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INFLAMMATORY DISORDERS

Adalimumab for juvenile idiopathic arthritis-associated uveitis

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Abstract
Purpose To assess the long-term outcomes and complications of patients with uveitis from juvenile idiopathic arthritis (JIA) treated with adalimumab.
Methods Prospective interventional case series. All patients who underwent treatment with adalimumab for JIA and anterior uveitis were prospectively included in the study. The anterior chamber inflammation was evaluated according to the Standardization of Uveitis Nomenclature criteria.
Results Twenty-one patients (16 females, five males, 38 eyes) were included in the study. Mean age of patients at referral was 11.1±3.8 (5–17) years. Before initiation of treatment, mean duration of arthritis was 7.0±5.5 (median, 6) months, mean duration of uveitis was 7.0±4.4 (median, 7) months. Oligoarticular arthritis was present in 15 cases (71 %), polyarticular arthritis in six cases (28 %). After a mean follow-up of 18.2±7.7 (9–41) months, resolution of anterior chamber inflammation was obtained in 29/38 eyes (76 %). The anterior uveitis flare rate during the 12 months prior to enrollment was 1.6 ± 0.4/year, and was reduced during adalimumab treatment to 0.7±0.3/year ($p<0.001$). A significant decrease of the number of relapses/month was present after onset of treatment with adalimumab (0.18±0.2 before versus 0.02±0.1 after treatment onset, $p<0.001$). No significant correlation was found between relapse number and age, sex, type of JIA and doses of previous steroid treatment ($p>0.05$).
Conclusion Adalimumab showed to be effective and relatively safe for treatment of JIA-associated uveitis.

Keywords Adalimumab, uveitis · Arthritis · Cataract · Ocular hypertension · Intraocular lens · TNF-α

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children [1, 2]. Uveitis has been reported in 10 %–20 % of patients with juvenile idiopathic arthritis, and may lead to significant ocular damage and even blindness [3, 4]. The time interval between arthritis and uveitis onset is the main predictor of severe course uveitis in JIA. [5]. Tumor necrosis factor-alpha (TNF-α) has been shown to play an important role in the development of uveitis [6]. TNF-α blockers have been used to treat uveitis and juvenile idiopathic arthritis, and especially uveitis associated with juvenile idiopathic arthritis in children who have failed conventional topical and second-line disease-modifying antirheumatic drug therapy [7, 8]. However, adequate data on the long-term safety and efficacy of the anti-TNFs are mainly for JIA patients with a polyarticular course, and refer to etanercept and infliximab [9–18]. A greater effectiveness of humanized monoclonal TNF-α antibody adalimumab for uveitis compared with etanercept has been shown [19, 20]. Herein, we evaluated the long-term outcomes and complications of patients with uveitis from JIA treated with adalimumab.

Methods

All patients who underwent treatment with adalimumab for JIA were prospectively included in the study. IRB approval was obtained, the ethics committee of the University Federico II granted the approval for this study, and the patients

and/or their guardians gave their informed consent to obtain the data. Inclusion criteria were diagnosis of JIA based on International League Against Rheumatology (ILAR) diagnostic criteria [21] before 16 years of age, non-responsiveness and/or non-compliance to topical therapy and second-line agents, and non-responsiveness and/or non-compliance to a different biologic drug. A pediatric rheumatologist evaluated juvenile idiopathic arthritis at 3- to 4-month intervals, depending on the severity of the disease. On each visit, the number of active and swollen joints as well as erythrocyte sedimentation rate and laboratory tests (routine blood examination, antinuclear antibodies, extractable nuclear antigen antibodies, immunoglobulins, and C-reactive protein) for drug safety were assessed. Improvement of arthritis was assessed using the American College of Rheumatology (ACR) Pediatric 30, 50, and 70 criteria [22].

Ophthalmic evaluation included best-corrected visual acuity (BCVA), intraocular pressure (IOP) measurement by applanation tonometry, anterior segment biomicroscopy, evaluation of cells and flare, fundus ophthalmoscopy. Fluorescein angiography, optical coherence tomography, and echography were performed when necessary. Ophthalmic examination was performed at monthly intervals. In case of relapse, patients were seen at 7- to 15-day intervals. The activity of the anterior chamber inflammation was evaluated according to the Standardization of Uveitis Nomenclature (SUN) criteria, where the activity of anterior chamber inflammation was graded from 0 to 4 (grade/cells in field: 0 = <1, 0.5+ = 1–5, 1+ = 6–15, 2+ = 16–25, 3+ = 26–50, 4+ = >50) [23]. An improved activity was defined as either a two-step decrease in the level of inflammation or a decrease to inactive (grade 0), a relapse as either a two-step increase in the level of inflammation or an increase to the maximum grade (4+), a stabilization as a change of <2 steps. If one eye improved, but the other eye worsened, the interpretation was increased activity. The flare in uveitis was defined as an episode with worsening activity in the anterior chamber inflammation during the follow-up. The number of flares was assessed from 1 year before adalimumab to baseline and from baseline to the end of the follow-up. The patients were initially given a standard dose of adalimumab subcutaneously every 2 weeks (40 mg to 18/20 patients, and 20 mg to two patients weighing <30 kg), and according to clinical response, up to a frequency of 24 mg/m^2 at 7-day intervals. Treatment was continued throughout the study period. Ocular hypertension was defined as intraocular pressure >21 on more than one examination. In patients with secondary cataract, after complete removal of the cataract, posterior capsulorexis and anterior vitrectomy were performed. At least 3 months of quiescence were requested prior to cataract surgery. Corticosteroids orally, in doses of 1–2 mg/kg/day, and topically were used before and after surgery. Postoperatively, dexamethasone was given eight times per day and a combination of cyclopentolate and phenylephrine three times per day, followed by a slow taper on an individual basis. When removal of secondary cataract was necessary, a hydrophobic acrylic IOL with polymethyl methacrylate haptics (VA-60BB; Hoya Corporation) was implanted into the capsular bag.

All statistical analyses were carried out with statistical software (STATA version 11, STATA Corp., College Station, TX, USA). The differences between the number of relapses before and during adalimumab therapy were compared using Cox regression. The differences between the patient characteristics on adalimumab with good or poor outcome were compared using the Mann–Whitney *U*-test (continuous variables) or Fisher's exact test (category variables). The 5 % significance level was used in all tests.

Results

Twenty-one patients (16 females, five males, 38 eyes) were enrolled during 24 months. Baseline characteristics of the 21 patients are showed in Table 1. Mean age of patients at referral to our visit was 11.1±3.8 (5–17) years. Mean duration of arthritis before starting treatment with adalimumab was 7.0±5.5 (median, 6) months, mean duration of uveitis was 7.0±4.4 (median, 7) months. Oligoarticular arthritis was present in 15 cases (71.4 %), polyarticular arthritis in six cases (28.6 %). In ten patients (47.6 %), the arthritis was diagnosed 2.5±2.0 months before the diagnosis of uveitis was made. In seven cases (33.4 %), uveitis was diagnosed 3.5±2.2 months before arthritis, while in four cases (19.0 %) arthritis and uveitis were diagnosed at the same time (11.7±2.6 months). Nine of 21 children (42.8 %) were antinuclear antibody positive (5/12 oligoarticular, 41.6 %; 2/6 poliarticular, 33.3 %). Treatment with adalimumab was started to treat the ocular disease in 12 patients (57 %), while in nine cases (43 %) it was administered due to relapses of uveitis and arthritis.

Outcomes

Mean follow-up after starting adalimumab was 18.2±7.7 (9–41)months. Nine months after starting therapy and during remaining follow-up, resolution of anterior chamber inflammation was obtained in 29/38 eyes (76 %), while 6/38 eyes (16 %) remained stable during follow up, without relapse, and in 3/38 eyes (8 %) inflammation increased. Mean BCVA improved from 20/50 at baseline to 20/40 at 9-month visit, and to 20/32 at 2-year visit, 3-year visit and at last visit. Overall, six patients showed a relapse of the uveitis 5.1±2.3 months after onset of treatment with adalimumab, and in two cases a concomitant active arthritis was

Table 1 Baseline characteristics and previous treatments in 21 patients with juvenile idiopathic arthritis (JIA) and uveitis on adalimumab

Patient no.	Age (years)	Eyes	Gender (M/F)	Type of JIA	Duration art/ uv (months)	Previous treatment	Reason to discontinue treatment	Involvementat treatment onset with ADA	Therapy
1	7	2	f	oligo	6/5	Dex	NR-adr	Uv	ADA
2	9	2	f	oligo	2/7	Dex	NR-adr	Uv	ADA
3	17	2	f	oligo	15/10	Dex/MTX	NR:uv	Uv	ADA
4	7	2	f	oligo	4/3	Dex/MTX	NR:art/uv	Art + Uv	ADA + MTX
5	17	2	f	poly	16/14	Dex/MTX/ETA	NR:art/uv	Art + Uv	ADA + MTX
6	9	2	f	poly	1/7	Dex/MTX	NR-adr	Uv	ADA + MTX
7	11	2	m	oligo	10/4	Dex	NR-adr	Uv	ADA
8	9	2	f	oligo	3/4	Dex/MTX/INF	NR:uv Adr:glauc	Uv	ADA + MTX
9	9	2	f	oligo	1/7	Dex/INF	NR:uv	Uv	ADA
10	10	1	f	oligo	7/2	Dex/MTX	NR:Art/uv	Art + uv	ADA + MTX
11	13	2	f	oligo	9/9	Dex/MTX	NR:uv	Uv	ADA + MTX
12	15	2	m	oligo	14/14	Dex/MTX/ETA	NR:art/uv Adr:tub	Art + uv	ADA + MTX
13	13	2	m	poly	3/2	Dex/MTX/ ETA/INF	NR:uv	Uv	ADA
14	5	2	m	oligo	1/3	Dex	NR-adr	Uv	ADA
15	17	1	f	oligo	14/14	Dex/MTX	NR:art/uv	Art + uv	ADA + MTX
16	12	1	m	oligo	10/8	Dex/MTX/ETA	NR:uv	Art + uv	ADA
17	17	2	f	poly	16/15	Dex/MTX/ Cicl/ETA/INF	adr/adr/NR/adr/in	Art + uv	ADA + MTX
18	6	1	f	oligo	1/2	Dex/INF	NR:uv	Uv	ADA
19	11	2	f	oligo	1/5	Dex/MTX/INF	NR:uv	Uv	ADA + MTX
20	8	2	f	poly	3/2	Dex/MTX/INF	NR:art/uv	Art + uv	ADA + MTX
21	11	2	f	poly	10/10	Dex/INF	NR:art/uv	Art + uv	ADA

ADA adalimumab; *MTX* methotrexate; *INF* infliximab; *ETA* etanercept; *dex* dexamethasone; *Art, art* arthritis; *Oligo* oligoathritis; *Poly* polyarthrits; *uv* uveitis; *NR* no/poor response; adr, adverse drug reaction

present. One of them stopped treatment. In the remaining 15 patients, an improvement of anterior chamber inflammation was present 6±3.2 weeks (2–12) after treatment onset. The anterior uveitis flare rate during the 12 months prior to enrollment was 1.6 ± 0.4/year, and was reduced during adalimumab treatment to 0.7±0.3/year ($p<0.001$). No differences were present between treatment with adalimumab alone and in association with methotrexate with regard to outcomes and relapses. A significant decrease of the number of relapses/month was present after onset of treatment with adalimumab (0.18±0.2 before versus 0.02±0.1 after treatment onset, $p<0.001$). No significant correlation was found between relapse number and age, sex, type of JIA, and steroid doses ($p>0.05$). All six patients who showed relapses presented with a longer history of uveitis (9.2±2.1 vs 6.1±2.6 months, $p=0.001$) and a wider articular involvement at treatment onset. All nine patients presenting with uveitis and arthritis at onset of treatment showed an ACR 50 response at 12-month visit. Arthritis resolved in 6/9 cases (66 %), remained stable in 1/9 case (11 %), and worsened in 2/9 cases (22 %). In all of the three cases that did not show improvement of arthritis, a diagnosis of polyarticular JIA was made.

Previous treatments

All patients had undergone oral steroid treatment before adalimumab treatment. Fourteen patients had been treated with methotrexate (15 mg/m^2 up to 20 mg weekly, in absence of side-effects). Of them, two patients had to stop methotrexate therapy because of intolerance, while treatment is still ongoing in association with adalimumab in 12 cases. Eleven patients (52.4 %) had been previously treated with a different biologic drug (etanercept in three cases, infliximab in six cases, etanercept and infliximab in two cases) but treatment had to be stopped because of low effectiveness or because of side-effects (1/5 on etanercept, 2/8 on infliximab). In one case, methotrexate, ciclosporin, salazopirin, etanercept, and infliximab had been administered before adalimumab. In this case,

even adalimumab was ineffective and now the patient is on abatacept [24].

Coexisting therapies

In 11 patients (52.4 %), concomitant methotrexate was administered. Two out of eight patients (25 %) who failed infliximab were not treated with concomitant methotrexate. In all patients undergoing coexisting therapies, the dosage of coexisting drug was lowered after a mean period of 1.2± 0.6 weeks, and in no case was an increase necessary. In 2/11 cases (18.2 %), treatment with methotrexate was reduced due to side-effects, but a constant clinical improvement was present. Topical steroids were reduced in 2/7 cases (28.6 %) and were stopped in 5/7 patients (71.4 %). In three out of four patients, oral steroids were stopped, while in one patient, continuation of oral steroidal treatment was necessary due to the aggressive course of the systemic and ocular disease.

Complications and side-effects

Before inclusion in the study, 15 patients (71 %) had shown complications of uveitis. Nine cases (42.8 %) had developed secondary cataract and had undergone cataract extraction. Of them, in seven cases intraocular lens (IOL) was implanted, while in two cases IOL was not inserted. After a mean follow up of 8.3 ±3.1 months, secondary ocular hypertension developed in all of the seven patients who underwent IOL implantation, while it did not develop when IOL implantation was not performed. Of the seven patients who developed secondary ocular hypertension, four patients underwent trabeculectomy with mithomicin C, and are still on antiglaucomatous treatment. The remaining three patients are on antiglaucomatous treatment with brimonidine 0.2 %, timolol 0.5 %, and brinzolamide 10 mg/ml.

Twelve patients (57 %) had developed uveitic ocular hypertension before inclusion in the study, and were on antiglaucomatous treatment at our first observation. Of them, five patients (42 %) had been treated with basal iridotomy and trabeculectomy. Four patients (19 %) had developed band-shaped keratitis. Of them, two underwent corneal disepithelization, ethylene-diaminetetraacetic acid (EDTA) chelation, and bandage contact lens. In six cases (28 %), a posterior involvement with macular edema was present. Of them, two cases showed cystoid macular edema since onset of the disease. A transient erythema was observed in 2/21 cases (9.5 %), and improved in 5 days without treatment.

Discussion

In this prospective study, we focused on adalimumab treatment for uveitis specifically from JIA and following the SUN criteria for improvement. Despite the small sample size mainly due to the rarity of the disease, and despite 52.4 % of patients having had prior anti-TNF therapy, nevertheless an improvement of the ocular symptoms was observed in 76 % of cases, stabilization in 16 % of cases and a relapse in 8 % of cases. Anterior uveitis flare rate reduced significantly after starting adalimumab treatment. Few retrospective studies have evaluated adalimumab for JIA-associated uveitis. In a recent large series, 39 out of 131 patients with refractory uveitis treated with adalimumab presented with JIA, and adalimumab showed to be well-tolerated and helpful in decreasing inflammatory activity [25]. In the study by Tynjälä et al., improvement was observed in 35 % of cases only after 18.7 months [26]. This low percentage may be due to the higher age of patients (13.4 years versus 11.3 years in our study), to the longer duration of uveitis before starting treatment with adalimumab (8.7 years), and to previous treatment with anti-TNF-α drugs in 95 % of cases. In the study by Kotaniemi et al., improvement of uveitis was observed in 58 % of 54 patients with JIA-associated uveitis [27]. This difference with our study may be due to the different sample size.

Several studies evaluated adalimumab for treatment of chronic uveitis not specifically associated with JIA. Vazquez-Cobian et al. reported an improvement of ocular symptoms in 81 % of cases, although they included both JIA-associated and idiopathic uveitis, and their definition of improvement did not follow SUN criteria [28]. Biester et al. reported an improvement of the ocular inflammation in 89 % of 18 patients (17 had juvenile idiopathic arthritis, one was without detectable underlying disease) [19]. However, in their study, improvement for uveitis was only defined as a reduction of at least 2+ cells in the anterior cells. Furthermore, age of patients at initiation of treatment was not clearly stated. In a recent prospective study over 3 years of treatment, Simonini et al. showed that adalimumab is more effective than infliximab in maintaining remission of chronic childhood uveitis in 16 patients (12 with JIA, three with idiopathic uveitis, and one with Behçet's disease) [29].

As in previous studies, serious side-effects and adverse events were absent [19, 28]. In adult studies, adalimumab has demonstrated an acceptable safety profile, and the rate of serious infections has also been low; 0.02/patient-year [30]. Adalimumab seems to cause fewer hypersensitivity reactions than infliximab, at least with the doses given in our patient cohort.

After cataract extraction, secondary ocular hypertension never developed when IOL implantation was not performed. On the other hand, all of the seven patients who underwent IOL implantation developed ocular hypertension. Ocular hypertension is a common complication of juvenile rheumatoid arthritis (JRA)-associated uveitis [31, 32], and in this series ocular hypertension had developed preoperatively in

three eyes. However after cataract extraction, ocular hypertension developed in all eyes that underwent IOL implantation, while it did not develop when IOL implantation was not performed. Of the seven eyes that developed high IOP, four were resistant to topical antiglaucomatous treatment, and needed hypotonising surgery. Despite the small population, our results may suggest that patients with uveitis, and especially those with chronic systemic disease, are at an especially high risk of increased IOP and uncontrolled inflammation after IOL implantation.

In all patients undergoing coexisting therapies, the dosage of coexisting drug was lowered, and in no case was an increase necessary. Despite being costly, adalimumab could therefore represent an adjuvant therapy for the treatment of uveitis, and our results probably confirm the effectiveness and relatively good safety of adalimumab for treatment of JIA-associated uveitis.

References

1. Levinson JE, Wallace CA (1992) Dismantling the pyramid. J Rheumatol 33(Suppl):6–10
2. Ruperto N, Levinson JE, Ravelli A, Shear ES, Link Tague B, Murray K, Martini A, Giannini EH (1997) Long term health outcomes and quality of life in American and Italian inception cohorts of patients with juvenile rheumatoid arthritis. I. Outcome status. J Rheumatol 24:945–951
3. Kanski JJ (1990) Juvenile arthritis and uveitis. Surv Ophthalmol 34:253–267
4. Kotaniemi K, Savolainen A, Karma A, Aho K (2003) Major review. Recent advances in uveitis of juvenile idiopathic arthritis. Surv Ophthalmol 48:489–502
5. Zannin ME, Buscain I, Vittadello F, Martini G, Alessio M, Orsoni JG, Breda L, Rigante D, Cimaz R, Zulian F (2012) Timing of uveitis onset in oligoarticular juvenile idiopathic arthritis (JIA) is the main predictor of severe course uveitis. Acta Ophthalmol 90:91–95
6. Santos Lacomba M, Marcos Martín C, Gallardo Galera JM, Gómez Vidal MA, Collantes Estévez E, Ramírez Chamond R, Omar M (2001) Aqueous humor and serum tumor necrosis factor-alpha in clinical uveitis. Ophthalmic Res 33:251–255
7. Smith JR, Levinson RD, Holland GN, Jabs DA, Robinson MR, Whitcup SM, Rosenbaum JT (2001) Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. Arthritis Rheum 45:252–257
8. Lovell D (2004) Biological agents for the treatment of juvenile rheumatoid arthritis: current status. Paediatric Drugs 6:137–146
9. Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN (2008) Biologics for the treatment of juvenile idiopathic arthritis: a systemic review and critical analysis of the evidence. Clin Rheumatol 27:67–76
10. Beresford MW, Baildam EM (2009) New advances in the management of juvenile idiopathic arthritis. 2: the era of biologicals. Arch Dis Child Educ Pract Ed 94:151–156
11. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, Baumgartner SW, Giannini EH, Pediatric Rheumatology Collaborative Study Group (2008) Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile idiopathic arthritis. Arthritis Rheum 58:1496–1504
12. Horneff G, De Bock F, Foeldvari I, Girschick HJ, Michels H, Moebius D, Schmeling H, German and Austrian Paediatric Rheumatology Collaborative Study Group (2009) Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German registry. Ann Rheum Dis 68:519–525
13. Prince FH, Twilt M, ten Cate R, van Rossum MA, Armbrust W, Hoppenreijs EP, van Santen-Hoeufft M, Koopman-Keemink Y, Wulffraat NM, van Suijlekom-Smit LW (2009) Long-term follow-up on effectiveness and safety of etanercept in JIA: the Dutch national register. Ann Rheum Dis 68:635–641
14. Tynjälä P, Lindahl P, Honkanen V, Lahdenne P, Kotaniemi K (2007) Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. Ann Rheum Dis 66:548–550
15. Kahn P, Weiss M, Imundo LF, Levy DM (2006) Favorable response to high-dose infliximab for refractory childhood uveitis. Ophthalmol 113:860–864, Epub 15 March 2006
16. Suhler EB, Smith JR, Wertheim MS, Lauer AK, Kurz DE, Pickard TD, Rosenbaum JT (2005) A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. Arch Ophthalmol 123:903–912
17. Rajaraman RT, Kimura Y, Li S, Haines K, Chu DS (2006) Retrospective case review of pediatric patients with uveitis treated with infliximab. Ophthalmology 113:308–314
18. Sukumaran S, Marzan K, Shaham B, Reiff A (2012) High dose infliximab in the treatment of refractory uveitis: does dose matter? Rheumatol Jan 5. doi:10.5402/2012/765380
19. Biester S, Deuter C, Michels H, Haefner R, Kuemmerle-Deschner J, Doycheva D, Zierhut M (2007) Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol 91:319–324
20. Foeldvari I, Nielsen S, Kümmerle-Deschner J, Espada G, Horneff G, Bica B, Olivieri AN, Wierk A, Saurenmann RK (2007) Tumor necrosis factor-alpha blocker in treatment of juvenile idiopathic arthritis associated uveitis refractory to second-line agents: results of a multinational survey. J Rheumatol 34:1146–1150
21. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A (1997) Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 40:1202–1209
22. Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P, Maldonado-Cocco J, Suarez-Almazor M, Orozco-Alcala J, Prieur AM (1998) Revision of the proposal classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 25:1991–1994
23. Jabs DA, Nussenblatt RB, Rosenbaum JT (2005) Standardization of Uveitis Nomenclature (SUN) working group. Standardization of Uveitis Nomenclature for reporting clinical data. Results of the first international workshop. Am J Ophthalmol 140:509–516
24. Zulian F, Balzarin M, Falcini F, Martini G, Alessio M, Cimaz R, Cimino L, Zannin ME (2010). Abatacept for severe anti-TNF alpha refractory juvenile idiopathic arthritis-related uveitis. Arthritis Care Res (Hoboken) 62(6):821–825
25. Díaz-Llopis M, Salom D, Garcia-de-Vicuña C, Cordero-Coma M, Ortega G, Ortego N, Suarez-de-Figueroa M, Rio-Pardo MJ, Fernandez-Cid C, Fonollosa A, Blanco R, Garcia-Aparicio AM, Benitez-Del-Castillo JM, Olea JL, Arevalo JF (2012) Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. Ophthalmology 119:1575–1581
26. Tynjälä P, Kotaniemi K, Lindahl P, Latva K, Aalto K, Honkanen V, Lahdenne P (2008) Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis. Rheumatology (Oxford) 47:339–344

27. Kotaniemi K, Säilä H, Kautiainen H (2011) Long-term efficacy of adalimumab in the treatment of uveitis associated with juvenile idiopathic arthritis. Clin Ophthalmol 5:1425–1429
28. Vazquez-Cobian LB, Flynn T, Lehman TJ (2006) Adalimumab therapy for childhood uveitis. J Pediatr 149:572–575
29. Simonini G, Taddio A, Cattalini M, Caputo R, De Libero C, Naviglio S, Bresci C, Lorusso M, Lepore L, Cimaz R (2011) Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab versus Infliximab. Arthritis Care Res (Hoboken) 63:612–618
30. Weinblatt ME, Keystone EC, Furst DE, Kavanaugh AF, Chartash EK, Segurado OG (2006) Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. Ann Rheum Dis 65:753–759
31. Wolf MD, Lichter PR, Ragsdale CG (1987) Prognostic factors in the uveitis of juvenile rheumatoid arthritis. Ophthalmology 94:1242–1248
32. Kanski JJ (1992) Lensectomy for complicated cataract in juvenile chronic iridocyclitis. Br J Ophthalmol 76:72–75