Adalimumab in the treatment of paediatric patients with chronic non-infectious anterior uveitis: a drug profile

Abstract

Introduction:

Adalimumab is established as an effective treatment for paediatric non-infectious uveitis refractory to methotrexate. However current use of the medication is empiric, according to fixed-dosing regimens and a significant proportion of patients will be non-responsive or sub-optimally responsive to adalimumab.

Areas covered:

There remains considerable scope to improve outcomes through tailoring treatment according to individual patient responsiveness. Monitoring of anti-drug antibodies and serum drug trough levels may assist in predicting which patients are likely to have a poor response to adalimumab and enable tailoring of regimens to individual patients.

Expert opinion:

We propose use of these biomarkers to individualise therapy in sub-optimally responding patients, and present an algorithm of treatment escalation for paediatric non-infectious uveitis.

Introduction

Background of context of the medical need

Paediatric non-infectious uveitis is a sight-threatening disease, and while there have been significant advances in treatment, there remains an unmet clinical need to prevent blindness through better diagnosis, prognostication and enhancement of treatment regimens.

The incidence of paediatric non-infectious uveitis (PNIU) is estimated at 4.9 per 100,000/year with a prevalence of 30 per 100,000/year in Europe and America (1-4). 29-63% of cases remain idiopathic and the most common systemic association is juvenile idiopathic arthritis (JIA) with high variability between referral centres across Europe, North America and Israel ranging from 15-67% of all PNIU cases (3, 5-7). Other systemic associations (rare) include Behcet's disease (0-15%), sarcoidosis (0-3%), Takayasu arteritis (0-2%), tubulo-interstitial nephritis-uveitis (0-2.4%), Vogt-Koyanagi-Harada disease (0-2%), Blau syndrome (0-1.8%), systemic lupus erythematosus (0-0.8%) and inflammatory bowel diseases (0-4%) (6, 8, 9).

PNIU can present with sight-threatening complications or develop these during follow up. Complications can occur from disease activity or treatment (in particular topical steroids). Common complications include cataract, band keratopathy, glaucoma, hypotony and macular oedema(3, 7, 10-13). Macular oedema and hypotony have the most significant impact on vision(3). A systematic review has found complications in 35.5-67% of children overall, with one third of these present at time of diagnosis(8). The review stated a final visual acuity (VA) of less than 20/50 was found in 11 to 31% and of less than 20/200 in 12% of eyes. It should be noted that this systematic review included studies from 1997 through to 2017, but there is a recognition of downwards trend in the numbers of complications in later publications(7).

Early detection and treatment of uveitis is key to reduce the risk of sight-threatening complications(14). Uveitis in children is most frequently asymptomatic. As mentioned above, JIA is the most common associated systemic disease. A recent meta-analysis found the prevalence of uveitis in JIA patients to be 11.8% (range 11.2-12.4%), therefore screening protocols are in place in most countries for children at risk, depending on their biomarkers(14-

16). Screening results in an improved overall outcome in visual acuity. One recent cohort study in JIA- uveitis (JIA-U) that enrolled in a screening protocol, showed a mean of VA at presentation between 20/32 and 20/20 depending on different small sized subgroups and over 95% retained 20/20 vision 1 year after diagnosis. Within this cohort 29.8% of patients had complications at first presentation and then 12.9% further developed complications during follow up.

With an isolated presentation of uveitis or where uveitis pre-dates the diagnosis of a systemic disease, there still remains a challenge for timely detection because of the relatively asymptomatic nature of the disease. However, there is only limited epidemiological data for non-JIA paediatric uveitis. One retrospective study at a regional referral centre, of a cohort of PNIU which included 166 children showed no significant difference between the rate of VA impairment between JIA-U and idiopathic uveitis; 18.6% and 17.1% of patients having a VA of less than 20/40 in these groups respectively. Children with JIA-U were more likely to develop raised IOP, while children with idiopathic uveitis were more likely to develop macular edema over the follow up period. However, in this cohort, more patients in the JIA-U group received adalimumab. In another retrospective study including 811 children with PNIU comparing JIA-U and non-JIA ANA positive uveitis in Germany, 72.9% of the non-JIA-U ANA positive patients presented with complications at initial diagnosis versus 39.9% in children with JIA-U (17). VA at presentation was most impaired in patients where uveitis pre-dated the diagnosis of JIA (mean 20/50) and in patients with non-JIA ANA-positive uveitis (mean 20/45). VA only recovered partially with treatment (mean of 20/50 and 20/40 respectively). Of note was the use of methotrexate was more frequent in the JIA cohort, whereas adalimumab was used in equal frequency.

To achieve optimise outcomes, a reliable assessment and monitoring of uveitis is required and to date the Standardisation of Uveitis Nomenclature (SUN) criteria is employed to define anatomical location and time course(18). Treatment algorithms for PNIU depend on associated systemic disease and to achieve maximal benefit are best managed by a specialised multi-disciplinary team of ophthalmologists and paediatricians(7). To this end, several consensus-based algorithms for JIA-U are available online and although

recommendations vary slightly, we commend the SHARE initiative acknowledging the current level of evidence base, whilst acknowledging where evidence gaps remain (14-16).

Whilst differences in approach to management exist, dependent upon type of uveitis, first line treatment consists of topical corticosteroids and cycloplegic and can be escalated to systemic corticosteroids, either oral or intravenous, in sight-threatening disease, which is then weaned over several weeks(14, 19-21). The primary indication for systemic immunosuppression for PNIU is failure of adequate control of inflammation after 3 months, evidenced as a need of topical treatment >2 drops daily, or conditional recommendations to escalate for 1-2 drop daily requirement in US guidelines(15, 16, 22, 23). Methotrexate is recommended as first second-line therapy in JIA-U (14, 15). There are no consensus-based guidelines for non-JIA paediatric uveitis. Disease modifying antirheumatic drug (DMARD) including Azathioprine, Mycophenolate mofetil, and Sulfasalazine might be considered as alternatives but there is only low-level evidence to support such an approach (see below). Current protocols, however, recommend escalation to anti-TNFα monoclonal antibodies (mAb) therapy when there is failure to control uveitis after 3 months on Methotrexate, with earlier or simultaneous introduction in very severe, sight-threatening cases(14). The SHARE initiative recommends primary escalation to adalimumab in case of methotrexate inefficacy or intolerance(14). The addition of a second non-biologic immunomodulatory therapy is not recommended as there is no substantive evidence to gain uveitis control and is associated with increase adverse effects and particularly with the advent of biologic therapy(24). In case of anti-TNFα mAb failure, other biologic agents that may be considered include Tocilizumab, or in-class switching to Infliximab or Golimumab, or further class switching to Rituximab (see below).

As the largest evidence base exists for the anti-TNFα therapy with adalimumab, this review synthesises the evidence behind the drug use and highlights the evidence gaps where future research may further optimise therapy.

Adalimumab profile and evidence for use in Paediatric non-infectious uveitis

The rationale

While multifactorial in origin, a current notion is that non-infectious uveitis develops with an environmental trigger in a genetically susceptible individual. There is loss of immune tolerance, resulting in a T-cell driven autoimmune response, orchestrating a cascade of inflammatory cells releasing tissue-damaging pro-inflammatory cytokines. Such cytokines include both T cell, dendritic cell and mononuclear cell derived cytokines, IL-23, IL-12 IL-1, IL-6 and TNFα, canonical Th1-derived Interferon-gamma and Th17-derived IL-17 (25-27).

TNFα has been implicated in many systemic and ocular immune-mediated diseases, including PNIU(9, 14, 25-31). Five anti-TNF biologic agents are currently available for treatment of immune-mediated inflammatory disease: adalimumab, etanercept, infliximab, golimumab and certolizumab.

The biologic

Adalimumab is a recombinant, fully human IGg1 monoclonal antibody against TNFα, binding to and blocking both transmembrane TNF as well as soluble TNF, thus preventing activation of both TNFRp55 and p75 receptors. The biologic is administered by subcutaneous injection and takes 131±56 hours to reach maximum concentration. The mean half-life of adalimumab is 2 weeks (range 10-20 days), reflected in the fortnightly dosing prescribed for the medication(25).

Adalimumab is usually given concurrently with non-biologic immunosuppressive agent most commonly, but not exclusively, methotrexate. However, Adalimumab may be administered as monotherapy particularly if there is poor tolerance of the non-biologic agent. There are variable reports, unlike rheumatoid arthritis, of the effect of concurrent methotrexate therapy for eye disease, with some authors suggesting reduced drug clearance and others reporting no effect(28).

Current indication

Adalimumab is licensed by the FDA(32) and EMA(33, 34) for the treatment of non-infectious uveitis in paediatric patients from 2 years of age. The indication is for uveitis refractory to treatment with corticosteroids, methotrexate or mycophenolate mofetil(31). In the context of PNIU, it is given in combination with methotrexate for patients who have persisting uveitis activity according to the SUN criteria(18), despite 12 weeks of stable-dose methotrexate, or who are unable to taper topical corticosteroid therapy below three times daily dosing.

Different dosing regimen have been described for systemic use, but in uveitis, dosage of adalimumab in adults is fixed at 40mg fortnightly via subcutaneous injection. Dosage in children is empiric based on weight, with children <30kg receiving 20mg fortnightly and children ≥ 30kg receiving 40mg fortnightly(25, 26).

Evidence of efficacy in pediatric non-infectious uveitis

Methotrexate is most commonly used as the first DMARD for pediatric non-infectious uveitis. For patients with ocular inflammation refractory to methotrexate, adalimumab has become the standard of treatment escalation. Evidence for the use of adalimumab in paediatric non-infectious uveitis followed successful outcomes in several case series, both prospective and retrospective(35-43) and then finally level 1 evidence from two randomized control trials SYCAMORE and ADJUVITE trials(30, 44).

SYCAMORE trial(30)

The SYCAMORE trial was a multicenter (17 UK centres), double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of adalimumab in pediatric patients aged 2 years or more with JIA-associated uveitis refractory to methotrexate. 90 adalimumab-naive patients who had active JIA-associated uveitis despite 12 weeks of stable-dose methotrexate were randomized 2:1 to receive either adalimumab (n=60) or placebo (n=30). Adalimumab dosing was weight-based, with patients <30kg receiving 20mg fortnightly, and patients ≥ 30kg receiving 40mg fortnightly via subcutaneous injection. The primary endpoint was time to treatment failure, assessed with a multicomponent intraocular inflammation score. Secondary end points included corticosteroid requirement, control of JIA and health-related quality of life scores. Treatment with adalimumab resulted in a significant delay in time to

treatment failure compared to placebo (P<0.0001). Median time to treatment failure was 24.1 weeks in the placebo group and was not reached in the treatment group over the 18-month trial period. Treatment failure occurred in 27% of the treatment group compared to 60% of the placebo group. Patients in the treatment group had significantly longer duration of inactive disease than those in the placebo group (179.3±16.9 days vs 14.5±23.9 days). None of the patients receiving adalimumab had a flare of arthritis during the trial period compared to 3 patients receiving placebo. There was no significant difference between the two groups in health-related quality of life scores. There was a higher rate of adverse events in those that received adalimumab, most commonly infections, minor respiratory disorders and gastrointestinal disorders.

ADJUVITE Trial(44)

The ADJUVITE trial was a multicentre, double-blind, 1:1 randomised, placebo-controlled phase III trial to assess the efficacy of adalimumab in the management of paediatric patients with early onset chronic, rheumatoid factor negative JIA-U or idiopathic uveitis, inadequately controlled on topical corticosteroids and stable-dose methotrexate.

31 patients aged ≥4 years with active ocular inflammation, defined by laser flare photometry (LFP) ≥30photon units/ms, despite were randomised 1:1 to receive either adalimumab or placebo. Adalimumab dose was 24mg/m2 in patients <13 years, and 40mg fixed dose in patients ≥13 years, given as a fortnightly subcutaneous injection. Primary outcome was response to treatment at 2 months, defined as a reduction of at least 30% of ocular inflammation quantified by LFP without worsening of inflammation according to SUN criteria. The study group used LFP in addition to slit lamp examination on the basis that neither the SUN criteria nor LFP have been validated in paediatric uveitis. Secondary outcomes included assessment of treatment efficacy, topical and/or systemic steroid use and dose adjustment, and JIA response or flare.

The double-blind phase of the trial had a 2-month follow-up, at which point it entered an open-label period where all patients received adalimumab with an additional 10 months follow-up. At 2 months, 9/16 patients had documented response to adalimumab, compared to 3/15 receiving placebo (P=0.038, RR=2.81, 95%CI 0.94-8.45). One patient in the placebo

group had worsening of their activity on both SUN and LFP assessment, but there was no significant difference in activity according to SUN grading between the two treatment arms, although most patients having relatively low anterior chamber cellular activity visible on slit lamp examination. One patient in the placebo group had a flare of JIA. 30 patients entered the open-label phase, with one patient discontinuing after 5.8 months due to a flare of both uveitis and arthritis. Most patients had either no inflammation or a reduction of inflammation throughout follow up, and with a concurrent reduction in or cessation of topical and systemic steroid use. There were no serious adverse events that were attributable to study treatment.

The ADJUVITE trial further supports the use of adalimumab in paediatric patients with JIA-U and idiopathic chronic anterior uveitis who are insufficiently controlled on topical steroid and stable-dose methotrexate. The study did raise a question of the ideal method of grading uveitis activity in paediatric patients. Patients may have low SUN cell count and high LFP activity, as evidenced in the ADJUVITE study. However, there remains uncertainty as to whether escalating treatment on the basis of flare alters disease outcome(45, 46). To this end, the SUN grading system remains widely accepted and accessible in the assessment of uveitis, although not validated in paediatric populations (45).

Systematic review and meta-analysis

In a recent systematic review and meta-analysis, Maccora et al assessed the evidence for anti-TNF therapy in childhood chronic uveitis across 37 articles encompassing 2 RCTs plus 487 patients enrolled in observational studies(9). 226 of these patients received adalimumab, 213 received infliximab and 48 received etanercept. The authors confirmed the findings of SYCAMORE and ADJUVITE in supporting the use of adalimumab in pediatric patients aged 2-16 years with chronic non-infectious uveitis. Systemic associations included JIA, sarcoidosis, Behçet's disease, Blau syndrome, Vogt-Koyanagi-Harada disease and chronic non-bacterial osteomyelitis, though many patients had idiopathic uveitis.

86% of patients demonstrated clinical response in ocular inflammation to adalimumab, and 68% had clinical response to infliximab, with adalimumab being significantly superior to infliximab for all forms of uveitis. 36% of patients were responsive to etanercept which was consistently found to be inferior to both adalimumab and infliximab. Visual acuity was

improved or stable/normal in 75.4% of patients receiving adalimumab and 73.7% of patients receiving infliximab. Corticosteroid discontinuation was achieved in 83.3% of patients receiving adalimumab and 80.2% of patients receiving infliximab.

Adverse events to anti-TNF agents include an increased risk of infections, including tuberculosis reactivation and opportunistic infection, gastrointestinal disorders and hyperlipidaemia(44). Paradoxical development of new autoimmune disease or exacerbation of existing autoimmune disease, especially demyelinating disorders, may develop during treatment with anti-TNF agents. Immune-mediated drug resistance may develop, associated with development of anti-drug antibodies(25). Injection site reactions have also been reported, including erythema, itching, haemorrhage, swelling and pain(25, 30).

Alternative biologics

While adalimumab has been demonstrated as an effective treatment for pediatric non-infective uveitis, some patients are refractory to adalimumab. Maccora et al reported adalimumab therapy being ceased in 15% of patients receiving therapy, in whom 44.4% had drug cessation due to lack of efficacy(9). The SYCAMORE study group found 27% of patients to be non-responsive to adalimumab and in the ADJUVITE trial 7/16 patients had not demonstrated response to adalimumab at the 2-month follow-up and one patient discontinued treatment in the open-label phase due to disease flare(30, 44). For these adalimumab-refractory patients, other biologic agents may be considered.

Summary of alternative biologic agents

Biologic	Target	Route of administration	Evidence for use	Conclusion
Tocilizumab	IL-6	IV/SC	APTITUDE (47) • 7/21 patients responded • Did not proceed to phase III Case series (48-51) Improvement in CMO observed	Evidence from controlled trial: may be beneficial Particular benefit for CMO
Rituximab	CD-20	IV	Case series (52) Reports of successful control of JIA-U	Low level evidence: May be beneficial
Infliximab	TNFα	IV	Case series (53-59) Shorter remission time when compared to adalimumab (58)	Low level evidence: may be beneficial
Etanercept	TNFα	SC	Lower efficacy than adalimumab and infliximab (9, 25) Case reports of development of uveitis and scleritis while receiving drug (23, 25, 59)	Not beneficial. Potentially harmful
Abatacept	CTLA-4	IV/SC	Double-blind placebo-controlled withdrawal trial (60) • Ineffective in achieving sustained remission	Not beneficial

IV = intravenous; SC = subcutaneous

Baracitinib

There is current interest in the potential role of the Janus kinase (JAK) inhibitor baricitinib in treatment of JIA-U. Baricitinib inhibits JAK1 and JAK2 and has been approved for use in rheumatoid arthritis(61). Recruitment is currently underway for assessment of baricitinib in paediatric patients with active JIA-U or chronic ANA-positive anterior uveitis(62).

We acknowledge that much of the evidence regarding the use of biologic agents in paediatric non-infectious uveitis exists in the form of case series, and as such we recommend caution in extrapolating and applying the findings to clinical practice. This level of evidence is prone to positive publication bias, with only successful outcomes being reported.

Evidence gaps to optimise Adalimumab therapy

While adalimumab has been shown to be an effective treatment for PNIU refractory to methotrexate, there remains minimal evidence who is more likely to respond (personalised treatment) and the ideal duration of treatment informing decision making with respect to treatment cessation. Moreover, there is no substantive evidence regarding the dose and frequency of therapy with respect to underlying disease activity when patients are partially or non-responsive to adalimumab.

Biomarkers for disease activity

Clinicians aim to distinguish between drug-induced remission and disease remission to assess the risk of disease flare on cessation of therapy. Ability to make this distinction would allow clinicians to tailor therapies to individual patient response and more safely predict ability to tolerate treatment cessation. Measurement of serum biomarkers that indicate underlying disease activity (including CD163 MRP8, MRP14, S100 proteins, IL-18 and IL-6) is gaining traction in the management of systemic JIA(63-66). While not currently utilised in ophthalmology this area of research may prove beneficial in tailoring treatment to individual patient needs. To achieve this, the CLUSTER Consortium (including industry) is a multi-disciplinary group interrogating childhood arthritis, JIA-uveitis through trial outcome data, multi-omic analysis of peripheral immune profiles and bioinformatics(67). CLUSTER's aim is to discover, replicate and validate biomarkers to predict response to treatment, to define novel therapeutic targets and to discover disease and treatment response measures to enable stratification of patients with childhood arthritis and JIA-U to guide treatment.

When to cease therapy

In cases where remission of uveitis is achieved whilst on Adalimumab, there is limited guidance on how and when to stop treatment. Questions are raised about the safety of Adalimumab in long term use, such as the increased risk of opportunistic infections and possible risk of malignancy(68-71). The financial burden for patients or health care systems must also be taken into consideration and often health authorities encourage the discontinuation of adalimumab in children who respond well to the treatment – without evidence that it is safe to do so. Only limited observational cohorts and retrospective case studies have been published regarding the discontinuation of anti-TNFα therapies for uveitis or other autoimmune diseases. Most of these have demonstrated high relapse rates. A recent meta-analysis on the efficacy of anti TNFα in PNIU found a relapse rate of 0-50% after termination of adalimumab(9).

The 5-year follow-up of 28 SYCAMORE trial patients showed a flare of JIA-U in 26 of the 28 patients after the conclusion of the trial and cessation of adalimumab, with median time to flare 188 days following their last trial treatment. 25 patients were recommenced on adalimumab which extended time to flare to 986 days(72). Another cohort with 335 children with polyarticular JIA or enthesis-related arthritis, showed a relapse rate of 89% within 12 months after discontinuation anti-TNFα treatment(73). A further cohort with 171 children with JIA showed a relapse rate of 78% within 12 months(74). A retrospective study including 50 children with controlled uveitis on either infliximab or adalimumab. 19 patients discontinued their anti-TNFα treatment which resulted in 63.8% suffering a reactivation within 12 months, versus 27.8% reactivation in the group which continued their treatment(75). In a cohort of 18 children with uveitis, 61% relapsed after discontinuing infliximab(76). Similar outcomes where reported in a retrospective cohort of 11 patients with JIA-U discontinuing their anti-TNFα treatment, where 82% relapsed(13). Median time to relapse in these cohorts ranged from a few months to nearly two years but there is a signal of a shorter duration for JIA-U.

A further issue lacking evidence is the opportune time point to discontinue treatment of adalimumab. As highlighted, we do not have any validated biomarkers to assist clinicians to distinguish between drug-induced or disease remission in PNIU. The SHARE initiative and ACR

consensus recommends at least 2 years of controlled disease before tapering(14, 15). In contrast to relapse of uveitis after withdrawal of methotrexate, (where a long period of disease inactivity on treatment was associated with higher remission rates after discontinuing treatment(77)), there is no evidence for a significant association between duration of anti-TNFα treatment and risk of relapse after withdrawal(13, 74).

To assist going forward there is currently one ongoing clinical trial examining the safety and efficacy of stopping adalimumab in controlled JIA-U cases (the ADJUST trial)(78). Participants with controlled ocular inflammation on adalimumab for more than twelve months are randomized 1:1 to continue with adalimumab or a placebo and are followed for at least twelve months.

Adalimumab trough levels and anti-drug antibodies

Key Points:

- Lower trough levels of adalimumab are associated with a worse clinical response
- Anti-drug antibodies (ADA) are associated with increased drug clearance and lower trough levels
- Increasing adalimumab from fortnightly to weekly dosing can improve trough levels and clinical response in ADA-negative patients
- ADA-positive patients are less likely to respond to adalimumab dose increase

While adalimumab has been shown to be an effective treatment in paediatric patients with non-infectious uveitis, there is a paucity of evidence guiding the appropriate dose and duration of therapy. Clinically, patients with non-infectious uveitis may have a variable response to adalimumab, a finding which is echoed in systemic immune-mediated diseases. Primary failure is described when there is no response to adalimumab, and secondary failure when there is an initial response that subsequently diminishes. Adalimumab pharmacokinetics and bioavailability evidenced in serum adalimumab trough levels have been implicated in the variability of patient response, along with development of anti-drug antibodies (ADA) against adalimumab(28, 79-84). While not routinely utilised in ophthalmology, we propose that monitoring of adalimumab trough levels and ADA titres may

allow clinicians to tailor treatment regimens to individual patients, particularly those with primary or secondary failure of adalimumab therapy(28).

Although less immunogenic than chimeric mAbs, approximately 14% of treated patients developing an immune response against adalimumab and subsequent formation of ADA(29, 85, 86). The development of ADA against adalimumab is likely to be T-cell mediated associated with IgG (IgG_4 and IgG_1) class and subclasses (87). Development of ADA is associated with decreased serum biologic levels and reduced clinical efficacy of adalimumab in addition to increased frequency of clinical adverse effects(29, 80-86). ADA usually develop within the first 6 months of treatment but may diminish over time with development of immune tolerance(29). Often ADA are directed against the region of adalimumab that binds to TNFα, thus are directly neutralizing, as well as directed against the Fc portion of adalimumab and are non-neutralizing(28, 29). Both forms of ADA form immunocomplexes with adalimumab, resulting in increased drug clearance and reduced serum drug levels(28), therefore implicated in loss of clinical response(86).

Antibody monitoring in ophthalmology

Cordero-Coma et al(28)

In a prospective observational study of 25 patients with non-infectious uveitis, ranging in age from 3-73 (2 paediatric patients with JIA-U), Cordero-Coma et al measured ADAs and adalimumab trough drug levels over a 24-week period. 44% of patients had a complete clinical response to adalimumab, 28% had a partial response and 28% were deemed non-responders. They found that patients who clinically responded to adalimumab had significantly higher drug trough levels than those non-responders (9550ng/ml vs 600ng/ml; $P<0.001$). There was no significant difference in trough levels between those who had a complete clinical response and those who had a partial clinical response. Concomitant treatment with other systemic immunosuppression did not seem to protect against ADA development, though this finding was not statistically significant, nor did concomitant immunosuppression have an effect on adalimumab trough levels in the absence of ADA. 4 of the 25 patients had “permanent” ADA; antibodies present on 2 or more occasions. In these patients, there was a significant inverse correlation between adalimumab trough level and ADA titre. In these patients with permanent ADA and corresponding undetectable adalimumab trough level, a worse uveitis

clinical outcome was observed (P = 0.014). 2 of the 4 patients with permanent ADA were adalimumab non-responders, one withdrew from the study due and the remaining patient was determined to have a complete clinical response which was suggested to be independent of adalimumab treatment. Another 4 patients had "transitory" ADA – an elevated antibody titre on one single measurement. In patients with transitory ADA there was no correlation between ADA titre and antibody trough level(28). With 24 weeks follow-up the longer-term implications of AA positivity and low drug levels are not known.

The role of monitoring adalimumab trough levels and ADA have been more widely explored in non-ocular immune mediated inflammatory diseases. For example:

Discipline	Source	Diagnosis	Key findings
Rheumatology	*Bartelds et al(80)*	Rheumatoid arthritis	28% developed ADA ADA developed in the first 28 weeks for 2/3 ADA = lower serum adalimumab concentration ADA = higher disease activity and worse outcome If trough level low, increasing adalimumab dose frequency to weekly improved adalimumab trough level and improved response
	Vogelzang et al(81)	Psoriatic arthritis	ADA = lower serum adalimumab concentration ADA = worse disease activity scores
Gastroenterology	*Karmiris et al(82)*	Crohn's disease	ADA = lower serum adalimumab concentration ADA = higher rates of treatment failure Lower serum adalimumab = worse outcome and treatment failure If trough level low, increasing adalimumab dose frequency to weekly improved

			adalimumab trough level and improved response in 71% Concomitant immunosuppression did not impact ADA formation
Dermatology	*Menting et al(84)*	Psoriasis	49% developed ADA ADA usually developed in the first 24 weeks ADA = lower serum adalimumab concentration ADA = higher rates of clinical non-response Concurrent methotrexate did not affect ADA formation Increasing dose frequency from fortnightly to weekly beneficial if trough level low and ADA-negative Increasing dose frequency from fortnightly to weekly less effective if trough level low and ADA-positive

Expert Opinion

Clinical implications for paediatric non-infectious uveitis

While direct conclusions cannot be made from these findings, the evidence regarding the role of ADA and drug trough level monitoring can be extrapolated to suggest a role for use in ophthalmology, particularly for the management of paediatric non-infectious uveitis.

Most of the available evidence is limited by small cohort sizes, or larger cohorts assessing the use of adalimumab in non-ocular immune mediated diseases. There is no current evidence for ADA and adalimumab trough level monitoring specific to paediatric non-infectious uveitis and further study in this population would be warranted if this practice were to be adopted.

Impact of ADA monitoring

While it has been established that ADA-positive patients are likely to have lower adalimumab trough levels and associated worse clinical outcomes. A further question is: are we able to

predict which patients are likely to develop ADA? Given naturally occurring antibodies may cross-react with adalimumab, thereby boosting ADA levels, or develop within the first 6 months of treatment, we propose there is merit in studying whether measuring antibody concentrations to predict likelihood of response to ongoing treatment is warranted. At present it is poorly understood which patients are at highest risk of developing ADA, or the degree to which ADA titre impacts clinical response. Whilst low ADA titres may have a lower impact on drug efficacy we should be concerned of the impact of high ADA titres sufficient to bind to available therapeutic antibody (29). van Schouwenburg et al(29) suggest ADA form due to a complex interplay between genetic, patient factors and treatment-related factors including dose, duration, administration route and co-treatment with other immunomodulatory agents. It is possible to also highlight molecular and cellular signatures predicting ADA formation. For example, Magill et al(88) analysed 332 cell surface markers on B and T cells in patients receiving adalimumab for rheumatoid arthritis. They found 7 differentially expressed markers (DEM) between antibody-positive and antibody-negative patients, with a significant, consistently reduced frequency of signal regulatory protein (SIRP)α/β-expressing memory B cells in antibody-positive patients compared to antibody-negative patients. Frequency of <9.4% of SIRPα/β-expressing memory B-cells prior to initiation of adalimumab was predictive for development of ADA and subsequent treatment failure. Finally, and although poorly understood, there has been a documented association between distinct IL-10 and TNF genotypes with ADA development(89).

Drug level monitoring

Current established practice in the management of paediatric non-infectious uveitis is to prescribe adalimumab on a fixed dosing regimen according to the weight and body surface area of the patient. However, as we have described above, the growing experience with respect to drug trough level monitoring, we suggest we develop to create evidence to tailor treatment to maintain adequate trough levels and provide superior disease control. Many authors have advocated using low adalimumab trough levels as a guide to increase dose frequency from fortnightly to weekly, and have demonstrated favourable clinical response to this approach. To support this assertion, proactive serum adalimumab trough monitoring has been described in 78 paediatric patients with Crohn's disease by Assa et al(90). In this non-blinded randomised controlled trial patients were randomised to prescribed adalimumab

trough level monitoring at weeks 4 and 8, then every 8 weeks until week 72, or to reactive monitoring with trough level assessment performed if there was a lack of clinical response. Both groups received dose and frequency adjustments to maintain adalimumab trough concentrations of 5µg/mL. The primary endpoint of corticosteroid-free disease remission at all visits (week 8-72) was achieved in 82% of patients in the proactive monitoring group versus 48% in the reactive monitoring group (P=0.002). 87% of patients in the proactive monitoring group had escalation of adalimumab therapy to maintain serum concentration compared to 60% of the reactive monitoring group (P=0.001). These patients had already demonstrated clinical response to adalimumab prior to study enrolment, and ADA were not recorded.

A recent review regarding ADAs in various biologic agents used in rheumatology - including adalimumab - highlights that ADAs reduce the efficacy of biologic agents and suggests monitoring of serum drug and ADA levels, but that cost effectiveness has yet to be proven(91). A suggested drug monitoring algorithm includes drug levels as first assessment followed by ADA levels. Interpretation of results depend on the type of assays used and needs education of clinicians requesting them as well as their patients. The authors further mention that in case of loss of efficacy of a TNF inhibitor with positive ADAs clinicians might consider switching to a different TNF inhibitor, but with negative ADAs might consider switching to another biologic class.

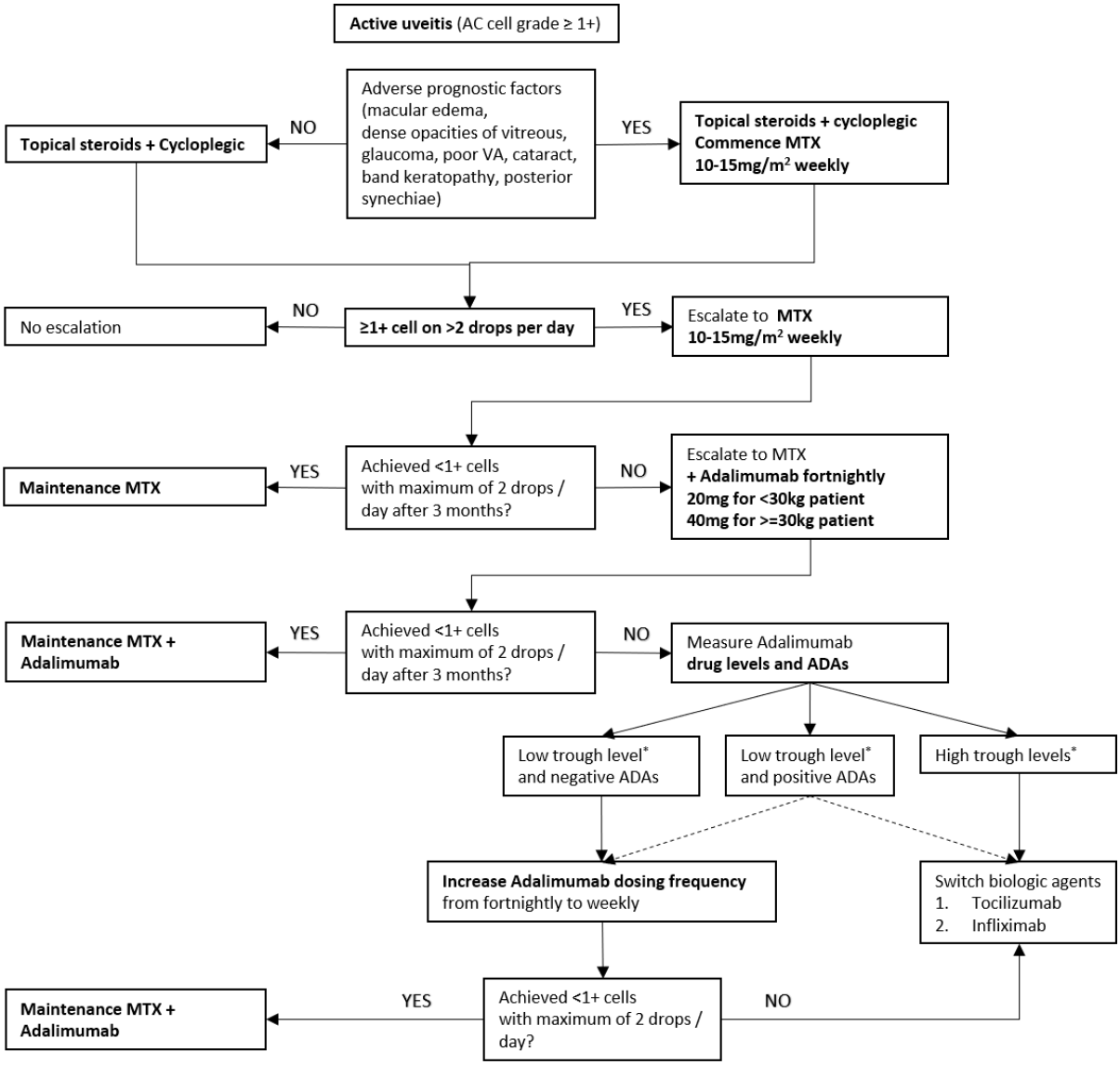
While it has been well-established across IMID that higher adalimumab trough levels are associated with an improved clinical outcome, and ADA monitoring can be a predictor of long-term response to treatment, the application in paediatric patients and ocular inflammation has yet to be established. There therefore remains no consensus on the ideal timing of measuring adalimumab and antibody levels, or what the target serum drug concentration should be (92).

Concluding Remarks

While adalimumab is an effective treatment for paediatric non-infectious uveitis refractory to methotrexate, there is considerable ability to improve outcomes through tailoring treatment to individual patient response at least in partial-responders or non-responders. The most

robust evidence is for adalimumab treatment of JIA-U and the management of non-JIA-U cases is extrapolative. Moving forward, the monitoring of ADA and serum trough levels may assist in predicting which patients are likely to have a poor response to adalimumab and with a hope to tailor regimens to individual patients. Further investigations on biomarkers are needed for improved clinical management especially when evaluating treatment cessation when remission is achieved.

The authors propose the following algorithm to guide escalation of treatment for paediatric non-infectious uveitis and optimise individualisation of treatment, particularly as relates to adalimumab therapy (Figure 1).



* Actual level depends on local laboratory values

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