

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 84994

Title: Dose escalation of adalimumab as a strategy to overcome anti-drug antibodies: A case report of infantile-onset inflammatory bowel disease

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00055521

Position: Peer Reviewer

Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Malaysia

Author's Country/Territory: Italy

Manuscript submission date: 2023-06-07

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-06-22 04:49

Reviewer performed review: 2023-06-29 06:54

Review time: 7 Days and 2 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In this case report, Ancona et al described a case of infantile-onset IBD with Crohn's-like phenotype. The development of anti-adalimumab antibodies leading to a loss of response to ADA treatment was encountered early in the course of disease. By increasing the dose of ADA, the author and team managed to overcome the anti-ADA and rendered the infant in remission again. As the author stated, management of infantile-onset IBD often poses a therapeutic challenge. Successful management of IO-IBD with escalation of biologics offers pediatric IBD specialists an alternative way of managing this challenging condition. I have a few comments: 1. The authors described a successful strategy of overcoming ADA antibody. However, it remains to be seen whether in the medium-term future, a recurrence of ADA antibody may happen again. This needs to be emphasised in the Discussion. 2. Similarly, overcoming formation of ADA antibody leading to clinical response is a short-term strategy. Cognisant of the lack of consensus in the management of IO-IBD, especially in cases of IO-CD, the authors may like to speculate any exit strategy for this child or just maintaining the current strategy for the patient. 3. The whole exome sequencing result is awaiting. What is the

likelihood of elucidating the genetic aspect of this case? If the result is expected to be available in the near future, it would make the manuscript more 'wholesome'. 4. There are some minor issues with the English, which I am sure can be easily overcome by carefully vetting the manuscript again.

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Peer-review model: Single blind

Reviewer's code: 05345731

Position: Peer Reviewer

Academic degree: BSc, MD, MSc

Professional title: Doctor

Reviewer's Country/Territory: Kazakhstan

Author's Country/Territory: Italy

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This review presents a case study focused on the treatment of infantile-onset inflammatory bowel disease (IO-IBD), which often poses challenges due to its aggressive disease course and resistance to standard therapies, necessitating the use of biologic agents. A common issue encountered in patients with IBD receiving biologic treatment is the development of anti-drug antibodies, leading to secondary loss of response. The case study highlights the use of therapeutic drug monitoring (TDM)-guided high-dose anti-tumor necrosis factor (TNF) therapy as a strategy to address the presence of anti-drug antibodies. In this particular case, dose escalation monitoring was employed to overcome the inhibitory effects of anti-drug antibodies and optimize treatment efficacy. The utilization of TDM, a technique that involves measuring drug levels and anti-drug antibody titers in the patient's blood, allowed for personalized treatment adjustments based on individual pharmacokinetic and immunogenic profiles. By closely monitoring drug levels and the presence of anti-drug antibodies, the clinicians were able to guide dose escalation to achieve therapeutic drug concentrations and restore treatment response in the patient with IO-IBD.

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

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Academic degree: DSc, MD, PhD

Professional title: Chief Doctor, Professor

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Author's Country/Territory: Italy

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Reviewer chosen by: Geng-Long Liu

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Reviewer performed review: 2023-07-05 08:26

Review time: 3 Days and 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
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SPECIFIC COMMENTS TO AUTHORS

To diagnose and treat Crohn's disease in infants can be very challenging. Ancona et al are describing a case of Crohn,s disease in a 5 months old infant and how they overcome the development of anti-drug antibodies to adalimumab by increasing the dose of the drug. It can be argued that the concept of restoring the effect of TNFalpha blockers in case of antidrug antibody development by increasing the drug dose is not new - at least not in "adult" gastroenterology. However I find the presented case interesting due to the severity of Crohn's disease in infants and because it may be rather new knowledge for many pediatric gastroenterologists treating these patients. The case is very well presented and the language is excellent. I have in fact only a very few comments.

Introduction: It is stated that TDM has revolutionized the treatment with biologics. I would suggest to use a more modest term. It is correct that TDM can in some cases guide the treatment but the fact is that it has been rather difficult scientifically to prove the value of TDM in the proactive setting. Further diagnostic work-up I presume that the endoscopic examination was an ileocolonoscopy. This should be clarified (not just endoscopy assessment)

Treatment What are the standard dosis of adalimumab when



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treating infants ? It may be known by pediatricians but it would be informative to other readers to add this information Discussion In the present case it was chosen to increase the dose af adalimumab to restore the effect of the drug. It would be informative in the discussion briefly to add information as to what other treatment modalities could be considered (eg other biologics)