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Give weekly adalimumab a chance before discontinuing it: a retrospective clinical and pharmacokinetic analysis in pediatric rheumatology

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Abstract

Background Subcutaneous adalimumab is the preferred treatment for most children with juvenile idiopathic arthritis (JIA) and non-infectious uveitis, usually administered every other week. Some patients do not respond or lose responsiveness over time, leading to dose escalation to weekly administration. This study evaluated the efficacy and pharmacokinetics of weekly subcutaneous adalimumab in children with JIA and idiopathic uveitis.

Methods This is a retrospective study on clinical and pharmacokinetic characteristics of patients treated with subcutaneous adalimumab for psoriatic arthritis or non-infectious uveitis (idiopathic or JIA-associated) who did not respond or ceased to respond to biweekly administration.

Results Four patients were enrolled: three females and one male, with a median age of 15 years (range 7–18; IQR 6). One had juvenile psoriatic arthritis, two had idiopathic uveitis, and one had JIA-related uveitis. They all presented a poor control of the disease on biweekly administrations, while it was successfully controlled on weekly administrations. None of them presented adverse events. Pharmacokinetic analyses identified two groups of patients: those with high clearance and those with low clearance. In both groups, weekly dosing increased the predicted drug concentrations, and in patients with high clearance only weekly administration provided the predicted concentration exceeding the therapeutic cut-off of 9.6 mg/L.

Conclusions Weekly adalimumab administrations were safe and effective in controlling both articular and ocular inflammation. In cases where the disease is poorly controlled with regular biweekly administrations, we encourage escalating adalimumab treatment to weekly administration before adding other therapies or switching to different biologics.

Keywords Adalimumab, Uveitis, Inflammation, Children, Pharmacokinetics

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Background

Juvenile Idiopathic Arthritis (JIA) is a prevalent rheumatic disease in children, with up to 30% of cases linked with uveitis [1]. Uveitis can be idiopathic or secondary to viral or bacterial infections, and non-infectious uveitis can be isolated or associated with systemic conditions. Effective management of non-infectious uveitis is challenging, as it can advance and cause serious eye damage if not promptly treated. Anti-Tumor Necrosis Factor alpha (TNFi) treatments and surveillance have significantly improved the quality of life and long-term prognosis for these patients. Subcutaneous adalimumab, a humanized monoclonal antibody that inhibits TNFα, is the treatment of choice for most people with JIA and severe non-infectious uveitis [2, 3]. It is usually administered every other week according to the patient's weight categories [2, 3]. Adalimumab's pharmacokinetics is complicated and depends on various variables, including target binding, endosomal recycling, and anti-drug antibodies (ADAs) [4, 5]. Age and body composition can affect drug metabolism, with obesity linked to poor response in patients with inflammatory disorders [4, 6]. Modelling of adalimumab pharmacokinetics can be useful to estimated patients exposure and pharmacodynamic target attainment but studies are still limited in JIA patients [7]. Patients with JIA and idiopathic uveitis may not respond or lose responsiveness over time, leading to dose escalation and increased TNF inhibitors (TNFi) doses [8].

Some authors have recently reported the safety and effectiveness of weekly adalimumab for JIA and refractory uveitis [2, 9, 10]. However, most studies on its effectiveness are related to inflammatory bowel diseases (IBD) [9]. Switching to other biological therapies has been associated with additional efficacy to decrease uveitis activity [11].

As for the treatment of JIA-associated uveitis and idiopathic anterior uveitis, recent recommendations suggest topical agents (e.g. dexamethasone 0.1%) as the first-line therapy [11]. If this approach fails, methotrexate (MTX) is usually the preferred synthetic disease-modifying antirheumatic drug, while mycophenolate mofetil may be considered in the absence of articular involvement [11]. In cases of inefficacy or intolerance, adding or switching to adalimumab is recommended [11]. If adalimumab fails, another TNFi or tocilizumab can be used. Finally, for patients refractory to these treatments, abatacept, JAK inhibitors, and/or rituximab may be considered [11].

This study aimed to evaluate the efficacy and pharmacokinetics of weekly subcutaneous adalimumab therapy in pediatric patients with JIA and idiopathic uveitis.

Methods

This retrospective case series examines patients with psoriatic arthritis and non-infectious uveitis who received weekly adalimumab treatment after a biweekly regimen was ineffective. Adalimumab was administered at a dose of 20 mg for patients weighing up to 30 kg, and 40 mg for patients weighing more than 30 kg, as per the in-label recommendation. The research was conducted at the Pediatric Rheumatology Service of the Institute for Maternal and Child Health Burlo Garofolo, Trieste, Italy. One patient with psoriatic arthritis and three patients with non-infectious uveitis – either idiopathic or JIA-associated – who were treated with weekly adalimumab were included. Three patients who escalated to weekly adalimumab administration with the concomitant addition of MTX were excluded, whereas those already on MTX were included.

Articular disease was estimated with the Juvenile Arthritis Disease Activity (JADAS) Score [12].

Anterior chamber inflammation was assessed and graded using the SUN criteria [13]. Vitreous, retinal and choroidal involvement was assessed with dilated indirect ophthalmoscopy, while optical coherence tomography (OCT) was performed in those cases with posterior pole involvement. Uveitis was considered inactive if the anterior chamber cells was < 1 (grade 0)[14].

Serum adalimumab concentration was quantified by ELISA sandwich with no restrictions on the timing of sampling (RIDA®QUICK ADM Monitoring Ref. GN3043, r-biopharm, Germany) and concentrations were considered adequate if they were higher than 9.6 mg/L concentration that should ensure a sufficient response to therapy, as suggested by recent scientific literature [15]. In cases of low serum adalimumab levels (< 1.5 mg/L), anti-drug antibodies were investigated. Adalimumab pharmacokinetics (PK) profiles were predicted using Bayesian estimation based on a previously reported pediatric Crohn's disease population PK model, using the MapbayrR package (version 0.10.0)[16]. To account for intra-patient PK variability during the course of treatment, an inter-occasion variability (IOV) of 40% was incorporated into the PK model. Average clearances were then calculated for each patient. For the modeling analysis, since we did not have the dates of each dose available, we considered the sampling time as pre-dose, given that, due to the long half-life of adalimumab, sampling times do not appear to affect the effectiveness of TDM, as already reported in previous studies [17, 18]. Patients were also genotyped, using Taqman® genotyping technique, for the rs396991 variant in the *FCG3RA* gene, associated with poor response and low concentrations of TNFi in patients with rheumatoid arthritis [19].

Adverse events (AEs) and serious adverse events (SAEs) were defined according to the International Council for

Table 1 Patients' characteristics

	Gender	Disease	Age (disease onset/ at adalimumab escalation, yrs)	Previous systemic treatments	Dosage (mg/m^2)[a]	Adalimumab serum concentrations (mg/L)	Other already ongoing treatments[a]	Side effects
1	F	Juvenile psoriatic arthritis	14/15	NSAIDs	18.5	2.70, 4.70 (during bi-weekly therapy from 3 and 6 months) 19.10, 15.0, 15.10 (during weekly therapy from 5, 8.5 and 13 months)	-	-
2	M	Idiopathic Uveitis	7/7	ADM 20 mg weekly	37	20.7, >25 (during 40 mg every 10 days from 20 days and 3 months) 24.60 (during bi-weekly therapy from 5 months)	dexamethasone and timolol	-
3	F	JIA + uveitis	2/15	ADM 40 mg every two weeks	23.4	11.5, 15.80, 10.20, 15.30, 15.40 (during bi-weekly therapy from 3, 10, 14 and 20 months)	dexamethasone and tropicamide	-
4	F	Idiopathic Uveitis	8/18	ADM 40 mg every three weeks	23.8	7.0 (during weekly therapy from 2 weeks)	-	-

NSAIDs Non-steroidal anti-inflammatory drugs, *ADM* Adalimumab, *MTX* Methotrexate

[a]At the time of escalated adalimumab dosage

Harmonisation Good Clinical Practice guidelines (ICH E6(R2)).

The study was approved by the Institutional Board Review (RC 23/2022) and written consent was obtained from all participants' guardians. The 18-year-old patient signed her own informed consent form.

Results

Four patients were enrolled: three females and one male, with a median age of 15.5 years (range 7–18; IQR 6). One had juvenile psoriatic arthritis, two had idiopathic uveitis, and one had JIA and related uveitis.

Patient's clinical characteristics are summarized in Table 1.

Patient #1 is a 15-year-old obese girl with psoriatic arthritis since the age of 14 years. The disease began in a polyarticular form, so treatment with MTX and adalimumab was started immediately. However, MTX was suspended after one month due to intolerance and refusal of the drug by the patient. Treatment with adalimumab was initiated at the standard dosage of 40 mg every two weeks. After three months, the disease was still active (JADAS score 7.1), so the therapy was escalated to weekly administrations. After three months, the disease was minimally active (JADAS score 2.5), obtaining subsequently disease remission according to Wallace criteria, without any side effects [20].

Adalimumab concentration was measured both before and after the change in dosage: the average level measured was 3.7 mg/L during biweekly therapy and 16.4 mg/L during weekly therapy. The average therapy duration during biweekly therapy at the time of sampling was 4.5 months, while during weekly therapy it was 8.8 months.

Patient #2 is a 7-year-old boy with idiopathic posterior bilateral uveitis without retinal involvement, who started the adalimumab treatment nine months ago. Given the lack of response to topical therapies (dexamethasone and timolol, anterior chamber flare 0, vitreous cells 2+, no retinal involvement), and considering the severity of the condition, adalimumab was directly initiated at weekly doses of 20 mg (weight: 29 kg). Due to further relapses, after three months the dosage was adjusted according to the patient's weight to 40 mg every 10 days, with a good response and no signs of side effects. After escalation to 40 mg (20 days later), the observed serum adalimumab concentration was 20.7 mg/L. Serum adalimumab concentrations prior to escalation to 40 mg was not measured.

Patient #3 is a 16-year-old girl with ANA-positive JIA and associated iridocyclitis since the age of two years. When she was ten, MTX and adalimumab were started at inlabel dosage of 40 mg every two weeks with a good response. By the age of 14 years, MTX and adalimumab were both gradually discontinued. However, six months later, both ocular and articular inflammation relapsed (anterior chamber flare 1+, vitreous cells 0, JADAS score 5.3) and adalimumab was started again with biweekly administrations at the dosage of 40 mg every two weeks, as well as daily topical dexamethasone and tropicamide. Three months later, because of the persistence of uveitis (anterior chamber flare 1+, vitreous cells 0), without

articular inflammation (JADAS score 0.8), the adalimumab schedule was changed to once a week, maintaining the ongoing topical treatment (dexamethasone and tropicamide), with prevention of further flares in the absence of side effect. The patient reached inactive disease. Average observed adalimumab serum concentration during 40 mg biweekly therapy (average therapy duration on this stable dosage: 11.7 months) was 13.6 mg/L. Model-based predicted steady-state pre-dose concentration for 40 mg every week regimen was 32.9 mg/L.

Patient #4 is an 18-year-old young woman with bilateral idiopathic panuveitis since the age of eight years. She was treated with MTX and adalimumab at the dosage of 40 mg every two weeks with a good response (anterior chamber flare 0, vitreous cells 0, no retinal involvement). After two years, MTX was successfully withdrawn, while she relapsed when adalimumab withdrawal was attempted. After one year without disease relapses and an attempt to taper adalimumab administrations to every three weeks, the woman experienced a relapse one month later (macular oedema, mild retinal detachment), so the medication was escalated to weekly administration, with benefit (anterior chamber flare 0, vitreous cells 0, mild bilateral choroidal neovascularization) and no side effects. Twelve days after escalation, before reaching steady state (which is reached in about 2 months, considering a half-life of 2 weeks), the observed serum concentration of adalimumab was 7.0 mg/L. Model-based predicted steady-state concentration for 40 mg every week regimen was 9.9 mg/L.

Estimation of adalimumab clearance for patient #1 to #4 were 0.0143, 0.0089, 0.0071, and 0.0310 L/h/70 kg, respectively. Patient #1 and #4 presented estimated steady state pre-dose concentration below therapeutic cut-off (9.6 mg/L) during biweekly therapy and above therapeutic cut-off during weekly therapy. Patient #2 and #3 presented estimated steady state pre-dose concentration above therapeutic cut-off both during biweekly and weekly therapy, with doubling of estimated drug concentration after intensification.

Genotyping for the rs396991 variant in the *FCGR3A* gene showed that no patients were homozygous wild-type, three patients were heterozygous, and one patient was homozygous variant (patient 4).

Discussion

We explored the administration of adalimumab through a weekly schedule, contrasting it with the conventional biweekly regimen. This adjustment has seemed to be effective in patients experiencing inadequate initial responses or a decline in efficacy over time. Some individuals initially showed insufficient responses to biweekly treatment but improved significantly when their regimen was shifted to weekly. In other cases, although conventional therapy had previously controlled the condition, there was a decline in management when treatment was briefly paused. The implementation of a weekly administration schedule has facilitated more consistent management for our patients.

In one critical instance, therapy commenced with a weekly dosage to address an aggressive condition promptly. A potential reason for suboptimal responses in some patients may arise from inaccurate subcutaneous dosing that doesn't align with the patient's weight, since adalimumab dose is not finely calibrated to body weight but dichotomised between patients weighing less or more than 30 kg (20 or 40 mg, respectively) [4]. Comparatively, other biologics such as infliximab provide a weight-based dosing schedule but require intravenous administration, which can be burdensome due to costs and the need for hospital visits. Intravenous methods also tend to involve a higher risk of adverse effects. Notably, weekly adalimumab dosing has been found non-inferior to infliximab for treating children with refractory non-infectious uveitis [9].

During the weekly regimen, serum adalimumab levels in pediatric patients remained above the established efficacy threshold, except for patient #4, initially not reaching adequate levels due to insufficient therapy duration but reached the therapeutic cut-off at steady state according to pharmacokinetic estimates [16]. Patient #1 exhibited significant enhancement in serum levels upon increasing from a biweekly to a weekly regimen, highlighting the potential of weekly dosing to augment medication concentration and effectiveness. Additionally, all the patients were either heterozygous or homozygous for the rs396991 variant in the *FCGR3A* gene, associated, in adult patients, with poor responses to TNFi, potentially explaining the inadequate responses to standard regimens in our pediatric patients [19, 21].

Notably, no patients presented adalimumab side effects during the treatment at escalated dosage.

A recent study indicates that disease severity can affect serum concentrations of adalimumab, with higher disease activity leading to increased medication clearance [22]. Notably, the co-administration of MTX with adalimumab may reduce drug clearance and immunogenicity [23]. In all patients of our series, adalimumab was escalated without adding MTX. Thus, we can assume that in all cases clinical improvement was achieved solely due to adalimumab.

Patients receiving adalimumab for uveitis might experience decreases in drug effectiveness, often tied to the formation of anti-drug antibodies (ADAs) [10, 24]. Nevertheless, weekly administration has been linked to a lower risk of ADA development, a trend that has been noticed in our patient cohort, none of whom developed

ADAs during the follow-up period, which lasted an average of 7.5 months per patient.

In this cohort, patients with slower estimated clearance required higher concentrations to achieve response, since they were above the therapeutic cut-off already before therapy intensification. We could hypothesize that patients with higher clearance may present higher TNF concentration; in these patients adalimumab probably works by conjugating TNF, while in patients with lower drug clearance, a different pharmacodynamic mechanism could be involved, such as proapoptotic effects, requiring higher drug concentrations [25, 26]. Interestingly, in this cohort, patients with higher clearance had different potential causes: #1 was obese and #4 was the only homozygous patients for the *FCGR3A* variant. Obesity is known to be a risk factor for adalimumab treatment failure compared to patients with normal body max index, as standard dosage may be insufficient [27, 28].

Our work reinforces the safety and effectiveness of weekly adalimumab therapy for children diagnosed with JIA and uveitis, particularly for those not responding to biweekly treatment. The measurement of adalimumab serum concentrations and pharmacokinetic estimations adds an essential dimension to treatment management, helping to highlight patients who may be at risk of therapeutic failure.

This study also suggests that initiating treatment with weekly adalimumab could be a strategic approach, allowing for tapering once remission is achieved—a method already utilized in IBD [29]. There are commonalities in the treatments across gastroenterology and rheumatology, indicating a need for enhanced collaboration between pediatric specialties to optimize the safe and effective use of biologics.

However, this study does acknowledge limitations, including the small and heterogeneous patient sample, which may impact the generalizability of the findings. Future research should aim to include larger and more diverse cohorts to strengthen the evidence to recommend weekly dosing of adalimumab.

Conclusions

In conclusion, this study emphasizes the effectiveness of weekly adalimumab thanks to clinical and pharmacokinetic findings and highlights the necessity of a personalized dosing approach to enhance patient response. These findings could pave the way for further studies on adalimumab pharmacokinetics in JIA, improving future clinical practice.

We encourage escalating adalimumab treatment to weekly administration before adding other therapies or switching to different biologics. This possibility could be included in the normal posology, not considering it as an off-label use.

Abbreviations

ADAs	Anti-drug Antibodies
ADM	Adalimumab
ANA	Anti-Nuclear Antibodies
IBD	Inflammatory Bowel Diseases
IOV	Inter-occasion Variability
JIA	Juvenile Idiopathic Arthritis
MTX	Methotrexate
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OCT	Optical Coherence Tomography
PK	Pharmacokinetics
TNFi	Tumor Necrosis Factor inhibitor

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Authors' contributions

SP, AITo and AnTa contributed to the diagnosis and follow-up of the patients involved in this study. GS, PDZ and DC contributed to the drug serum concentrations and pharmacogenetic analysis. TM and KI contributed to the pharmacokinetics modelling and estimations. FB wrote the first draft of the manuscript. SP, AITo, AnTa and GS revised it. All authors read and approved the last version of the manuscript.

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Data availability

The dataset supporting the conclusions of this article is included within the article.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Board Review at the IRCCS Burlo Garofolo (RC 23/2022). All parents of children involved in the study gave the consent to participate in the study.

Consent for publication

Informed consent was obtained from all parents of children involved in the study.

Competing interests

The authors declare no competing interests.

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