

Golimumab in uveitis previously treated with other anti-TNF-alpha drugs: a retrospective study of three cases from a single centre and literature review

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Abstract

Objective

The aim of this paper is to assess the clinical response to golimumab (GLM) in patients with non-infectious uveitis from a single centre that had previously been treated with other anti-TNF- α drugs.

Methods

A retrospective chart review was carried out of patients with immune-mediated uveitis refractory to standard synthetic immunosuppressive drugs who were treated with GLM at Hospital Universitario Marqués de Valdecilla, Santander (Spain). Patients were included in this study if they had previously been treated with other anti-TNF- α drugs. A literature review of patients with immune-mediated uveitis undergoing GLM therapy was conducted.

Results

Three patients (2 men and 1 woman) were included in this study. Two of them were refractory to other anti-TNF- α drugs. The median age of patients was 26 years (range 20–42). Uveitis was bilateral in two patients. The underlying diseases were uveitis associated with HLA-B27 and psoriasis in one case and sarcoidosis in the other two cases. Improvement of the main ocular parameters following GLM therapy was achieved in all cases. After a median follow-up of 3 (range 1–9) months using GLM therapy, none of the patients had experienced new relapses of uveitis. None of them had side effects during treatment with this drug. A literature review disclosed that our observations were in keeping with other reports that showed good response to GLM in 13 of 16 patients with immune-mediated uveitis refractory to other biologic agents.

Conclusion

Although the follow-up was too short in our series, GLM could be an effective and safe therapy for the management of patients with uveitis previously treated with other anti-TNF- α drugs.

Key words

uveitis, immune-mediated diseases, anti-TNF- α agent, golimumab

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Received on October 17, 2013; accepted in revised form on April 8, 2014.

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*Funding: This work was partially supported by RETICS Programs, RD08/0075 (RIER) and RD12/0009/0013 from "Instituto de Salud Carlos III" (ISCIII) (Spain).
 Competing interests: non declared.*

Introduction

Uveitis includes a series of different clinical syndromes characterised by an intraocular inflammatory disease that, without appropriate treatment, may lead to blindness (1-3). Although the aetiology of non-infectious uveitis is often unknown, it may be the result of a wide spectrum of conditions, including autoimmune diseases such as spondyloarthropathies, Behçet's disease or sarcoidosis.

Several studies have demonstrated the presence of high levels of TNF- α in serum and aqueous humor of patients with uveitis (4-7). In the last years the use of biologic agents has improved the prognosis of patients with refractory uveitis (8). The switch to an anti-TNF-alpha drug has just shown a good efficacy in adult and paediatric patients (9-11). Off-label use of these agents, mainly infliximab (IFX) and adalimumab (ADA), has constituted an important breakthrough in the treatment of immune-mediated uveitis refractory to conventional immunosuppressive drugs (3).

Golimumab (GLM) is a novel fully humanised anti-TNF- α monoclonal antibody that has been approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis (12-14). However, information related to the efficacy of this biologic agent in the treatment of uveitis is limited to a few studies, most of them including a small number of patients (22-24).

Taking into account all these considerations, in the present study we aimed to evaluate the clinical response to GLM in patients with non-infectious uveitis from a single centre that had previously been treated with other anti-TNF- α drugs.

Patients and methods

A retrospective chart review was made of patients with immune-mediated uveitis refractory to standard synthetic immunosuppressive drugs who were treated with GLM at Hospital Universitario Marqués de Valdecilla, Santander (Spain).

Patients were included in this study if they had previously been treated with other anti-TNF- α drugs. As previously described (3), patients were defined as having refractory uveitis when it was not in remission despite receiving anti-

TNF- α drugs or when the use of these drugs was not sufficient to maintain the disease under control.

Before GLM onset, evidence of malignancy or systemic infection, including hepatitis B or hepatitis C, was excluded. As indicated in the Spanish National Guidelines, in all patients receiving anti-TNF- α drugs, latent tuberculosis was excluded by a tuberculin skin testing (PPD) and/or quantiferon and chest radiograph. Following this procedure, in patients with latent tuberculosis prophylaxis with isoniazid is initiated at least 4 weeks before the onset of the biologic agent. Overall, prophylaxis with isoniazid is maintained for 9 months.

Uveitis was classified anatomically according to the International Uveitis Study Group (IUSG) classification (19). GLM was given subcutaneously at the dose of 50 mg monthly. Since GLM is an off-label indication in uveitis, written informed consent was requested and obtained from all the patients.

Results

Three patients with uveitis refractory to conventional immunosuppressive therapy who were treated with GML were studied. They had previously been treated with other anti-TNF- α drugs. The main demographic and therapeutic data are described in Table I. Two of them were men. The median age of patients was 26 years (range 20-42). Uveitis was bilateral in two patients. The underlying diseases were HLA-B27 uveitis associated with psoriasis without axial or peripheral joint involvement in 1 patient, and uveitis in the setting of sarcoidosis in two patients. In both patients with sarcoidosis bilateral hilar lymphadenopathy were revealed on computed axial tomography. One of them also had impairment of pulmonary function tests.

Besides oral corticosteroids (maximum prednisone daily dosage 60 mg/day; mean \pm standard deviation 33.3 \pm 23.6 mg/day) and before the onset of the first biologic agent they were treated with MTX (3 patients), AZA (1 patient), Hydroxychloroquine (1 patient) and Sulfasalazine (1 patient).

Anti-TNF- α drugs were the first-choice biologic therapy in all cases; in two of

Table I. Main demographic, clinical features and treatment of 3 patients treated with golimumab because of refractory uveitis.

| Patient number | Sex / age (years) | Associated rheumatic disease | Synthetic immunosuppressant before first biologic drug | Biologic drugs before GLM | Associated synthetic immunosuppressant with GLM | Follow-up with GLM (months) | Active uveitis at the last visit on GLM therapy | BCVA at GLM onset; BCVA at last visit on GLM (OD/OS) |
|----------------|-------------------|------------------------------|--|---------------------------|---|-----------------------------|---|--|
| 1 | Male / 42 | HLA-B27+ and psoriasis | SSZ, MTX | ADA | None (monotherapy) | 3 | no | 0.05/1; 0.05/1 |
| 2 | Female / 20 | Sarcoidosis | MTX | IFX | MTX | 1 | no | 0.4/0.6; 0.9/0.9 |
| 3 | Male / 26 | Sarcoidosis | MTX, Hydroxychloroquine | IFX | AZA | 9 | no | 1/1; 1/1 |

SSZ: sulfasalazine; MTX: methotrexate; ADA: adalimumab; IFX: infliximab; GLM: golimumab; BCVA: best corrected visual acuity; OD: right eye; OS: left eye; ND: no data.

them IFX and in the other one ADA. In two cases anti-TNF- α was administered in combination with conventional immunosuppressive therapy (MTX and AZA, respectively).

One of the patients (Patient 1 from Table I) with uveitis associated with HLA-B27 and psoriasis was switched from ADA to GLM because of recurrent (relapsing) unilateral anterior uveitis. He had previously been treated with ADA therapy for 6 years. When ADA therapy was initiated the ophthalmological examination revealed a significant loss of vision in the right eye due to a cataract secondary to repeated episodes of intraocular inflammation and increased intraocular pressure in this eye. Because of that, ADA was given every week. After controlling intraocular inflammation with ADA 40 mg/week, a trabeculotomy was performed, leading to normalisation of the intraocular pressure in the eye. Regrettably, during the follow-up there were new episodes of anterior uveitis and also an urticarial local re-

action following ADA administration. Because of that, ADA was switched to GLM 50 mg/sc, achieving good control of intraocular inflammation.

The second patient (Patient 2 from Table I) presented with bilateral panuveitis and exudative retinal detachment due to sarcoidosis. She was initially treated with MTX and high dose oral corticosteroids. Due to persistent ocular activity, IFX was started at a loading dose of 5 mg/kg at 0, 2, 6 followed by a maintenance regimen of 5 mg/kg every 8 weeks. However, due to persistence of active bilateral panuveitis two months after the onset of IFX, she was switched to GLM 50 mg/month/sc. Intraocular inactivity was achieved one month after GLM onset (Fig. 1).

Patient 3 (Table I) was also diagnosed with sarcoidosis, IFX had been used because of persistent panuveitis with relapses in the left eye. IFX was started at a loading dose of 5 mg/kg at 0, 2, 6 followed by a maintenance regimen of 5 mg/kg every 8 weeks. Due to

successful response with persistent intraocular inactivity and also because the patient wished to stop biologic therapy, IFX was discontinued after 23 months of therapy. Regrettably, 2 years later the patient suffered a recurrence of sarcoidosis clinically manifested by dyspnea and dry cough. In addition, mild posterior uveitis was observed in the left eye. Because of that, anti-TNF- α therapy was again considered. Since the patient preferred to receive subcutaneously rather than intravenously the administration of the biologic therapy, GLM 50 mg/month/sc was started leading to complete ocular and respiratory improvement. However, 9 months after GLM onset the patient experienced newly worsening of respiratory symptoms. Thus, GLM was switched to IFX therapy achieving complete improvement of the respiratory symptoms.

Overall, the following ocular complications were observed in this series of patients at the time of GLM onset: macular oedema (2 eyes), cataract (1 eye), glaucoma (1 eye), irido-lenticular synechiae (1 eye). By the use of GLM the best corrected visual acuity (BCVA) remained stable in 4 eyes, and improved in 2 eyes.

After a median follow-up of 3 months (range 1–9) using GLM therapy, none of the patients experienced new relapses of uveitis. Moreover, no side effects were observed during treatment with this drug.

Discussion

In this retrospective study we report on 3 cases of non-infectious uveitis refractory to synthetic conventional

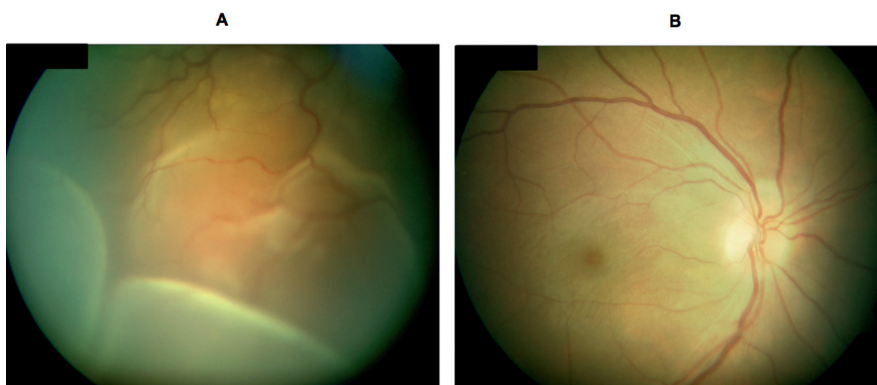


Fig. 1. Patient 2: Images of the right eye before (A) and after (B) golimumab therapy.

Table II. Literature review of patients with refractory uveitis treated with golimumab including the present series*.

| | Calvo-Río <i>et al.</i> present series* | Cordero <i>et al.</i> Spain (13) | Mesquida <i>et al.</i> Spain (15) | William <i>et al.</i> Boston, USA (12) | Miserocchi <i>et al.</i> Italy (14) |
|--|---|--|--------------------------------------|--|---|
| Number of cases | 3 | 2 | 1 | 3 | 10 |
| Underlying disease | HLA-B27+ and psoriasis, and 2 Sarcoidosis | JIA idiopathic retinal vasculitis | Behçet's disease | JIA | 6 JIA 4 HLA-B27 associated uveitis |
| Age (mean±SD), years | 29.3 | 29.5±2.1 | 28 | 17.3±8.7 | 34.2±10.3 |
| Uveitis pattern | AU OD, panuveitis OS, panuveitis bilateral | AU recurrent OD PU | Panuveitis OS | bilateral AU, AU OS | 4 bilateral AU 7 bilateral panuveitis |
| Previous treatment | MTX, SSZ, Hydroxychloroquine, ADA, IFX | MTX, SSZ, CsA, ETN, IFX, ADA | CsA, IFX | MTX, AZA, IFX, mycophenolate mofetil, ADA, ETN, daclizumab, abatacept | MTX, ETN, IFX, ADA, abatacept |
| Reason for using GLM | Recurrent uveitis, persistence of panuveitis, change of route of administration of anti-TNF | Uveitis relapse, severe macular edema | Uveitis relapse | Persistent active ocular inflammation, relapses of arthritis, ocular and joint symptoms | 4 active uveitis and arthritis 6 active uveitis |
| Ocular inflammation following GLM therapy | Inactivity | Inactivity | Inactivity | 2 Inactive 1 relapse | 8 inactive 2 active |
| Adverse effects by GLM | None | None | None | None | None |
| Months in treatment with GLM (mean±SD) | 4.3 | 6.5±0.7 | 6 | 9.3±7.5 | 8.2±2.3 |
| GLM withdrawal | 1 case because of worsening of respiratory symptoms | no | no | 1 case because of joint inflammation and uveitis relapse | no |

JIA: juvenile idiopathic arthritis; AU: anterior uveitis; PU: posterior uveitis; OD: right eye; OS: left eye; SSZ: sulfasalazine; MTX: methotrexate; CsA: cyclosporine A; ETN: etanercept; AZA: azathioprine; ADA: adalimumab; IFX: infliximab; GLM: golimumab.

immunosuppressive drugs that had previously been treated with other anti-TNF- α drugs. All of them responded favourably to GLM. This fact was of particular relevance since 2 of them had also been refractory to anti-TNF- α drugs different from GLM.

There are a number of studies demonstrating the efficacy of anti-TNF- α drugs, in particular ADA and IFX, in the treatment of non-infectious refractory uveitis (3, 20, 21). However, information on GLM therapy in uveitis is scarce because GLM is a relatively new drug in the market and also because anti-TNF- α drug therapy is an off-label indication for uveitis (15-18). Nevertheless, several clinical trials have demonstrated the efficacy of GLM in the management of autoimmune and inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis (22-24). Large scale studies on these entities have

also shown that GLM is well tolerated, having a safety profile similar to other commercially available anti-TNF- α drugs (12-25).

In comparing with the most commonly used anti-TNF- α drugs, GLM has advantages in terms of the route and the periodicity of administration. Moreover, GLM is a fully human monoclonal antibody. This fact may reduce potentially the risk of developing neutralising antibodies and allergic reactions (14-17). Interestingly, GLM is the only anti-TNF- α drug that has proved efficacy in prospective double-blind randomised controlled trials for the treatment of patients with rheumatoid arthritis refractory to other anti-TNF- α drugs (13, 14, 26).

Our results indicate that GLM could be effective and safe in patients with non-infectious uveitis previously treated with other anti-TNF- α drugs. In our hands this drug proved efficacy to

maintain intraocular inflammation inactivity. GLM was also useful to prevent further relapses in patients with recurrent episodes of uveitis.

Our observations are in keeping with former reports that showed good response to GLM in 13 of 16 patients with immune-mediated uveitis refractory to other biologic agents, including in some cases improvement of extraocular manifestations (15-18). These studies are summarised in Table II. With respect to this, Miserocchi *et al.* (17) assessed 10 patients with uveitis refractory to anti-TNF- α drugs (6 with juvenile idiopathic arthritis and 4 with HLA-B27-associated uveitis). The main complications at the time of GLM onset were macular oedema (6 eyes), cataract (6 eyes) and glaucoma (4 eyes). At last visit, uveitis remained inactive in 8 patients and active in 2 patients who underwent cataract extraction surgery. The other 3 studies analysed results on GLM in 3,

2 and 1 patient with refractory uveitis secondary to juvenile idiopathic arthritis, Behçet's disease and idiopathic retinal vasculitis, respectively (15, 16, 18). The main ocular complications of these patients at the time of GLM onset were cystoid macular oedema (2 patients), posterior synechiae (2 patients) and cataracts (2 patients). GLM therapy led to improvement of ocular and extraocular manifestations in all but one patient diagnosed with juvenile idiopathic arthritis. This patient had a good initial response to GLM. However, a relapse of ocular and joint inflammation was observed after 6 months of treatment with this biologic drug.

Conclusion

In conclusion, although the follow-up was too short in our series, in keeping with former reports, our results indicate that GLM could be an effective and safe therapy for the management of patients with uveitis previously treated with other anti-TNF- α drugs. Nevertheless, further research on the efficacy of GLM in uveitis refractory to classic anti-TNF- α agents is warranted.

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