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Kyle Gress

Julie A. Bass
Children's Mercy Hospital

Ryan S Funk

Ryan Morrow
Children's Mercy Hospital

Rachel Hasenkamp
Children's Mercy Hospital

See next page for additional authors

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OPINION
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Facing Real-World Challenges of Immunogenicity in Pediatric Inflammatory Bowel Disease

Kyle Gress[1], *Julie A. Bass*[2,3], *Ryan S. Funk*[4], *Ryan P. Morrow*[2,3], *Rachel Hasenkamp*[3] *and Valentina Shakhnovich*[2,3]*

[1] Georgetown University School of Medicine, Washington, DC, United States, [2] Department of Pediatrics, University of Missouri-Kansas City School of Medicine, Kansas City, MO, United States, [3] Children's Mercy Kansas City, Kansas City, MO, United States, [4] Department of Pharmacy Practice, University of Kansas Medical Center, Kansas City, KS, United States

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INTRODUCTION

The advent of biological therapies drastically altered the landscape of inflammatory bowel disease (IBD) treatment, making long-term steroid-free remission possible for thousands of patients living with this chronic inflammatory condition that compromises the integrity of the gastrointestinal mucosa. Unfortunately, up to 65% of patients with IBD develop anti-drug antibodies to biologics (1). This is especially problematic for pediatrics, where treatment options are substantially more limited than for adult patients. Currently, only two biologics have approval from the United States (U.S.) Food and Drug Administration (FDA) for pediatric indications in IBD, anti-TNF-α agents infliximab (IFX), and adalimumab (ADM). The fear of losing these two agents to immunogenicity is very real for the providers and the families of the ∼70,000 children affected by IBD in the U.S. (2).

GENERAL FACTORS CONTRIBUTING TO IMMUNOGENICITY

Immunogenicity, or the development of anti-drug antibodies (ADAs), is a major contributor to loss of treatment response to anti-TNF-α agents. Multiple factors play a role in ADA development and are frequently divided into drug properties, drug pharmacokinetics, and individual patient characteristics.

Drug properties, including compound structure and derivation, formulation and route of administration, play a significant role in immunogenicity. Briefly, compounds that are non-glycosylated, non-pegylated and/or non-human derived (i.e., chimeric) are more likely to elicit an immune response and be recognized as "non-self" by a patient's immune system, triggering ADA formation (3). Similarly, ADA formation is more likely to occur when drug concentrations are low (e.g., trough before the next dose) and the addition of new drug may challenge the host immune system to recognize the drug as "foreign." Known factors associated with low trough concentrations are low drug dose, infrequent dosing, and accelerated drug clearance, observed when inflammatory burden is high and serum albumin (a marker of reduced Fc Receptor-mediated protein recycling) is low (4, 5). Lastly, compared to less concentrated intravenous formulations administered directly into the intravascular space, biologics administered subcutaneously are prone to protein aggregation and more likely to predispose to ADA development due to prolonged contact time with cutaneous and subcutaneous immune cells (3, 6).

Interestingly, when comparing the subcutaneously administered humanized biologic, ADM, to the intravenously administered chimeric biologic, IFX, data from multiple clinical trials, early on, demonstrated similar degree of immunogenicity for these two anti-TNF-α agents in patients

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***Correspondence:**
Valentina Shakhnovich
vshakhnovich@cmh.edu

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with IBD (5). However, a more recent review of the IBD literature suggests that immunogenicity is up to two-fold greater for IFX than ADM (1), mirroring our clinical experience with these agents. Importantly, compared to all other autoimmune, inflammatory conditions treated with anti-TNF-α agents (e.g., rheumatoid arthritis, psoriasis, etc.), immunogenicity to IFX is highest in IBD (7).

IMMUNOGENICITY FACTORS UNIQUE TO IBD

Mucosal erosion of the gastrointestinal epithelium, characteristic of IBD, predisposes patients with IBD to protein losing enteropathy, a condition that results in significant, abnormal protein losses in the stool, including the loss of protein-based therapies (8). In patients with IBD, increased stool losses of IFX have been linked to lower circulating IFX drug concentrations and increased propensity for IFX ADA development, with subsequent therapeutic failure and the need for total parenteral nutrition dependence, surgical intervention, and permanent bowel resection (9). Thus, ADA development in IBD goes beyond clinical manifestations of infusion reaction, serum sickness, and decreased drug efficacy (10), and poses a serious threat to patient morbidity and mortality.

With loss of treatment response estimated as 13% per patient-year of IFX therapy (11), children, who inherently have longer treatment duration than patients with adult-onset disease, are at greatest risk for losing biological treatment options, especially when those options are already limited to anti-TNF-α agents.

IMMUNOGENICITY IN CHILDREN

Although, generally, the pharmacokinetics of anti-TNF-α agents are believed to be similar between adults and children (12–14), data specifically comparing immunogenicity in adult vs. pediatric patients are lacking, and are confounded by the use of different ADA assays across studies. Nevertheless, it is well-established that therapeutic immunogenicity susceptibility varies with age, with highest susceptibility observed in the elderly and the young (3). Anecdotally, younger children also appear to clear anti-TNF-α agents faster, requiring higher, more frequent drug dosing in order to avoid immunogenicity and maintain treatment response (15). One proposed mechanism for this increased drug clearance is age-related differences in metabolic rate (16, 17), which, on a kilocalorie-per-kilogram basis, is highest during childhood.

Unlike conventional low-molecular weight drugs (i.e., $\leq$ 1 kDa), systemic clearance of protein-based therapies depends on proteolytic degradation (i.e., catabolism), determined in large part by metabolic rate, which depends on age, size and body mass composition (18). Highest proteolytic catabolism is expected in young, small, thin children—the typical clinical phenotype of pediatric patients with IBD, whose growth is frequently stunted by disease (19). Indeed, it has been suggested that close therapeutic drug monitoring and ADA surveillance for biologics may be most important for those pediatric patients who weigh less (4).

THERAPEUTIC DRUG MONITORING

In our opinion, aside from medication adherence, therapeutic drug monitoring (TDM) is the single, most critical step for both preventing and overcoming immunogenicity in clinical practice. Clinical trial results from as early as 2014, demonstrate the cost-effectiveness of TDM for anti-TNF-α agents (20) and recent reports in pediatrics provide evidence that close TDM can help not only detect, but also reverse immunogenicity, with appropriate TDM-based dose adjustments (15).

At our center, between 2015 and 2018, TDM was performed 677 times for the ∼350 children receiving anti-TNF-α therapy for IBD (21). Forty-five children (13%) were identified to have ADAs, and anti-TNF-α therapy was salvaged in 33% (14 IFX, 1 ADM) by increasing drug dose, shortening the dosing interval, and/or adding an immunomodulator to clear ADAs, as described by others (22). The other 30 children required prior authorization and appeals to third-party payers (e.g., letters of medical necessity, peer-to-peer communications) to secure off-label treatment with agents other than anti-TNF-α (e.g., ustekinumab, vedolizumab). To date, we have not detected immunogenicity with these newer agents.

ADA DETECTION PLATFORMS

In practice, the issue of testing for immunogenicity as part of proactive TDM is complicated by the availability of multiple ADA detection platforms. The intricacies of different ADA assay types are often unfamiliar to medical providers, with assay selection sometimes driven by third-party payer preference, or payment-support programs available to patients, especially if paying out of pocket. For example, based on financial considerations, providers at our institution alternate ordering ligand binding immunoassays, homogenous mobility shift and gene-reporter assays for therapeutic drug monitoring of biologics.

Of the currently available assays, providers are likely most familiar with ligand binding immunoassays (i.e., EIA, ELISA, ECLIA); however, there have been a number of novel ADA detection platforms developed, including homogenous mobility shift assays, gene-reporter assays, surface plasmon resonance, bio-layer interferometry, and mass spectrometry-based approaches (23). Although the overall correlation across these assays is acceptable (24), a major challenge in interpreting assay comparability is the use of different analytical standards and outcome measures that make interpretation of each assay highly dependent on the individual assay utilized (25). A major source for the observed variation amongst assays is the positive controls used in the assay, which commonly represent polyclonal ADAs developed through immunization of different animal species with the biological agent. The lack of uniform controls and reagents limits the comparability of results across assays and reveals the need for the development of ADA "standards" for the calibration and comparison of the various assays. This issue is perhaps best illustrated by comparing immunogenicity data from biosimilar development programs for IFX, which, overall, have failed to demonstrate a significant difference in the incidence of immunogenicity between the biosimilar and the innovator

product. However, if one reviews the actual reported ADA incidence from study to study, it varies from 26 to 60%, based on the immunogenicity assay used (26–29). One consequence of the deficiency in uniform assay standards is dissemination of assay-specific treatment recommendations (25), which are not always clinically useful or applicable.

An added challenge in immunogenicity interpretation is the issue of drug tolerance, or unreliable ADA detection when free drug is present in the blood sample being tested. Some ADA platforms have improved the drug tolerance of immunoassays by adding an acid dissociation step to liberate ADAs bound to drug, while others have not, making comparisons across assays difficult.

Another important consideration in evaluating the clinical implications of immunogenicity is the differentiation of neutralizing vs. non-neutralizing ADAs. The differentiation is based on the ability of an ADA to directly interfere with the binding site of the biological agent, preventing its intended function at the drug target and, effectively, neutralizing drug activity/efficacy. Although neutralizing ADAs are believed to have the most clinical relevance, as they affect drug pharmacodynamics, non-neutralizing ADAs may also have significant impact on pharmacodynamics through pharmacokinetic alterations that result in lower drug exposure, secondary to reduced drug bioavailability and/or enhanced drug clearance mediated by ADA binding (30). To our knowledge, differentiation of ADA types is not routinely communicated in clinical immunogenicity reports. Although this information may be of benefit for clinical decision making, it could potentially drive up assay costs as three separate, validated methods would need to be applied in a tiered fashion to provide meaningful drug concentration, neutralizing and non-neutralizing ADA data.

Lastly, although the turn-around time for immunogenicity reports has improved greatly, results may still take up to 5 business days and point-of-care platforms, though available (31), are not yet integrated into routine clinical care.

DISCUSSION

In summary, despite the outlined evidence that pediatric patients with IBD are at increased risk for immunogenicity, and the knowledge that approved biologic treatments for children are limited to anti-TNF-α, clinicians face many challenges in implementing judicious, proactive therapeutic drug monitoring to detect immunogenicity in every-day IBD practice. A common barrier to implementing TDM is third-party payers denials to cover testing (21), despite the growing number of publications describing the clinical benefit and cost-effectiveness of TDM, specifically for anti-TNF-α therapy in IBD. (20, 32, 33) In practice, assay selection for TDM is often driven by financial considerations, and multiple ADA platforms may be used interchangeably for a given patient, confounding both the reliability and interpretability of test results.

In our opinion, uniformly validated ADA detection methods (e.g., standard reagents and positive controls), and provider education regarding limitations of different ADA assay types, could facilitate comparability of results across the different ADA platforms available. While, language regarding treat-to-target approaches and routine ADA assessment in the drug label, along with integration of point-of-care assays into clinical practice, could facilitate accessibility and affordability of TDM and ADA surveillance for patients and providers, preserving drug efficacy over time.

AUTHOR CONTRIBUTIONS

VS conceived the original idea for manuscript. JB, RF, RH, and VS provided expert opinion. KG, JB, RF, RM, RH, and VS conducted pertinent literature review, wrote and edited the manuscript, reviewed, and approved the final manuscript.

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REFERENCES

1. Vermeire S, Gils A, Accossato P, Lula S, Marren A. Immunogenicity of biologics in inflammatory bowel disease. *Ther Adv Gastroenterol.* (2018) 11:1–13. doi: 10.1177/1756283X17750355
2. Rosen MJ, Dhawan A, Saeed SA. Inflammatory bowel disease in children and adolescents. *JAMA Pediatr.* (2015) 169:1053–60. doi: 10.1001/jamapediatrics.2015.1982
3. U.S. HHS, FDA. *Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products.* US Dep Heal Hum Serv Food Drug Adm. (2014). Available online at: www.fda.gov/media/85017/download
4. Fasanmade AA, Adedokun OJ, Ford J, Hernandez D, Johanns J, Hu C, et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. *Eur J Clin Pharmacol.* (2009) 65:1211–28. doi: 10.1007/s00228-009-0718-4
5. Ordás I, Mould DR, Feagan BG, Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. *Clin Pharmacol Ther.* (2012) 91:635–46. doi: 10.1038/clpt.2011.328
6. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. *J Pharm Sci.* (2004) 93:2645–68. doi: 10.1002/jps.20178
7. Strand V, Balsa A, Al-Saleh J, Barile-Fabris L, Horiuchi T, Takeuchi T, et al. Immunogenicity of biologics in chronic inflammatory diseases: a systematic review. *Biodrugs.* (2017) 31:299–316. doi: 10.1007/s40259-017-0231-8
8. Levitt DG, Levitt MD. Protein losing enteropathy: comprehensive review of the mechanistic association with clinical and subclinical disease states. *Clin Exp Gastroenterol.* (2017) 10:147–68. doi: 10.2147/CEG.S136803

9. Zitomersky NL, Atkinson BJ, Fournier K, Mitchell PD, Stern JB, Butler MC, et al. Antibodies to infliximab are associated with lower infliximab levels and increased likelihood of surgery in pediatric IBD. *Inflamm Bowel Dis.* (2015) 21:307–14. doi: 10.1097/MIB.0000000000000284
10. Schellekens H. Factors influencing the immunogenicity of therapeutic proteins. *Nephrol Dial Transplant.* (2005) 20:3–9. doi: 10.1093/ndt/gfh1092
11. Gisbert JP, Panés J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. *Am J Gastroenterol.* (2009) 104:760–7. doi: 10.1038/ajg.2008.88
12. AbbVie HUMIRA (adalimumab) injection, solution for subcutaneous use. *Handb Ther Antibodies.* (2008) 3:696–732. doi: 10.1002/9783527619740.ch27
13. Janssen Biotech Inc. *REMICADE (Infliximab) Lyophilized Concentrate for Injection, for Intravenous Use Product Label,* Vol. 50 (1998). p. 1–25.
14. Fasanmade AA, Adedokun OJ, Blank M, Zhou H, Davis HM. Pharmacokinetic properties of infliximab in children and adults with crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. *Clin Ther.* (2011) 33:946–64. doi: 10.1016/j.clinthera.2011.06.002
15. Kang E, Khalili A, Splawski J, Moses J. Reversal of immunogenicity in pediatric inflammatory bowel disease patients receiving anti-tumor necrosis factor medications. *Pediatr Gastroenterol Hepatol Nutr.* (2018) 21:329–35. doi: 10.5223/pghn.2018.21.4.329
16. Goldman J, Davis H, Zhou H, Kearns G. Infliximab clearance in children: potential association with resting energy expenditure. *Ann Paediatr Rheumatol.* (2012) 1:120–5. doi: 10.5455/apr.042120121033
17. Lee SK. Resting energy expenditure and the clearance of therapeutic proteins in pediatric subjects. *Pharmacology.* (2014) 93:225–8. doi: 10.1159/000362562
18. Butte NF, Moon JK, Wong WW, Hopkinson JM, Smith EO. Energy requirements from infancy to adulthood. *Am J Clin Nutr.* (1995) 62:1047S−52S. doi: 10.1093/ajcn/62.5.1047s
19. Wang W, Wang E, Balthasar J. Monoclonal antibody pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther.* (2008) 84:548–58. doi: 10.1002/9780470485408.ch19
20. Steenholdt C, Brynskov J, Thomsen OØ, Munck LK, Fallingborg J, Christensen LA, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. *Gut.* (2014) 63:919–27. doi: 10.1136/gutjnl-2013-305279
21. Shakhnovich V, Meibohm B, Rosenberg A, Kierzek AM, Hasenkamp R, Funk RS, et al. Immunogenicity in clinical practice and drug development : when is it significant? *Clin Transl Sci.* (2019) 13, 219–23. doi: 10.1111/cts.12717
22. Kothari MM, Nguyen DL, Parekh NK. Strategies for overcoming anti-tumor necrosis factor drug antibodies in inflammatory bowel disease: case series and review of literature. *World J Gastrointest Pharmacol Ther.* (2017) 8:155–61. doi: 10.4292/wjgpt.v8.i3.155
23. Vande Casteele N. Assays for measurement of TNF antagonists in practice. *Frontline Gastroenterol.* (2017) 8:236–42. doi: 10.1136/flgastro-2016-100692
24. Steenholdt C, Ainsworth MA, Tovey M, Klausen TW, Thomsen OO, Brynskov J, et al. Comparison of techniques for monitoring infliximab and antibodies against infliximab in Crohn's disease. *Ther Drug Monit.* (2013) 35:530–8. doi: 10.1097/FTD.0b013e31828d23c3
25. Bendtzen K. Immunogenicity of anti-TNF-α biotherapies: II. Clinical relevance of methods used for anti-drug antibody detection. *Front Immunol.* (2015) 6:109. doi: 10.3389/fimmu.2015.00109
26. Yoo DH, Racewicz A, Brzezicki J, Yatsyshyn R, Arteaga ET, Baranauskaite A, et al. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. *Arthritis Res Ther.* (2016) 18:1–12. doi: 10.1186/s13075-016-0981-6
27. Smolen JS, Choe JY, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, et al. Comparing biosimilar SB2 with reference infliximab after 54 weeks of a double-blind trial: clinical, structural and safety results. *Rheumatology.* (2017) 56:1771–9. doi: 10.1093/rheumatology/kex254
28. Alten R, Batko B, Hala T, Kameda H, Radominski SC, Tseluyko V, et al. Randomised, double-blind, phase III study comparing the infliximab biosimilar, PF-06438179/GP1111, with reference infliximab: Efficacy, safety and immunogenicity from week 30 to week 54. *Open Hear.* (2019) 6:1–9. doi: 10.1136/rmdopen-2018-000876
29. Lila AM, Mazurov VI, Denisov LN, Nesmeyanova OB, Ilivanova EP, Eremeeva AV, et al. A phase III study of BCD-055 compared with innovator infliximab in patients with active rheumatoid arthritis: 54-week results from the LIRA study. *Rheumatol Int.* (2019) 39:1537–46. doi: 10.1007/s00296-019-04359-9
30. Gunn GR III, Sealey DCF, Jamali F, Meibohm B, Ghosh S, Shankar G. From the bench to clinical practice: understanding the challenges and uncertainties in immunogenicity testing for biopharmaceuticals. *Clin Exp Immunol.* (2016) 184:137–46. doi: 10.1111/cei.12742
31. Curci D, Lucafo M, Cifu A, Bramuzzo M, Martelossi S, Favretto D, et al. Determination of serum infliximab concentration by point-of care devices in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* (2019) 69, 474–5. doi: 10.1097/MPG.0000000000002410
32. Mitrev N, Vande Casteele N, Seow CH, Andrews JM, Connor SJ, Moore GT, et al. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. *Aliment Pharmacol Ther.* (2017) 46:1037–53. doi: 10.1111/apt.14368
33. Vasudevan A, Gibson PR, Van Langenberg DR. Systematic review: cost-effective strategies of optimizing anti-tumor necrosis and immunomodulators in inflammatory bowel disease. *Inflamm Bowel Dis.* (2019) 25:1462–73. doi: 10.1093/ibd/izy399

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