# Anti-Adalimumab Antibody Development in Children and Young People treated for Non-infectious Uveitis and Rheumatic Diseases

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## Introduction

Adalimumab is a monoclonal antibody that inhibits the action of Tumour Necrosis Factor-alpha and downregulates inflammation. It is an effective, evidence-based, biologic therapy approved for use in National Health Service England (NHS England) in the UK to treat Children and Young People (CYP) with non-infectious uveitis regardless if the CYP has juvenile idiopathic arthritis (JIA) or not.

However, development of anti-Adalimumab antibodies (AAA) is an emerging recognised phenomenon and has previously been linked to treatment failure and disease relapse.

Currently, there is limited evidence and guidance on the use of AAA testing to inform treatment management, and the factors influencing AAA development; prompting our observational cohort study at a single tertiary referral centre, in a national children's hospital in the UK.

## Methods

All 390 CYP treated with Adalimumab within a specialist paediatric rheumatology service, between 2015-2023, were included in this retrospective observational study.

Potential factors influencing AAA development and its implications for CYP were explored.

Data was collected from hospital systems including patient databases, clinical records and blood test result software; clinical diagnosis, length of treatment, concurrent use and dosage of disease modifying anti-rheumatic drugs (DMARDs), reason for testing, AAA levels, and outcomes following results.

## Results

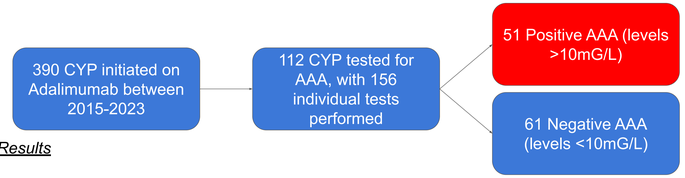



*Figure 1: AAA Results*

390 CYP were initiated on Adalimumab treatment between 2015-2023. 112/390 (28.7%) CYP were tested for AAA, with 156 individual tests performed. 135/156 (86.5%) tests were performed due to flare of disease. Other reasons for testing included suspected non-compliance with medication, clinical interest, and monitoring.

51/112 (45.5%) CYP had AAA detected (defined as >10mG/L) after an average of 2.4 years (range: 0.3-5.8yrs) of being treated with Adalimumab.

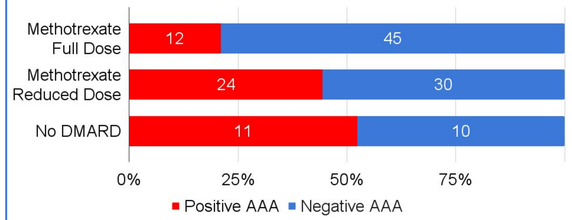



*Figure 2: AAA Results with DMARD Use*

- 21/156 (13.5%) CYP were not prescribed concurrent DMARDs alongside Adalimumab.
- **52.3%** (11/21) CYP had detectable AAA in those not prescribed concurrent DMARD.
- **44.4%** (24/54) CYP had detectable AAA while on sub-therapeutic methotrexate dosage (<15mg/m$^2$).
- **21.1%** (12/57) CYP had detectable AAA while on full therapeutic dosage of methotrexate (15-20mg/m$^2$).

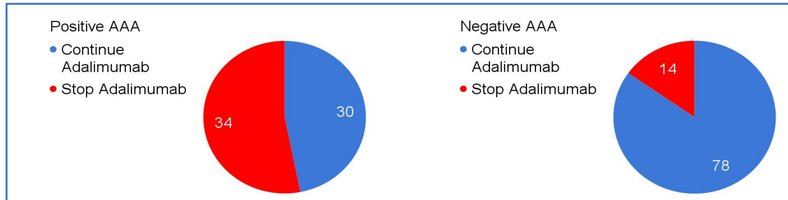



*Figure 3: Effect on Adalimumab Continuation*

53.1% (34/64 individual tests) tested positive for AAA resulting in discontinuation of Adalimumab, compared to 15.2% (14/92 individual tests) of those with negative AAA.

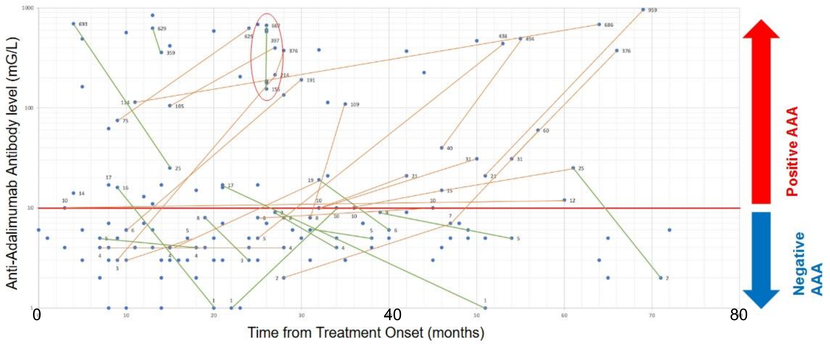



*Figure 4: Relationship between AAA Level and Treatment Onset Time. Orange line indicates an increase in AAA levels and green line indicates a decrease in AAA over time.*

7/34 (20.6%) CYP demonstrated large fluctuations in AAA levels (range: 13-522mG/L) despite no changes to regular medications; 1 CYP had a level of 677mG/L which decreased to 155mG/L one week later, despite no change to treatment - the reason for this is unknown.

There was no demonstrable direct correlation between AAA level and time from treatment onset; some CYP showed high antibody levels within the first 4 months of starting Adalimumab.

34 of CYP had repeat AAA tests:

- 14/34 (41.2%) had increased AAA levels on subsequent testing.
- 14/34 (41.2%) had negligible changes to AAA levels (<10mg/L change).
- 6/34 (17.6%) had decreased AAA levels, and 3/6 (50%) CYP had large reductions in AAA levels (>100mg/L) within weeks.

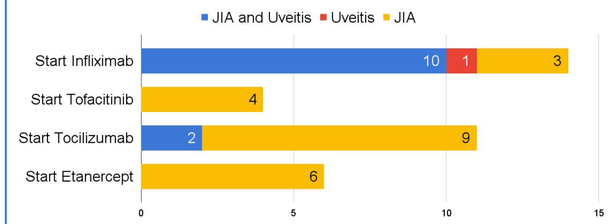



*Figure 5: Changes made to Treatment after Positive AAA Results in CYP with JIA and Uveitis, Uveitis only, and JIA only.*

## Conclusion

There is notable AAA incidence amongst CYP receiving Adalimumab, with no difference found between non-infectious uveitis and JIA cohorts. Concurrent use of DMARD, at full therapeutic dosage, alongside Adalimumab appeared to reduce the risk of developing AAA (52.3% vs 21.1%).

45.5% of those tested had detectable AAA with large variability in antibody level and can develop at any time from starting Adalimumab. Large fluctuations of AAA levels were found at sequential testing in a subgroup, despite no changes made to their treatments.

Those with positive AAA were 3.5x more likely to result in discontinuing Adalimumab compared to those with a negative AAA, 53.1% vs 15.2% due to loss of clinical effectiveness in treating uveitis in CYP.

Collaborative multi-centre study looking into the factors affecting antibody formation and ways to suppress AAA development would be useful given the pivotal role of Adalimumab in controlling inflammatory eye and joint disease.

Decisions regarding Adalimumab discontinuation should be based on comprehensive clinical review, AAA level as well as serum trough drug level.

## References

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