MAR Gastroenterology (2025) 4:06

Case Series

Dose Escalation Reverses Antibody Formation and Loss of Response in Children with Inflammatory Bowel Disease Treated with Adalimumab.

Elmunzir Ali MD* [1], Ahmed Saeed MD [1], Nazira Ibrahim RN [1], Fatma Al-Mudahka MD [1], Anthony Akobeng MD MPH [1], Hatim Abdulrhman [1], Mamoun Elawad MD [1]

1. Division of Gastroenterology, Hepatology and Nutrition, Sidra Medicine, Doha, Qatar.

***Correspondence to:** Dr. Elmunzir Ali, 1Division of Gastroenterology, Hepatology and Nutrition, Sidra Medicine, Doha, Qatar.

Received: 03 Sep 2025

Published: 19 Sep 2025

DOI: https://doi.org/10.5281/zenodo.17337599

Abstract

In this study, we describe 4 children with inflammatory bowel disease (IBD) who had a reversal of adalimumab antibodies (AA) and regained clinical response following dose escalation of adalimumab. We observed in our cases that all of them benefitted from adalimumab dose escalation in terms of achieving clinical and laboratory remission as well as achieving desirable adalimumab trough level and reversal of adalimumab antibodies.

Keywords: *Inflammatory bowel disease, adalimumab antibodies, dose escalation.*

Introduction

Inflammatory bowel diseases (IBD) are a spectrum of chronic gut inflammatory diseases which carry significant variations in pathology location, depth, and behavior.1

Neutralization of the biologic activity of tumor necrosis factor-alpha (TNF-α), using monoclonal antibodies such as adalimumab is an effective strategy for the induction and maintenance of remission in IBD.2 The reported adalimumab antibodies (AA) detection rate after median of 34 weeks in Crohn's patients on maintenance adalimumab therapy is up to 20%.3 These antibodies, together with the accompanying low trough serum drug concentrations, have been implicated as pre-disposing factors for loss of response ending up with switching to another biologic agent.4,5 A potential strategy to reverse AA is adalimumab dose intensification.6

In this study, we describe 4 children with IBD who had a reversal of AA and regained clinical response following dose escalation of adalimumab.

Methodology

This study is a retrospective case series conducted through an electronic medical record (EMR) review. It investigates the occurrence and management of AA in pediatric patients with IBD undergoing adalimumab therapy. The focus is on evaluating the impact of dose escalation on antibody levels and clinical outcomes. Out of 25 patients on adalimumab therapy in our institution, 4 developed AA. These patients were selected for detailed analysis based on their development of AA and the effect of dose escalation.

Ethics, human subjects Issues, conflict of interest and Funding

All authors have no conflicts of interest to declare. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Cases

Patient 1

The first patient was a 9-year-old boy with ulcerative colitis. He was in clinical remission whilst receiving maintenance treatment of adalimumab 20 mg every other week. 3 months after being on this regime, he developed significant symptoms, high inflammatory markers (CRP 40.1 mg/l, reference value <7.5 mg/l, ESR 40 mm/hr, reference value <20 mm/hr) and therapeutic drug monitoring (TDM) revealed a low adalimumab concentration (2 mcg/ml) accompanied by positive AA (72.1 AU/ml, reference value <14 AU/ml). Following double-dose escalation of his treatment to 20 mg weekly, the patient's symptoms improved within 2 months. Six months after dose escalation serum adalimumab concentration had increased significantly to 17.7 mcg/ml (reference >5 mcg/ml) with no AA detected and normal inflammatory markers (CRP 0.9 mg/l, reference value <7.5 mg/l, ESR 10 mm/hr, reference value <20 mm/hr, calprotectin 50 mcg/g, reference value <50 mcg/g).

Patient 2

The second patient was a 17-year-old boy with ileo-colonic Crohn's disease. He was initially treated with Infliximab but developed resistant antibodies for it and was switched over to adalimumab on which he was in clinical remission whilst receiving maintenance treatment of 40 mg every other week. 11 months after being on this treatment, he developed significant symptoms, high markers (ESR 36 mm/hr, calprotectin 1800 mcg/g) and TDM revealed low adalimumab levels (0.8 mcg/ml, reference value >5 mcg/ml) accompanied by positive AA (>500 AU/ml, reference <14 AU/ml). Following double-dose escalation of his adalimumab to 40 mg weekly and within 4 months, adalimumab levels had increased significantly to 20.9 mcg/ml (reference >5 mcg/ml) with no AA detected. The patient became asymptomatic after 2 months of the dose escalation and his markers trended down nicely (ESR 6 mm/hr, calprotectin 186 mcg/g).

Patient 3

The third patient was an 8-year-old girl with very early onset IBD and IgM deficiency who was started on infliximab, however she developed allergic reaction while receiving second dose, thus her treatment was changed to adalimumab. She was started on induction of 40 mg then maintenance 20 mg every other week (EOW). She continued to have symptoms (frequent loose motion and a poor weight gain) along with elevated inflammatory markers (CRP 37.6 mg/l, Platelets 428 *109 /L, ESR 76 mm/hr, calprotectin 543 mcg/g). TDM revealed a low adalimumab concentration (<0.8 mcg/ml; reference value >5 mcg/ml) accompanied by positive AA (>500 AU/ml, reference value <14 AU/ml). Adalimumab dose was escalated to 40 mg EOW, then to 40 mg weekly as she continued to have low adalimumab concentration (<0.8 mcg/ml; reference value >5 mcg/ml) accompanied by positive AA (>500 AU/ml, reference value <14 AU/ml). Following double-dose escalation of her adalimumab, the patient's disease activity improved significantly and within 5 months, serum adalimumab concentration had increased significantly to 26.8 mcg/ml with no anti-adalimumab antibodies detected. There was also notable drop in her markers (CRP 1.1 mg/l, platelets 378 *109 /L, ESR 9 mm/hr, calprotectin 296 mcg/g) and excessive weight gain likely because of symptom resolution and immobility.

Patient 4

The fourth patient was 15-year-old girl with IBD-unclassified (IBD-U). She was maintained on mesalamine and azathioprine after achieving remission with steroids, however she developed new symptoms of rectal bleeding, high fecal calprotectin level (2268 mcg/g; reference value 5-50 mcg/g) and weight loss. She was started on adalimumab with induction of 80 mg followed by maintenance of 40 mg EOW. 2 years after being on this treatment (weekly adalimumab 40 mg), TDM revealed low adalimumab levels (7 mcg/ml, reference value >8 mcg/ml) accompanied with positive AA (16.4 AU/ml, reference <14 AU/ml), she was in clinical remission and low inflammatory markers but persistent elevation in Calprotectin >2500 mcg/g. Following double-dose escalation of her adalimumab to 80 mg weekly, adalimumab levels had increased within 5 weeks to 15.3 mcg/ml (reference >5 mcg/ml) with no AA. Her calprotectin trend down to 146 mcg/g.

Discussion

The annual loss of response in ulcerative colitis patients was reported in a systematic review and meta-analysis as 10% for infliximab and 13% for adalimumab, with higher rates during the first year.7 Higher percentage of 38.5% was reported for pediatric patients with Crohn's disease.8 For Infliximab, this loss of response and development of anti-drug antibodies was associated with low drug level.9 Our study observed that all the patients who required adalimumab dose escalation, were found to have low adalimumab level and developed AA, with loss of clinical response in 4-6 month which similar to other studies.10 Moreover, adalimumab dose escalation (doubling of the dose) lead to clearance of AA and regain of clinical response. Similar to notable studies with variable success rates.3,9,11

Although dose de-escalation after achieving clinical response was successful in 1 notable study,11 it was not assessed in our study, it is something that could be evaluated in the follow up of our patients.

It is not clear why escalating adalimumab dose would have such an effect, but we suggested increasing drug levels to overcome the antibody response, ensuring effective drug concentrations, and potentially altering immune system dynamics to reduce the formation of anti-drug antibodies, thereby restoring clinical efficacy.6,7

Conclusion

Development of anti-adalimumab antibodies is one of the main factors that leads to loss clinical response as well as low drug trough level. Reversal of these antibodies could be achieved by adalimumab dose escalation which leads to achieving desirable trough drug level and regaining of clinical remission.

Acknowledgement

We confirm that informed consent for publication of the case details was obtained from each patient (or from the parent/guardian in the case of a minor).

References

1. Overstock B, Bressler B, Martinez-Lozano H, McGovern D, Silverberg MS. Time to revisit disease classification in inflammatory bowel disease: is the current classification of inflammatory bowel disease

good enough for optimal clinical management? Gastroenterology 2022;162:1370-82.

2. Khoury T, Ilan Y. Introducing patterns of variability for overcoming compensatory adaptation of the immune system to immunomodulatory agents: a novel method for improving clinical response to anti-TNF therapies. Front. Immunol. 2019;10:2726.

3. Baert F, Kondragunta V, Lockton S et al. Antibodies to adalimumab are associated with future inflammation in Crohn's patients receiving maintenance adalimumab therapy: a post hoc analysis of the Karmiris trial. Gut. 2016;65:1126-31.

4. Yanai H, Hanauer SB. Assessing response and loss of response to biological therapies in IBD. Am J Gastroenterol. 2011;106:685-98.

5. Ben-Horin S, Mao R, Chen M. Optimizing biologic treatment in IBD: objective measures, but when, how, and how often? BMC Gastroenterol. 2015;15:178.

6. Ungar B, Kopylov U, Engel T et al. Addition of an immunomodulator can reverse antibody formation and loss of response in patients treated with adalimumab. Aliment Pharmacol Ther. 2016;45:276-82.

7. Savelkoul EHJ, Thomas PWA, Derikx LAAP, den Broeder N, Römkens TEH, Hoentjen F. Systematic review and meta-analysis: loss of response and need for dose escalation of infliximab and adalimumab in ulcerative colitis. Inflamm Bowel Dis. 2023;29:1633-47.

8. Qiu Y, Chen B, Mao R et al. Systematic review with meta-analysis: loss of response and requirement of anti-TNFα dose intensification in Crohn’s disease. J Gastroenterol. 2017;52:535-54.

9. Ben-Horin S, Yavzori M, Katz L, et al. The immunogenic part of infliximab is the F(ab’)2 fragment, but measuring antibodies to the intact infliximab molecule is more clinically useful. Gut. 2011;60:41-8.

10. Taxonera C, Iglesias E, Muñoz F, et al. Adalimumab maintenance treatment in ulcerative colitis: outcomes by prior anti-TNF use and efficacy of dose escalation. Dig Dis Sci. 2017;62:481-90.

11. Van de Vondel S, Baert F, Reenaers C, et al. Incidence and predictors of success of adalimumab dose escalation and de-escalation in ulcerative colitis: a real-world Belgian cohort study. Inflamm Bowel Dis. 2018;24:1099-105.

Medtronic