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Alimentary Tract

Infliximab therapy intensification upon loss of response: Is there an optimal trough level?

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ABSTRACT

Introduction: Loss of response (LOR) to infliximab occurs in ~30% of IBD patients. At time of LOR, lower infliximab-trough-levels (TL), in the absence of anti-drug-antibodies (ATI), have been associated with the need for therapy escalation. Nevertheless, few studies have examined the outcome of infliximab-therapy intensification, based on different TL.
Aim: To evaluate the impact of infliximab-TL on efficacy of therapy intensification (dose-elevation/interval-shortening).
Methods: This was a retrospective observational study performed at two tertiary-centers between 2013–2017. Study population included IBD patients who underwent infliximab therapy escalation (dose elevation/interval shortening) due to clinical LOR. Patients with TL < 3 μg/ml or positive ATI were excluded. TL and clinical scores before intensification and after 6, 12 months were obtained prospectively.
Results: Forty-eight IBD patients were included; 23(49%), and 29(60%) reached clinical remission by 6, 12 months before intensification. TL among patients in clinical remission were significantly lower than among those clinically active, both at 6 (p = 0.001, median TL 4.7,8.7 μg/ml, IQR 3.6–8.1, 5.9–16 μg/ml) and 12 months (p = 0.005, median TL 4.6,8.7 μg/ml, IQR 3.6–8, 5.3–16 μg/ml), respectively.
Conclusions: In IBD patients experiencing clinical LOR to infliximab in the absence of ATI, success of doubling the dose was inversely associated with baseline TL. Patients with baseline TL above 9 mcg/ml were very unlikely to reach clinical remission.

1. Introduction

Loss of response (LOR) to infliximab occurs in approximately 30% of IBD patients within the first year of therapy, with an annual rate of 13% [1]. At time of LOR, lower infliximab trough levels, in the absence of anti-drug antibodies, have been associated with the need for dose escalation, while higher drug levels guide towards an out-of-class switch [2,3]. Therapeutic drug monitoring (TDM) of anti-TNF drug/anti-drug antibody trough levels upon LOR has bee proven useful for guiding the management of more than two thirds of patients [4,5]. Moreover, it has recently been demonstrated that in a clinical practice setting, a TDM based strategy for patients losing response to infliximab was more cost-effective than an empirical approach, with similar clinical effectiveness [6].

Most recent studies have defined 3–10 μg/ml as the range of infliximab trough levels associated with optimal clinical outcome[7–10]. Dose escalation is suggested below 3 μg/ml, while out of class switch is recommended above the range of 3–10 μg/ml [10]. Several recent studies have put into question the clinical utility of using this range for TDM of infliximab therapy, and it has not been proven separately among CD and UC patients [9,11]. Moreover, many physicians, especially at clinical centers where trough levels are not measured routinely, perform dose intensification regardless of trough levels. Therefore, we decided to perform a retrospective analysis of all dose intensifications performed upon LOR at two tertiary centers, and to define optimal infliximab levels for successful dose escalation.

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2. Methods

2.1. Patient population

This was a retrospective observational study of all IBD patients receiving scheduled infliximab therapy at two tertiary medical centers in Israel and in France, between 2013 and 2018. This study is a validation cohort for a previous study by Yanai and colleagues, which analyzed the association between trough levels of anti-TNF agents and outcomes of interventions for patients with loss of response [4]. In the previous study, patients treated with infliximab between 2009–2013 in several medical centers in Israel were included. In the current study, we focused on patients starting infliximab after 2013. Only patients who received infliximab dose intensification (either dose elevation to 10 mg/kg every 8 weeks or interval shortening to 5 mg/kg every 4/6 weeks) due to clinically documented loss of response were included. Contrary to the previous study, patients who developed anti-infliximab-antibodies (ATI) were excluded, as well as patients with infliximab trough levels lower than 3 μg/ml upon loss of response. Patients' demographics and clinical characteristics were obtained from the medical records. Clinical scores were recorded prospectively for each patient before each infusion. The study was approved by the medical centers' ethics committees. All patients signed an informed consent for sera analyses and review of medical records.

2.2. Clinical scores

Clinical status was determined by HBI (Harvey-Bradshaw index) for Crohn's disease (CD) and by SCCAI (Simple Clinical Colitis Activity Index) for ulcerative colitis (UC) patients [12,13]. Clinical remission was defined as HBI <5 for CD patients and SCCAI ≤3 for UC patients [14].

2.3. Inflammatory markers

High sensitivity CRP serum levels were measured with the use of the CardioPhase hsCRP particle enhanced immunoephelometric assay (Siemens Medical Solutions Diagnostics, Malvern, PA) and the immunoturbidimetric assay for the in vitro quantitative determination of CRP in human serum CRP measurement (Immunoturbimetry Cobas, Roche).

2.4. Therapeutic drug monitoring

The serum samples were routinely and systematically collected at trough, before infliximab infusions. Infliximab and anti-infliximab-antibodies' levels were measured by a previously described drug-sensitive ELISA assay at Saint-Ettiene and a drug-tolerant assay at Sheba medical center [15,16].

2.5. Statistical analysis

Continuous variables were expressed as the median and interquartile range (IQR). Mann–Whitney test was used to compare continuous variables and Fischer's exact test was used for categorical data. A receiver-operating characteristic (ROC) analysis was performed for infliximab trough levels using clinical remission after therapy escalation as a classification variable. Multivariable analysis was performed using backward logistic regression. Kaplan Meier curves were plotted to assess the temporal rate of events and log rank test was computed for the comparison between survival free durations. All reported P values were 2-sided, and a p value less than .05 was considered statistically significant. All statistics were performed with MedCalc software (version 12.2.1.0, Mariakerke, Belgium).

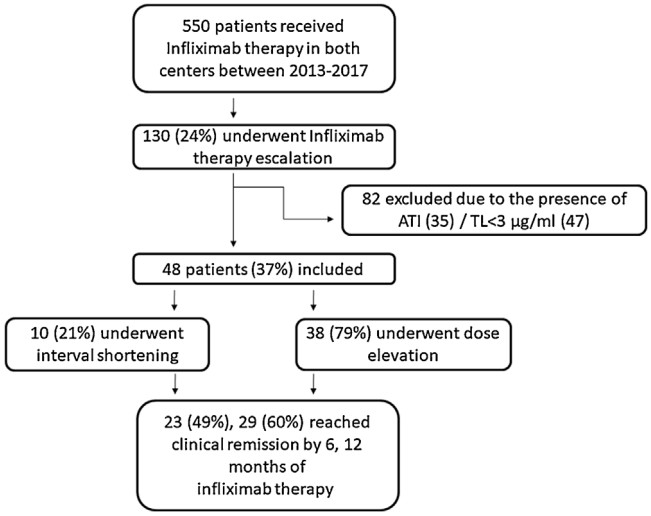

Fig. 1. Flow chart demonstrating patients' inclusion into the study.

Table 1
Patients' demographic and clinical characteristics.

N	48
CD, n(%)	31 (65)
UC, n(%)	17 (35)
Age at intensification, years (median, IQR)	36.5 (29.5–50.5)
Age at diagnosis, years (median, IQR)	23 (20–30)
Disease duration, years (median, IQR)	8 (3–12.5)
Male/Female ratio	0.7
Infliximab therapy duration prior intensification, years (median, IQR)	3 (1.8–4)
Smoking at induction, n(%)	8 (26)
Previous surgery, n(%)	14 (30)
Weight (median, IQR)	67 (58–76)
Extra-intestinal manifestations, n (%)	10 (35)
Previous biological therapy, n (%)	13 (30)
Previous immunomodulator therapy, n (%)	31 (72)
Concomitant immunomodulator therapy, n (%)	19 (40)
Clinical remission 6 months post intensification, n (%)	23 (48)
Clinical remission 12 months post intensification, n (%)	29 (60)

CD — Crohn's disease, UC — ulcerative colitis, TNF — Tumor Necrosis Factor, TL — trough levels, IQR — interquartile range.

3. Results

550 patients received scheduled infliximab therapy at both centers between 2013 and 2017. Of those 130 patients (24%) underwent infliximab therapy escalation due to clinical loss of response. 82 patients (63%) were excluded due to the presence of ATI/TL below 3 μg/ml upon LOR. Thus, 48 patients were included in the analysis (10, and 38 underwent interval shortening and dose elevation respectively, Fig. 1). Table 1 demonstrates the patients' clinical and demographic characteristics. Dose escalation resulted in clinical remission in 23 (49%), 29 (60%) of the patients by 6, 12 months of scheduled infliximab therapy. Table 2 demonstrates infliximab TL and CRP (C-reactive protein) values before and at the two timepoints after escalation. It is of note, that median CRP values before escalation were increased (15 mg/dl), but normalized 6 and 12 months post intervention (5, 4 mg/dl respectively).

TL of patients who underwent clinical remission post-intensification were significantly lower than those who were clinically active, both at 6 ($p = 0.001$, median TL 4.7, 8.7 μg/ml, IQR 3.6–8.1, 5.9–16 μg/ml respectively, Fig. 2a) and at 12 months ($p = 0.005$, median TL 4.6, 8.7 μg/ml, IQR 3.6–8, 5.3–16 μg/ml

Table 2
Infliximab TL & protocol at the different time-points.

Median infliximab TL at intensification, μg/mL (median, IQR)	7.8 (4.5–9.2)
Median CRP at intensification, mg/dl (median, IQR)	15 (4–23)
Infliximab therapy protocol at intensification — 5 mg/kg/8 weeks	48 (100%)
Infliximab TL 6 months post intensification, μg/mL (median, IQR)[a]	7.9 (4.7–11.1)
Median CRP 6 months post intensification, mg/dl (median, IQR)	5 (3.8–12)
Infliximab therapy protocol at 6 months (dose elevation to 10 mg/kg)	38 (79%)
Infliximab TL 12 months post intensification, μg/mL (median, IQR)[b]	6.7 (4.8–11.2)
Median CRP 12 months post intensification, mg/dl (median, IQR)	4 (3–6)
Infliximab therapy protocol at 12 months (dose elevation to 10 mg/kg)	38 (79%)

TL — trough levels, IQR — interquartile range.
[a] Patients who lost response and stopped infliximab therapy before the 6 months' period were excluded (n = 19).
[b] Patients who lost response and stopped infliximab therapy before the 12 months' period were excluded (n = 28).

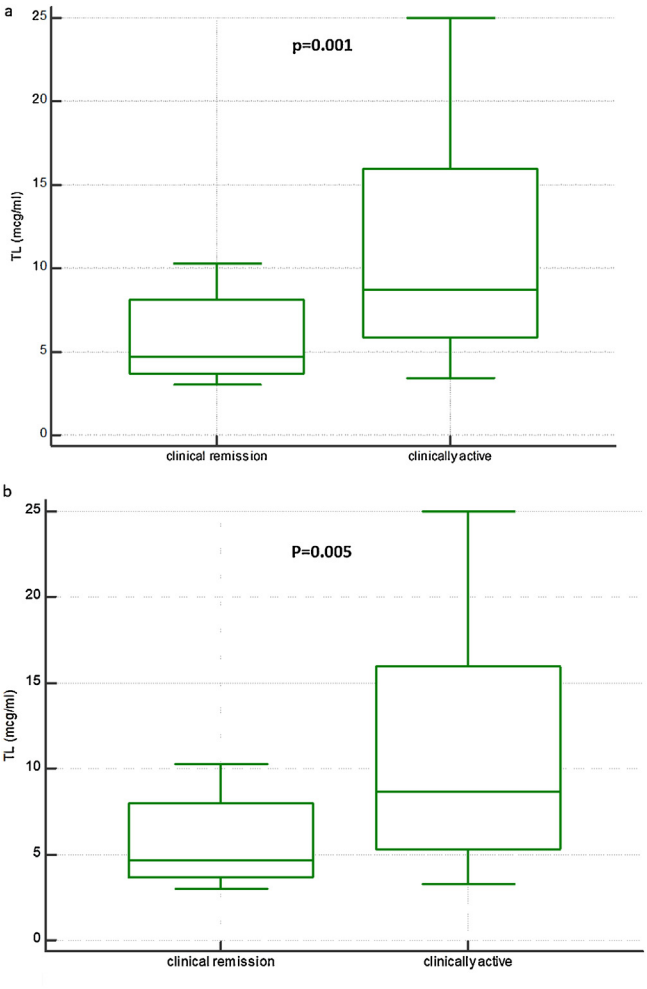

Fig. 2. (a) TL of patients who underwent clinical remission 6 months post-intensification were significantly lower than those who were still clinically active. TL — trough level. (b) TL of patients who underwent clinical remission 12 months post-intensification were significantly lower than those who were still clinically active. TL — trough level.

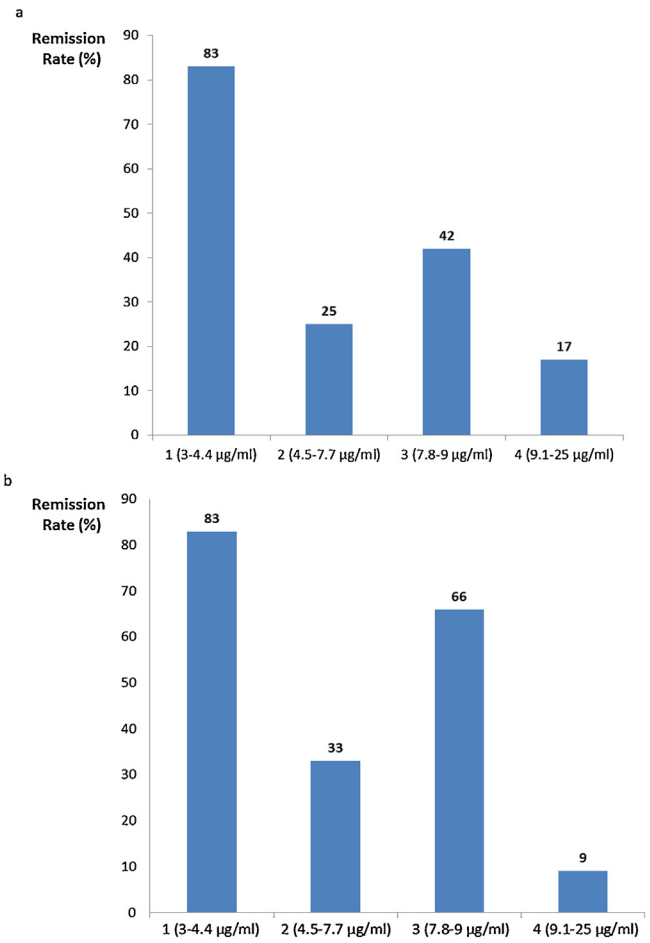

Fig. 3. (a) Rate of clinical remission 6 months post therapy intensification in relation to infliximab level quartiles at time of LOR. LOR — clinical loss of response. (b) Rate of clinical remission 12 months post therapy intensification in relation to infliximab level quartiles at time of LOR. LOR — clinical loss of response.

respectively, Fig. 2b) after the intervention. Subsequently, an analysis of infliximab trough level quartiles in association with clinical outcome was performed for both time-points. Clinical remission at both six and 12 months was significantly more prevalent for patients with infliximab levels at the first quartile (<4.54 μg/ml) before therapy intensification, compared to second and fourth quartiles (for 6 months' remission: p = 0.02, OR = 0.1, 95%CI 0.01–0.7, p = 0.003, OR = 0.02, 95%CI 0.001–0.26, for 12 months' remission: p = 0.02, OR = 0.11, 95%CI 0.02–0.7, p = 0.008, OR = 0.07, 95%CI 0.009–0.5, Fig. 3a, b).

An incremental gain analysis was also performed, to demonstrate alternations in clinical remission rate one year after intensification, in relation to infliximab TL upon LOR. While infliximab TL < 5 μg/ml upon LOR resulted in successful intensification in 60% of patients, only 10% of intensified patients with TL of 11 and over gained clinical remission (Supplementary Fig. 1). On ROC analysis, infliximab trough levels <4.8 μg/ml before treatment escalation were found to be optimal for dose intensification, both for clinical remission at 6 months (AUC = 0.77, p = 0.0001, 91% sensitivity, 66% specificity) and at 12 months (AUC = 0.74, p = 0.001, 83% sensitivity, 58% specificity, Fig. 4a, b).

In view of the possible differences between CD and UC in response to dose optimization and in pharmacokinetics, a subanalysis according to IBD type was performed; Median TL in CD patients who underwent clinical remission following dose intensification were significantly higher than among those who were still clinically active 6 months post-intervention (p = 0.01, median 4.5, 8.7 μg/ml,

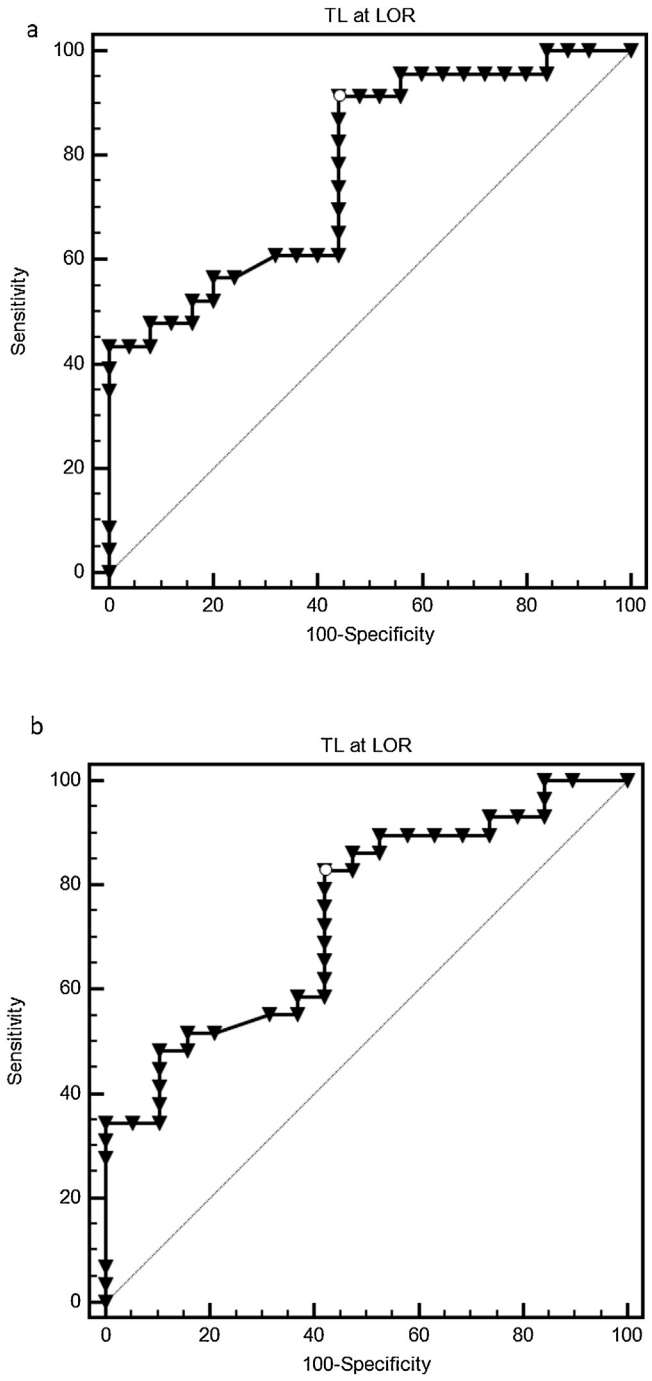

Fig. 4. (a) Infliximab trough levels below 4.8 μg/ml were optimal for clinical remission at 6 months (AUC = 0.77, p = 0.0001, 91% specificity, 66% sensitivity). (b) Infliximab trough levels below 4.8 μg/ml were optimal for clinical remission at 12 months (AUC = 0.74, p = 0.001, 83% specificity, 58% sensitivity).

IQR 3.8–8.3, 5.7–16 μg/ml respectively) and of borderline statistical significance 12 months post-intervention (p = 0.08, median 4.6, 8.3 μg/ml, IQR 4–8.2, 5.2–15 μg/ml respectively). Findings were quite similar for UC; Median TL in UC patients who underwent clinical remission following dose intensification were significantly higher than among those who were still clinically active 6 months post-intervention (p = 0.026, median 4.8, 8.9 μg/ml, IQR 3.4–8.1, 6.3–16 μg/ml respectively), as well as 12 months post intensification (p = 0.02, median 4.2, 8.7 μg/ml, IQR 3–8, 5.8–14.3 μg/ml respectively).

In order to map out all factors associated with optimal clinical outcome after infliximab therapy intensification univariate and multivariable analyses were performed. On univariate analysis, lower infliximab TL and longer disease duration were associated with clinical remission 6 months post intensification, while only lower infliximab TL was associated with clinical remission at 12 months. On multivariable analysis, only infliximab TL predicted both 6 and 12 months clinical remission. Supplementary Tables 1a, 1b demonstrate all associations on univariate and multivariable analyses.

4. Discussion

The direct association between infliximab TL and optimal clinical and endoscopic outcome has been proven in numerous studies [3–6,11]. Nevertheless, only few studies examined the effect of increasing infliximab TL on outcome of various interventions for LOR [4,17]. Yanai et al. demonstrated that infliximab TL greater than 3.8 μg/mL identified patients who failed to respond to an increase in drug dosage or a switch to another anti-TNF agent with 90% specificity. In that study, TL guided therapeutic decisions for more than two-thirds of IBD patients with clinical LOR [4].

The current study focused on the more specific subgroup of IBD patients, who developed LOR, with positive TL (and sufficient according to some studies, >3 μg/ml) and no identifiable ATI (i.e. non-immunogenic LOR). This study was designed to address a clinical dilemma many physicians face when an infliximab therapy patient experiences LOR; As the therapeutic arsenal for moderate – severe IBD is limited, should we always try to intensify infliximab therapy before switching to another drug? In which cases would intensification hardly be effective? Should we try to intensify even if infliximab levels are over 3 μg/ml? This study demonstrated that we should definitely try to intensify when infliximab TL is over 3 μg/ml. TL below 4.8 μg/ml are best associated with clinical remission, both 6 and 12 months after the intervention, but intensification can still be effective in most patients when applied in patients with TL < 7 μg/ml. It is of note, that in this study, in order to strengthen the validity of the findings, patients with positive ATI were excluded from the analysis. This was done on the grounds that the existence of ATI is associated with lower infliximab levels (through immune complex formation) [2,18].

In our study, dose escalation was performed in 24% of the cohort (55/130 patients). According to a recent meta-analysis, the mean percentage of patients on infliximab who needed dose escalation ranged from 14% to 54%, with a mean of 41.8% (585/1397 patients). The annual risk was 14.9% (585/3918) per patient-year. Another study demonstrated a dose escalation rate of 30%, which is similar to ours [19,20]. Notwithstanding, the rate of dose escalation differs between medical centers and depends not only on clinical judgement, but also on access to and acceptance of therapeutic drug monitoring for routine management of IBD patients.

In the present study infliximab therapy escalation resulted in clinical remission in 23 (49%), 29 (60%) of the patients by 6, 12 months. Quite similarly, in previous studies and case-series, dose-intensification has been shown to restore clinical response in 60–90% of patients in the short term, and in 35–50% in the long term (>12 months) [21,22]. A previous randomized — controlled study demonstrated that infliximab therapy intensification resulted clinical remission in 53–58%. In that trial, performing intensification in cases of low drug levels and no ATI, resulted in significantly reduced average treatment costs per patient, compared with routine infliximab dose escalation, and without any apparent negative effect on clinical efficacy [22]. In light of those findings, and the outcomes of our study, it seems that performing infliximab dose escalation with

lower infliximab TL, perhaps lower than 7 μg/ml, would not only be more clinically effective, but would also save treatment costs.

Several studies have evaluated association between infliximab TL and outcome of therapy in CD and UC separately. It has been shown that negative TL are associated with LOR in moderate/severe UC patients, regardless of immunogenicity. Few studies have compared LOR and dose escalation events in UC versus CD, and demonstrated that dose escalation may occur earlier and more often in UC patients. Nevertheless, exact optimal threshold for dose escalation of infliximab therapy in UC patients has not been described [23]. In a review which compared studies assessing proportion of patients not in remission above a certain threshold, for UC and CD separately, higher numbers of patients with UC were unlikely to be in remission at infliximab trough concentrations above ≥3 mg/mL[24], although head to head trials of infliximab pharmacokinetics upon LOR in both IBD types have not yet been performed [25]. In the current study, median TL upon intensification were significantly lower among those in remission by 6, 12 months, similarly for UC and for CD separately. On multivariate analysis, IBD type was not a factor, which affected outcome of intensification. It is of note, that an exact cut-off for UC, CD separately could not be calculated, due to the limited number of patients in each subgroup.

Multivariable analyses were performed in order to assess predictors of clinical remission after infliximab therapy intensification for both time-points (6, 12 months after intensification). The only factor significantly associated with successful intensification was lower infliximab TL. Few previous studies examined predictors of successful infliximab therapy intensification. In one study, smoking was demonstrated as the only modifiable predictive factor for failure to re-gain response by dose escalation. Age of diagnosis between 16 to 40 years and normal CRP at LOR were also associated with sustained 12-month response to intensification [26].

In the current study, no difference was detected between dose elevation to 10 mg/kg in comparison with interval shortening (to 5 mg/kg every 4 or 6 weeks). There is little agreement about the optimal protocol for dose-intensification. Pharmacokinetic modeling suggested that that interval shortening would result in greater effective drug level AUC compared to equivalent dose-increasing [27]. However, several previous studies have found both strategies similarly effective [26,28,29].

Our study has several limitations; Firstly, as this is a very specific cohort (infliximab therapy patients who underwent therapy intensification due to LOR, with TL > 3 μg/ml and without development of antibodies), the sample size is small, which affects subgroup and multivariate analysis. Secondly, as this is a retrospective study, confounders related to patients' selection cannot be excluded. Nonetheless, this is a 'real-life' cohort from two tertiary centers, with prospective clinical scores and TL measurements. A further limitation is the use of two different ELISA assays in the two centers, which may impact accuracy of the findings. Although it has been shown previously that both assays demonstrate a high level of agreement for measurement of infliximab trough levels, some of the ATI measured in infliximab positive patients using the drug-sensitive assay can be unidentified [30].

In conclusion, this study demonstrates that in patients experiencing non-immunogenic LOR, dose intensification would be significantly more effective in patients with lower infliximab TL, both in the short and in the long term. Patients with baseline TL above 9 μg/ml were very unlikely to reach clinical remission upon doubling the dose of infliximab. In fact, the only factor significantly associated with successful intensification was lower infliximab TL. This demonstrates once again that therapeutic drug monitoring assists us in selection of the optimal intervention for each specific patient.

Conflict of interest

Bella Ungar received consultation fees from Janssen and Abbvie. Shomron Ben-Horin received consulting and advisory board fees and/or research support from AbbVie, MSD, Janssen, Takeda and CellTrion. Uri Kopylov received speaker and advisory fees from Abbvie, Jannsen, MSD, Takeda and Medtronic, and research support from Jannsen, Medtronic and Takeda. Rami Eliakim received consultant and speaker fees from Janssen, Abbvie, Takeda and Medtronic. None of the other authors have any conflicts to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2019.02.013.

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