Adalimumab for the treatment of non-infectious uveitis: a real life experience

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Abstract

Objective: To describe the efficacy and safety of adalimumab for the treatment of non-infectious uveitis (NIU) in four Uveitis Units from tertiary Spanish hospitals.

Methods: Multicenter and retrospective clinical cohort study including all patients with NIU treated with adalimumab from January 2012 to October 2022 in four uveitis units was performed. Efficacy was measured with the number of relapses, ocular inflammation and reduction in immunosuppression and corticosteroid dosage before and after adalimumab use. We collected data regarding adverse effects and examined the immunogenicity of adalimumab.

Results: One hundred and twenty-two patients (59% females), with a mean age of 48.6 years (SD = 14.8) accounting for 217 eyes were included. The majority (92.6%) were Caucasian. Uveitis analyzed were predominantly panuveitis (34.7%), bilateral (77.9%), acute (41.5%), and non-granulomatous (90%). Most of them were inmune mediated (42.6%) and the main reason to initiate adalimumab was refractory disease (96.7%). The analysis was statistically significant for the reduction in the number of immunosuppressive drugs as well as the dose of oral corticosteroids and the number of relapses during follow-up ($p<0.001$). The decrease in ocular inflammation parameters and the improvement in visual acuity ($p<0.05$) were also significant. There were no deaths due to the drug and only one reported case of serious infection. In total, 10.9% of 73 patients tested developed anti-adalimumab antibodies and 4.1% lupus-like.

Conclusions: We consider adalimumab as a leading drug in the treatment of NIU with high safety and efficacy.

Key words

Uveitis, adalimumab, immunogenicity.

Introduction

Uveitis is a heterogeneous group of diseases characterized by intraocular inflammation, and, in general, is classified as infectious and non-infectious (NIU), including those that are specific ocular syndromes (limited to eye), those associated with systemic diseases and those idiopathic. To perform an adequate etiological classification, multidisciplinary diagnostic approach is essential that should include a complete ophthalmological evaluation, followed by an exhaustive clinical history, physical examination, and complementary studies according to the results of etiological assessment[1,2,3].

The Standardization of Uveitis Nomenclature (SUN)[3] working group classified uveitis according to their onset, location, time course, duration, and activity. This classification defines different uveitis patterns with diagnostic, prognostic, and therapeutic implications[4].

Currently, uveitis continue to be a public health problem, not only because of the high economic and social burden, but also because of its morbidity, being the cause of 10-15% of blindness in developed countries, and the fifth or sixth cause of blindness in the world[5].

Treatment of NIU includes regional therapy (topical, intravitreal and periocular corticosteroids), systemic treatment (corticosteroids, immunosuppressants agents, and biologics), or a combination of them[5]. In general, the anatomical location of uveitis will determine the initial uveitis therapy. In addition, the course of the disease and the association with systemic disease will determine the duration of treatment and the need for chronic immunosuppression[5]. The ultimate goal of treatment should

be the control of ocular inflammation and to minimize visual loss while avoiding treatment toxicity[6].

In 2016, adalimumab received the European Medicine Agency approval for the treatment of non-anterior NIU (intermediate, posterior uveitis and panuveitis) in adults and children over two years-old based on the favorable results of two multicentre, randomized, placebo controlled clinical trials (VISUAL-I and VISUAL-II)[7,8]. Adalimumab, in patients with active and inactive uveitis, achieved a ~50% reduction in relapse rate (prolonged time to relapse) and vision impairment as well as a rapid taper off oral corticosteroids with a good safety profile[7,8].

As an adverse effect, the drug is immunogenic by eliciting anti-drug antibodies that can decrease its therapeutic level and effectiveness[9]. In this sense, monitoring serum adalimumab levels and detecting antibodies has been considered as a clinically cost-effective means of guiding the treatment, specially the event of primary or secondary loss of response[10,11]. However, the reported percentage of patients with development of anti-adalimumab antibodies varies between different studies, the cost of serum drug level and antibodies monitoring is non-trivial, and there is no consensus whether or when to test for serum drug levels and anti-drug antibodies in patients on anti-TNF therapies[11].

The aim of this study was to describe the efficacy, safety and immunogenicity of adalimumab in a cohort of patients with NIU from different Spanish Uveitis Units.

Methods

Patients

Adults with NIU treated with adalimumab between January 2012 and October 2022 were identified in the Uveitis Units from four specialized Spanish hospitals. Patients with uveitis of purely infectious etiology and those with incomplete data were excluded. This study was approved by the local ethics committees of Hospital Virgen de las Nieves of Granada (0055-N-23) and was conducted in compliance with the Good Clinical Practices and Declaration of Helsinki principles. Ethics Committee waived requirements for written consent because the retrospective nature of the study.

Variables

Data on demographics, uveitis location, uveitis diagnosis, associated systemic disease, age at uveitis onset, previous and concurrent immunosuppressant and biologic treatments including dose of oral corticosteroids, age at start and end of adalimumab and main indication of adalimumab were collected. In all cases, adalimumab was administered subcutaneously in accordance with NICE (UK) guidelines, 80 mg induction followed by 40 mg at week 1 and every 2 weeks thereafter[12].

The SUN Working Group[4] criteria were used to anatomically classify the uveitis and also to describe the grade of inflammation in anterior chamber. For laterality, those patients with alternating unilateral involvement or synchronous involvement were considered as ‘bilateral’. For the etiological classification of NIU, we divided them into following groups: immune-mediated (associated to systemic disease), ocular primary syndromes or white dot syndromes, idiopathic, masquerades, and others.

The term ‘idiopathic’ uveitis was applied to any NIU not associated with any known systemic disease or that did not meet any described specific ocular syndrome after appropriate extensive examinations.

In terms of adalimumab efficacy, visual acuity and intraocular inflammation parameters at baseline (adalimumab starting) and at 3, 6 and 12 months after starting adalimumab, with a margin of ± one month at each time interval were collected. The assessment of visual acuity has been collected and analyzed on a decimal scale. Intraocular inflammation parameters analyzed were anterior chamber inflammation measured as anterior chamber cells[4], vitreous haze assessed by the Nussenblatt scale[13], macular edema (absent/present) measured by optical coherence tomography (OCT), choroiditis, retinitis, and vasculitis measured by fundus photography and fluorescein angiography, synechiae, and relapses or flares defined as the presence of inflammatory ocular activity in patients who had reached remission[4,13]. Number of uveitis relapses at 24, 12, 6 and 3 months before starting adalimumab and 3, 6, 12 and 24 months after adalimumab initiation were included.

Side effects associated to adalimumab were also identified such as infections with location and microorganism, as well as withdrawal rate and reason for discontinuing the drug. In addition, development of other systemic diseases, antinuclear antibodies, and anti-drug antibodies were also collected. Regarding the development of antinuclear antibodies, only those with a negative determination prior to starting the drug were considered positive.

For the comparative analysis of the treatments, immunosuppressive drugs were grouped together, excluding corticosteroids (topical, oral, intraocular and/or periocular therapy, and bolus), which were analyzed independently.

Statistical analysis

Descriptive statistics included sample size, percentages, mean and standard deviation. Categorical variables were presented as absolute numbers and proportions. Normally distributed continuous variables were summarized as mean, standard deviation (SD) and range. Non-normally distributed variables were summarized as median, interquartile range (IQR) and range.

The association between qualitative variables was analyzed using the Chi-square test or Fisher exact test. For the quantitative variables, if they met the conditions of normality and homoscedasticity, the Student T-test was used and if not the Mann-Whitney U-test. In the case of more than two groups, the analysis of variance (ANOVA) and Kruskal-Wallis test were used. For two-to-two comparisons, the Bonferroni correction was considered.

Paired data analysis was performed to compare pretreatment measurements with adalimumab for treatments, visual acuity, and ophthalmologic parameters with post measurements. The Wilcoxon test for related data was used to compare the means between dependent data.

The unit of analysis for the general characteristics of the sample, the treatments, and the number of uveitis flares was the total number of patients, while for visual acuity and ocular inflammation parameters we considered the number of eyes.

For statistical analysis, the statistical program SPSS version 28.0 was used. p value of < 0.05 was considered as statistically significant.

Results

General characteristics

Overall, the number of patients with NIU was 122 accounting for a total of 217 affected eyes. Sixty patients (49.2%) were from Hospital Clinic, Barcelona, 24 (19.7%) from Hospital Universitario Central de Asturias, Oviedo, 21 (17.2%) from Hospital de Navarra, Pamplona, and 17 patients (13.9%) from Hospital Virgen de las Nieves, Granada.

The main demographic characteristics of patients, location and features of uveitis, and previous treatments are depicted in Table 1. The mean age was 48.6 years (SD = 14.8), 59% of patients were female and 92.6% Caucasian (Table 1).

The most frequent uveitis etiologies are depicted in Table 2. The most common were the immune-mediated uveitis (42.6%). The main reason to initiate adalimumab was refractory disease in 118 (96.7%) patients, followed by intolerance to previous treatments in one (0.8%) or both causes in the remaining three (2.5%).

Originator biologic was started in 74 patients and adalimumab biosimilar in 48 patients.

Before starting adalimumab, all patients had been treated with topic, intraocular, periocular, and/or oral glucocorticoids, and 88 (72.1%) patients had been received at least one immunosuppressor (Table 1). This number decreases to 63 (51.6%) at the start of adalimumab, 53 (43.4%) at 3 months, 44 (36.7%) at 6 months, and 36 (33.6%) at 12 months of starting adalimumab.

Mean follow-up under adalimumab treatment was 42.6 ± 34.9 months. All patients were still on adalimumab at 3 months, 120 (98.4%) were on adalimumab at 6 months and 107 (87.7%) patients at 12 months. At the end of follow-up, 71 (58.2%) patients are still on treatment.

Ocular outcomes

To analyze ocular outcomes after adalimumab starting, a total of 217 affected eyes were evaluated. Regarding the number of relapses, the differences between all time intervals before and after adalimumab were statistically significant ($p<0.001$) (Table 3).

Mean visual acuity improved after adalimumab starting at 3 months (0.62 ± 0.34), and then maintained at 6 months (0.62 ± 0.33) and 12 months (0.64 ± 0.34), compared with visual acuity at adalimumab starting (0.58 ± 0.32) ($p<0.05$ at all time intervals) (Table 3).

When the ocular inflammation parameters were considered jointly for each eye, the eyes with at least one ocular inflammation parameter decreased from 134 (64.1%) before starting adalimumab (with a maximum of 6 inflammation parameters in the same eye) to 70 (38.9%) at 3 months, 61 (31.8%) at 6 months and 50 (29.9%) at 12 months respectively. The mean number of ocular inflammation parameters decreased from 1.17 ± 1.16 before adalimumab to 0.62 ± 0.99 at 3 months, 0.45 ± 0.75 at 6 months and 0.39 ± 0 .68 at 12 months, respectively (Table 3).

With respect to number of cells in anterior chamber, significant differences were observed between the different periods in terms of the percentage of eyes with positive *Tyndall* ($p<0.001$), although these differences are no longer significant if we compare the last two time points (6 months vs. 12 months). Significant results were also observed in terms of vitreous haze, macular edema, choroiditis, retinitis and vasculitis, as reflected in Figure 1 and Supplementary Table.

Interestingly, no significant differences were found in the improvement of visual acuity and ocular inflammation parameters in the different time intervals according to the different etiologies or depending on whether it was a originator biologic or adalimumab biosimilar.

Previous and final treatments

The mean number of immunosuppressive drugs were compared before, at baseline and at 3, 6 and 12 months after adalimumab (Table 3). Of note, it decreased from a mean 1.31 ± 1.16 immunosuppressive drugs to 0.3 ± 0.5 at 12 months (global p-value <0.001). The differences were also statistically significant at 3 and 6 months, respectively. Twenty-three out of 107 (21.5%) patients in whom this data was available, immunosuppressant drug could be withdrawn at 12 months.

At the start of adalimumab, the median oral corticosteroid (prednisone) dose was 2.5 mg/day (range 0-60 mg/day). Interestingly, the median dose decreased at 3 months (0 mg/day; p<0.001) (range 0-40 mg/day), and it was maintained at 6 months (0 mg/day; p<0.001) (range 0-20 mg/day) and at 12 months (0 mg/day, range 0-30 mg/day) (Table 3). Of note, in 34 out of 101 (33.4%) patients for whom this data was available, corticosteroids could be withdrawn at 12 months. Table 3 shows the percentage of patients who received topical, regional and oral corticosteroids, as well as those with one or more immunosuppressants at different time points.

Safety profile

Overall, 18 (14.8%) patients presented some adverse event associated to adalimumab, which led 6 (4.9%) of them to withdraw treatment (Table 4). There were

two cases of severe adverse events consisting of a central nervous system infection without documenting the causative microorganism and a severe sensory neuropathy. There were three cases of non-severe infections, one cutaneous infection by varicella-zoster virus (VZV), one herpetic keratitis and a urinary infection by *Klebsiella pneumoniae*, respectively. There was no death in this cohort.

Other non-infectious adverse events were documented in 14 (11.5%) patients consisting of flu-like symptoms (one case), skin reaction at the injection site (6 cases), arthralgia (2 cases), gastrointestinal effects (2 cases), distal sensory neuropathy (2 cases), and headache (1 case). These side effects didn't required admission, and required withdrawal in 4 patients (3.3%), without implying death in any case.

Treatment after adalimumab

Overall, of the 50 (41.3%) patients in whom adalimumab was discontinued, 21 (42%) were due to inefficacy (active uveitis despite treatment but no immunogenicity data), 10 cases (20%) due to stability (inactive uveitis), 6 cases (12%) due to adverse effects, 6 cases (12%) due to immunogenicity (development of anti-adalimumab antibodies), 2 cases (4%) due to an alternative diagnosis (masquerade syndrome) that forced the discontinuation of the drug, 2 cases (4%) due to the pregnancy desire of the patient, one case (2%) due to activity and development of lupus-like, and one case (2%) due to stability and desire of the patient.

After discontinuation of adalimumab, other biologics were started in 34 patients (27.9%), infliximab in 10 patients (29.4%), golimumab in 9 (26.5%), tocilizumab in 5

(14.7%), certolizumab in 3 (8.8%), rituximab in 3 (8.8%), switch from adalimumab biosimilar to originator in 3 (8.8%), and etanercept and anakinra (each one case).

Immunogenicity

Overall, anti-adalimumab antibodies were positive in 8 (10.9%) out of 73 patients in whom they were tested. In three of them adalimumab had been administered in combination with methotrexate (n=2) and azathioprine (n=1). In addition, 5 (4.1%) patients were diagnosed with lupus-like syndrome after starting adalimumab. Positive antinuclear antibodies (at titer of 1/160 or more) were detected in 8 patients (6.6%) after starting the drug.

Discussion

Uveitis remains a challenge for the physicians due to the multivariable etiologies that can be hidden behind ocular inflammation, and those with an immune-mediated profile are becoming increasingly prominent. As we can see in our study, 42.6% of uveitis was immune-mediated, and, in addition, some classified as 'idiopathic' (17.2%) was probably also immune-mediated, given their good response to immunosuppressive treatment. Even so, our study presents a lower percentage of idiopathic uveitis than in other series, probably in relation to the progresess in diagnostic tests, clinical research and implementation of multidisciplinary uveitis units[2].

Our work evaluates the effectiveness, safety and immunogenicity of adalimumab in NIU from a comprehensive and multicenter perspective, and it includes patients from four Multidisciplinary Uveitis Units from different geographical locations in Spain

(Granada, Barcelona, Oviedo and Navarra) which contributes great variability and richness to the study. This is one of the largest real-world series available[14], with a greater long-term follow-up under treatment of adalimumab compared to previous studies[13], and the first study in our country of a retrospective nature and more than six months of follow-up period[15,16].

In line with major multicentric clinical trials, VISUAL-I[7] and VISUAL-II[8], conducted among patients with active and inactive uveitis respectively, our study concludes a significant decrease in the risk for uveitic flare or vision impairment, an improvement in ocular prognosis and a reduction of corticosteroid treatment and other immunosuppressors, with low safety concerns. That is, compared to these and subsequent studies of a retrospective nature[14,17] as well as recent meta-analysis of randomized controlled trials[18], adalimumab appears to be effective and safe.

The most frequent reported side effects associated with treatment with adalimumab is local reaction in relation to injection, although potentially serious effects such as infections, anaphylactic reactions, and neoplasms have also been reported[7,8,17]. In our study, the adverse reactions described were mostly mild and non-infectious, in accordance with what was described in previous studies. No demyelinating process was detected, in contrast to that detected in VISUAL III study, in which a rate of 0.5/100 patient-years was observed[19], and no neoplasms or severe anaphylactic reactions were recorded. Yet, there was one case of serious infection that required hospital admission and forced the withdrawal of the drug, however the rest of the infections detected were mild and did not lead to hospital admission or suspension of adalimumab.

As far as the inclusion and exclusion criteria are concerned, our study included patients with active and inactive uveitis, as well as anterior uveitis, that were excluded from major clinical trials[7,8].

Our patient cohort had a similar duration of uveitis at baseline (mean 4 years) compared with VISUAL-I (mean < 4 years), VISUAL-II (mean 5 years) and most recent retrospective clinical cohort studies[17], probably due to the number of patients diagnosed before adalimumab availability for treatment of NIU.

The main indication for adalimumab in our sample was refractory to previous treatments, so it is likely that adalimumab was started in a greater number of severe, refractory, and chronic cases in which other immunosuppressive therapies had already failed. The results presented in our work and the rest of the available evidence suggest the consideration of earlier adalimumab in patients refractory to corticosteroid treatment.

In this study, more than 50% patients still used adalimumab at the end of follow-up and due to our long-term follow-up (3.5 years), the causes of cessation of adalimumab were analized. The major cause was inefficacy (41.2%) followed by stability (19.6%), immunogenicity (14%) and adverse events (11.8%). This is in line with other real-world data studies where inefficacy was the main cause of discontinuation[20], and contrasts with the results of the most recent retrospective study with long-term follow-up, where the main cause of drug discontinuation was remission, followed by adverse events and relapse and where no cases of cessation due to immunogenicity were detected[17].

The efficacy of adalimumab has been related to significant inter-individual variability in the systemic concentrations of biological drugs, and this in turn with the

development of anti-drug antibodies, the use of concomitant immunomodulatory treatments, and alterations in biochemical parameters[21].

Due to the high rate of patients presenting with primary or secondary failure with treatment, early identification of non-response or loss of response is very important, and this is closely related to serum drug concentration, immunogenicity and presence of anti-drug antibodies[21]. Immunogenicity has been related to an increase in the clearence of the drug and a decrease in its serum levels[21].

In our cohort, anti-adalimumab antibodies were detected in the 10.9% of patients (its determination was only performed in 73 patients), and more often (62.5%) in patients on adalimumab monotherapy compared with patients with additional immunosuppressors. In relation to this, concomitant treatment of adalimumab with immunosuppressants has shown a protective effect against the appearance of immunogenicity, which results in an increase in systemic drug levels and therefore a higher probability of clinical response[22,23].

In addition, in our work we report a percentage of patients (6.6%) who developed positive antinuclear antibodies after starting the drug. The development of antinuclear antibodies had been previously reported in patients with rheumatoid arthritis or Crohn's disease receiving selective TNF inhibitors[24], and although the development of antinuclear antibodies seems to be related to a worse clinical response to TNF inhibitors and development of anti-drug antibodies, the correlation between autoimmunity, immunogenicity and therapeutic response has not been established[25].

Our work highlights the need for clinical studies to establish the usefulness and cost-effectiveness of determining drug levels and antibodies to guide treatment adjustment with adalimumab in the treatment of NIU.

In summary, in accordance with the main clinical trials, our study proposes adalimumab as the leading drug in the treatment of NIU with a high rate of safety and efficacy, and addresses aspects that may be useful when making decisions in daily clinical practice. Some of them are the multidisciplinary diagnostic and therapeutic approach to patients, the inclusion of patients with anterior uveitis, and, above all, the detection of anti-adalimumab antibodies and the development of autoimmunity phenomena in a cohort in real life of patients with NIU.

Acknowledgements: We thank the Research Support Unit of A Coruña and her statistician, Vanesa Balboa, for their help and great work.

Declaration of interest statement: All authors declare no conflicts of interest.

Funding: There has been no financial support for this work.

Financial Disclosures: No financial disclosures.

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Legends

Table 1: Demographic characteristics, location and type of uveitis, reason to initiate adalimumab, and previous treatments of patients with uveitis.

Table 2: Causes of uveitis.

Table 3: Main ocular outcomes before and after adalimumab.

Table 4: Adverse events during adalimumab treatment.

Figure 1 and Supplementary Table: Ocular inflammation parameters before and after adalimumab in terms of the percentage of eyes affected.