The Safety and Efficacy of Noncorticosteroid Triple Immunosuppressive Therapy in the Treatment of Refractory Chronic Noninfectious Uveitis in Childhood

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ABSTRACT. ***Objective.*** To assess the safety and efficacy of noncorticosteroid triple immunosuppressive therapy in the treatment of refractory chronic noninfectious childhood uveitis.

Methods. Subjects were retrospectively selected from a database. Patients were included if they were diagnosed with chronic, noninfectious uveitis at 16 years of age or under and treated with triple immunosuppressive therapy for at least 6 months (following failure of a combination of 2 immunosuppressants). Patient demographics, diagnoses, duration of uveitis, drug dosages, active joint inflammation, and ophthalmologic data were recorded. Efficacy outcomes for triple therapy were recorded at 6 months.

Results. Thirteen patients with bilateral uveitis were included. Using Standardized Uveitis Nomenclature (SUN) criteria, at 6 months only 11 eyes (42%) had a 2-step improvement in anterior chamber cell inflammation (n = 26). In addition, 2 patients required additional oral corticosteroid treatment. There were 4 significant infectious adverse events during a total of 21.9 patient-years (PY) on triple therapy (0.18 events per PY).

Conclusion. In this group of children with refractory uveitis, addition of a third immunosuppressive agent did not confer substantial benefit in redressing ocular inflammation and was associated with significant infections in a minority of patients. (First Release Oct 1 2013; J Rheumatol 2014; 41:136–9; doi:10.3899/ jrheum.130594)

Key Indexing Terms:
UVEITIS JUVENILE ARTHRITIS IMMUNOSUPPRESSION

Childhood chronic noninfectious uveitis is a rare disease that, despite immunosuppression, may be recalcitrant to therapy[1,2]. It is associated with significant morbidity and ocular complications occur in about 40% of patients[3]. Some patients fail to respond to conventional treatment with 2 immunosuppressive agents [conventionally methotrexate (MTX) and an anti-tumor necrosis factor-α (TNF-α) agent] and therefore remain at risk of developing severe visual disability. Increasingly, an additional immunosuppressive drug is introduced in these refractory cases[3,4]. However, the efficacy and safety of this treatment remains controversial. Here we present data from a cohort of patients with refractory chronic uveitis who have been treated with triple immunosuppressive therapy.

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MATERIALS AND METHODS

Study subjects were identified from a prospective database of patients who attended a combined Pediatric Rheumatology and Ophthalmology clinic at a single center in the UK since January 2008. Clinical information was recorded contemporaneously at 3 monthly intervals using a standard pro forma, and patients were included if they were diagnosed with chronic, noninfectious uveitis at 16 years of age or under and treated with triple immunosuppressive therapy for at least 6 months. Data collection endpoints were (1) cessation of triple therapy, (2) loss to followup, or (3) continued triple therapy at a defined census date in August 2012.

In patients with juvenile idiopathic arthritis (JIA), the diagnosis was made in accordance with International League of Associations for Rheumatology criteria[5]. Uveitis was diagnosed and documented according to Standardization of Uveitis Nomenclature (SUN) criteria[6]. "Triple therapy" was defined as the use of any 3 immunosuppressive agents (not including corticosteroids) simultaneously, for example, MTX, an anti-TNF-α agent, and mycophenolate mofetil (MMF) or tacrolimus. The decision to start triple immunosuppressive therapy was based on uncontrolled uveitis despite treatment with 2 immunosuppressive agents. Uncontrolled uveitis

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was defined as persistent inflammation of SUN grade 1+ or more anterior chamber cells.

Our study was part of an institutionally approved service evaluation project. Patient demographics, diagnoses, duration of uveitis, drug dosages, and active joint inflammation were recorded. Ophthalmologic data, including visual acuity and anterior chamber (AC) cells, were also recorded according to the SUN group's criteria. Inactive uveitis was defined as < 1 cell per field in the anterior chamber on slit lamp examination (grade 0). Ocular inflammation was said to be improved if there were a 2-step reduction in AC cell grade (or a decrease to inactive), and worsened with a 2-step increase in AC cell grade (or increase to grade 4)[6]. Data were reported for each eye separately.

Efficacy outcomes are reported at 6 months and data from all patients were available at this timepoint. In contrast, for our safety analysis, because adverse events were rare, the rate of significant adverse events that occurred during the total followup time was recorded per patient-year (PY) and calculated by this formula: event rate/PY = $\sum$ (number of events) / $\sum$ [time (since starting triple therapy) to event or data collection endpoint].

A significant adverse event was defined as one that was life-threatening, resulted in significant disability, or required a prolonged hospital admission. An infection was noted as significant if it required intravenous antibiotics or hospital admission[7]. Adverse events that were not significant were not reported, because these were not included in the clinical pro forma and our records will therefore be incomplete. Reasons for stopping triple therapy were reported as written in patients' clinical records.

RESULTS

Characteristics of study population. Nineteen patients were identified as receiving triple therapy since January 2008. Of these, 6 were excluded because they had been using 3 agents for < 6 months. Therefore, 13 patients (8 female, 62%; median age 13 yrs) were included. Eleven had JIA, 1 had Blau syndrome, and 1 had idiopathic uveitis. Twelve of the patients identified had bilateral anterior uveitis and 1 had bilateral pan-uveitis. Triple therapy was started for control of uveitis in 7 patients and for both uveitis and arthritis in 6 patients. The median duration of uveitis when triple therapy was started was 3 years.

The combinations of triple therapy are shown in Table 1. Because of inadequate control of uveitis (and arthritis in 2 patients), 1 of the medications was changed in 4 patients during followup. The median length of followup was 14 months (range 6–54 months). The total followup after starting triple therapy was 21.9 PY.

Visual acuity and uveitis activity. Before starting triple therapy, the median visual acuity was logMAR 0.18, 23.1% of eyes had a visual acuity of logMAR 0.4 or worse, and 3.8% of logMAR 1.0 or worse (n = 26). At 6 months these values were 15.4% and 7.7%, respectively (n = 26). Two eyes had reduced visual acuity before triple therapy began (hypermetropic amblyopia/amblyopia and aphakia), accounting for those with a visual acuity of logMAR > 1.0 that did not improve over the course of followup.

At baseline, 22 (84.6%) of the 26 eyes had active uveitis. All 4 inactive eyes were in patients with active uveitis in their fellow eye, and of these, 2 remained inactive for the entire followup period. Six months after commencing triple therapy, ocular inflammation had improved in 11 eyes (42.3%), but 17 eyes (65.4%) still had active anterior uveitis.

A total of 4 surgical procedures on 4 eyes were performed to treat uveitis or its complications during the followup period (3 trabeculectomies, 1 intraocular triamcinolone injection). Surgery was also required for 1 eye with strabismus.

Use of corticosteroids. Prior to starting triple therapy, 22 (84.6%) of the 26 eyes were treated with topical corticosteroids. After 6 months of using triple therapy (n = 26), 15 of the eyes (57.7%) were treated with a tapered dose, 8 (30.8%) remained the same, and an increased dose of topical corticosteroids was administered to 3 (11.5%). At that time topical corticosteroid drops were used in a total of 17 eyes (65.4%).

At baseline 2 patients were taking oral prednisolone and another 2 had received orbital floor corticosteroid injections. These patients were able to stop taking corticosteroids after 3 months of triple therapy.

At the first 6-month followup, 2 (15.4%) of the 13 patients had to have additional corticosteroids administered (oral prednisolone, methylprednisolone by IV) to control persistent ocular inflammation.

Adverse events and discontinuation of triple therapy. At the time data collection ceased, 7 patients were still taking triple therapy, while 6 had stopped taking at least 1 agent. Of these 6 patients, 1 patient was tapered off MMF therapy because the disease had become inactive, another patient stopped owing to subtherapeutic levels of tacrolimus, 3 stopped because of intolerance to 1 of the drugs (n = 2 for MTX and n = 1 for MMF), and 1 patient chose to stop MTX.

Over a total of 263 months of followup time, there were 16 adverse events recorded from patient notes. We classified 4 of these as significant since they required a prolonged hospital admission. These occurred in 3 patients: 1 had an episode of chicken pox, another had swine flu (H1N1), and another developed pneumonia on 2 separate occasions. The significant adverse event rate was 0.18/PY (rate of patients affected was 0.14/PY). Other studies using mono and duotherapy appear to show lower adverse event rates; however, there is a paucity of data available on adverse events in duotherapy papers[4,8,9,10,11].

DISCUSSION

We have presented 13 children with noninfectious chronic uveitis who had refractory uveitis, despite treatment with topical corticosteroids and 2 other systemic immunosuppressants. Our results show that despite some improvement in visual acuity, ocular inflammation improved in only 42% of the eyes at 6 months with the addition of a third immunosuppressant, but this was associated with a significant adverse event rate of 0.18/PY.

All but 1 of the patients was treated with MTX, and 11 of these 12 also received MMF. Other studies have highlighted the effectiveness of immunosuppressive agents as monotherapy, such as MTX[8] and MMF[12], or in combination

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Table 1. Patient characteristics, previous treatments, and clinical features before and after starting triple therapy.

Sex	Age, yrs	Diagnosis	Duration of Uveitis When TT Started	Age, yrs, When TT Started	Previous Treatment	Third Drug Started	Medication		Medication Changes During Followup	Eye	Visual Acuity (LogMAR)		Anterior Chamber Cells	
							0 mos	6 mos			0 mos, n = 26	6 mos, n = 26	0 mos, n = 26	6 mos, n = 26
M	13	Psoriatic polyarticular JIA, chronic bilateral AU	3 yrs	10	MTX 17.5 PO, MMF 300	ADA 40	MTX 17.5 PO, MMF 300, TS 2 hourly RE/QDS LE	MTX 17.5 PO, MMF 300, ADA 40, TS BD BE		RE LE	0.00 0.78	0.00 1.00	3+ 3+	3+ 0
F	14	Oligoarticular JIA, chronic bilateral AU	4 yrs, 5 months	10	MTX 7.5 PO, INF	MMF 300	MTX 7.5 PO, INF, TS 6 × day RE, Pred	MTX 7.5 PO INF, MMF 300, TS QDS RE		RE LE	0.30 2.00	0.18 2.00	2+ 0	0 0
F	6	Oligoarticular JIA, chronic bilateral AU	1 yr, 8 months	6	MTX 12.5 PO, MMF 500	ADA 20	MTX 12.5 PO, MMF 500, TS BD BE	MTX 12.5 PO, MMF 500, ADA 20, TS TDS RE		RE LE	0.40 0.10	0.18 0.00	2+ 1+	0.5+ 0.5+
F	15	Idiopathic chronic bilateral AU	3 yrs	14	MTX 25 PO, TAC 3	ADA 40	MTX 25 PO, TAC 3, TS 6 × day BE	MTX 25 PO, TAC 3, ADA 40, TS QDS BE		RE LE	0.00 0.30	–0.08 0.00	1+ 2+	1+ 1+
M	16	Blau, chronic bilateral granulomatous PU	6 yrs, 4 months	13	MTX 20 SC, ADA 30	MMF 800	MTX 20 SC, ADA 40	MTX 20 PO, ADA 40, MMF 800	ADA to INF at 29 mos	RE LE	0.78 0.00	0.78 0.00	2+ 0	0 0
F	10	Polyarticular JIA, chronic bilateral AU	1 yr, 8 months	6	MTX 10 PO, MMF 480	ADA 20	MTX 10 PO, MMF 480, TS BD BE	MTX 10 PO, MMF 480, ADA 20, TS BD LE/ 8 × day RE		RE LE	0.18 0.78	0.30 0.60	1+ 3+	1+ 0.5+
F	8	Polyarticular JIA, chronic bilateral AU	3 yrs, 1 month	7	MTX 10 PO, ADA 20	MMF 300	MTX 12.5 PO, ADA 20, TS TDS RE	MTX 12.5 PO, MMF 300, TS QDS RE	ADA to ABT at 5 mos	RE LE	0.20 0.10	0.20 0.00	1+ 0	2+ 0.5+
M	13	Polyarticular JIA, chronic bilateral AU	5 yrs, 1 month	12	MMF 750, ADA 40	MTX 20 PO	ADA 40, MMF 750, TS 2 hourly BE	ADA 40, MMF 750, MTX 20 SC, TS TDS BE	ADA to ABT at 9 mos	RE LE	0.30 0.00	0.18 0.00	2+ 2+	2+ 0.5+
M	13	Polyarticular JIA, chronic bilateral AU	1 yr, 6 months	8	MTX 10 PO, INF	MMF 500	MTX 10 PO, INF, TS QDS BE	MTX 20 PO, MMF 500, ADA 20, TS QDS BE, Pred	INF to ADA at 3 mos	RE LE	0.00 0.00	0.00 0.00	2+ 2+	2+ 3+
F	14	Polyarticular JIA, chronic bilateral AU	8 yrs	13	MMF 850, ABT 440	TAC 1.5	ABT 400, MMF 850, TS QDS BE	ABT 440, MMF 850, TAC 4.5, TS RE OD		RE LE	0.18 0.00	0.00 0.00	1+ 0	0 0
M	19	Polyarticular psoriatic JIA, chronic AU	10 yrs	16	MTX 20 SC, MMF 1000	ADA 40	MTX 20 SC, MMF 1000, TS BE hourly	MTX 20 SC, MMF 1000, ADA 40		RE LE	0.00 0.48	0.00 0.18	1+ 1+	0 0
F	11	Polyarticular JIA, chronic bilateral AU	2 yrs	7	MTX 12.5 SC, ADA 20	MMF 250	MTX 12.5 SC, ADA 20, TS BE 4 hourly, Pred	MTX 12.5 SC, ADA 20, MMF 500, TS BE TDS		RE LE	0.18 0.30	0.18 0.00	1+ 3+	1+ 1+
F	19	Oligoarticular JIA, chronic bilateral AU	n/a	15	MTX 15 PO, MMF 1000	ADA 40	MTX 15 SC, MMF 1000, TS QDS BE	MTX 15 SC, MMF 1000, ADA 40, TS QDS RE		RE LE	–0.08 0.00	–0.08 0.30	0.5+ 2+	0.5+ 0.5+

ABT: abatacept (dose in mg, IV, monthly); ADA: adalimumab (dose in mg, subcutaneously, fortnightly); AU: anterior uveitis; BE: both eyes; INF: infliximab (dose 6 mg/kg, IV, every 8 weeks); JIA: juvenile idiopathic arthritis; LE: left eye; MMF: mycophenolate mofetil (dose in mg, PO twice daily); MTX: methotrexate (dose in mg, once weekly); Pred: oral prednisolone; PU: pan-uveitis; RE: right eye; TAC: tacrolimus (dose in mg, PO twice daily); TS: topical corticosteroids; TT: triple therapy.

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with a single biologic agent, including adalimumab[13,14,15,16], infliximab[9,17], or abatacept[18,19]. The use of tacrolimus for uveitis has been studied in adults[20] but not in children. Although evidence suggests that three-quarters of childhood uveitis responds to MTX[8], there is a subgroup that is refractory to a combination of 2 immunosuppressive agents.

It is evident that triple therapy did not obviate the need for corticosteroids, although 57.7% of patients were able to reduce the frequency of topical corticosteroid eyedrops during the first 6 months of followup, which is a key surrogate measure of efficacy[21,22]. The combination of 3 immunosuppressants in these 13 patients was, however, associated with 4 significant adverse events, all infections that are therefore potentially causally linked to the addition of further immunosuppression.

We acknowledge several limitations of our study and the conclusions drawn: first, the relatively small sample size and variable followup times for the adverse event data reported; second, the absence of a comparator control group; and third, the heterogeneity of the combination of therapies used, although 9 of the 13 patients did receive a single combination (MTX, MMF, and adalimumab). Given the small numbers, statistical analysis in an attempt to identify differences between subgroups would not be valid. It is not possible from the data presented here to assess the efficacy of any particular combination of triple therapy, but rather to comment in general on the effect and safety of the addition of a third immunosuppressant in this patient population.

Bearing in mind the above caveats, our study suggests that in children with refractory chronic noninfectious uveitis already receiving 2 immunosuppressive drugs, the addition of a third agent does not confer substantial benefit in redressing ocular inflammation and is associated with an increased risk of infectious adverse events. Therefore, we suggest that early intervention with first-line and second-line immunosuppressive agents, including biologics, may be more beneficial than attempts at late triple therapy rescue for established refractory disease.

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