.02-3.84], p=0.045) were associated with complete response to anti-TNFα. Side effects were reported in 28% of patients, including 12% of serious adverse events. IFX and ADA did not differ significantly in terms of occurrence of complete response (SHR=0.65 [0.25;1.71], p=0.39), serious side effects (SHR= 0.22 [0.04-1.25], p=0.089) or event free survival (SHR=0.55 [0.28;1.08], p=0.083).

Conclusions: Anti-TNFα are highly effective in refractory inflammatory uveitis. Behçet's disease is associated with increase odds of response. IFX and ADA seem equivalent in terms of efficacy.

INTRODUCTION

Non infectious inflammatory uveitis is a heterogeneous group of diseases, characterized by inflammation of intra-ocular structure. They can be associated with systemic autoimmune diseases, with syndromes involving several ocular structures or be a sporadic disease of unknown etiology. With an incidence of 52/100 000 person-years (1) inflammatory uveitis are responsible of 10-20% of blindness cases in developed nations. (2)

TNFα is a cytokine that has a major role in regulating the functions of cells involved in the inflammatory process (3) and seems to play a key role in ocular inflammatory diseases. Indeed, the intraocular injection of TNFα to mice induces a **break down** of the blood–retinal barrier (4) and high levels of TNFα and TNF-receptor were observed in **serum** and aqueous humor of patients with uveitis. (5,6)

There is an unmet need for additional effective therapies in patients with non infectious uveitis beyond corticosteroids which are the mainstay of treatment despite their well-known adverse effects. (7) A better understanding of the mechanisms involved in the inflammatory response and regulation of adaptive immunity led to the development of biotherapeutics including anti-Tumor Necrosis Factor alpha (anti-TNFα). (8) A recent review of 61 studies and 1093 patients concluded that infliximab (IFX) and adalimumab (ADA) are effective in the treatment of noninfectious inflammatory uveitis with a medium level of evidence, whereas etanercept (ETA) seems to be ineffective. (9) Furthermore, a committee of the American expert generated guidelines for the management of biotherapies in ocular inflammatory diseases recommended the use of ADA and/or IFX as first or second line therapy according to uveitis etiologies. (10) **IFX and ADA were strongly recommended early in management of patients with sight threatening ocular manifestations of Behçet's disease and in second intention for children with vision-threatening uveitis secondary to JIA.** (10)

However, data regarding factors associated with response to anti-TNFα and comparison of safety and efficacy of IFX and ADA are lacking in non infectious uveitis. In this nationwide study from the French uveitis network, our aim was to analyze and to compare the efficacy and safety of IFX and ADA in a large cohort of patients with non infectious refractory uveitis.

MATERIAL AND METHODS

Patients

Multicenter **retrospective** observational study, from the French Uveitis Network, conducted from 2001 to 2013 and including patients with a refractory uveitis. Uveitis was considered as refractory in case of failure of at least 1 immunosuppressive and/or immunomodulator treatment, **defined as fulfilling one of the two following criteria at inclusion: a. Active inflammatory chorioretinal and/or inflammatory retinal vascular lesions (fluorescein angiogram) or b. A reduction of visual acuity due to vitreous haze or macular edema (Optical Coherence Tomography, OCT).** Infliximab was given intravenously at a dose of 5 mg/kg at weeks 0, 2, 6, and then every 5-6 weeks. Adalimumab (ADA) was used at the dose of 40mg every 2 weeks subcutaneously. **The choice of anti TNF was left to the discretion of the physicians in charge of the patients (in France IFX and ADA can be prescribed in second line of treatment in inflammatory uveitis).** The local ethics committee of Pitié Salpétrière hospital, Paris VI University, approved this study. Patients were excluded from the study if they had an infectious uveitis, if they were naïve of immunosuppressant before using anti-TNFα agent or if they were treated with other anti-TNFα than IFX or ADA.

Collected data included demographic characteristics (age, sex, geographical origin), date of diagnosis, etiology of uveitis, previous treatments (corticosteroids and immunosuppressive treatment), date of anti-TNFα agent introduction, characteristic of uveitis at anti-TNFα agent introduction, indication of anti-TNFα treatment, type and dosage of anti-TNFα used in first and second line, glucocorticosteroids dose and associated treatments and outcome. Uveitis were characterized with their anatomic localization, their course (acute or chronic), the presence of granuloma, retinal vasculitis and/or macular edema according to the Standardization of Uveitis Nomenclature (SUN) Workgroup criteria. (11) **All patients had a**

fluorescein angiogram to diagnosed retinal vasculitis and optical coherence tomography (OCT) to detect macular edema.

Primary objective

The response to anti-TNFα and the factors associated to complete response were considered as the primary objective of this study. The response to treatment was evaluated according to the SUN Workgroup criteria. (11) 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 and with corticosteroids dose ≤10mg/day at 6 months. Partial response was defined as an improvement of at least 50% of inflammation and/or a significant regression of retinal vasculitis **(i.e. notably asymptomatic peripheral retinal vascular leakage)** and of macular edema and a reduction of >50% of initial corticosteroids dose at 6 months. All other situations were considered as non -response.

Secondary objectives

Secondary objectives included safety, corticosteroids sparing at 6 and 12 months, event free survival (*e.g* survival without failure, relapse and serious side effects), and comparison of clinical response, event free survival and serious side effects between IFX and ADA. Corticosteroid sparing was assessed by comparing corticosteroid daily dose between the day of anti-TNFα introduction and after 6 and 12 months of treatment. Relapses were defined as a new ocular inflammation and/or worsening of a preexisting manifestation requiring treatment intensification. 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

Data for categorical variables are summarized as frequencies and percentages; quantitative variables are presented as the medians, 25th and 75th percentiles and were compared using Wilcoxon's rank sum test. Time to response, relapse and serious side effects were considered as outcomes in a competing risks framework; they were examined from the date of antiTNFα initiation. Partial response or end of first line antiTNFα without response were considered as competing events in the analysis of complete response; remission or treatment failure as competing events with relapse under antiTNFα; end of antiTNFα without serious side effect as competing event with the occurrence if a serious side effect. The cumulative incidences of complete response, relapse and serious side effects were estimated using Gray's method and factors associated with complete response were assessed using subdistribution hazard ratios (SHR) in Fine and Gray's models. (12) Event free survival was estimated using the Kaplan-Meier method; association of anti-TNFα with event free survival was assessed in a Cox proportional hazard model. Because of the non-randomized design, the comparison of anti-TNFα agents on complete response, serious side effect and event free survival was performed using a propensity score approach, with a matching procedure. (13) Propensity score was estimated in a logistic regression model as the probability of receiving either IFX or ADA, conditionally on baseline characteristics at the anti-TNFα introduction. A 1:1 matched sample was selected by matching IFX patients to ADA patients, within a range of 0.30 standard deviation of the logit of the estimated propensity score, without replacement. The balance in the baseline risk factors was evaluated in the matched sample by computing the standardized differences for these variables. All tests were two-sided and P-values lower than 0.05 were considered as indicating significant association. Analyses were performed using the R statistical software version 3.2.2.

RESULTS

Characteristics of the 160 patients with refractory uveitis

Two hundred and three patients with noninfectious uveitis were screened (**Figure 1**). Forty three were excluded because of a non-refractory uveitis or because of the use of another anti-TNFα than IFX or ADA (**Figure 1**). Finally, 160 patients were included of whom 98 (61%) were treated with IFX and 62 (39%) with ADA (**Figure 1**). Main characteristics are summarized in **Table 1**. The median age at anti-TNFα agent introduction was of 31 [21-42] years. The median time between diagnosis of uveitis and the initiation of anti-TNFα treatment was of 51 [24-113] months. Most of uveitis were bilateral (n=132; 82%), chronic (n=140; 90%), panuveitis (n=99; 62%) and 21% of them were granulomatous. Retinal vasculitis was observed in 34% of patients and macular oedema in 49% of patients. The main etiology of uveitis were Behçet's disease (BD) (n=58; 36%), juvenile idiopatic arthritis (JIA) (n=35; 22%), spondyloarthropathy (n=16; 10%), sarcoidosis (n=10; 6%), and idiopatic uveitis (n=23; 14%). The other etiologies included Vogt-Koyonagi-Harada disease (n=5), Birdshot chorioretinitis (n=6), sympathetic ophthalmia (n=2), granulomatosis with polyangitis (n=1), IRVAN syndrome (n=1), serpiginous choroiditis (n=1), systemic lupus erythematous (n=1) and relapsing polychondritis (n=1).

One hundred twenty four (84%) and 102 (64%) patients received corticosteroids and an immunosuppressant treatment, respectively, in association with anti-TNFα agent (**Table 1**). The median follow-up was of 36 [15-62] months after anti-TNFα initiation.

Efficacy

The cumulative incidence of overall response (complete and partial) was of 87% (CI95%: 80-91), 93% (CI95%: 87-96) and 95% (CI95%: 90-98) at 6, 12 and 24 months, respectively (**Figure 2A**). Among the complete responders, the median time to complete response was 2 (0-12) months. The cumulative incidence of complete response was 26% (CI95%: 19-34), 28% (CI95%: 21-36) and 29% (CI95%: 22-37) at 6, 12 and 24 months, respectively. The overall response of IFX and ADA was 97% and 95%, respectively. **At anti-TNFα initiation, the median visual acuity (LogMar chart) was 0.4 [0.1-1.0] for the right and 0.3 [0.0-0.8] for the left eyes. The median visual acuity improved at 6 months (0.3 [0.0-0.8] for the right and 0.1 [0.0-0.5] for the left eyes). Then visual acuity stabilized at 12 and 24 months (0.2 [0.1-0.6] and 0.1 [0.0-0.5], respectively for the right eyes and 0.1 [0.0-0.7] and 0.1 [0.0-0.4], respectively for the left eyes.**

In univariate analysis, the factors associated to complete response to anti-TNFα included BD (SHR=2.78 [1.55-4.99]), number of uveitis flares before anti-TNFα treatment (more than 5 flares) (SHR=1.90 [1.00-3.64]), a daily corticosteroid dosage higher than 20mg (SHR=2.10 [1.13-3.93]), and immunosuppressant treatment in association with anti-TNFα agent (SHR=0.46 [0.25-0.84]) (**Table 2)**. In multivariate analysis, factors independently associated with complete response to anti-TNFα included the number of uveitis flares before anti-TNFα treatment (SHR=1.97 [1.02-3.84), p=0.045), and BD (SHR=2.52 [1.35-4.71], p=0.004).

The cumulative incidence of relapse was 7% (CI95%: 3-12), 21% (CI95%: 15-29) and 25% (CI95%: 18-33) at 6, 12 and 24 months respectively.

Corticosteroid sparing

Anti-TNFα agents had a significant corticosteroid sparing effect. The median (IQR) daily prednisolone dose was of 20 [10-50] mg at time of initiation of anti-TNFα and of 10 [5-15] mg and of 7 [4-10] mg at 6 and 12 months, respectively, (both $p<0.0001$ compared to baseline).

Safety

Safety related data are summarized in **Table 3**. Forty five (28%) patients presented at least one side effect during anti-TNFα treatment of whom twenty (12%) had at least one serious side effect. Most frequent type of side effects in patients were infection (n=18), hypersensitivity reaction (n=10), auto-immune disease (n=5) and neoplasia (n=4). The cumulative incidence of serious side events was 1% (CI95%: 0-4), 7% (CI95%: 4-12) and 8% (CI95%: 4-13) at 6, 12 and 24 months, respectively. There was a trend toward higher serious side effects with IFX (16%) compared to ADA (6%) including more infections (n=5 with IFX, n=0 with ADA), hypersensitivity reactions (n=5 with IFX, n=1 with ADA), autoimmune-diseases (n=3 with IFX, n=1 with ADA) and neoplasia (n=2 with IFX, n=1 with ADA). We analysed the factors associated with the occurrence of severe side effects with anti-TNFα. In multivariate analysis, though not significantly, incidence of severe side effects tended to be higher in older patients (SHR=1.02 [0.98-1.06]), in patients with more than 5 episodes of uveitis flare prior anti-TNFα initiation (SHR=2.76 [0.76-9.99]) and in patients with a daily corticosteroid dosage greater than 20mg (SHR=2.38 [0.69-8.20]).

Event free survival

The event free survival was of 90% (CI95%: 85-95) at 6 months, 70% (CI95%: 63-78) at 1 year and 59% (CI95%: 51-68) at 2 years (**Figure 2B**).

Comparison of IFX and ADA using a propensity score approach.

Eighty two patients were selected after the matching procedure 1:1. The two groups of patients (IFX vs ADA) were comparable in term of age, sex, geographic origin, uveitis characteristics, etiology, previous type of immunosuppressive treatment and associated treatment at time of anti-TNFα initiation. The cumulative incidences of complete response and serious side effects were not significantly different regardless of anti-TNFα treatment (SHR= 0.65 [0.25-1.71], p=0.39) and 0.22 [0.04-1.25], p=0.089 respectively) (**Figure 3A and 3C**). The event free survival under IFX and ADA was not significantly different (SHR: 0.55, [0.28-1.08],p=0.083)(**Figure3B**).

DISCUSSION

In this multicenter study form the French uveitis network, we analyzed a large cohort of patient treated with anti-TNFα for refractory uveitis. The most relevant messages were: 1. BD is associated with a three times higher rate of complete response to anti-TNFα therapy. 2. Efficacy seems equivalent between IFX and ADA. 3. Trend toward higher serious adverse event was observed with IFX.

In this study, anti-TNFα agents were highly effective in the treatment of refractory uveitis with 87% and 93% of improvement at 6 and 12 months, respectively. The median time to complete response was of 2 months. A significant corticosteroïd sparing effect was evidenced with a 50% reduction of the daily dose at 6 months. These results were concordant with the published literature. Indeed, several studies reported a high rate with 68 to 82% of clinical response rate and a significant corticosteroïd sparing effect. (14–18)

We showed that BD and the number of previous uveitis flares were highly associated with complete response to anti-TNFα. The efficacy of anti-TNFα in uveitis of patients with BD was known. A study has reported an increase level of inflammatory cytokines, such as interferon γ, interleukins 2-6-17 and TNFα, in ocular fluid from uveitis patients with BD, whereas ocular fluid from patients being treated with anti-TNFα did not contain any inflammatory cytokines. They concluded that anti-TNFα agents suppress effector T cell differentiation, notably Th17 differentiation, in uveitis patients with BD. (19) In 2011, a large literature review concerning the efficacy of anti-TNFα in BD reported an uveitis improvement in 89% and 100% of patients with IFX and ADA respectively. (20) More recently, a cohort study of about 124 uveitis patients with BD treated with anti-TNFα reported that 68% of patients were inactive at 1 year. (21) All these results have conducted the expert group of the Executive Committee of the American Uveitis Society to generate guidelines for the

management of biotherapies in ocular inflammatory disease. They recommended the use of IFX and/or ADA early in the management of vision threatening uveitis in BD. (10) **In univariate analysis poorer response was observed in patients being on an immunosuppressant. However, this parameter was not independently associated with complete response to anti TNFα in multivariate analysis**.

Additionally, the use of anti-TNFα is likely to be effective in active uveitis, as suggested by the association found between the number of uveitis flares before anti-TNFα and the incidence of complete response. Several studies showed an increased level of TNFα in the serum and ocular fluids of patients with active uveitis. (6,22) Moreover, levels of TNFα seems to be correlated with recurrent uveitis. (6) **Recently, a prospective study concluded that ADA improved significantly the visual functioning in patients with non-anterior noninfectious uveitis**. (23)

Twenty eight percent of patients presented at least one side effect, of whom 12% had to discontinue the treatment. Data concerning safety of anti-TNFα in uveitis are lacking. Our results are in line with other studies that found an overall side effect rate of 10% to 36%. (18,20) The most common side effects in our study were infections and hypersensitivity reaction. Bronchopneumonia, (20) viral infections, (16,20) abscess, (20) tuberculosis, (20) cutaneous rash (18) and other hypersensitivity reaction (20,24) were already described in uveitis patients treated with IFX or ADA. We also report several cases of neoplasia and auto-immune disease. A pharmacovigilance study about safety of anti-TNFα in uveitis reported an increased risk of infections, auto-immune disease and neoplasia with IFX and ADA. (25) Similar results were reported with IFX and ADA in other inflammatory diseases. (26–29) Thus, the decision of anti-TNFα treatment initiation always needs to consider the risk-benefit-balance.

In the present study, the efficacy and safety seems similar between IFX and ADA. No

significant difference was found in terms of complete response or event free survival.

Few data are available regarding comparison of IFX and ADA. Two study have compared efficacy between IFX and ADA in childhood refractory chronic uveitis. (30,31) The first study concluded that IFX and ADA were similar regardless of time to achieve remission and time to steroid discontinuation but ADA was superior to maintain a long term remission. (30) The second one showed a higher overall remission rate with ADA compared to IFX. (31) In ulcerative colitis, a recent meta-analysis showed that IFX was more effective than ADA to induced remission but efficacy of the two anti-TNFα was comparable at one year. (32) Our study is, at the best of our knowledge, the first to compare the efficacy between IFX and ADA in a large cohort of non infectious uveitis. IFX and ADA seems equivalent in terms of efficacy with an overall response of 97% and 95% respectively. However, trend toward higher incidence of serious side effects was observed with IFX. Although no data are available about the safety comparison of IFX and ADA in noninfectious uveitis, two recent studies in chronic inflammatory bowel disease, including a meta-analysis, concluded that IFX and ADA presented a similar safety profile. (33,34) However, a trend toward a higher association between IFX and autoimmune disease and between ADA and neoplasia was found. (25)

Although further studies are needed to confirm our results, this information could be interesting notably because of the different route of administration of these two agents. In fact, subcutaneous administration with ADA should be less constraining for patients, for it does not require hospitalization. By contrast, intravenous administration with IFX requires hospitalization and allows for a better monitoring of uveitis and patients overall. Moreover, the treatment cost is slightly lower for ADA than IFX (12.731 euros per year for ADA at the dose of 40 mg every 2 weeks vs 15.799 euros per year with vial optimization for IFX dosed at 5 mg/kg was administered at weeks 0, 2, and 6 and then every 8 weeks). (35)

We acknowledge some limitations in our 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 these anti-TNFα agents based on observational non-randomized observations, we used a propensity score approach to minimize potential confusion bias. (13)

In conclusion, anti-TNFα is highly effective in this large series of refractory inflammatory uveitis, with a similar incidence of complete response regardless of anti-TNFα agent (IFX or ADA). Behçet's disease is positively associated with complete response.

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Contributions:

HV and DS contributed to the conception of the study. HV collected the data. HV, LB, PAB, MRR and DS analyzed the data. PS, JBF, PB, LP, BB, SA, AR, AD, DS, AP, IM, EF, EH, OF, GC, SR, JG, GP, PLH, PC, BB and DS followed the patients. HV, PS, LB, MRR, BB and DS drafted the manuscript and contributed to the writing of the article.

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Table 1: Demographic and main clinical characteristics of 160 patients with refractory uveitis

	All
	n=160
Age (years)	31 [21 to 42]
Male gender	63 (39)
Geographic origin[¥]	
Europe	82 (64)
North Africa	31 (24)
Sub-saharian Africa	12 (9)
Asia	3 (2)
Uveitis	
Location	
Panuveitis	99 (62)
Posterior	31 (19)
Anterior	24 (15)
Intermediary	6 (4)
Bilateral	132 (82)
Chronic[$]	140 (90)
Granulomatosis[‡]	32 (21)
Retinal vasculitis[#]	53 (34)
Macular edema[†]	67 (49)
Etiology	
BD	58 (36)
JIA	35 (22)
Idiopathic	23 (14)
Spondyloarthropathy	16 (10)
Sarcoidosis	10 (6)
Other	18 (11)
Previous immunosuppressive treatment	
MTX	87 (54)
AZA	79 (49)
INFγ	39 (24)
CYC	25 (16)
MMF	21 (13)
Ciclosporine	17 (11)
Associated treatment with anti-TNFα	
Corticosteroid[¤]	124 (84)
Immunosuppressant	102 (64)
MMF[Θ]	8 (5)
MTX[Θ]	67 (45)
AZA[Θ]	24 (16)

Data are median [25-75 interquantile range], or number (percentage), aTNF: Tumor Necrosis Factor alpha antagonist, AZA: azathioprine, CYC: cyclophosphamide, MTX: methotrexate, INFγ: interferon gamma, MMF: mycophenolate mofetil, BD: Behçet disease JIA: Juvenile Idiopatic Arthritis, [#] 4 [$] 4 [‡] 11 [Θ] 12 [¤] 13 [†] 23 [¥] 32 missing values.

Table 2 : Factors associated to complete response

	Univariate analysis		Multivariate analysis	
	SHR [95%CI]	P-value	SHR [95%CI]	P-value
Age	1.01 [0.99-1.02]	0.44		
Male gender	0.97 [0.52-1.78]	0.91		
Geographic origin				
Sub-saharian Africa	1			
Europe	0.49 [0.21-1.13]	0.092		
North Africa	1.31 [0.56-3.11]	0.53		
Uveitis				
Acute	1.47 [0.60-3.56]	0.40		
Granulomatosis	1.19 [0.43-3.30]	0.73		
Vascularitis	0.88 [0.46-1.69]	0.70		
Macular edema	1.03 [0.50-2.12]	0.93		
≥ 5 uveitis flares before anti-TNFα	1.90 [1.00-3.64]	0.052	1.97 [1.02-3.84]	0.045
Etiology - Behçet disease	2.78 [1.55-4.99]	0.0006	2.52 [1.35-4.71]	0.004
Associated treatment				
Corticosteroid ≥20mg/d	2.10 [1.13-3.93]	0.019		
Immunosuppressant	0.46 [0.25-0.84]	0.012		

SHR: Subdistribution Hazard Ratio, CI: Confidence interval, TNFα: Tumor Necrosis Factor alpha antagonist,

Table 3.: Description of side effects during anti-TNFα treatment

	n* (%)
Sides effects	45 (28)
Infections	18
Pneumonia	2
Bronchitis	4
Pyelonephritis	2
Cystitis	2
Herpes infections	3
Zoster	1
Anal abscess	3
Cholecystitis	1
Tuberculosis	1
Hypersensitivity reaction	10
Injection site reaction	1
Auto-immune disease	6
Serum sickness	2
Systemic Lupus Erythematosus	1
Psoriasis	2
Graves' disease	1
Neoplasia	4
Cervical dysplasia	2
Melanoma	1
Cutaneous squamous cell carcinoma	1
Others[¥]	11
Cytolytic hepatitis	1
Diarrhea	1
Lower Urinary Tract Symptoms	1
Headache	1
Nausea	1
Isolated Fever	1
Orthostatic hypotension	1
Serious side effects	20 (12)
Treatment interruption	20
Death	0

**n: number of patients with at least one side effect as described*

Figures legends:

Figure 1: Flow chart of the study

Figure 2: Cumulative incidence of response (complete or partial) to anti-TNF (A) and event free survival (B)

Figure 3: Comparison of the cumulative incidence of complete response (A), event free survival (B) and cumulative incidence of serious side effects (C) between IFX (solid line) and ADA (dashed line) using a propensity score methods

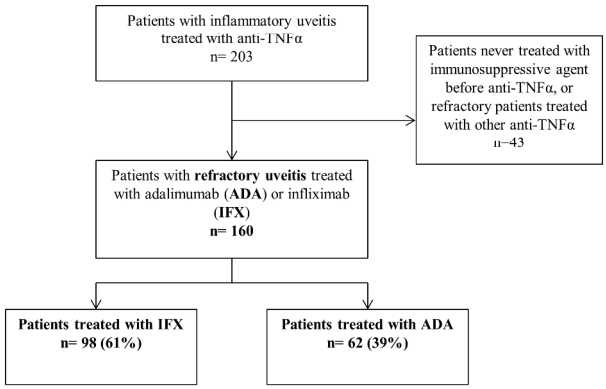

Figure 1: Flow chart of the study
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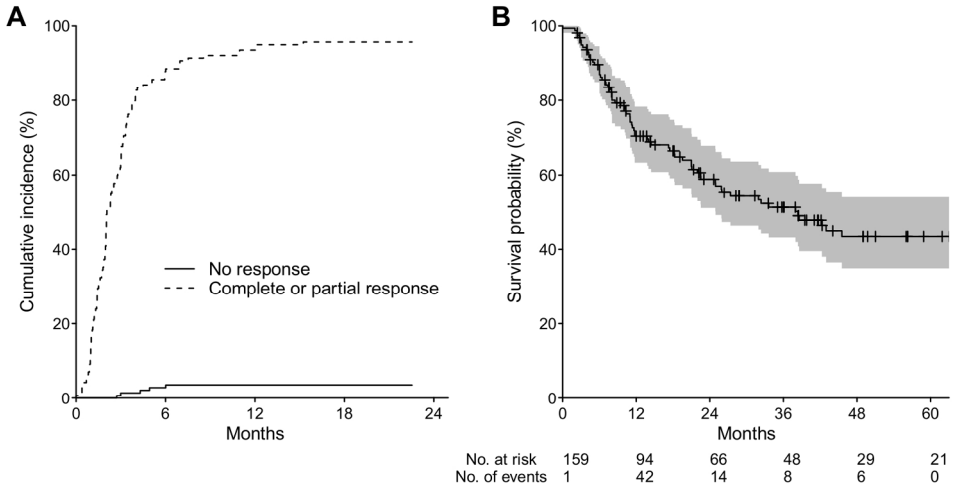

Figure 2: Cumulative incidence of response (complete or partial) to anti-TNF (A) and event free survival (B)
177x91mm (300 x 300 DPI)

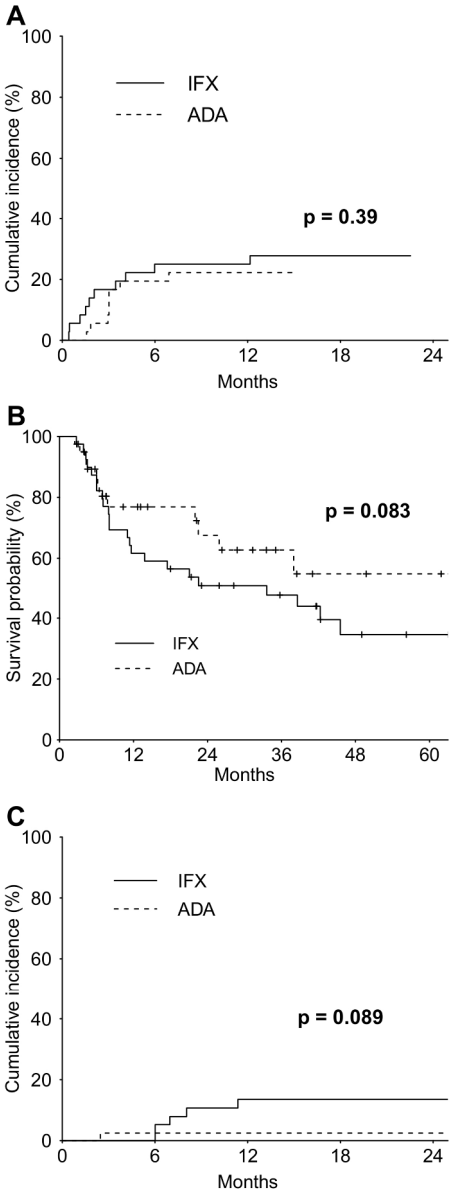

Figure 3: Comparison of the cumulative incidence of complete response (A), event free survival (B) and cumulative incidence of serious side effects (C) between IFX (solid line) and ADA (dashed line) using a propensity score methods
101x251mm (300 x 300 DPI)