

Golimumab in refractory uveitis associated to juvenile idiopathic arthritis: multicentre study of 7 cases and literature review

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ABSTRACT

Objective. To assess the efficacy of golimumab (GLM), a fully humanised anti-TNF- α monoclonal antibody, in refractory juvenile idiopathic arthritis (JIA)-associated uveitis.

Methods. This was a multicentre study of JIA-associated uveitis refractory to standard synthetic immunosuppressive drugs and in most cases to other anti-TNF- α agents.

Results were expressed as mean \pm standard deviation or as median (range or interquartile range). The Wilcoxon signed-rank test was used to compare continuous variables. A literature review of the efficacy of GLM in uveitis related to JIA was also conducted.

Results. We studied 7 patients (5 females; mean age 21.7 ± 7.5 years; 13 affected eyes). Uveitis was bilateral in 6. Cystoid macular oedema (CME) occurred in 3 patients (5 eyes). Besides corticosteroids and synthetic immunosuppressive drugs, patients had received before GLM a median of 2 biologic agents (range 0–3) including adalimumab ($n=6$), etanercept ($n=2$), infliximab ($n=3$) and abatacept ($n=2$). GLM dose was 50 mg/sc every 4 weeks. After 6 months of therapy the number of anterior chamber cells decreased from 1 [0.25–1.5] to 0 [0–0.5] ($p=0.02$) and optical coherence tomography (in patients with CME) from 313.6 ± 77.05 to $261.4 \pm 75.1 \mu\text{m}$ ($p=0.03$). The best-corrected visual acuity increased from 0.5 to 0.62 ($p=0.018$). Complete remission of uveitis was achieved in 4 of 7 patients after 16.8 ± 11.4 months of follow-up. However, 2 of the seven patients had to be switched to tocilizumab due to inefficacy. Local erythema at the injection site was observed in 2.

Conclusion. GLM may be considered in the management of refractory JIA-related uveitis.

Introduction

Uveitis is a potentially sight-threatening complication of juvenile idiopathic arthritis (JIA) (1). Lack of control of JIA-associated uveitis can lead to the development of cataracts, macular oedema, band keratopathy and glaucoma (2). The goal of treatment is to achieve a complete and rapid remission of uveitis. Besides topical therapy, oral corticosteroids, and several conventional immunosuppressive drugs, including methotrexate (MTX), cyclosporine A (CsA), azathioprine (AZA) and mycophenolate mofetil (MMF), have been used in the management of this complication (2). Infliximab (IFX) and adalimumab (ADA) can be used in JIA-related uveitis refractory to conventional immunosuppressive therapy (3). However, inadequate response to these biologic agents, due to either intolerance or inefficacy, may be observed.

Golimumab (GLM) is a fully humanised anti-TNF- α monoclonal antibody that has been approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and ulcerative colitis (4). GLM has a safety profile comparable to other anti-TNF- α drugs (4–6). Compared to IFX, GLM is administered by subcutaneous route and has a lower risk for developing neutralising antibodies. Unlike ADA that is prescribed every other week, is administered every month (5–6). However, information on the efficacy of GLM in JIA-related uveitis refractory to IFX or is scarce and based on single cases (7–9).

Taking all these considerations into account, our aim was to assess the efficacy of GLM in patients with JIA-associated uveitis refractory to conventional immunosuppressive drugs and at least to one anti-TNF- α agent. In addition, a literature review of JIA-uveitis treated with GLM was performed.

Patients and methods

Design and enrolment criteria

We set up an interventional case series, open-label, multicentre study that included patients diagnosed with JIA-associated uveitis with partial or no response to corticosteroids, and refractory to at least one standard synthetic immunosuppressive drug and, in most cases to one anti-TNF- α agent. Patients were studied at the outpatient clinics of the Uveitis Units of several referral centres. JIA was diagnosed according to the 2001 revised International League Against Rheumatism (ILAR) classification criteria (10). The diagnosis was always confirmed by a paediatric rheumatologist.

The dose of immunosuppressive drugs used before GLM therapy were as follows: cyclophosphamide (1g/kg/IV), CsA (<5 mg/kg/day), MTX (10–15 mg/m²/week), IFX (5 mg/kg/intravenously at 0, 2 and 4 weeks followed by a maintenance dose every 4 weeks), ADA (24 mg/m²/subcutaneously/2 weeks) and etanercept (0.8 mg/kg up to 50 mg per dose, once a week subcutaneously).

Malignancy or infectious diseases, including hepatitis B or hepatitis C infection, were ruled out before GLM onset, as previously described (11–17). To exclude latent tuberculosis, a tuberculin skin testing (PPD) and/or an interferon- γ assay (quantiFERON) and a chest radiograph were performed to all the patients receiving biologic drugs, as recommended by the Spanish National Guidelines. If present, prophylaxis with isoniazid was initiated at least 4 weeks before the onset of the biologic agent and maintained for 9 months.

Uveitis was anatomically classified according to the Standardisation of Uveitis Nomenclature (SUN) Working Group (18). Remission was defined as the presence of inactive disease for at least 3 months.

Table I. Main epidemiological and ophthalmologic features of seven patients treated with Golimumab.

n.	7
Age (mean \pm SD; years)	21.7 \pm 7.5
Sex (female/male)	5/2
Number of affected eyes	13
Pattern of uveitis (n)	
Bilateral/unilateral	6/1
Anterior	7
Previous conventional IS agents (n)	
MTX	6
CsA	1
LFN	1
CYM	1
Number of biologic agents before GLM	
1	2
2	1
3	3

MTX: Methotrexate; CsA: Cyclosporine A; CYM: Cyclophosphamide; LFN: Leflunomide; IS: Immunosuppressive; GLM: Golimumab.

Since GLM is an off-label indication for uveitis, written informed consent was requested and obtained from all the patients.

Outcome variables

Intraocular inflammation, macular thickness, visual acuity, and sparing corticosteroid effect were the outcome variables. They were assessed in each centre according to a predefined follow-up protocol and recorded at baseline, 1 week and 1, 3, 6 and 12 months.

The degree of intraocular inflammation was evaluated according to the SUN Working Group (18). Nussenblatt scale

was used to evaluate the degree of vitritis (19). Retinal vasculitis was defined as retinal angiographic leakage, staining and/or occlusion on Fluorescein angiogram (FA).

Macular thickness was measured by high-definition optical coherence tomography (HD-OCT). All HD-OCT scans were performed by means of Cirrus HD-OCT (Carl Zeiss, Ca, USA). Scans were obtained using the 512x128 scan Pattern. Macular thickening was defined as a macular thickness greater than 250 μ m, and CME was considered to be present when it was greater than 300 μ m.

The best-corrected visual acuity (BCVA) was determined using the Snellen test. A relapse was considered when an asymptomatic patient experienced a new flare of uveitis (19).

Statistical analysis

Results were reported as mean \pm SD or as median (interquartile range [IQR]) as appropriate. The Wilcoxon signed-rank test was used to compare continuous variables before and after GLM onset. Statistical analysis was performed by using the STATISTICA software (StatSoft Inc. Tulsa, Oklahoma, USA).

Results

Baseline general features of the patients

We assessed 7 (5 females/2 males) patients with 13 affected eyes. The mean

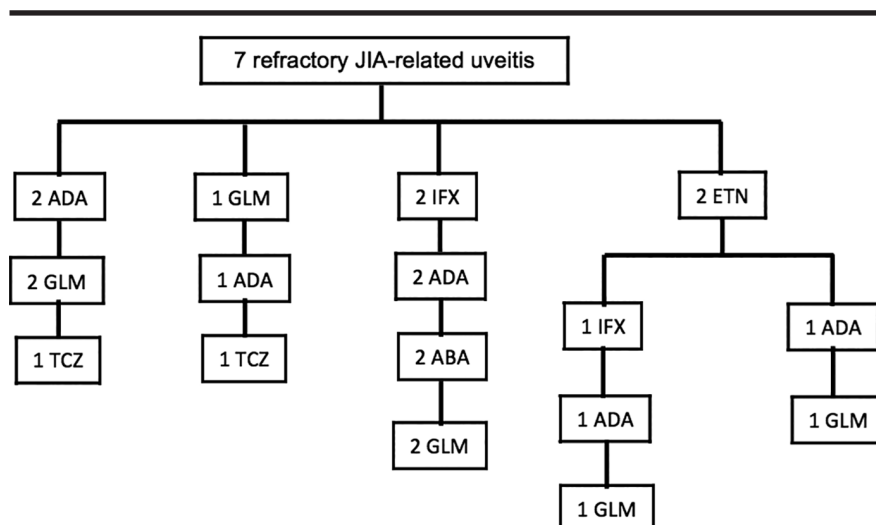


Fig. 1. Flow-chart showing the biologic therapy used in 7 patients with refractory JIA-associated uveitis that required GLM.

age was 21.7 ± 7.5 years. Uveitis was bilateral in 6 cases. Cystoid macular oedema (CME) was present in 3 patients (5 eyes). Baseline epidemiological and clinical features of patients are shown in Table I.

Therapy before GLM onset

In addition to corticosteroids and synthetic immunosuppressive drugs, patients had received a median of 2 biological agents (IQR, 0-3): ADA (n=6), etanercept (n=2), IFX (n=3), and abatacept (n=2). Figure 1 shows the biologic agents prescribed to these patients.

Clinical efficacy of GLM, follow-up and side effects

GLM was administered as a 50 mg subcutaneous injection once a month. Following this procedure clinical improvement was rapidly observed. In this regard, 6 months after the onset of the therapy the number of anterior chamber cells decreased from a median of 1 [0.25–1.5] to 0 [0–0.5] ($p=0.02$), vitritis from 0 [0–1] to 0 [0–0] ($p=0.6$) and optical coherence tomography (in 3 patients, 5 eyes with CME) from 313.6 ± 77.05 to 261.4 ± 75.1 μm ($p=0.03$) (Fig. 2). Moreover, the best-corrected visual acuity in the whole group increased from 0.5 to 0.62 ($p=0.018$) (Fig. 3).

After a median follow-up of 16.8 ± 11.4 months, complete remission of uveitis was achieved in 4 of 7 (57.1%) patients. However, GLM had to be withdrawn in two of the seven patients due to inefficacy (Fig. 1). One of them was switched to ADA due to lack of response after six months of therapy with GLM: However, ADA did not yield clinical improvement and, because of that, the patient was switched to tocilizumab (TCZ). Following TCZ therapy the patient achieved complete remission of the visual complications. The other patient who failed to GLM was the only patient who was treated with GLM as the first biologic agent. However, there was no improvement after 5 months of therapy with this anti-TNF- α agent. Because of that the patient was switched to TCZ (Fig. 1). As occurred in other case TCZ yielded clinical improvement.

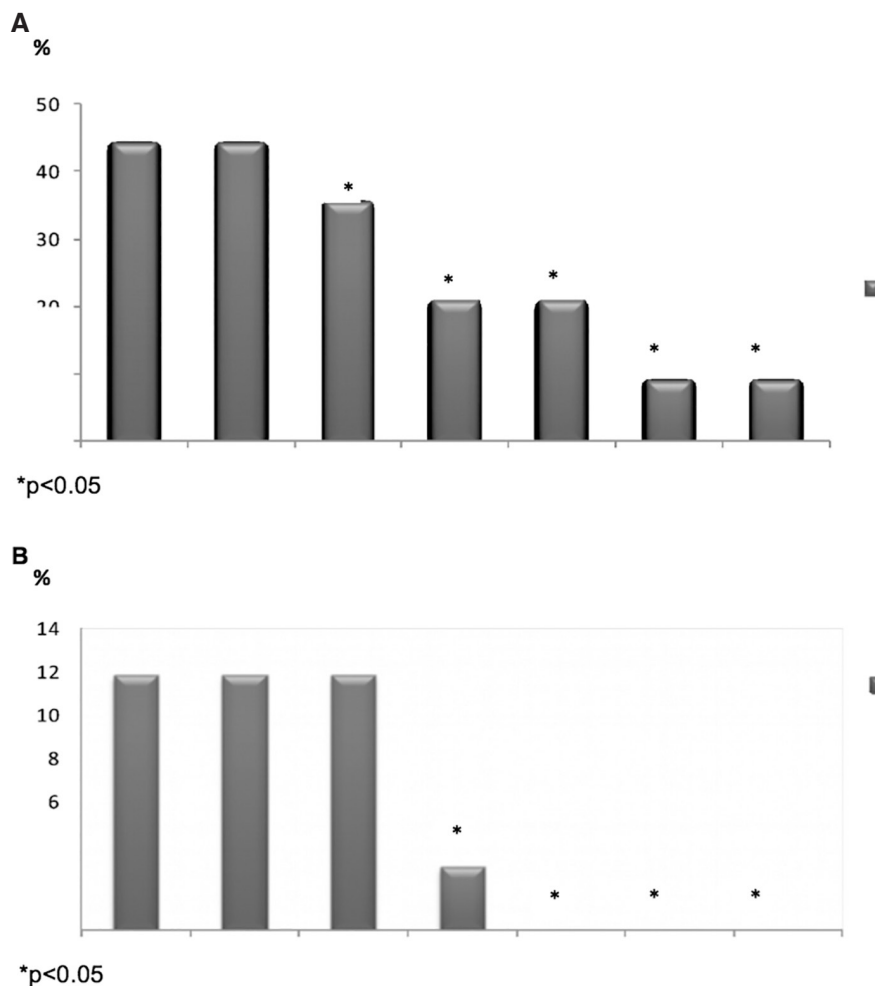


Fig. 2. Golimumab therapy led to global improvement of active inflammation of: (A) Anterior chamber cells (AC cells), and (B) vitritis. Data were expressed when any score of activity was present as percentage of affected eyes. Active inflammation was considered if: AC cells > 0, vitritis > 0.

The mean corticosteroid dose was reduced from 34.4 mg/day at baseline to 16.39 mg/day and 9.98 mg/day at 6 months ($p=0.001$) and 12 months ($p=0.001$), respectively (Fig. 4). GLM was well tolerated in most of the patients. Only transient and mild skin reactions at the site of injection were observed in 2 patients.

Discussion

We herein report a series of 7 patients with severe JIA-associated uveitis refractory to conventional immunosuppressive drugs and in all but in one also refractory to at least one biologic agent including anti-TNF- α drugs. Complete remission was observed in 4 of them. However, 2 had to be switched to other biologic agents due to lack of response. In both cases a successful response to TCZ was achieved. The data are inter-

esting and may give further information to clinical practice.

Ocular involvement is the most severe extraarticular manifestation in JIA (1-2). Several factors have been proposed to be related to a poor visual prognosis in these patients. They include the grade of uveitis (20, 28-31), the presence of visual manifestations before or at the same time of JIA diagnosis, a shorter time interval between the arthritis onset and the ocular involvement (21), and a male gender (22). One of the most frequent (3-47% of the patients) and threatening ocular complications is macular oedema, (32) that is considered the cause of blindness in 8% of children with active uveitis (23). The mainstay of therapy of JIA-associated uveitis is topic or oral corticosteroids. However, in about one-third of the cases, ocular inflammation or vis-

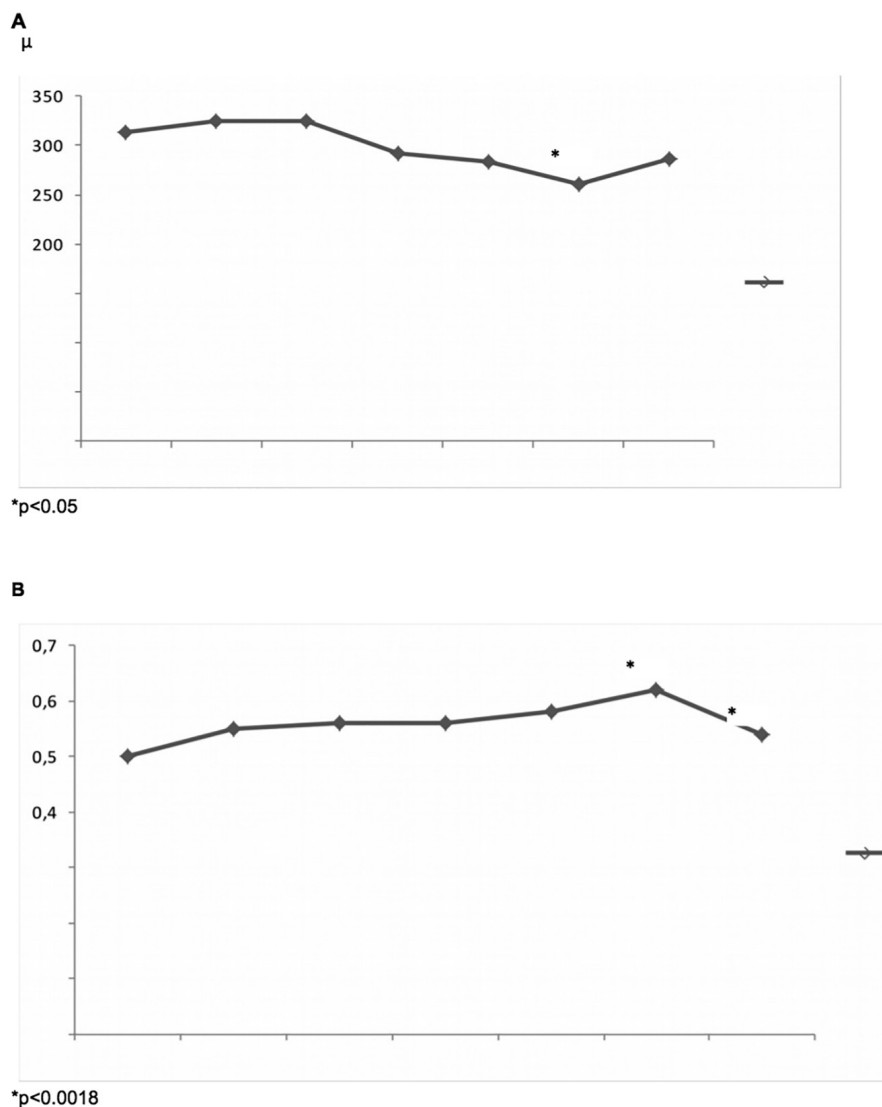


Fig. 3. Global improvement following use of Golimumab therapy (data expressed as mean values compared with basal results): (A) macular thickness and (B) best corrected visual acuity (BCVA).

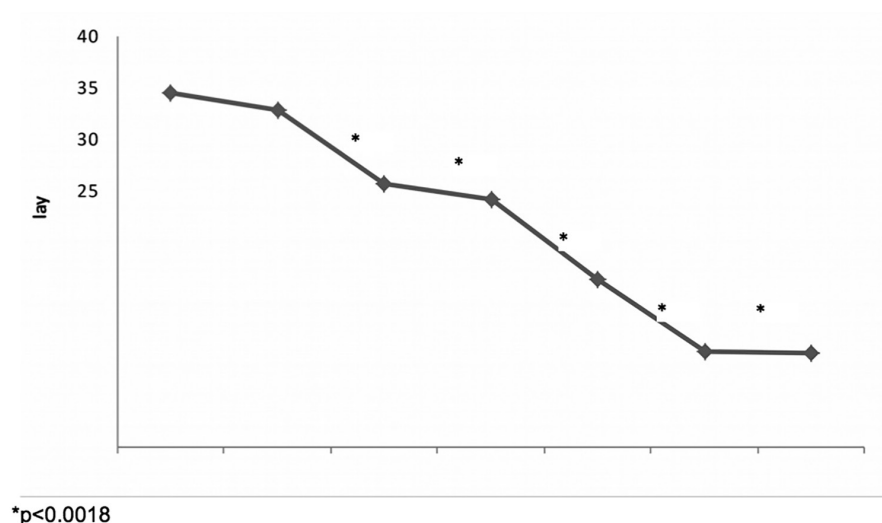


Fig. 4. Corticosteroid-sparing effect following GLM therapy in a series of refractory JIA related uveitis (values are expressed as mean of prednisone/day).

ual complications are severe requiring immunosuppressive agents (22). Based on the current guidelines (22), if local steroid eye drops cannot be reduced after 12 weeks or systemic corticosteroid dosage cannot be reduced to less than 15 mg/kg/weight after 4 weeks, administration of immunosuppressive drugs, mainly MTX (10–15mg/m²/week) orally or subcutaneous or azathioprine, should be started. If uveitis remains active after 3–4 months of conventional immunosuppressive therapy, ADA 24 mg/m² every 2 weeks sc or IFX 3 mg/kg/day IV every 4–8 weeks can be used (22, 24). With respect to this, TNF- α is one of the main proinflammatory cytokines involved into the pathogenesis of JIA-associated uveitis (25). Although IFX or ADA, have been shown to be useful to control the disease (25), nearly 30–40% of patients with JIA-associated uveitis patients do not achieve clinical ocular remission and became unresponsive to these first line TNF- α blockers (25). These patients represent a true challenge for the clinicians, since no clear therapeutic scheme is available. Other therapies have been used in these patients. They include rituximab, an antibody against CD-20 surface marker in B lymphocytes, which has been assessed in a pilot study and also in two retrospective case series with promising results in patients with JIA-associated uveitis (27).

Tocilizumab (TCZ), a humanised recombinant antibody that binds IL-6 receptor and inhibits intracellular signal, approved to treat polyarticular JIA (32), has also been evaluated in some case series of severe JIA-associated uveitis with excellent results (32, 34–37). In this regard, our group has recently reported a retrospective multicentre study of 25 patients diagnosed with JIA-associated uveitis refractory to anti-TNF- α therapy, concluding that TCZ appears to be a useful drug for these patients (17).

Abatacept, a biologic agent that inhibits the co-stimulation and activation of T lymphocytes, has also been approved for the treatment of polyarticular JIA in children over six-year-old. Several recent studies have demonstrated the efficacy of abatacept in JIA-related uveitis unresponsive to conventional immuno-

Table II. Literature review of patients with refractory JIA related uveitis treated with golimumab.

	Cordero-Coma M <i>et al.</i> , 2014, (7)	Miserocchi E <i>et al.</i> , 2014, (8)	William M <i>et al.</i> , 2012, (9)	Present series, Palmou-Fontana <i>et al.</i>
Number of cases, n	4	13	3	7
Sex (women/men)	3/1	10/3	2/1	5/2
Age (mean±SD, years)	25.5± 5.80	25± 5.37	17.33± 8.73	21.71±7.48
Uveitis pattern (bilateral/unilateral)	3/1	13/0	2/1	6/1
Previous treatment	MTX, SSZ, AZA, ETN, IFX, ADA.	MTX, ETN, IFX, ADA, RTX ABA	MTX, AZA, IFX, DCZ, ADA, ETN, ABA	CFM, CyA, MTX, IFX, ETN, ADA
GLM regimen	50 mg /sc every 4 weeks	50 mg /sc every 4 weeks	50 mg /sc every 3 weeks	50 mg /sc every 4 weeks
Ocular remission after GLM, n	4	11	2	4
Adverse effects related to GLM	None	1 pulmonary infection 1 skin reaction	none	skin reaction
Months in treatment with GLM (mean±SD)	6 months	22.38±7.47 months	10±6.92 months	16.83±11.43 months
GLM withdrawal	no	no	One patient for inefficacy	Two patients for inefficacy

MTX: Methotrexate; SSZ: Sulfasalazine; AZA: Azathioprine; IFX: Infliximab; ETN: Etarcept; ADA: Adalimumab; ABA: Abatacept; RTX: Rituximab; CyA: Cyclosporine; CFM: cyclophosphamide.

suppressive drugs and other biologic agents (38, 39, 40).

There are several reports showing the efficacy of GLM in severe recurrent uveitis related to spondyloarthropathies, Behçet’s disease, sarcoidosis and psoriatic arthritis (7, 11-13, 16, 41, 42). However, the use of GLM in JIA-associated uveitis with inadequate response to previous TNF-α blockers or other biologic agents has been scarcely reported (9). Table II summarises the main findings of these studies.

According to our results, GLM may be potentially useful in the management of severe JIA-associated uveitis refractory to conventional immunosuppressive and biologic drugs, including anti-TNF-α and other biologic agents such as rituximab or abatacept. In our study, we observed a global improvement in all the ocular parameters analysed. Four of the seven patients achieved complete remission. However, two of the seven patients did not experience any improvement with GLM and they had to be switched to other biologic agents. It is worth noting that both patients experienced clinical improvement with TCZ. These findings are not unexpected as we already reported efficacy of TCZ in patients with severe JIA-associated uveitis refractory to anti-TNF-α therapy, including GLM (17).

With regard to the safety profile, GLM was generally well tolerated in most patients, being skin reaction at the in-

jection site the only adverse effect observed.

In conclusion, GLM appears to be a potential alternative therapy for patients with refractory JIA-associated uveitis. However, the absence of response to GLM in two of our patients support the need of further studies to better identify the ideal biologic agent required in JIA-uveitis. Based on our own experience we feel that a biologic agent with a mode of action different from a TNF-α inhibitor should be used in cases of failure to anti-TNF-α therapy.

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