World Journal of Gastroenterology

Manuscript

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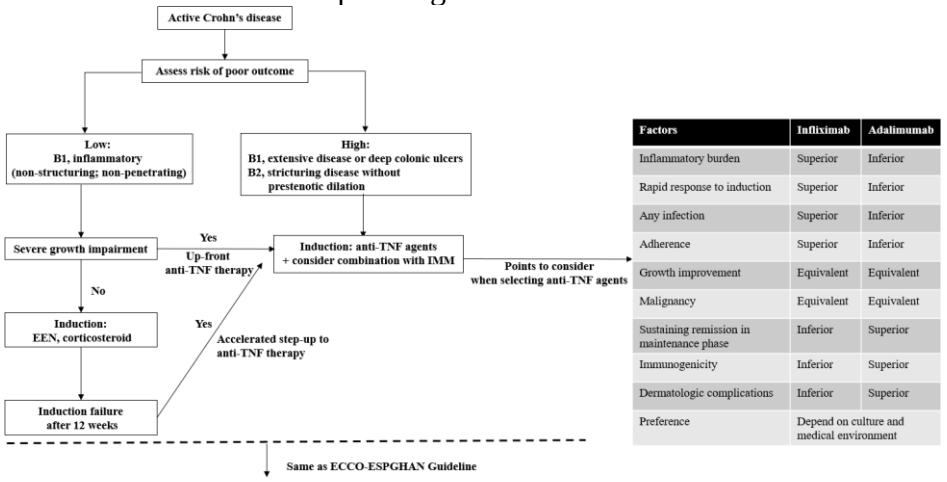
Manuscript title: **Infliximab versus Adalimumab: Points to Consider When Selecting Anti-Tumor Necrosis Factor Agents in Pediatric Patients with Crohn's Disease**

REVIEWERS' COMMENTS TO AUTHOR:

Reviewer:

REVIEWER COMMENT	AUTHOR RESPONSE	PAGE NU-MBER
1. Indications can include at what point the anti TNF to be commenced [within <3 months after diagnosis - higher corticosteroid- and surgery-free remission rates at 1 year than induction with EEN or corticosteroids followed by immunomodulator therapy]	Thank you for your comment. We added the indications for early induction of anti-TNF agents and outcomes of top-down therapy. " However, the guidelines recently published by the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommended early anti-TNF treatment within <3 months after diagnosis for the induction of remission in moderate-to-severe pediatric CD with a high risk of complications such as extensive disease, deep colonic ulcers, perianal disease, stricturing [B2], or penetrating disease [B3], growth impairment, the so-called top-down strategy[20]. The RISK study demonstrated that early induction therapy with anti-TNF agents was associated with higher corticosteroid- and surgery-free remission rated at 1 year compared to induction with EEN and corticosteroids. Kugathasan et al. also reported that early induction therapy with anti-TNF agents significantly lowered the risk of penetrating [B3] complications, however did not seems to reduce the risk of stricturing [B2] complications."	Page 6-7, line 126-136
2. Also, other indicative features to be considered such as those who do not reach clinical [PCDAI <	Thank you for your recommendation. As you pointed out, we added the additional indication of anti-TNF agents.	Page 7, line 136-139

10] and biochemical remission [faecal calprotectin <250 μg/g] after induction with EEN or corticoster oids	"In addition, even in patients with low risk of poor outcome, anti-TNF therapy should be considered in patients with severe growth i mpairment or who have not achieved clinical [Pediatric Crohn's di sease activity index (PCDAI) <10] and biochemical remission [feca l calprotectin <250 μg/g] despite induction therapy with EEN or c orticosteroids."	
3. Any dosing modifications to be done based on the weight / other investigations [children < 30 kg, and those with extensive disease and low serum al bumin levels, require higher induction doses up to 10 mg/kg, shorter dosing intervals, or both, to rea ch target trough levels]	Thank you for your comment. We revised our manuscript as your recommendation and added the indication of dose escalation in induction phase. "Especially, children at risk for accelerated IFX clearance during i nduction [i.e., patients < 30kg, those with extensive disease, and t hose with low serum albumin] require dose escalation to achieve t arget trough levels (TLs) or their first proactive therapeutic drug monitoring (TDM) at the second or third anti-TNF infusion"	Page 8, line 159-162
4. Use of Methotrexate in addition to Azathioprin has been noted in literature.	Thank you for your critical comments. We added information on methotrexate and infliximab combination therapy to the manuscript in terms of anti-drug antibodies development. " For patients starting on IFX, combination therapy with IMM incl uding azathioprine (AZA) and methotrexate (MTX) is recommende d.~ Likewise, it was revealed that the combination of IFX plus MTX had a lower ADA development [4% vs. 20%, *P* = 0.01] an d higher IFX TLs [6.35 μg/mL vs. 3.75 μg/mL, P = 0.08] than IF X monotherapy in the COMMIT trial conducted in adult.[72] ~ Similarly, pediatric studies comparing combination of IFX plus IMM (including AZA and MTX) and IFX monotherapy reported re sults similar to those in adult studies.[59,74,75]"	Page 16-17, line 368~389
5. Practical guidelines of when to combine immun omodulators, end point and outcome can be added [patients with perianal disease, stricturing or penetr ating behaviour, or severe growth retardation shoul d be considered for up-front anti-TNF agents in c ombination with an immunomodulator]	Thank you for your comment. We added the indication of up=front anti-TNF + immunomodulators in our manuscript as your recommendation. " Therefore, up-front anti-TNF agents in combination with IMMs s hould be considered in patients with high risk of poor outcomes s uch as perianal disease, structuring [B2] or penetrating [B3] diseas e behaviour or severe growth impairment."	Page 17, line 387-392
6. Monitoring of drug levels (well within the targ et range and treatment targets) and scopy findings (endoscopic and transmural healing) serve as excel	Thank you for your comment. We agree that TDM, fecal calprotectin and endoscopic findings are considered to be important tools for evaluating endoscopic remission. Therefore, we revised our manuscript	Page 10, line 222-224 Page 13, line 280-283

lent tools.	as follows: “Although the cut-off values of post-induction TLs for regulating t he inflammatory burden at anti-TNF initiation are different for IFX and ADL, it is anticipated that the higher the post-induction TLs, the higher the clinical and endoscopic remission rate.” “As can be inferred from the above studies, clinical remission and endoscopic healing can be achieved when the drug concentrations are sustained above the threshold despite the difference in the cut-off values for withstanding the inflammatory burden in the mainten ance phase between IFX and ADL.” However, as our review article focused the difference between IFX and ADL, not general management of pediatric CD, methods for assessing and predicting endoscopic remission were not described in detail.	
7. Guidelines in the form of algorithms would provid e a quick grasp / summary of the review.	Thank you for your recommendation. As your recommendation, we summarized our manuscript in Figure 3.  	Figure 3

Factors	Infliximab	Adalimumab
Inflammatory burden	Superior	Inferior
Rapid response to induction	Superior	Inferior
Any infection	Superior	Inferior
Adherence	Superior	Inferior
Growth improvement	Equivalent	Equivalent
Malignancy	Equivalent	Equivalent
Sustaining remission in maintenance phase	Inferior	Superior
Immunogenicity	Inferior	Superior
Dermatologic complications	Inferior	Superior
Preference	Depend on culture and medical environment	