Uveitis occurrence in patients with ankylosing spondylitis according to the type of tumour necrosis factor inhibitor: a cohort study of 175 patients

E.Y. Choi[1], M. Lee[2], C.S. Lee[1]

[1]Department of Ophthalmology, The Institute of Vision Research, Severance Eye Hospital, Yonsei University College of Medicine, Seoul, Korea;
[2]Department of Ophthalmology, The Institute of Vision Research, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea.

Abstract

Objective

To compare the occurrence of non-infectious uveitis based on the type of tumour necrosis factor (TNF) inhibitor used to manage spondyloarthritis in ankylosing spondylitis (AS) patients.

Methods

The occurrence (new-onset and recurrence) of uveitis was reviewed retrospectively in AS patients receiving different TNF inhibitor therapies (adalimumab [ADA], infliximab [IFX], etanercept [ETN], and golimumab [GOL]) for the management of spondyloarthritis from 2005 to 2018. Kaplan-Meier analysis was performed to calculate the cumulative occurrence rates of uveitis during TNF inhibitor therapy, and a log-rank test was used to analyse differences between the survival curves. Multivariable Cox proportional-hazards models were used to compute hazard ratios (HRs) of different TNF agents for uveitis occurrence after adjusting for concurrent confounding factors.

Results

The three-year cumulative occurrence rates of uveitis were significantly different according to the type of anti-TNFs used (23.1% in IFX, 18.5% in ETN, and 11.9% in ADA+GOL group) (p=0.020). The risk of new-onset uveitis was similar for different drugs. However, the IFX group showed a 5.4 times higher risk of recurrence than the ADA+GOL group (p=0.022). After adjusting for other confounding factors, IFX use was independently associated with a more frequent occurrence of uveitis in AS patients (HR=2.01; p=0.011).

Conclusion

A significant number of AS patients who received anti-TNF therapy developed uveitis. Different types of anti-TNF drugs were associated with uveitis recurrence. Particularly, chimeric mouse-human monoclonal antibody (IFX) was found to increase the risk of uveitis occurrence compared to humanised monoclonal antibody (ADA or GOL).

Key words

uveitis, tumour necrosis factor inhibitor, adalimumab, infliximab, etanercept, golimumab, ankylosing spondylitis

Eun Young Choi, MD
Minwoo Lee, MD
Christopher Seungkyu Lee, MD, PhD

Please address correspondence to
Christopher Seungkyu Lee,
Department of Ophthalmology,
Severance Eye Hospital,
Yonsei University College of Medicine,
50-1 Yonseiro, Seodaemun-gu,
Seoul 03722, Korea.
E-mail: sklee219@yuhs.ac

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Introduction

Tumour necrosis factor (TNF) inhibitors block various immune related action pathways of TNF cytokines, leading to inflammation and pain (1, 2). Various types of TNF blockers are used clinically. Adalimumab (ADA) and golimumab (GOL) are fully human monoclonal anti-TNF-α IgG antibodies. Infliximab (IFX) is a chimeric mouse-human monoclonal antibody, and etanercept (ETN) is a soluble TNF receptor fusion protein that binds to TNF-α and TNF-β (3). TNF inhibitors have shown excellent anti-inflammatory properties and are now considered as an advanced therapeutic option for ankylosing spondylitis (AS) (4, 5).

Increasing evidence has been collected suggesting anti-TNF agents as efficacious therapeutic options for non-infectious uveitis (intraocular inflammation) (6-8). In addition to the anti-inflammatory effects, steroid-sparing effects have also been reported in a long-term follow-up (9). However, there is still a lack of consensus on whether TNF antagonists used for systemic purposes have prophylactic effects on uveitis. Several observational studies have suggested that ETN is less effective than other agents in preventing uveitis (10-13) or even promotes uveitis (14) in patients with AS. However, previous studies involved heterogeneous data collection methods and designs. Additionally, the analyses were usually based on small numbers of observable populations or on large national data lacking disease level clinical data. Furthermore, comparison results among anti-TNF agents have not been presented through meta-analyses or as randomised controlled trials (15-17).

Therefore, this study was designed to comprehensively compare the occurrence (new-onset and recurrence) of non-infectious uveitis during TNF inhibitor therapy (ADA, ETN, IFX, or GOL) to manage spondyloarthritis, in a large cohort with underlying AS.

Materials and methods

Study design and participants

This was a retrospective comparative cohort study. Since January 2019, we reviewed the medical records of patients who were diagnosed with AS (18) and received TNF inhibitors (ADA, ETN, IFX, and GOL) for more than 6 months to manage their spondyloarthritis in the Department of Rheumatology, Severance Hospital (Shinchon and Gangnam, Seoul, Korea) between November 2005 and December 2018. We collected information on cases in which the patients underwent ophthalmologic examinations for more than 6 months. Therefore, all patients with AS who were diagnosed with or without non-infective uveitis during anti-TNF treatment to manage their spondyloarthritis were selected. Patients with concurrent uveitis at the time of initiation of anti-TNF therapy were excluded for analysis, while a previous history of uveitis during the anti-TNF-naïve period was not an exclusion criterion. Cases, in which the first TNF inhibitors were subsequently changed with other anti-TNF agents or discontinued for more than 3 months, were excluded. Patients with a diagnosis of other rheumatic diseases except AS were excluded. The study was approved by the Institutional Review Board of Severance Hospital. Informed consent was not obtained from the participants because of the retrospective nature of the study.

Data collection and main outcome measures

In addition to the basic demographic information (age and sex), we recorded the duration of underlying AS, types of anti-TNF agents used as first-line treatment, duration of TNF inhibitor therapy, types of combined systemic immunosuppressive therapies [oral steroids and other disease modifying anti-rheumatic drugs (DMARDs)], and the total follow-up period. A detailed history of non-infectious uveitis was also recorded, including information regarding the onset time, type according to the Standardization of Uveitis Nomenclature (SUN) Uveitis classification, involved eye, duration, treatment, and outcome. A "favourable" outcome was recorded if the uveitis resolved within 1 month after local treatment or systemic steroids. Human leukocyte antigen (HLA) B27 positivity and C-reactive protein (CRP) levels at uveitis onset were also investigated.

Table I. Demographic data of patients and characteristics of uveitis events with different anti-tumour necrosis factor (TNF) agents.

	Adalimumab	Etanercept	Infliximab	Golimumab	*p*-value
Patients	62 (29.1)	37 (42.5)	49 (33.3)	27 (50.9)	N/A
Age, years	38.5 (17.4)	41.2 (16.1)	36.4 (15.1)	35.7 (14.5)	0.23*
Male sex	46 (74.2)	25 (67.6)	34 (69.4)	18 (66.7)	0.20†
Follow-up period, months	48.1 (18.4)	43.2 (18.5)	39.7 (15.4)	57.3 (18.7)	0.37*
Duration of TNF inhibitor therapy, months	49.0 (18.5)	33.2 (18.1)	48.2 (47.2)	37.1 (14.9)	0.11*
Occurrence of uveitis	10 (16.1)	5 (13.5)	10 (20.4)	2 (7.41)	0.81†
First-onset	3 (7.69)	1 (3.85)	2 (5.71)	0 (0)	0.58†
Recurrence	7 (30.4)	4 (36.4)	8 (57.1)	2 (28.6)	0.13†
SUN Classification of uveitis					0.39†
Anterior,	6 (60.0)	2 (40.0)	6 (60.0)	2 (100)	
Intermediate, or posterior	4 (40.0)	3 (60.0)	4 (40.0)	0 (0)	
Localisation					0.12†
Unilateral	6 (60.0)	1 (20.0)	7 (70.0)	2 (100)	
Bilateral	4 (40.0)	4 (80.0)	3 (30.0)	0 (0)	
Interval onset underlying disease-uveitis, years	9.3 (5.7)	9.6 (6.2)	9.5 (5.5)	9.1 (6.0)	0.18*
Interval of initiation of TNF therapy and uveitis onset, months	35.4 (12.1)	18.0 (8.6)	23.7 (12.3)	28.0 (-)	0.63*
Interval of the last uveitis recurrences, days	20.7 (13.6)	66.5 (16.7)	41.3 (12.3)	25.6 (16.3)	**0.045***
CRP levels at uveitis onset, mg/L	7.55 (14.75)	4.81 (5.10)	4.14 (5.06)	2.22 (2.15)	0.61*
Response to uveitis treatment					0.44‡
Favourable	8 (80.0)	3 (60.0)	6 (60.0)	2 (100.0)	
Not favourable	2 (20.0)	2 (40.0)	4 (40.0)	0	
Mean duration of uveitis, months	2.62 (3.78)	1.96 (1.56)	2.81 (3.44)	0.92 (0.25)	0.29*

SUN: Standardization of Uveitis Nomenclature; CRP: C-reactive protein.
Values are expressed as mean (± standard deviation), except where indicated as number (percentage) of subjects.
*ANOVA (Bonferroni *post hoc* test), †Fisher's exact, and ‡chi-square test.
A *p*-value in bold indicates a statistical significance (*i.e.* $p < 0.05$).

Based on the results of the examination performed by an ophthalmologist, we calculated the rate of new-onset (developing in patients with no previous history of uveitis) and recurrence (developing in patients with a previous history of uveitis) of uveitis during TNF inhibitor therapy. To compare the cumulative occurrence (new-onset and recurrence) rate of uveitis, the patients were classified into three groups according to the type of first-line anti-TNF agents used as follows: ADA or GOL users (ADA+GOL), ETN users, and IFX users. For adjusting confounding factors, we selected age, sex, previous uveitis history, duration of AS, HLA B27 positivity, CRP level, duration and types of TNF inhibitor therapy, and concomitant use of immunosuppressive agents as potential confounders.

Statistical analyses

Mean ± standard deviations are presented for continuous variables. To compare baseline characteristics among the four groups, Fisher's exact or chi-square test was performed for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. Kaplan-Meier analysis was used to calculate the cumulative occurrence rates of developing uveitis among the anti-TNF groups, and log-rank test was used to analyse differences between the survival curves. Thereafter, univariable Cox proportional-hazards models were performed to estimate factors associated with uveitis occurrence by computing hazard ratios (HRs). We then performed a multivariable Cox analysis including only those factors that were significant with a p-value <0.10 in the univariable analysis. All statistical analyses were performed using SPSS v. 21.0 (SPSS Inc., Chicago, Illinois, USA). A p-value of <0.05 was considered statistically significant.

Results

Patient characteristics

Among 203 patients who were reviewed for this study, a total of 175 patients were finally included in the analysis. We excluded 7 patients with concurrent uveitis at the time of initiation of anti-TNF therapy, 8 patients with diagnosis of other rheumatic diseases in addition to AS (*e.g.* Behçet's syndrome, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus), 6 patients because of the subsequent change of anti-TNF agents, and 7 patients because of a short TNF inhibitor therapy period of less than 6 months. Table I shows the basic characteristics of the patients. Among these, 62 (29.1%) patients received ADA, 37 (42.5%) received ETN, 49 (33.3%) received IFX, and 27 (50.9%) received GOL. The mean age of patients in the TNF inhibitor groups was similar (ranging from 38.5 years for ADA to 41.2 years for ETN, p=0.23). Sex ratios were similar among the groups. The mean follow-up period was similar in each group (ranging from 39.7 months for IFX to 57.3 months for GOL, p=0.37)

Twenty-three (37.1%) patients had a history of one or more uveitis episodes before receiving ADA, 11 (29.7%) patients before ETN, 14 (28.6%) before IFX, and 7 patients (25.9%) before GOL treatment (p=0.54). The mean duration of use of TNF inhibitors was 41.0 months. The mean duration of an-

ti-TNF treatment showed no significant difference among the groups (p=0.11).

Events of uveitis with anti-TNF therapy

We summarised the characteristics of uveitis based on the use of TNF inhibitors in Table I. Overall, 27 of 175 (15.4%) patients developed uveitis during the mean follow-up period of 46.7 months. The overall incidence and recurrence rates were 5.0% and 38.2%, respectively. There was no difference in the overall occurrence, incidence, and recurrence rates of uveitis according to the different drug types (p=0.81, p=0.58, and p=0.13, respectively). Among the patients who developed uveitis, the ratio of intermediate/posterior involvement (p=0.39) and bilaterality (p=0.12) were not significantly different among the anti-TNF groups.

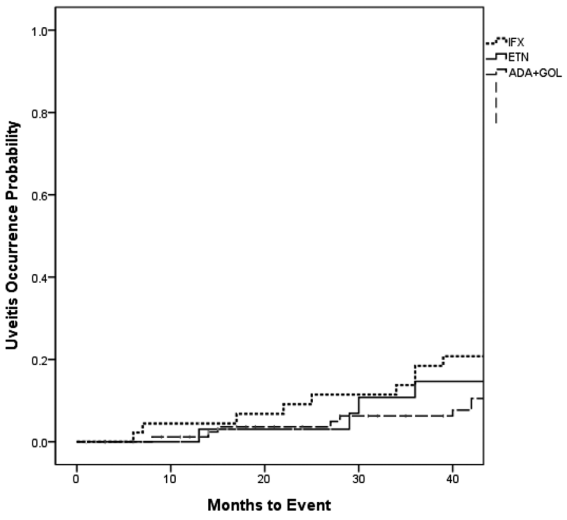
The duration of the underlying AS diseases before the development of uveitis was similar among the four anti-TNF groups (p=0.18). The mean interval between the initiation of TNF inhibitor therapy to the development of uveitis was similar for different drugs (35.4 months for ADA, 28.0 months for GOL, 23.7 months for IFX, and 18.0 months for ETN, respectively; p=0.63). Among patients who developed a recurrence, the mean interval since the last occurrence of uveitis was the longest for ETN (66.5 days), followed by IFX (41.3 days), GOL (25.6 days), and ADA (20.7 days, p=0.045).

The rate of concurrent oral steroid use did not differ among the different groups (p=0.97). Use of other DMARDs (methotrexate, azathioprine, mycophenolate mofetil, cyclosporin, sulfasalazine, hydroxychloroquine) was also comparable among groups (p=0.23). A favourable response to uveitis treatment was rated from 60.0% in patients receiving ETN and IFX to 100.0% in patients receiving GOL, while there were no significant differences among the four groups (p=0.44). The mean duration of uveitis ranged from 0.9 months in patients receiving GOL to 2.8 months in patients receiving IFX, which was not significantly different (p=0.29). The difference in the mean CRP level at the onset of uveitis was not statistically significant among the groups (p=0.61).

Fig. 1. Estimated occurrence rates of non-infectious uveitis at each year and estimated years of uveitis occurrence according to anti-tumour necrosis factor (TNF) treatment in patients with ankylosing spondylitis (p=0.020).

Anti-TNFs	Uveitis			
	Estimated Years*	Estimated Occurrence at Year (%)*		
	[95% CI]	1	2	3
IFX	2.9 [1.7-4.1]	4.8	13.8	23.1
ETN	3.4 [2.3-4.5]	3.0	3.8	18.5
ADA + GOL	6.3 [4.6-7.8]	2.4	4.3	11.9

CI: confidence interval; ADA: adalimumab; GOL: golimumab; IFX: infliximab; ETN: etanercept. *Estimated incidence and years from Kaplan-Meier analysis, and p-value from a log-rank test.



Time of occurrence and risk of uveitis

We used Kaplan-Meier survival analysis to examine the cumulative occurrence rates of uveitis among the anti-TNF groups (ADA+GOL, ETN, and IFX) (Fig. 1). A log-rank test revealed statistically significant differences among the anti-TNF drugs (p=0.020). The estimated occurrence rate of uveitis was 4.8% at 1 year, 13.8% at 2 years, and 23.1% at 3 years in the IFX group; 3.0% at 1 year, 3.8% at 2 years, and 18.5% at 3 years in the ETN group; and 2.4% at 1 year, 4.3% at 2 years, and 11.9% at 3 years in the ADA + GOL group. The new-onset risk of uveitis showed no significant difference among the anti-TNF drugs (p=0.49). The risk of recurrence of uveitis was 5.4 times higher in patients with AS receiving IFX than in those receiving ADA or GOL (HR=5.41; 95% CI=1.28–22.83) (p=0.022).

The results of Cox proportional-hazards models are presented in Table II. Significant risk factors for uveitis occurrence were duration of AS (HR= 1.78; p=0.020), HLA B27 positivity (HR=1.72; p=0.056), and the type of anti-TNF agent used (HR= 2.48; p=0.009) in the univariable Cox analysis. Multivariable Cox analysis including three significant clinical variables determined the use of IFX (HR=2.01; p=0.011) as a significant risk factor. The duration of AS showed marginal significance (HR=1.93; p=0.058).

Discussion

To the best of our knowledge, this is the largest hospital-based comparative cohort study on the occurrence of uveitis in AS patients during treatment with different types of TNF inhibitors. The three-year cumulative occurrence (new-onset + recurrence) rates of uveitis were significantly different according to the type of anti-TNFs used: 23.1% for IFX, 18.5% for ETN, and 11.9% for ADA+GOL.

Table II. Factors associated with the occurrence of uveitis during tumour necrosis factor (TNF) inhibitor therapy to manage spondyloarthritis in patients with ankylosing spondylitis (AS).

	Univariable		Multivariable	
	HR [95% CI]	*p*-value*	HR [95% CI]	*p*-value*
Age, years	0.99 [0.94-1.05]	0.79		
Male sex	1.54 [1.21-3.14]	0.14		
Previous uveitis event before TNF inhibitor therapy	1.47 [1.27-1.76]	0.55		
Duration of AS, years	1.78 [0.62-2.96]	0.020	1.93 [0.86-3.51]	**0.058**
HLA B27+	1.72 [0.20-2.41]	0.056	1.53 [0.65-2.70]	0.06
CRP levels at uveitis onset	0.40 [0.28-2.59]	0.50		
TNF inhibitor therapy				
Duration, months	0.96 [0.89-1.02]	0.19		
Agent types				
ADA + GOL	Ref		Ref	
ETN	1.68 [0.55-3.15]	0.36	1.53 [0.51-3.58]	0.44
IFX	2.48 [1.36-4.36]	0.009	2.01 [0.85-4.15]	**0.011**
Concomitant systemic treatment at uveitis event				
Corticosteroids	1.31 [0.30-1.56]	0.72		
DMARDs	1.08 [0.56-1.22]	0.12		

HR: hazard ratio; CI: confidence interval; HLA: human leukocyte antigen; CRP: C-reactive protein; ADA: adalimumab; GOL: golimumab; IFX: infliximab; ETN: etanercept; DMARDs: disease-modifying anti-rheumatic drugs.
**p*-value from the Cox proportional-hazards model. A *p*-value in bold indicates a statistical significance (*i.e.* $p < 0.05$).

Although the reasons behind our findings are unclear, speculation is possible in several directions. In addition to binding and neutralising soluble TNF-α, anti-TNF agents have various biological effects against transmembrane TNF-α- and Fc-receptor-expressing cells (19). As a soluble receptor, ETN not only blocks TNF-α but also TNF-β (20, 21). The action toward the transmembrane TNF-expressing cells was generally superior with monoclonal IgG antibodies than with ETN (22, 23), whereas only ETN showed binding and neutralisation of lymphotoxin-α3 (24). Therefore, ETN along with other TNF inhibitors might have similar protective effects against uveitis in patients with AS and other rheumatic diseases.

Moreover, TNF inhibitors have distinct pharmacological characteristics such as half-life, distribution, and degradation (25, 26). In uveal tissues, whether a significant difference exists between TNF blockers remains unknown. The development of permanent antibodies against IFX (27, 28) and ADA (29) was reported as a possible cause of poor pharmacokinetic outcomes. GOL, a human anti-TNF monoclonal antibody, has greater affinity for soluble TNF than IFX or ADA (30). The efficacy of GOL has been reported in severe uveitis that was refractory to other anti-TNFs (31, 32). The difference in the method and interval of administration of the drugs could also affect the occurrence of uveitis. IFX is administered by intravenous infusion, while other anti-TNF agents are injected subcutaneously. GOL, administered monthly, is expected to have better drug compliance.

In previous studies with general AS populations, the annual incidence of uveitis varies substantially, although it was reported to be approximately 15.6% in a meta-analysis (15). A systematic review presented the prevalence as 12.3% for a mean disease duration of <5 years and 43.0% for a mean disease duration of 30 years (33). Recurrence of uveitis occurred in 50.6% of patients (33). In our study, the rate of new-onset and recurrence during the follow-up period of 46.7 months were 5.0% and 38.2%, respectively. Considering the long AS duration of our cohort, the incidence and recurrence rates were relatively lower than those in the general AS population. This seems to be due to the effect of long-term TNF inhibitor therapy. HLA B27 positivity and heel pain are known to be associated with a more frequent appearance of uveitis in AS (34). In addition to this, our results are important because we identified a possible risk factor with regard to the therapeutic factors.

Previous studies have suggested that ETN might not show similar effects to that of monoclonal antibodies (35, 36). However, our study revealed that the receptor fusion protein ETN does not elevate the risk of occurrence of uveitis compared with monoclonal TNF antibodies, which were used for the treatment of spondyloarthritis in AS patients. This is probably due to the difference in the research design between the studies. Most previous studies used national databases, which were registered from multiple institutions without disease level data, whereas a more detailed analysis of the effects on uveitis was possible in our hospital-based data sets.

This study has some limitations. First, a more detailed analysis of the clinical data was not possible because the information was collected retrospectively. Changes in the incidence and severity of uveitis before and after treatment with TNF inhibitors could not be analysed. Further prospective controlled studies are needed to validate our results. Secondly, a retrospective comparison among TNF inhibitors used at different time periods can be a potential bias. However, we confirmed that the patient's basic demographic profile and concurrent immunosuppressive treatments at the time of uveitis events were not significantly different between the TNF groups.

In summary, among three different types of new-onset TNF inhibitors in-

cluding monoclonal antibodies (ADA, GOL), a chimeric antibody (IFX), and a receptor fusion protein (ETN) used to manage spondyloarthritis in AS patients, IFX showed the highest occurrence rate of uveitis. There was no difference in the rate of new-onset uveitis among the different drugs, but the recurrence rate of uveitis was highest in IFX. These results could serve as an important reference in selecting biologicals to treat AS, especially in patients with previous or concurrent non-infectious uveitis.

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