Ther Adv Gastroenterol
2022, Vol. 15: 1–12
DOI: 10.1177/17562848221083395

Delaying an infliximab infusion by more than 3 days is associated with a significant reduction in trough levels but not with clinical worsening

Zohar Ben-Shatach, Tomer Ziv-Baran, Ella Fudim, Miri Yavzori, Orit Picard, Asaf Levartovsky, Limor Selinger, Batia Weiss, Uri Kopylov, Rami Eliakim and Bella Ungar

Abstract

Background: Higher infliximab trough levels (TLs) correlate with better clinical, inflammatory, and endoscopic outcomes among inflammatory bowel disease (IBD) patients. Although standard scheduled infliximab therapy regimen consists of infusions at pre-defined time-points (weeks 0, 2, 6, and every 8 weeks), short-period deviations from therapeutic schedule are common in 'real life', but the pharmacokinetic impact of these deviations has not been explored. In this study, we aim to determine whether short-period deviations from infusion schedule affect infliximab-TL.

Methods: A retrospective analysis of all IBD patients receiving infliximab maintenance therapy every 8 weeks was conducted in a tertiary medical center. Patients with anti-drug antibodies, deliberate interval shortening and <3 sequential maintenance sera available were excluded. Associations between time since last infusion and TL were studied. Statistical analysis was performed using generalized estimating equations.

Results: Out of over 10,000 sera, 2088 sera of 302 maintenance period stable infliximab-therapy-patients met inclusion criteria (median TL 4.1 μg/mL, interquartile range (IQR) 2.3–6.5 μg/mL). A delay beyond 3 days in infusion schedule (n > 59 days since last infusion) was found to significantly affect TL (mean difference in TL 0.9 μg/mL, 95% confidence interval (CI): 0.03–1.9 μg/mL, $p < 0.04$). Furthermore, among patients with delayed infusions, 80% had TL below 5 μg/mL, in comparison to 55% of patients who were not late (odds ratio (OR): 2.81, CI: 2.02–3.92, $p < 0.0001$).

Conclusion: Real-life delays of ⩽3 days from infusion protocol can probably be allowed. Delays >3 days culminate in measurable decrease of TL, although effect on clinical outcome is unclear. This needs to be taken into account when interpreting drug-level test results.

Summary: A total of 2088 sera of 302 maintenance period inflammatory bowel disease (IBD) patients treated with infliximab were analyzed, to assess effect of small deviations from infusion schedule on TLs. A significant decline in patients' trough level (TL) was noted as early as 3 days after scheduled infusion.Keywords: biologics, IBD, IFX, maintenance therapy, patient adherence, pharmacokinetics, TL

Received: 8 November 2021; revised manuscript accepted: 8 February 2022.

Correspondence to:
Zohar Ben-Shatach
Department of Gastroenterology, Sheba Medical Center, Tel Hashomer, 52621, Israel. Sackler School of Medicine, Tel Aviv University, Tel Aviv, 6997801, Israel.
zoharbens@gmail.com

Ella Fudim
Miri Yavzori
Orit Picard
Asaf Levartovsky
Limor Selinger
Uri Kopylov
Rami Eliakim
Bella Ungar
Department of Gastroenterology, Sheba Medical Center, Tel Hashomer, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Tomer Ziv-Baran
Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Batia Weiss
Department of Pediatric Gastroenterology, Sheba Medical Center, Tel Hashomer, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Introduction

Infliximab (IFX) is a chimeric monoclonal antibody against tumor necrosis factor alpha (TNFα), used extensively for the last two decades in the treatment of inflammatory bowel disease (IBD). However, loss of response (LOR) to IFX occurs in approximately 30% of IBD patients within the first year of therapy, with an annual rate of approximately 13%.[1] Several patient-related factors have been found to associate with LOR, including anti-drug antibodies (ADAs) and lower IFX TL, IFX monotherapy, low baseline albumin levels, and male gender.[2]

IFX trough levels (TLs), regardless of ADA, are considered one of the main factors associated with response to therapy in IBD patients treated with scheduled IFX infusions.[3–5] Accordingly, patients with detectable IFX levels showed higher clinical and endoscopic remission rates and lower C-reactive protein (CRP) values in comparison to patients with undetectable IFX levels.[3] The TAXIT and TAILORIX randomized controlled trials, as well as additional retrospective studies, recommended that a 'therapeutic window' of TL between 3 and 7 μg/mL is achieved, although the benefit of proactively adjusting dose according to TL in clinical remission still remains inconclusive.[6–12] In another recent study, it was demonstrated that IFX levels between 6 and 10 μg/mL were associated with mucosal healing in up to 80% of Crohn's disease (CD) patients.[13]

Patient compliance is a cardinal factor in terms of therapy success. Among IBD patients, it has been demonstrated that non-adherence seems to contribute to approximately 20% of cases of LOR to anti-TNFs.[14] Non-adherence was associated with increased total healthcare costs, including inpatient, outpatient, and emergency room costs and increased rates of hospitalizations.[15,16] However, 'real-life' data on day-to-day variability in infusion schedules is currently lacking. Thus, it has not yet been assessed if deviations from infusion schedules due to holidays, vacations, work, sickness, and so on might affect serum TLs. Therefore, we decided to perform a retrospective analysis of all maintenance period sera of IBD patients receiving IFX maintenance therapy to determine which, if any, deviations may result in changes in IFX TLs.

Materials and methods

Study design

Sera were prospectively collected immediately before infusions from all IBD patients receiving IFX therapy at Sheba, a single tertiary medical center. In our center, all patients treated with IFX are routinely monitored for TLs before infusions since 2009. Clinical scores (HBI/SCCAI) were determined on the day of infusion. A retrospective cohort study analyzing the associations between inter-infusion intervals and drug levels was performed for all IBD patients receiving IFX maintenance therapy. The reporting of this study conforms to the STROBE statement.[17]

Study population

Venous trough serum samples were prospectively obtained from patients with CD and ulcerative colitis (UC) receiving IFX infusions at Sheba Medical Center between the years 2009 and 2018.

Inclusion criteria

- Sera samples of patients receiving scheduled IFX therapy every 8 weeks after completion of standard induction dose (from week 14 onward).
- Sera samples of patients who had at least three consecutive IFX infusions within the maintenance period.

Exclusion criteria

Sera samples were excluded in the following cases:

- Patients with less than three consecutive TL measurements.
- Patients who underwent interval shortening (i.e. receiving IFX 6 or 4-weekly), either during induction period or during maintenance.
- Patients on episodic therapy (i.e. not following a standard infusion protocol).
- Patient's infusions given at a deviation of over seven days from scheduled therapy (the seven-day limit was chosen as the fact that large deviations from infusion protocol affects drug levels is well known. The study aimed to assess subtle deviations).

- Patients with positive antibodies to IFX (ATI, levels > 2.5 μg/mL, measured by a previously described drug-tolerant anti-lambda ELISA assay 18).
- Missing clinical data.

Ethics

The study was approved by Sheba medical center's ethics committees (N. 4530).

Therapeutic drug monitoring

IFX serum samples were routinely and systematically collected before IFX infusions. IFX and anti-IFX antibodies' levels were measured by a previously described drug-tolerant assay.[18,19]

Clinical scores

Clinical status was determined by HBI (Harvey–Bradshaw index) for CD and by SCCAI (Simple Clinical Colitis Activity Index) for UC patients.[20,21] Clinical remission was defined as HBI < 5 for CD patients and SCCAI ⩽ 3 for UC patients.[22] Clinical scores were prospectively determined on the day of infusion by the IBD nurse. Clinical remission status was defined as clinical and/or endoscopic remission during the last 3 months of IFX therapy.

Study endpoints

The primary analysis examined the association between time since last IFX infusion and TL in patients receiving scheduled IFX therapy every 8 weeks.

The secondary analysis was a sub-group analysis, for patients with >10 consecutive maintenance period IFX level measurements (n = 60), among those treated every 8 weeks. The analysis was adjusted for several basic patient-related parameters, including age, gender, concomitant immunomodulatory therapy, weight, and IFX dose (5/10 mg per kg). The association between time since last IFX infusion and TL, clinical score and clinical/endoscopic remission were assessed. All parameters were obtained from the medical records. The analysis was performed per sera and not per patients. All patients in the study had one delay or more and the generalized estimating equations (GEEs) analysis takes into account different numbers of intervals per different patients—sera corresponding to early/late infusions were analyzed accordingly.

Statistical analysis

Continuous variables were expressed as the median and interquartile range (IQR). All reported p values were two-sided, and a p value less than 0.05 was considered statistically significant. GEEs were used to study the association between TL and days from previous infusion, the effect of different patient-related parameters on TL, and association of disease activity with TL and infusion timing. Difference in TL (μg/mL) was calculated by subtracting the median IFX TL, calculated for all every-8-weeks patients, from TL at day of interest. All statistical analyses were performed using SPSS (SPSS statistics for windows, version 24, IBM Corporation, Armnok, NY, USA, 2016).

Results

A total of 10,635 trough sera from 2257 IFX-treated patients were collected and analyzed at Sheba Medical Center between 2009 and 2018. In total, 2088 sera from 302 maintenance period IFX therapy patients were included (Figure 1). All sera were collected within ±7 days of therapeutic schedule. Median TL among all scheduled maintenance therapy patients was 4.1 μg/mL (IQR: 2.3–6.5 μg/mL, Figure 2).

Delays from IFX infusion schedule among maintenance period patients were then analyzed in association with actual IFX TLs. A delay of more than 3 days from the every-8-weeks infusion protocol (n > 59 days since last infusion) significantly affected TL (mean difference in TL was 0.9 μg/mL, 95% confidence interval (CI): 0.5–1.2 μg/mL, $p < 0.001$, Figure 3). With regard to earlier than scheduled arrival for an infusion, shortening the interval between infusions up to 6 days was not significantly associated with a change in TL; however, shortening the interval from last infusion by 1 week (49 days from previous infusion) showed significant increase in TL (mean difference in TL was 0.93 μg/mL, 95% CI 0.3–1.5 μg/mL, $p < 0.003$).

A sub-analysis was performed for maintenance period IFX therapy patients with >10 consecutive TL measurements each. Sixty patients with 1226

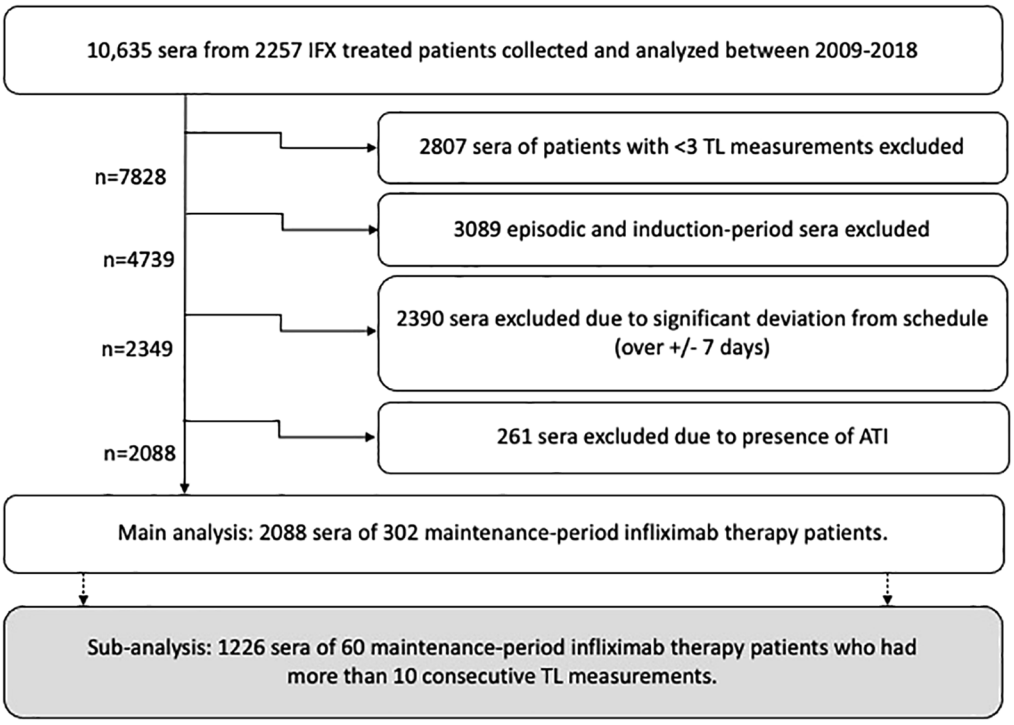

Figure 1. Flow chart demonstrating patients' inclusion into the study.
ATI, antibodies to infliximab; IFX, infliximab; TL, trough level.

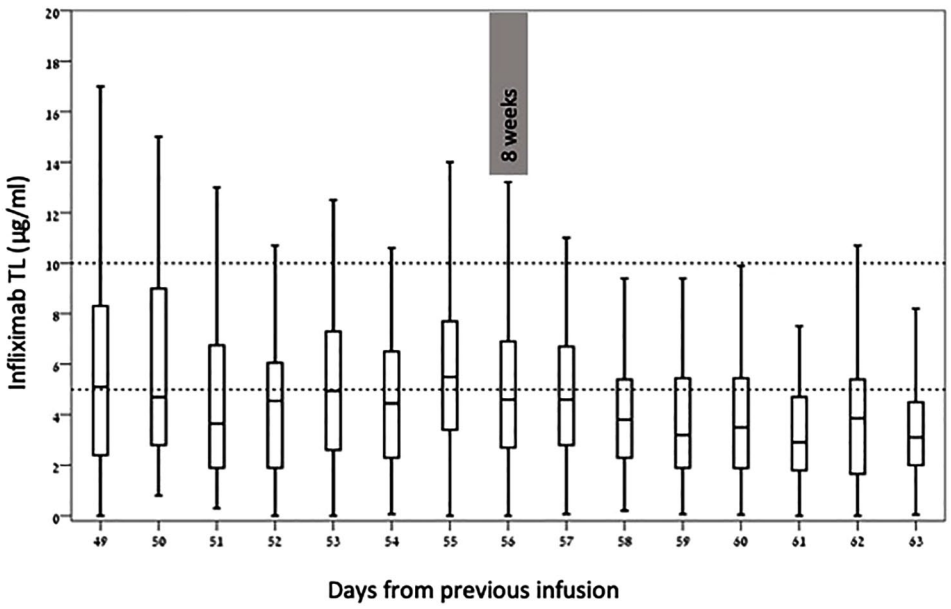

Figure 2. 2088 TL measurements of 302 patients receiving scheduled IFX therapy, stratified by days from previous infusion. Median TL at exactly 8 weeks (56 days) from previous infusion was 4.1 µg/mL, as marked by the gray '8 weeks' square.
TL, trough level.

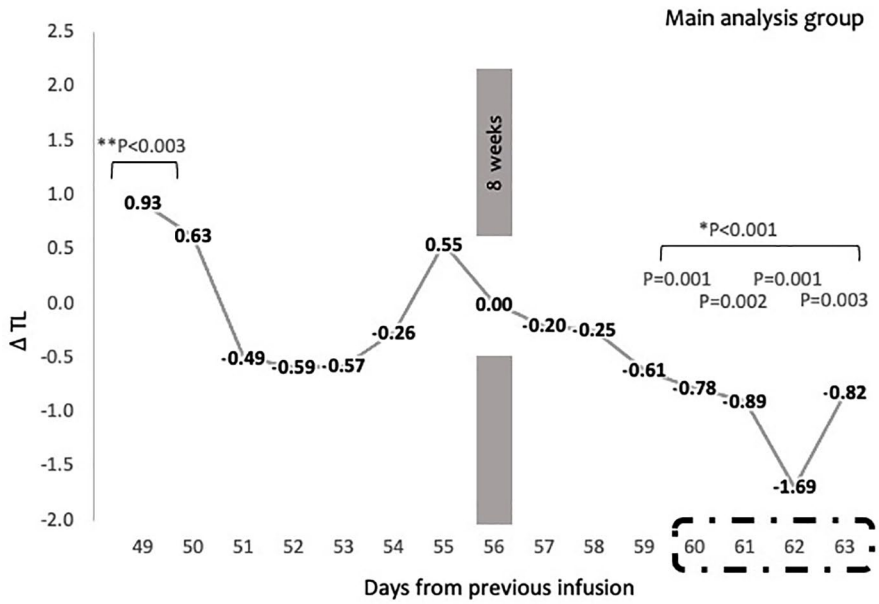

Figure 3. Delaying infusions by >3 days (>59 days from previous infusion) resulted in a significant decline in infliximab drug levels. *Delayed infusions by more than 3 days. **Shortening the interval by 1 week (49 days from previous infusion) showed significant increase in TL.
Δ TL, the difference in TL (μg/ml) from scheduled therapy.

samples in total were included in the analysis (Supplementary Figure 1). Among these patients, adjustment for basic background parameters was performed to account for possible confounders including patient gender, IFX dose (either the standard 5 mg/kg dose or an escalated dose of 10 mg/kg, disease type, concomitant immunomodulator, age, or weight at induction (Table 1). Among the sub-analysis group, 42% of visits were exactly as per schedule, while 37.3% arrived late and 20.7% arrived earlier than scheduled. Median serum TL at 8 weeks for the sub-analysis population was 5.19 μg/mL (IQR 2.8–6.7 μg/mL). Among these patients, a delay of more than 3 days from infusion schedule also resulted in a statistically significant decline in IFX TL (Figure 4, mean difference in TL 0.8 μg/mL, 95% CI 0.25–1.36 μg/mL, $p < 0.005$). Shortening the interval between infusions by 4–7 days from regular 8-week interval (i.e. arriving 49–51 days from previous infusion), was significantly associated with an increase in TL (mean difference in TL was 1.97 μg/mL, 95% CI 0.5–3.44 μg/mL, $p < 0.008$).

A multivariate analysis was performed to detect factors affecting TL. A test of model effects demonstrated that of the parameters collected, only interval between infusions affected TL (Table 2, $p = 0.001$). No significant difference in TL was attributed to patients' gender ($p = 0.53$), patient age ($p = 0.07$), disease type (CD/UC, $p = 0.15$), concomitant immunomodulator therapy ($p = 0.49$), or weight at induction ($p = 0.13$).

Next, an analysis was performed to assess whether patients arriving late for infusions have lower trough IFX levels compared to those arriving early or on-time. The lower threshold for IFX TLs,[3,10] 3 μg/mL, was used as a cut-off point for the analysis. Among patients with delayed infusions (4 days late or over), 43.6% had TL below 3 μg/mL, in comparison to 25% of patients that were not late (Figure 5(a), OR: 1.88, CI: 1.33–2.66, $p < 0.001$). We also examined the cut-off of 5 μg/mL, which is considered optimal in terms of IFX therapy outcome.[23] Among patients with delayed infusions, 80% had TL below 5 μg/mL, in comparison to 55% of patients that were not late (Figure 5(b), OR: 2.18, CI: 1.63–2.92, $p < 0.001$).

We then analyzed the associations between delays in infusion schedule and prospective same time-point clinical scores. The clinical scores on infusion day were analyzed for the 60 patients included in the adjusted analysis. 834 clinical scores (HBI/SACCAI) were available at the same

Table 1. Sub-analysis population: demographic and clinical characteristics.

*N**	60
Total number of sera	1226
Number of TL measurements per patient (median, IQR)	18.5 (14–25)
Male, *n* (%)	32 (53.3)
CD, *n* (%)	48 (80)
UC, *n* (%)	12 (20)
Age at diagnosis, years (median, IQR)	22 (16–25)
Weight at induction, kg (median, IQR)	64.5 (55–78)
Infliximab dose, *n* (%)	5 mg/kg – 52 (86.7)
	10 mg/kg – 7 (11.7)
Concomitant immunomodulator therapy, *n* (%)	23 (38.3)
Previous immunomodulator therapy, *n* (%)	49 (81.7)

CD, Crohn's disease; IQR, interquartile range; TL, trough-levels; UC, ulcerative colitis.
*Number of patients with over 10 consecutive infliximab trough level measurements within scheduled therapy patients.

time-points of TL measurements (68% of sub-analysis visits) and were analyzed accordingly. In our cohort, neither TL below 3 μg/mL nor below 5 μg/mL were associated with active disease (OR: 1.22, CI 0.78–1.9, $p=0.37$, and OR: 0.92, CI: 0.58–1.45, $p=0.73$, respectively). Deviations from infusion schedule were also analyzed in association with clinical remission status. No significant correlation was seen between arriving late or early for an infusion (up to ±7 days from the scheduled 8 weeks interval) and disease activity (OR: 1.01, CI: 0.73–1.39, $p=0.94$). Finally, an analysis of clinical/endoscopic remission status, based on the previous 3 months was performed in association with being late for infusions. Hence, patients with >55% of total infusions being overdue (>3 days delay) were classified as late. No association was detected between arriving mostly late for infusions and the patients remission status in our cohort ($p=0.15$, CI: 0–1.99).

Discussion

Higher IFX levels, and specifically, IFX TL higher than 3 μg/mL, have been associated with better

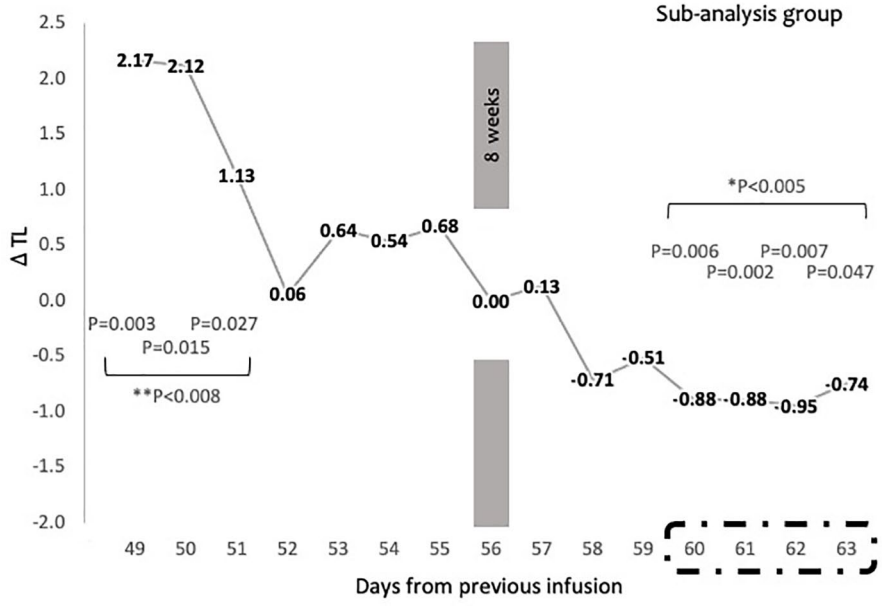

Figure 4. Delaying infusions for >4 days results in a significant decline in infliximab drug levels in the sub-analysis population. *Delayed infusions by more than 3 days. **Shortening the interval between infusions by 4 to 7 days from regular eight-week interval, showed significant increase in TL.
TL, trough level; ΔTL, the difference in TL (μg/mL) from scheduled therapy.

therapeutic outcomes.[24–29] The optimal TL range was suggested by prospective studies to be 3–7 μg/mL, although many others suggest that even higher TL are required to achieve mucosal healing.[10,13,30] At any rate, measuring TL upon clinical worsening (i.e. reactive therapeutic drug monitoring) has been proven to result in better therapeutic decision-making in both adult and pediatric patients with IBD[31] and thus to improve patient outcome and to save costs.[32] Episodic IFX therapy and remarkable delays from infusion routine have been associated with immunogenicity and detrimental outcomes.[33,34] Furthermore, it was shown in many studies that marked deviations from scheduled infusion protocol (due to concurrent illness/infection/lack of adherence) result in lower drug levels, worse clinical outcomes, and increased disability.[35–39] However, scarce data exist as to the effect of minor deviations on patient outcome. As this study aimed to explore subtle changes, patients with a deviation of over 7 days from scheduled therapy (above 9 or less than 7 weeks since last infusion) were excluded.

A Canadian study reported that adherence to maintenance IFX therapy was as low as 32%;[40] however, no distinction was made between patients late for infusions, versus those skipping infusions. Moreover, it has been shown that only one-third of CD patients were compliant with maintenance schedule, in comparison to induction therapy, when three quarters of patient were adherent to schedule.[40] In another study, patients who were late for purchasing their subcutaneous biologics (adalimumab/certolizumab) by over 2 days, had significantly increased risk of flares.[41] As we encourage patients to lead a normal daily routine, with minimal interferences due to their chronic illness, it is important to define how much flexibility is allowed in terms of deviations from infusion protocol. Our results suggest that for patients on long-term IFX maintenance therapy, deviations from infusion protocol by 3 days or less can probably be allowed. However, larger gaps between IFX infusions could result in lower

Table 2. Association of demographic factors with infliximab trough levels.

Parameter	Wald-chi square	Significance level (*p*)
Time from last visit	58.51	0.001
Age at diagnosis	3.28	0.07
Gender	0.38	0.535
IBD type (CD/UC)	1.98	0.159
Weight at induction	2.19	0.138
Infliximab dose (5/10 mg/kg)	0.21	0.646
Concomitant immunomodulator therapy	0.46	0.496

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

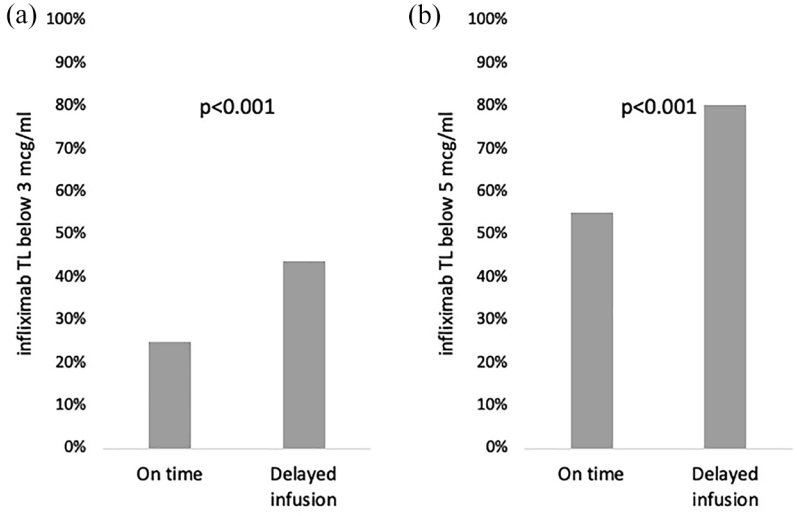

Figure 5. Patients arriving more than 4 days late of schedule had a greater prevalence of subtherapeutic levels: (a) infliximab TL below 3 μg/mL and (b) TL below 5 μg/mL, than patients that were not late.
TL, trough level.

trough serum levels (lower by a median of 0.9 μg/ml at 4 to 7 days from schedule) which could be associated with deleterious therapeutic outcome. To our knowledge, our study is the first to address the association of time between infusions versus IFX levels in serially treated IFX patients. These results should also be borne in mind by physicians interpreting results of TDM measurements in real life, where exact infusion dates may be often be overlooked but may impact the interpretation of TLs obtained.

In this study, inspecting small deviations from infusion protocol, there was no clear correlation between being late or early for an infusion and the patient's clinical status. This counter-intuitive finding suggests that clinical factors mainly drive patients to receive an earlier-then-scheduled infusion. It seems that some of the patients schedule their own infusions based on their clinical status. Thus, additional studies are required to determine whether patients allow larger delays in therapy when they are in remission, and schedule earlier infusions when they feel worse. Previous publications have also suggested that patients in remission can often withdraw/delay biological therapy, without significant worsening.[42] Moreover, it has been shown that in patients who are in clinical and endoscopic remission despite low IFX levels, drug discontinuation probably does not lead to detrimental outcomes.[43] This goes in line with our findings that patients who were doing well were more often late for infusions, which resulted in lower TLs. It is of note that a causative effect has been identified between TL and clinical outcome. However, we presume that when performing same-point analysis of TL and clinical score, the cause and effect relationship cannot be assessed and the effect of delaying an infusion on drug levels is not possible to assess. Furthermore, as deviations in drug levels have been subtle following minor delays in infusions (median 4.1, IQR 2.3–6.5μg/ml), they were mostly within the therapeutic range, thus probably not affecting response to therapy in most cases.

Interval between infusions was the only significant factor affecting IFX levels in our study. This goes in line with known pharmacokinetics,[44] whereby after intravenous administration, slow degradation of IFX takes place by non-specific proteases, in a linear manner with no accumulation of the drug in body compartments between intervals.[45] Concomitant immunomodulator use was previously associated with decreased ATI formation and IFX clearance in both adult and pediatric CD patients.[46,47] However, no clear association between combination immunomodulatory use and IFX TL was detected in our cohort. This may be due to the fact we focused on patients on long-term maintenance therapy, whereas the use of immunomodulators probably affects immunogenicity and IFX TL[48–50] most notably during induction period/first 6 months of therapy.[51,52] Furthermore, as measurements of metabolites (6TGN/6MMP) of immunomodulators were not regularly performed in our medical center, compliance issues may have affected the outcomes of this analysis. The effect of patient gender on serum TL was described elsewhere for a variety of monoclonal antibodies.[53,54] It was previously suggested that gender and weight often correlate and the increased clearance may actually be related to the patient weight;[2] however, it was demonstrated by prospective studies that higher clearance rate and central compartment concentration of IFX [55] and lower TL was seen in men.[56] This association was demonstrated inconsistently,[29] and no effect of gender on patient IFX TL was seen in our sub-analysis group. IFX dosage is adjusted according to patients' weight. Nevertheless, it seems to have a non-linear effect on the clearance of monoclonal antibodies[2] in a mechanism not entirely clear, thought to involve the proinflammatory effect of mesenteric fat in the production of inflammatory mediators such as TNF-α.[57] At any rate, in our cohort patient weight did not impact the drug TL, similarly to previous publications.[58] IFX dose has been previously positively associated with higher IFX levels.[59] In our study, no such association was found, probably because in this real-life observational study drug levels were reactively adjusted according to serum levels in individual patients.

Our study has several limitations. Although our database included over 10,000 sera, some of the sub-analyses were limited by serum numbers, such as the adjusted sub-analysis among UC patients. Patient's albumin and CRP levels were not routinely measured with TL at time of infusion and therefore were not included in this study. Furthermore, different numbers of sera were analyzed per each patient. To overcome this, GEEs was utilized. Moreover, it is debatable whether arriving late for an infusion can be considered as a violation of adherence, particularly when

adapted on other grounds than patient wishes; therefore, no implication on patient adherence could be deduced from our data, nor the reason for individual delays from schedule. Finally, in this study, clinical scores were evaluated at the same time-point of TL measurements. Although this enables evaluation of association between the two parameters, causality is lacking when performing same time-point analysis.

To conclude, real-life delays from maintenance infusion protocol of 30 days or less can probably be allowed. Delays beyond that would notably decrease TL, which should be borne in mind when interpreting drug levels. Furthermore, it seems that patients allow larger delays in therapy when they are in remission and prompt the staff to schedule earlier infusions when they feel worse. This suggests that most patients navigate therapy according to personal well-being. Corroborating studies ought to explore associations between delays in infusion protocol and endoscopic scores. A comparison with an infusion center where infusions are scheduled by the staff solely might demonstrate a different aspect as to the significance of delays in IFX therapy schedule.

Acknowledgements

All authors approved the final version of the article, including the authorship list.

Author contributions

Zohar Ben-Shatach: Conceptualization; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Tomer Ziv-Baran: Data curation; Formal analysis.

Ella Fudim: Data curation.

Miri Yavzori: Data curation.

Orit Picard: Data curation.

Asaf Levartovsky: Data curation.

Limor Selinger: Data curation; Methodology.

Batia Weiss: Data curation; Writing – review & editing.

Uri Kopylov: Methodology; Writing – review & editing.

Rami Eliakim: Methodology; Writing – review & editing.

Bella Ungar: Conceptualization; Formal analysis; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: UK received speaker fees from Abbvie, Janssen and Takeda, research support from Takeda and Janssen and consulting fees from Takeda and CTS. BU received consultation fees from Neopharm, Takeda, Janssen and Abbvie. BW received in the past lecture fee from Abbvie and consultation fee from Janssen. None of the other authors have any conflicts to declare.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Zohar Ben-Shatach https://orcid.org/0000-0001-7225-9765

Asaf Levartovsky https://orcid.org/0000-0003-1235-1927

Uri Kopylov https://orcid.org/0000-0002-7156-0588

Supplemental material

Supplemental material for this article is available online.

References

1. Ben-Horin S and Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. *Aliment Pharmacol Ther* 2011; 33: 987–995.
2. Ordás I, Mould DR, Feagan BG, *et al.* Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. *Clin Pharmacol Ther* 2012; 91: 635–646.
3. Maser EA, Villela R, Silverberg MS, *et al.* Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol* 2006; 4: 1248–1254.

4. Colombel JF, Sandborn WJ, Reinisch W, *et al*. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; 362: 1383–1395.
5. Ben-Horin S and Chowers Y. Tailoring anti-TNF therapy in IBD: drug levels and disease activity. *Nat Rev Gastroenterol Hepatol* 2014; 11: 243–255.
6. Yanai H, Lichtenstein L, Assa A, *et al*. Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. *Clin Gastroenterol Hepatol* 2015; 13: 522–530.
7. Velayos FS, Kahn JG, Sandborn WJ, *et al*. A test-based strategy is more cost effective than empiric dose escalation for patients with Crohn's disease who lose responsiveness to infliximab. *Clin Gastroenterol Hepatol* 2013; 11: 654–666.
8. Mitrev N, Vande Casteele N, Seow CH, *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: 1037–1053.
9. Gomollón F, Dignass A, Annese V, *et al*. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. *J Crohns Colitis* 2017; 11: 33–25.
10. Vande Casteele N, Ferrante M, Van Assche G, *et al*. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology* 2015; 148: 1320–1329.e3.
11. Papamichael K, Gils A, Rutgeerts P, *et al*. Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD. *Inflamm Bowel Dis* 2015; 21: 182–197.
12. Khanna R, Sattin BD, Afif W, *et al*. Review article: a clinician's guide for therapeutic drug monitoring of infliximab in inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; 38: 447–459.
13. Ungar B, Levy I, Yavne Y, *et al*. Optimizing anti-TNF-α therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2016; 14: 550–557.e2.
14. Ben-Horin S. Loss of response to anti-tumor necrosis factors: what is the next step? *Dig Dis* 2014; 32: 384–388.
15. Wan GJ, Kozma CM, Slaton TL, *et al*. Inflammatory bowel disease: healthcare costs for patients who are adherent or non-adherent with infliximab therapy. *J Med Econ* 2014; 17: 384–393.
16. Kane SV, Chao J and Mulani PM. Adherence to infliximab maintenance therapy and health care utilization and costs by Crohn's disease patients. *Adv Ther* 2009; 26: 936–946.
17. Von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.
18. Ben-Horin S, Yavzori M, Katz L, *et al*. The immunogenic part of infliximab is the F(ab')2, but measuring antibodies to the intact infliximab molecule is more clinically useful. *Gut* 2011; 60: 41–48.
19. Roblin X, Rinaudo M, Del Tedesco E, *et al*. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. *Am J Gastroenterol* 2014; 109: 1250–1256.
20. Higgins PDR, Schwartz M, Mapili J, *et al*. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. *Gut* 2005; 54: 782–788.
21. Harvey R and Bradshaw J. A simple index of Crohn's-disease activity. *Lancet* 1980; 315: 514.
22. Vermeire S, Schreiber S, Sandborn WJ, *et al*. Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. *Clin Gastroenterol Hepatol* 2010; 8: 357–363.
23. Vande Casteele N, Herfarth H, Katz J, *et al*. American Gastroenterological Association Institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. *Gastroenterology* 2017; 153: 835–857.e6.
24. Amiot A, Hulin A, Belhassan M, *et al*. Therapeutic drug monitoring is predictive of loss of response after de-escalation of infliximab therapy in patients with inflammatory bowel disease in clinical remission. *Clin Res Hepatol Gastroenterol* 2016; 40: 90–98.
25. Vaughn BP, Martinez-Vazquez M, Patwardhan VR, *et al*. Proactive therapeutic concentration monitoring of infliximab may improve outcomes for patients with inflammatory bowel disease: results from a pilot observational study. *Inflamm Bowel Dis* 2014; 20: 1996–2003.
26. Papamichael K and Cheifetz AS. Therapeutic drug monitoring in IBD: the new standard-of-

care for anti-TNF therapy. *Am J Gastroenterol* 2017; 112: 673–676.

27. Lega S, Phan BL, Rosenthal CJ, *et al*. Proactively optimized infliximab monotherapy is as effective as combination therapy in IBD. *Inflamm Bowel Dis* 2019; 25: 134–141.
28. Bortlik M, Duricova D, Malickova K, *et al*. Infliximab trough levels may predict sustained response to infliximab in patients with Crohn's disease. *J Crohns Colitis* 2013; 7: 736–743.
29. Yarur AJ, Kanagala V, Stein DJ, *et al*. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Aliment Pharmacol Ther* 2017; 45: 933–940.
30. Drobne D, Kurent T, Golob S, *et al*. Success and safety of high infliximab trough levels in inflammatory bowel disease. *Scand J Gastroenterol* 2018; 53: 940–946.
31. Van Hoeve K, Dreesen E, Hoffman I, *et al*. Higher infliximab trough levels are associated with better outcome in paediatric patients with inflammatory bowel disease. *J Crohns Colitis* 2018; 12: 1316–1325.
32. Steenholdt C, Brynskov J, Thomsen OØ, *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: 919–927.
33. Sprakes MB, Ford AC, Warren L, *et al*. Efficacy, tolerability, and predictors of response to infliximab therapy for Crohn's disease: a large single centre experience. *J Crohns Colitis* 2012; 6: 143–153.
34. Lee LYW, Sanderson JD and Irving PM. Anti-infliximab antibodies in inflammatory bowel disease: prevalence, infusion reactions, immunosuppression and response, a meta-analysis. *Eur J Gastroenterol Hepatol* 2012; 24: 1078–1085.
35. Kane S, Huo D, Aikens J, *et al*. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. *Am J Med* 2003; 114: 39–43.
36. Rutgeerts P, Feagan BG, Lichtenstein GR, *et al*. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004; 126: 402–413.
37. Perry J, Chen A, Kariyawasam V, *et al*. Medication non-adherence in inflammatory bowel diseases is associated with disability. *Intest Res* 2018; 16: 571–578.
38. Lakatos PL. Prevalence, predictors, and clinical consequences of medical adherence in IBD: how to improve it? *World J Gastroenterol* 2009; 15: 4234–4239.
39. Steenholdt C. Use of infliximab and anti-infliximab antibody measurements to evaluate and optimize efficacy and safety of infliximab maintenance therapy in Crohn's disease. *Dan Med J* 2013; 60: B4616.
40. Ma C, Evaschesen CJ, Gracias G, *et al*. Inflammatory bowel disease patients are frequently nonadherent to scheduled induction and maintenance infliximab therapy: a Canadian cohort study. *Can J Gastroenterol Hepatol* 2015; 29: 309–314.
41. Govani SM, Noureldin M, Higgins PDR, *et al*. Defining an optimal adherence threshold for patients taking subcutaneous anti-TNFs for inflammatory bowel diseases. *Am J Gastroenterol* 2018; 113: 276–282.
42. Reenaers C, Mary JY, Nachury M, *et al*. Outcomes 7 years after infliximab withdrawal for patients with Crohn's disease in sustained remission. *Clin Gastroenterol Hepatol* 2018; 16: 234–243.e2.
43. Ben-Horin S, Chowers Y, Ungar B, *et al*. Undetectable anti-TNF drug levels in patients with long-term remission predict successful drug withdrawal. *Aliment Pharmacol Ther* 2015; 42: 356–364.
44. Orfanoudaki E, Gazouli M, Foteinogiannopoulou K, *et al*. Infliximab trough levels are decreasing over time in patients with inflammatory bowel disease on maintenance treatment with infliximab. *Eur J Gastroenterol Hepatol* 2019; 31: 187–191.
45. Klotz U, Teml A and Schwab M. Clinical pharmacokinetics and use of infliximab. *Clin Pharmacokinet* 2007; 46: 645–660.
46. Fasanmade AA, Adedokun OJ, Blank M, *et al*. 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: 946–964.
47. Ben-Horin S, Waterman M, Kopylov U, *et al*. Addition of an immunomodulator to infliximab therapy eliminates antidrug antibodies in serum and restores clinical response of patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013; 11: 444–447.
48. Danese S, Vuitton L and Peyrin-Biroulet L. Biologic agents for IBD: practical insights. *Nat Rev Gastroenterol Hepatol* 2015; 12: 537–545.

49. Sokol H, Seksik P, Carrat F, *et al.* Usefulness of co-treatment with immunomodulators in patients with inflammatory bowel disease treated with scheduled infliximab maintenance therapy. *Gut* 2010; 59: 1363–1368.

50. Jones JL, Kaplan GG, Peyrin-Biroulet L, *et al.* Effects of concomitant immunomodulator therapy on efficacy and safety of anti-tumor necrosis factor therapy for Crohn's disease: a meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol* 2015; 13: 2233–2240. e1–e2; quiz e177–178.

51. Steenholdt C, Bendtzen K, Brynskov J, *et al.* Optimizing treatment with TNF inhibitors in inflammatory bowel disease by monitoring drug levels and antidrug antibodies. *Inflamm Bowel Dis* 2016; 22: 1999–2015.

52. Bor R, Farkas K, Fábián A, *et al.* Clinical role, optimal timing and frequency of serum infliximab and anti-infliximab antibody level measurements in patients with inflammatory bowel disease. *PLoS One* 2017; 12: e0172916.

53. Ng CM, Bruno R, Combs D, *et al.* Population pharmacokinetics of rituximab (anti-CD20 monoclonal antibody) in rheumatoid arthritis patients during a phase II clinical trial. *J Clin Pharmacol* 2005; 45: 792–801.

54. Nestorov I, Zitnik R and Ludden T. Population pharmacokinetic modeling of subcutaneously administered etanercept in patients with psoriasis. *J Pharmacokinet Pharmacodyn* 2004; 31: 463–490.

55. Fasanmade AA, Adedokun OJ, Ford J, *et al.* Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. *Eur J Clin Pharmacol* 2009; 65: 1211–1228.

56. Papamichael K, Rakowsky S, Rivera C, *et al.* Association between serum infliximab trough concentrations during maintenance therapy and biochemical, endoscopic, and histologic remission in Crohn's disease. *Inflamm Bowel Dis* 2018; 24: 2266–2271.

57. Karagiannides I and Pothoulakis C. Neuropeptides, mesenteric fat, and intestinal inflammation. *Ann N Y Acad Sci* 2008; 1144: 127–135.

58. Dotan I, Ron Y, Yanai H, *et al.* Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis* 2014; 20: 2247–2259.

59. Steenholdt C, Bendtzen K, Brynskov J, *et al.* Changes in serum trough levels of infliximab during treatment intensification but not in antiinfliximab antibody detection are associated with clinical outcomes after therapeutic failure in Crohn's disease. *J Crohns Colitis* 2015; 9: 238–245.