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Direct transition from rapid-infusion originator to rapid-infusion biosimilar tumor necrosis factor inhibitor in children with inflammatory bowel disease: A case series

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Purpose: Biosimilar tumor necrosis factor inhibitors (b-TNFi) reduce healthcare costs and maintain equal efficacy when compared to their originator counterparts (o-TNFi). Current practice is to start patients on a slower standard infusion rate during the initial transition from an o-TNFi to a b-TNFi. There is a knowledge gap around switching from rapid originator infusion to rapid biosimilar infusion in the pediatric inflammatory bowel disease (IBD) population.

Summary: We present a case series of 8 pediatric patients with IBD who were switched from a rapid-infusion o-TNFi to a rapid-infusion b-TNFi from 2016 through 2022. Our primary interest was safety, which we evaluated based on the occurrence of infusion reactions or need for new premedications within the first 6 months of starting a b-TNFi. We also examined effectiveness through the incidence of IBD-related hospitalizations, TNFi failure, and need for co-medication or dose escalation over the same period. In our cohort, 4 patients had Crohn's disease and 4 had ulcerative colitis. All patients were switched to a biosimilar for nonmedical reasons. During the follow-up period, no patients had infusion reactions necessitating new premedications, serious adverse events, or medication nonresponse.

Conclusion: Patients who directly transitioned from a rapid-infusion o-TNFi to a rapid-infusion b-TNFi did not experience serious adverse events. Given the fiscal and patient experience advantages of rapid-rate infusions, larger studies are needed to consider a change in practice.

Keywords: biologics, biosimilar agents, infliximab, infliximab-dyyb, pediatric inflammatory bowel disease.

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Inflammatory bowel disease (IBD) is one of the most expensive gastrointestinal conditions to treat, placing tremendous financial strain on healthcare systems around the globe.[1] In the era of biologic therapies, the cost burden has shifted from inpatient to outpatient management; however, significant social and quality-of-life impacts on patients remain.[2,3] As healthcare providers and payors team up to provide cost-effective, patient-centered care, further research is needed to optimize accelerated infusion protocols for biosimilar agents. Biosimilar tumor necrosis factor inhibitors (b-TNFi) have drastically reduced treatment costs while maintaining equivalent efficacy in pediatric and adult cohorts.[4-6] Similarly, rapid-infusion protocols that decrease the administration time for TNFi medications from 120 to 60 minutes have improved healthcare resource utilization, therapy adherence, patient satisfaction, and infusion center throughput.[7-11] Large studies in children and adults have shown that rapid TNFi infusions are safe and well tolerated without increased risk of infusion reactions or adverse events.

International guidelines support the transition from an originator TNFi (o-TNFi) to a b-TNFi to promote

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broader access to therapy.[9-14] During these transitions, patients maintained on rapid o-TNFi infusions (60 minutes) are commonly reverted to a b-TNFi infusion with a standard rate (120 minutes), although there are limited data to validate this conservative approach. Previous studies have demonstrated no increase in the incidence of infusion reactions when following a transition protocol converting patients to a rapid rate after receiving and tolerating a minimum of 3 standard-length infusions.[15] To our knowledge, no study has reported the efficacy of direct transition to a 60-minute b-TNFi infusion in the pediatric population.

This case series delineates the experience of a single center when directly transitioning pediatric patients from a rapid-infusion o-TNFi to a rapid-infusion b-TNFi and serves as a pilot study to evaluate the safety and effectiveness of this novel approach. We included children and young adults (<21 years old) with IBD who were transitioned from rapid o-TNFi infusions directly to rapid b-TNFi infusions from 2016 through 2022. All patients were followed at the Pediatric Inflammatory Bowel Disease Center at the University of California San Francisco (UCSF) Benioff Children's Hospital, and information included in our study was extracted from the electronic health record. We excluded patients who were transitioned to a standard-rate infusion of b-TNFi, even if they were later started on a rapid-infusion biosimilar. Data were stored in a secure REDCap server. The UCSF Benioff Children's Hospital institutional review board approved data collection for this study (13-12137).

Case descriptions

Case 1. Case 1 was a 15-year-old female with pan-colonic ulcerative colitis (UC) without previous severe episodes. She was diagnosed at age 13, started on infliximab, and quickly achieved clinical remission in the same year. After 9 months on o-TNFi therapy, she was switched from infliximab 10 mg/kg every 8 weeks to infliximab-dyyb 10 mg/kg every 8 weeks. Her infliximab-dyyb level after switching was 7.7 µg/mL (goal of >5 µg/mL). In the 6 months after the switch, she did not have an infusion reaction, require a change in premedications, have a hospitalization for a flare, or return to the standard infusion length. Findings for all cases are presented in Table 1 and Table 2.

Case 2. Case 2 was a 17-year-old male with inflammatory Crohn's disease (CD) without growth delay. He was diagnosed at age 11, started on infliximab at age 13, and achieved clinical remission at age 16. After 41 months on o-TNFi therapy, he was switched from infliximab 10 mg/kg every 8 weeks to infliximab-dyyb 10 mg/kg every 8 weeks. His infliximab-dyyb level after switching was 8.5 µg/mL. In the 6 months after the switch, he was continued on rapid infusions and did not have any infusion reactions, changes in premedications, or IBD-related hospitalizations.

Case 3. Case 3 was a 19-year-old female with inflammatory CD with growth delay and perianal disease. She was diagnosed at age 16, was started on infliximab at age 16, and achieved clinical remission at age 17. After 28 months on o-TNFi therapy, she was switched from infliximab 10 mg/kg every 8 weeks to infliximab-dyyb 10 mg/kg every 8 weeks. Her infliximab-dyyb level after switching was 9.0 µg/

KEY POINTS

- Rapid infusions of tumor necrosis factor inhibitors improve patient satisfaction, decrease nursing time required, and increase infusion center throughput.
- In this case series pilot study, direct transition from rapid-infusion infliximab to rapid infusion with the biosimilar infliximab-dyyb was not associated with increased risk of adverse events, and no patient had medication loss of response within the 6-month follow-up period.
- Larger studies are needed to validate the safety and efficacy of this protocol.

Table 1. Primary Endpoints

Endpoint	Patients (N = 8)
Infusion reaction within first 6 months of starting biosimilar, %	0
New need for premedications, %	0

Table 2. Medication Effectiveness

Parameter	Patients (N = 8)	*P* value
Infliximab level before switch, median (IQR), µg/mL	13.3 (8.6-23.6)	0.11
Infliximab-dyyb level after switch, median (IQR), µg/mL	8.1 (7.5-9.3)	
IBD-related hospitalizations, %	0	
TNFi loss of response, %	0	
Changes in IBD therapy[a], %	0	
TNFi dose escalation, %	0	

Abbreviations: IBD, inflammatory bowel disease; IQR, interquartile range; TNFi, tumor necrosis factor inhibitor.
[a]Defined as initiation of corticosteroids, thiopurines, methotrexate, or new biologic therapy within 6 months of starting biosimilar infusions.

mL. In the 6 months after the switch, she was continued on rapid infusions and did not have any infusion reactions, changes in premedications, or IBD-related hospitalizations.

Case 4. Case 4 was a 21-year-old male with inflammatory CD without growth delay. He was diagnosed at age 16, started on infliximab at age 16, and achieved clinical remission at age 17. After 55 months on o-TNFi therapy, he was switched from infliximab 9 mg/kg every 6 weeks to infliximab-dyyb 9 mg/kg every 6 weeks. His infliximab-dyyb level after switching was 7.4 µg/mL. In the 6 months after the switch, he was continued on rapid infusions and did not have any infusion reactions, changes in premedications, or IBD-related hospitalizations.

Case 5. Case 5 was a 14-year-old male with pan-colonic UC with previous severe episodes. He was diagnosed at age 9, started on infliximab at age 9, and achieved clinical remission at age 10. After 58 months on o-TNFi therapy, he was switched from infliximab 9 mg/kg every 8 weeks to infliximab-dyyb 9 mg/kg every 8 weeks. His infliximab-dyyb level after switching was 14.3 µg/mL. In the 6 months after the switch, he was continued on rapid infusions and did not have any infusion reactions, changes in premedications, or IBD-related hospitalizations.

Case 6. Case 6 was a 19-year-old female with stricturing CD with growth delay. She was diagnosed at age 13, started on infliximab at age 13, and reached clinical remission at age 15. After 56 months on o-TNFi therapy, she was switched from infliximab 10 mg/kg every 7 weeks to infliximab-dyyb 10 mg/kg every 7 weeks. Her infliximab-dyyb level after switching was 7.5 µg/mL. In the 6 months after the switch, she was continued on rapid infusions and did not have any infusion reactions, changes in premedications, or IBD-related hospitalizations.

Case 7. Case 7 was a 10-year-old male with pan-colonic UC without previous severe episodes. He was diagnosed at age 7, started on infliximab, and quickly achieved clinical remission in the same year. After 23 months on o-TNFi therapy, he was switched from infliximab 10 mg/kg every 7 weeks to infliximab-dyyb 10 mg/kg every 7 weeks. His infliximab-dyyb level after switching was 10.3 µg/mL. In the 6 months after the switch, he was continued on rapid infusions and did not have any infusion reactions, changes in premedications, or IBD-related hospitalizations.

Case 8. Case 8 was a 20-year-old female with pan-colonic UC with previous severe episodes. She was diagnosed at age 14, started on infliximab at age 15, and reached clinical remission at age 16. After 57 months on o-TNFi therapy, she was switched from infliximab 12 mg/kg every 7 weeks to infliximab-dyyb 12 mg/kg every 7 weeks. Her infliximab-dyyb level after switching was 6.3 µg/mL. In the 6 months after the switch, she was continued on rapid infusions and did not have any infusion reactions, changes in premedications, or IBD-related hospitalizations.

Case summary. Of 124 pediatric patients with IBD on TNFi therapy at our center, 8 children (4 with CD and 4 with UC) met the inclusion criteria. The mean age at diagnosis was 14 years (range, 10-21 years), and 50% were female (Table 3). All patients were switched from the o-TNFi infliximab to the b-TNFi infliximab-dyyb and were switched to a biosimilar for nonmedical reasons. According to their Paris classification, all patients with UC had pancolitis, with 50% having a history of a severe episode.[16] All patients with CD had ileocolonic involvement, and 75% had disease proximal to the ligament of Treitz (Paris classification of L3 and L4a, respectively).[16] The majority of patients with CD had inflammatory disease, with one patient having stricturing disease.

We used Wilcoxon matched-pairs signed-rank tests to evaluate within-person changes in TNFi trough levels. The median infliximab trough level directly before the switch was 13.3 µg/mL, while the median infliximab-dyyb trough level after the switch was 8.1 µg/mL (P = 0.11). In keeping with consensus guidelines recommending a goal TNFi trough level of 3 to 7 µg/mL,[17] 100% of patients included in this case series had trough levels above the goal of 5 µg/mL after switching to the biosimilar.

In the 6 months after starting rapid-infusion biosimilar therapy, no patients had new premedication requirements, infusion reactions, or resumption of standard-length infusion times. No patients had IBD-related hospitalizations, medication loss of response, thiopurine or steroid initiation, TNFi dose escalation, or a need to switch to a different biologic.

Discussion

Our case series pilot study is the first to show that direct transition from rapid-infusion o-TNFi to rapid-infusion b-TNFi therapy in the pediatric population is not associated with increased risk of serious adverse events or medication loss of response. These results are congruent with established safety data. This study serves as hypothesis-generating work for future larger trials. As additional biosimilar agents become available, these studies are essential in optimizing a cost-effective and patient-centric approach that bolsters well-being and improves compliance with chronic disease management.

Accelerated TNFi infusion protocols significantly decrease patient time in the hospital setting and have the potential to directly impact patient satisfaction and aid in treatment adherence. Shorter infusions are associated with higher patient-reported measures of well-being,[18] while treatment-related constraints, including time spent at an infusion center, are predictive of treatment noncompliance.[19] Poor adherence to biologic therapy can result in hospitalizations, steroid use, treatment failure, and higher healthcare costs.[20]

Rapid-infusion TNFi regimens also carry system-wide financial implications. Faster infusions decrease nursing workload and improve infusion center throughput by 50%.[15] In addition to a 35% decrease

Table 3. Patient Characteristics

Characteristic	Patients (N = 8)
Race, No. (%)	
Caucasian	6 (75)
Asian	2 (25)
Ethnicity, No. (%)	
Non-Hispanic	8 (100)
Female, No. (%)	4 (50)
Commercial insurance, No. (%)	8 (100)
Diagnosis, No. (%)	
Ulcerative colitis	4 (50)
Crohn's disease	4 (50)
Age at diagnosis, mean (SD), years	14 (3.0)
Age at starting biosimilar, mean (SD), years	16.6 (3.0)
UC Paris classification, No. (%)	
Extent: pancolitis (E4)	4 (100)
Severity (S1)	2 (50)
CD location (Paris classification), No. (%)	
L3: ileocolonic	4 (100)
L4a: disease proximal to ligament of Treitz	3 (75)
CD behavior (Paris classification), No. (%)	
Inflammatory	3 (75)
Stricturing, nonpenetrating	1 (25)
Hospital-based treatment facility[a], No. (%)	8 (100)
Reason for switching (nonmedical), No. (%)	8 (100)
Duration on infliximab, median (IQR), months	48 (27-56)
Infliximab/infliximab-dyyb laboratory level, No. (%)	
Prometheus	3 (37)
ARUP	5 (62)
Baseline co-medications[b], %	0

Abbreviations: CD, Crohn's disease; IQR, interquartile range; UC, ulcerative colitis; ARUP, Associated Regional and University Pathologists.
[a]One patient received home and hospital-based treatment.
[b]Co-medications included oral corticosteroids and immunomodulators.

in healthcare costs for b-TNFi vs o-TNFi,[15] recent data have indicated a 50% reduction in nursing costs following transition to a rapid infusion.[21] Indeed, non–drug-related expenses associated with TNFi infusion may even exceed the cost of the TNFi itself, with one analysis finding that the costs for personnel required to administer TNFi amounted to 77% of the total healthcare cost for each infusion.[22] The decreased cost associated with rapid TNFi infusion has been corroborated across other chronic diseases.[23,24]

We acknowledge the limitations of our study, mostly stemming from its retrospective nature and limited sample size. Because infusion reactions to TNFi occur in less than 10% of patients, it is possible that we did not capture an event.[25] It is also possible that future adverse events or loss of response could occur after our 6-month follow-up period, although any such events would be less likely to be related to the transition to a rapid infusion. Our case study design is dependent on complete and accurate documentation in the electronic medical record.

Conclusion

Given the fiscal and patient experience advantages of rapid-rate infusions, additional case series and larger prospective studies are needed to further evaluate the safety and patient perceptions of a direct transition when switching to a biosimilar. Such work will be essential to developing future infusion protocols for pediatric IBD.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Disclosures

Dr. Patel is a fellow physician on a National Institutes of Health T32 grant. The research is supported by grant T32-DK007762. The remaining authors have declared no potential conflicts of interest.

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