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Brief Report

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A Real-World Comparison of Drug Trough Levels between Patients Experiencing a Secondary Nonimmune Loss of Response and Those Maintaining a Response to Infliximab on Long-Term Maintenance Therapy for Inflammatory Bowel Disease

Michael Farber[a, b] Jeremy Polman[c] Nina Kohn[b] Vincent Chua[b]
Arun Swaminath[c] Keith Sultan[b]

[a]College of Osteopathic Medicine, New York Institute of Technology, Old Westbury, NY, USA; [b]Northwell Health North Shore University Hospital, Manhasset, NY, USA; [c]Northwell Health, Lenox Hill Hospital, New York, NY, USA

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Abstract
Introduction: A secondary loss of response (LOR) to infliximab (IFX) therapy for inflammatory bowel disease (IBD) is typically associated with low IFX trough levels, often with high levels of neutralizing antibodies to IFX (ATI). A small subset of patients on long-term therapy experience a "nonimmune" LOR, without ATI and with desired IFX trough levels ≥5 μg/mL, regarded as a LOR to the mechanism of action of IFX. However, this currently accepted IFX goal level is largely derived from observations of patients within the first year of therapy and may not apply to those on treatment beyond 1 year. ***Methods:*** Retrospective review of all IBD patients receiving IFX infusions for ≥12 months with at least 1 IFX trough and ATI measurement beyond 12 months was conducted. Chart review of all patients with absent ATI and an IFX trough ≥5 μg/mL classifies as LOR versus non-LOR based on physician assessment, with a comparison of IFX troughs between the two groups. ***Results:*** Of 167 patients using IFX ≥12 months, 13 (7.8%) experienced a nonimmune secondary LOR. The mean duration of IFX use was over 3 years for both LOR and non-LOR patients. The mean IFX trough for those with LOR was greater than for those without LOR, 18.5 μg/mL versus 13.1 μg/mL, $p = 0.110$. ***Conclusion:*** Our results did not demonstrate lower IFX levels among patients experiencing secondary nonimmune LOR on long-term therapy. Our results do not redefine the therapeutic IFX goal levels for those patients on long-term therapy and suggest that underdosing of IFX is not the cause of secondary LOR.

karger@karger.com
www.karger.com/iid

Correspondence to:
Michael Farber, mfarbe01@nyit.edu

Introduction

Infliximab (IFX) was approved for Crohn's disease (CD) treatment in 1998 and for ulcerative colitis (UC) in 2005, and targets the pro-inflammatory cytokine TNF-α [1]. IFX is rapidly effective, with over 50% achieving response by week 8 and almost 40% maintaining remission at week 52 [1, 2]. Those not responding to initial IFX treatment are regarded as primary nonresponders. It is believed that these patients have a mechanism of inflammation less related to TNF-α activity or that higher doses of IFX may be required to induce an initial response.

For those patients initially responding to IFX, many will subsequently suffer a "secondary" loss of response (LOR). The mechanism of this secondary LOR is definable by blood testing for IFX drug trough and antibody to IFX (ATI) levels. The currently accepted therapeutic IFX minimum trough is 5.0 μg per mL (μg/mL) [3]. For a low IFX trough level in the setting of high ATI, the mechanism of LOR is regarded as immune mediated, and guidelines suggest switching to a non-IFX anti-TNF-α to bypass these drug-specific ATI. Conversely, patients with a secondary LOR demonstrating a low IFX trough <5.0 μg/mL and an absence of a high ATI are not immediately regarded as refractory to the anti-TNFα mechanism of IFX, and guidelines recommend increasing the dose of IFX to restore an effective trough level [3, 4].

Another scenario of secondary LOR includes those patients with therapeutic IFX trough levels ≥5 μg/mL and without high ATI. For these patients, it is believed that TNF-α is no longer the mechanism driving their inflammation, and guidelines recommend a switch to an entirely different class of inflammatory bowel disease (IBD) treatment. It is notable however that the minimum goal IFX trough level of ≥5 μg/mL guiding this recommendation is derived from retrospective patient observations within the first year of therapy [5–8]. As such, the current goal IFX trough level of ≥5 μg/mL may not be valid for IFX patients failing treatment at time points beyond 1 year. We investigated all patients on >12 months of IFX treatment who maintained an IFX level >5.0 μg/mL. Patients with LOR despite an adequate trough were regarded as having an IFX mechanism-related LOR and were compared to those maintaining clinical response. Our goal was to determine if those patients defined as experiencing an IFX mechanism LOR had lower absolute IFX trough levels than those maintaining clinical response. We hypothesized that observing a difference between the two groups would suggest an alternate/higher goal IFX trough level for those patients on long-term treatment.

Methods

Patient Selection and Data Extraction

A retrospective analysis of outpatients with IBD who were treated within the Northwell Health system was conducted with IRB approval. A bioinformatics search was completed identifying IBD outpatients by ICD9 and ICD10 codes for CD, UC, or IBD unspecified between January 09, 2002, and January 09, 2022, and with a minimum of 12 months of IFX therapy, confirmed by manual chart review. Inclusion of patients with a minimum of 12 months of IFX therapy was independent of response status at 1 year. Patients with an IFX level <5.0 μg/mL were excluded as such levels did not meet the current threshold for judging IFX mechanism response or LOR. All patients included for analysis were required to demonstrate an IFX trough ≥5 μg/mL on their last documented IFX trough level. Patients were then excluded if their last documented ATI was as high, defined as >1,000 ng/mL by the Labcorp®-based assay, or >3.1 U/mL by the Prometheus®-based assay, respectively.

Patients meeting these criteria were then defined as LOR versus non-LOR by physician global assessment. LOR was defined as either any patient who discontinued IFX for IBD-related complaints or those who temporarily continued IFX but were experiencing complaints regarded as IBD related. Non-LOR was classified as any patient who continued IFX treatment and did not report IBD complaints. Any patient who discontinued IFX for reasons besides LOR was excluded from the final analysis. As all included patients needed to have an IFX trough ≥5 μg/mL, patients with LOR were regarded as suffering an IFX mechanism LOR, rather than inadequate dosing of IFX.

Relevant clinical and demographic data were extracted manually from patients' electronic record, including the final documented IFX dosing regimen. Any patient receiving maintenance IFX at either higher than standard dose of 5 mg per kilogram or more frequently than the standard 8 weeks between infusions was regarded as a patient who had undergone a dose escalation.

Statistical Analysis

The MEANS procedure was used to calculate the mean and standard deviation of IFX level for both the LOR and non-LOR groups. The Wilcoxon two-sample

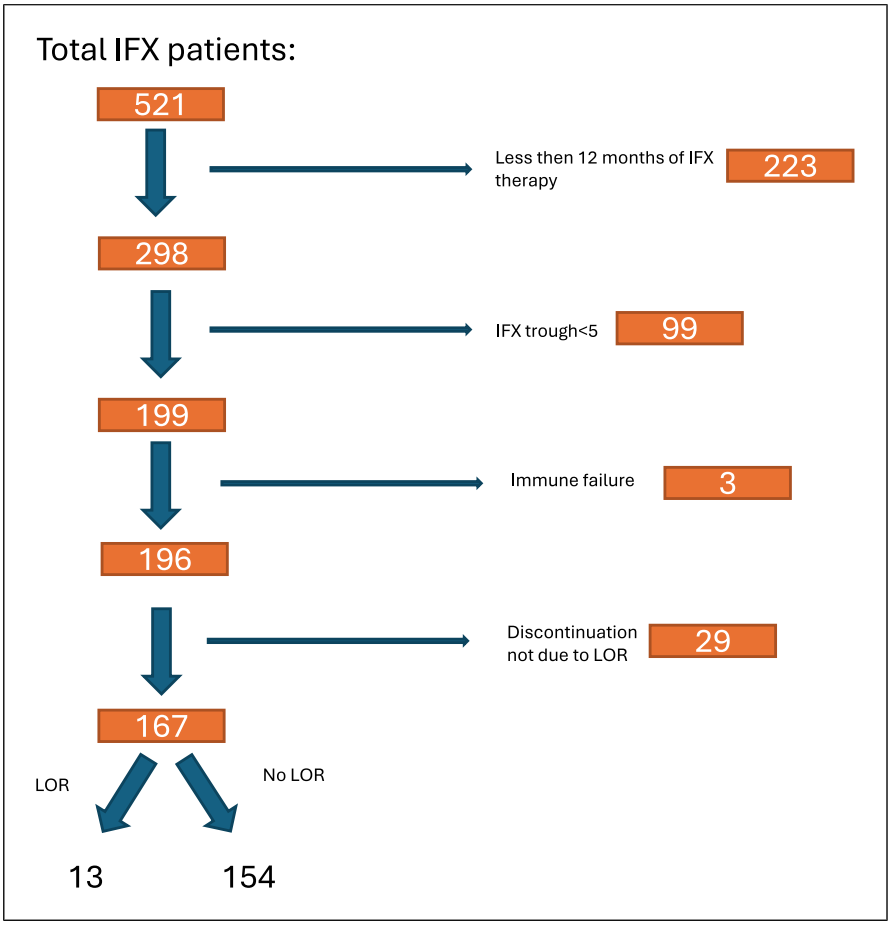

Fig. 1. Patient identification.

test was then performed to analyze for any significant differences between the LOR and non-LOR groups across the entire population, as well as for CD and UC separately.

Results

A total of 521 patients were initially identified who received IFX for the treatment of IBD, of whom 167 patients remained following application of all inclusion and exclusion criteria (shown in Fig. 1). After performing a review of each patient's chart notes, it was determined that only a small subset of patients, 13 (7.8%), experienced a secondary LOR and 154 (92.2%) did not experience a LOR. LOR and non-LOR groups were similar by race ethnicity and smoking status (shown in Table 1). The LOR group showed a greater proportion of UC patients, with 38%, compared to 18% in the non-LOR group (p = 0.331). The LOR group displayed an older age at 24.77 ± 10.35 years compared to the non-LOR group at 22.72 ± 11.92 years (p = 0.047). The LOR group had a greater proportion of patients who received a dose escalation at 9 (69%) patients versus 29 (19%) patients in the non-LOR group (p = 0.692). Use of a biologic prior to IFX was uncommon in both groups, with 1 (8%) patient in the LOR group and 8 (5%) patients in the non-LOR group (p = 0.702). The LOR group had 11 (85%) patients in remission at 1 year of follow-up compared to 144 (94%), and p = 0.233 in the non-LOR group had in remission.

The mean duration of IFX use in both groups was over 3 years, with an average of 3.85 ± 1.72 years in the LOR group, and 3.33 ± 1.71 years in the non-LOR group (p = 0.134). Concurrent immunomodulator use at last follow-up showed low rates, with 15% for those with secondary LOR versus 2% for those maintaining response. There was a nonsignificant trend toward longer mean duration of concomitant immunomodulator use in those without LOR at 2.39 years versus 1.08 years for those with LOR, p = 0.252. The mean IFX troughs were noted to be in the

Table 1. Demographics and clinical characteristics

	LOR	No LOR	*p* value
N (%)	13 (7.8)	154 (92.2)	
Age, mean (range), years	24.77 (18–47)	22.73 (16–77)	$p = 0.048$
Gender	Male: 7 Female: 6	Male: 82 Female: 72	
Race			
White	10	105	
African American	2	21	
Asian/Pacific Islander	1	10	
Other	0	18	
Ethnicity			
Hispanic	0	7	
Non-Hispanic	13	145	
Declined	0	2	
Disease type			$p = 0.331$
CD	8	122	
UC	5	29	
Indeterminate	0	3	
Duration IFX use, years	3.85	3.33	$p = 0.134$
Trough IFX last measured, μg/mL			$p = 0.110$
Mean	18.50	13.10	
Range	5.8–48.0	5.1–59.0	
Antibody level, ng/mL	Mean: 65.00 Range: 65.0–65.0	Mean: 92.97 Range: 25.0–324.0	$p = 0.857$
Disease activity at 1 year of treatment	Remission: 11 Non-remission: 2	Remission: 144 Non-remission: 10	$p = 0.233$
Dose escalation	Yes: 9 No: 4	Yes: 29 No: 125	$p = 0.692$
Biologic tried before IFX	Yes: 1 No: 12	Yes: 8 No: 146	$p = 0.702$
Smoker			
Active	0	3	
Prior	2	11	
Never	11	140	
BMI	28.85	24.34	$p = 0.299$
IMM ever			
AZA	1	5	
6-MP	2	19	
MTX	3	25	
Multiple	0	2	
IMM at time of last IFX level			
AZA	1	0	
6-MP	0	0	
MTX	1	3	
Multiple	0	0	
Concomitant IMM duration, years	1.08	2.39	$p = 0.252$

IMM, immunomodulator; AZA, azathioprine; 6-MP, 6-mercaptopurine; MTX, methotrexate.

Table 2. Demographics and clinical characteristics: CD

CD patients	LOR	No LOR	*p* value
N (%)	8 (6.2%)	122 (93.8%)	
Age, mean (range), years	24.75 (18–47)	22.08 (18–74)	$p = 0.033$
Gender	Male: 4 Female: 4	Male: 71 Female: 51	
Race			
White	5	85	
African American	2	15	
Asian/Pacific Islander	0	8	
Other	1	14	
Ethnicity			
Hispanic	0	6	
Non-Hispanic	8	114	
Declined	0	2	
Duration IFX use, years	3.38	3.34	$p = 0.980$
Trough IFX last measured, μg/mL			$p = 0.201$
Mean	16.05	12.31	
Range	5.8–40.0	5.1–33.0	
Antibody level, ng/mL	Mean: 0.00 Range: 0.0–0.0	Mean: 88.92 Range: 27.0–271.0	$p < 0.001$
Disease activity at 1 year of treatment	Remission: 7 Non-remission: 1	Remission: 115 Non-remission: 7	$p = 0.441$
Dose escalation	Yes: 6 No: 2	Yes: 24 No: 98	$p < 0.001$
Biologic tried before IFX	Yes: 0 No: 8	Yes: 8 No: 114	$p = 0.455$
Smoker			
Active	0	3	
Prior	1	8	
Never	7	111	
BMI	28.63	24.18	$p = 0.022$
IMM ever			
AZA	1	4	
6-MP	1	13	
MTX	3	19	
Multiple	0	2	
IMM at time of last IFX level			
AZA	1	0	
6-MP	0	0	
MTX	1	3	
Multiple	0	0	
Concomitant IMM duration, months	5.00	31.22	$p = 0.040$

IMM, immunomodulator; AZA, azathioprine; 6-MP, 6-mercaptopurine; MTX, methotrexate.

supra-therapeutic range of >10.0 μg/mL for both groups. Those with LOR had a mean IFX trough level of 18.50 μg/mL (range: 5.8–48.0 μg/mL) versus 13.10 μg/mL (range: 5.1–59.0 μg/mL) for those without LOR, $p = 0.110$. Mean ATI levels were also similar for those with and without LOR, 62 ng per mL (ng/mL) versus 93 ng/mL, $p = 0.857$.

Table 3. Demographics and clinical characteristics: UC

UC patients	LOR	No LOR	*p* value
N (%)	5 (14.7%)	29 (85.3%)	
Age, mean (range), years	24.80 (18–40)	25.52 (17–77)	$p = 0.777$
Gender	Male: 3 Female: 2	Male: 9 Female: 20	
Race			
White	5	19	
African American	0	4	
Asian/Pacific Islander	0	2	
Other	0	4	
Ethnicity			
Hispanic	0	1	
Non-Hispanic	5	28	
Declined	0	0	
Duration IFX use, years	4.60	3.24	$p = 0.071$
Trough IFX last measured, μg/mL		14.96	$p = 0.448$
Mean	22.30	5.3–59.0	
Range	7.5–48.0		
Antibody level, ng/mL	Mean: 65.00 Range: 65.0–65.0	Mean: 115.00 Range: 25.0–324.0	$p = 1.000$
Disease activity at 1 year of treatment	Remission: 4 Non-remission: 1	Remission: 27 Non-remission: 2	$p = 0.340$
Dose escalation	Yes: 3 No: 2	Yes: 4 No: 25	$p = 0.018$
Biologic tried before IFX	Yes: 1 No: 0	Yes: 0 No: 29	$p = 0.015$
Smoker			
Active	0	0	
Prior	1	2	
Never	4	27	
BMI	29.20	24.90	$p = 0.252$
IMM ever			
AZA	0	1	
6-MP	1	6	
MTX	0	4	
Multiple	0	0	
IMM at time of last IFX level			
AZA	0	0	
6-MP	1	0	
MTX	0	0	
Multiple	0	0	
Concomitant IMM duration, months	18.33	8.60	$p = 0.250$

IMM, immunomodulator; AZA, azathioprine; 6-MP, 6-mercaptopurine; MTX, methotrexate.

Stratified by disease type, CD patients with LOR had a mean IFX trough level of 16.05 μg/mL (range 5.8–40.0 μg/mL) versus 12.31 μg/mL (range 5.1–33.0 μg/mL) for those without LOR, $p = 0.201$, as shown in Table 2. No patient with LOR had measurable ATI, as compared to a mean ATI of 88.92 ng/mL in those without LOR, $p < 0.001$. UC

patients with an LOR had a mean trough level of 22.30 μg/mL (range 7.5–48.0 μg/mL) versus 14.96 μg/mL (range 5.3–59.0 μg/mL) in the non-LOR group (p = 0.448), as shown in Table 3, and no significant difference of mean ATI levels of 65 ng/mL versus 115 ng/mL, p = 1.000.

Discussion

Though the phenomenon of secondary LOR during the first year of IFX therapy is well studied, the frequency and mechanism of LOR beyond this point are less well defined. In our analysis of patients on long-term IFX treatment for IBD, we observed a very low rate of IFX mechanism LOR of just 7.8%, consistent with prior studies. Using the currently accepted/minimum IFX level of 5 μg/mL as a cutoff for inclusion, our comparison of IFX levels for those with versus without LOR did not demonstrate any significant difference in trough levels and in fact showed a trend toward higher levels for those with LOR.

In their recent retrospective review, Schultheiss et al. [9] also investigated the phenomenon of long-term IFX use, focusing on the frequency and predictors of LOR. Their multicenter study looked at the experience of 708 patients treated with anti-TNFα therapy over a median duration or 2.4 years, of which 518 received IFX. LOR was as high as 17.2% per patient-year (95% CI: 13.7–21.2) during the first year of treatment, but declined to 4.8% per patient-year (95% CI: 3.1–7.2) after 4 years, closely mirroring our own experience. Overall, 211 patients experienced LOR, 66 (31.3%) episodes with detectable antibodies to anti-TNFα. The remaining 145 (68.7%) cases were classified as LOR *without* anti-TNFα antibodies, 114 of whom had an available drug trough level for analysis. Of these, the IFX patients demonstrated a median trough level of 6.0 mg/L, and an IQR of 3.9–8.5. As such, their definition of nonimmune LOR included a large number of patients with an IFX trough <5.0 mg/L (5.0 μg/mL). Current practice would not regard these patients as experiencing a nonimmune LOR, but rather in need of IFX dose optimization.

Our own analysis looked at the nonimmune LOR phenomenon from a slightly different angle, re-asking the question of what constitutes the optimal dose/IFX level during later years of therapy among patients meeting the current standard accepted minimum IFX trough threshold of 5 μg/mL. The lack of significantly different trough levels between responders and nonresponders meeting this strict criteria prevented any redefining of target IFX levels during long-term therapy. Additionally, the trend toward higher IFX levels in the LOR group further suggests that more IFX is *not* the answer to nonimmune LOR.

Our study had several limitations. First, our sample size was small, with only 167 patients, including 13 in the LOR group. These small numbers reflect the low rates of secondary nonimmune LOR on long-term treatment, and prevented a more detailed analysis of factors that might predict this phenomenon. Second, though our data drew on patients from multiple centers, the population is still geographically defined and may not apply to different patient populations or medical settings. Additionally, our analysis depended upon the last available IFX trough level, leading to a possibility of bias as levels were not drawn by any standard protocol or timing. While some appear to have been performed reactively, most appeared to be for "routine" proactive drug monitoring. Also, chart review revealed that documentation of concurrent medications such as mesalamine and corticosteroids was inconsistent and could not be incorporated into the formal analysis. Finally, as objective clinical disease activity scores for CD and UC were not documented in patients' chart notes, disease activity was based on physician global assessment rather than a standardized disease activity score such as the Mayo score.

Once again, our analysis of IFX troughs of patients experiencing a secondary nonimmune LOR during longer courses of therapy does not suggest an alternate goal trough level over those currently in use. Our findings point away from the benefits of further dose escalation in these patients and more toward a true shifting of the mechanism promoting inflammation. Experiencing a LOR after years of successful therapy is disappointing and confusing to patients and providers alike. Our data provide further useful information to aid counseling and management of this small subset of patients, and support current guidelines advocating for the use of alternate therapeutic classes.

Statement of Ethics

This study protocol was reviewed and approved by Northwell Health Institutional Review Board (IRB), Approval No. 22-0307. Informed consent was not required, as exempt status was granted by the Northwell Health IRB.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.F.: investigator on the project, performed chart review, organized figures, and wrote the first draft of the manuscript. J.P.: performed chart review and editor of the manuscript. N.K.: statistician. V.C.: data curation. A.S.: editor of the manuscript. K.S.: principal investigator and editor of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from M.F. upon reasonable request.

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