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Systematic Review: Efficacy of Escalated Maintenance Anti-Tumour Necrosis Factor Therapy in Crohn's Disease

Running title: Escalated Anti-TNF Therapy in Crohn's Disease

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Summary

Background: Loss of response to anti-TNF agents is a common clinical problem. Dose escalation may be effective for re-establishing clinical response in Crohn's disease (CD).

Aims: To perform a systematic review assessing the efficacy of escalated maintenance anti-TNF therapy in CD.

Methods: EMBASE, MEDLINE, Web of Science, and CENTRAL databases were searched for English language publications through to April 25, 2021. Full-text articles evaluating escalated maintenance treatment (infliximab or adalimumab) in adult CD patients were included.

Results: A total of 4733 records were identified, and 68 articles met eligibility criteria. Rates of clinical response (33-100%) and remission (15-83%) after empiric dose escalation for loss of response to standard anti-TNF therapy were high but varied across studies. Dose intensification strategies (doubling the dose versus shortening the therapeutic interval) were similarly efficacious. Dose-escalated patients tended to have higher serum drug levels compared to those on standard dosing. An exposure-response relationship following dose escalation was found in a number of observational studies. Randomised controlled trials comparing therapeutic drug monitoring (TDM) to empiric treatment intensification have failed to reach their primary end-points. Strategies including Bayesian dashboard-dosing and early treatment escalation targeting biomarker normalisation were found to be associated with improved long-term outcomes.

Conclusions: Empiric escalation of maintenance anti-TNF therapy can recapture clinical response in a majority of patients with secondary loss of response to standard maintenance doses. Proactive optimisation of maintenance dosing might prolong time to loss of response in some patients.

Keywords: Crohn's disease, infliximab, adalimumab, dose escalation, therapeutic drug monitoring

1. Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract which causes progressive intestinal damage and disability.[1] Anti-tumour necrosis factor alpha (anti-TNF) monoclonal antibodies are the mainstay of treatment for moderate to severe CD when conventional treatments have failed.[2] The introduction of these agents (infliximab, adalimumab and certolizumab pegol) has revolutionised the treatment of CD, making control of inflammation and mucosal healing attainable therapeutic targets.[3,4]

However, despite robust efficacy data, not all patients respond to anti-TNF therapy, and many lose response over time.[5] Rates of primary nonresponse range from 10 to 30%, with secondary loss of response by 12 months as high as 23 to 46% (dose escalation rates) or 5 to 13% (drug discontinuation rates).[5] Immunogenicity is an established mechanism of treatment failure,[6] with antidrug antibodies developing within the first 12 months of treatment in most cases.[7] The implications of treatment failure are significant, including the risks of disease progression, complications and surgery,[1,5] as well as the economic consequences.[8]

With each subsequent biologic therapy, clinical response rates fall.[6] Therefore, it is important that each anti-TNF agent be optimised prior to switching to an alternative. Standard dosing of infliximab (5mg/kg every eight weeks) and adalimumab (40mg every other week), as defined in registration studies,[9-11] is efficacious for maintaining remission in CD. However, emerging strategies for optimising anti-TNF therapy support dose escalation in certain clinical scenarios.[3,4,6,7,12] Such strategies may achieve early control of disease activity and longer-term remission,[12] with the potential to limit disease progression and alter the natural history of this condition.[4]

Therapeutic drug monitoring (TDM) may be used to guide clinical decision-making in response to treatment failure, often referred to as 'reactive' TDM.[6,7] 'Proactive' TDM, or dose adjustments to

meet drug level targets in the absence of clinical or biochemical loss of response, remains a controversial strategy.[6,7] Various treatment algorithms based on serum drug levels and the presence or absence of antidrug antibodies have been described.[5-7] Subtherapeutic drug levels are associated with an increased risk of antibody formation.[13] In turn, the development of antibodies is associated with lower drug levels and an increase in disease activity.[14-16]

Loss of response to anti-TNF therapy and the subsequent need for dose intensification have been well described,[5] however, the evidence for dose escalation in CD (with or without guidance from TDM) remains controversial. In this systematic review, we aimed to assess the clinical efficacy of dose escalation in CD patients receiving maintenance infliximab or adalimumab therapy. We also aimed to compare the efficacy of dose escalation strategies and evaluate the role of TDM based dosing. Finally, we sought to identify predictors of response to dose-escalated therapy.

2. Materials and methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[17] (Table S1) using an *a priori* established protocol. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration ID: CRD42020206069).

2.1 Data sources and search strategy

We performed a systematic search of English language articles from inception through to 26 August 2020 using six electronic databases: EMBASE+EMBASE Classic (Ovid), MEDLINE, MEDLINE In-Process, Epub Ahead of Print, Web of Science and, the Central Cochrane Register of Controlled Trials (CENTRAL). The search was then updated on 25 April 2021. The search strategy used a combination of free-text and medical subject heading (MeSH) terms to capture the following concepts: i) Population: adult patients with CD (eg “Crohn’s disease” [MeSH]); ii) Intervention: anti-TNF drugs (eg “infliximab” or “adalimumab”); iii) Anti-TNF dose optimisation (eg

"dose escalation" or "dose intensification" or "empiric dose escalation" or "therapeutic drug monitoring")

The full search strategy for each database is shown in Tables S2-5. We also manually searched reference lists of key publications and the proceedings from Digestive Disease Week, United European Gastroenterology Week and European Crohn's and Colitis Organisation for the past five years to identify additional studies and emerging data. The clinicatrials.gov and controlled-trials.com databases were searched for ongoing trials. All search results were imported into a reference management software (Endnote X8, Clarivate Analytics) and duplicates were removed. Two authors (VYM and EKW) independently screened records by title and abstract, followed by full text, using predefined eligibility criteria, on Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Any disagreements between the authors were resolved by discussion, with third-party input as required.

2.2 Selection criteria

Studies were eligible for inclusion if they met all of the following criteria: i) full text publications; ii) study design: interventional (randomised or nonrandomised) or observational (prospective, retrospective or case-control); iii) adult population (age ≥18 years); iv) patients with luminal and/or perianal CD on maintenance anti-TNF therapy (infliximab or adalimumab)**;** v) At least 10 patients on escalated dosing (regular maintenance doses exceeding 40mg every other week for adalimumab and 5mg/kg every eight weeks for infliximab); vi) Reporting on at least one of the following outcomes of interest defined as per authors in individual studies:

- Primary outcome: clinical response and clinical remission after dose escalation
- Secondary outcomes: biochemical response, biochemical remission, endoscopic response, endoscopic remission, radiologic response, radiologic remission, fistula healing, fistula closure, change in anti-TNF drug level, change in antidrug antibody titre

Exclusion criteria were as follows: i) studies only available in abstract form; ii) case reports, case series, reviews and meta-analyses; iii) studies that only provided pooled analyses for patients with CD and UC

2.3 Data extraction

Data from included studies were extracted in duplicate into a standardised data table in Excel (Microsoft software) by two independent authors (VYM and EKW). Any disagreements were resolved by consensus and reference to the original paper. The following predefined data were extracted: first author, year of publication, country where study was conducted, study design, single or multicentre, study duration, sample size, duration of follow up, population characteristics (disease phenotype, disease duration, prior anti-TNF exposure, concomitant therapy). The following data about the study intervention were extracted: biologic agent(s) used, anti-TNF optimisation strategy (empiric or TDM guided), escalated dosing schedule(s), time to dose escalation, proportion of patients on escalated dosing. Data on clinical, biochemical, endoscopic and/or radiologic outcomes after anti-TNF dose escalation were extracted. If available, pharmacokinetic data including anti-TNF drug levels, antidrug antibody titres and type of assay used were also recorded.

2.4 Risk of bias assessment

Two authors (VYM and EKW) independently evaluated the RCTs using the Cochrane Collaboration's tool for assessing risk of bias in randomised studies.[18] Bias was assessed across six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias using Review Manager (RevMan version 5.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Colaboration, 2020). The RCTs were considered at low risk of bias if all domains were rated low risk of bias, at high risk of bias if one or more domains were rated high risk of bias, and at unclear risk of bias if one or more domains were rated unclear risk of bias with no high risk domains. Observational studies and post hoc analyses of RCTs were assessed using

the Newcastle-Ottawa scale (NOS).[19] Bias was evaluated across three domains: selection of study groups, comparability of groups and, ascertainment of exposure and outcomes. Studies were considered at low risk of bias if rated 7-9 stars on the NOS (out of a total maximum of 9 stars), at moderate risk of bias if rated 4-6 stars, and at high risk of bias if rated 0-3 stars. Any discrepancies in the risk of bias assessment were resolved by discussion and reference to the original paper.

2.5 Data synthesis

Data from included studies were summarised in a qualitative synthesis. We did not perform a meta-analysis due to substantive heterogeneity in study design, therapeutic strategy and protocol for anti-TNF optimisation, and duration of follow-up in the included studies.

3. Results

3.1 Search results and study characteristics

The search results are summarised in Figure 1. All eligibility criteria were met in the 68 articles included. Of the included studies, nine were RCTs, nine were post-hoc analyses of the RCTs, and five were single-arm trials. We included two reports of the Steenholdt RCT, with a 12 week follow up[20] and a 20 week follow up.[21] In addition, 44 observational studies were reviewed, of which only 10 were prospective studies. Of the retrospective studies, one was a follow-up study of the Trough Concentration Adapted Infliximab Treatment trial (TAXIT).[22]

Adalimumab was dose escalated to 40mg weekly in most studies (n= 27), although a small number of studies escalated patients to 80mg every other week (n= 4), 80mg weekly (n= 1) or 40mg every ten days (n= 2). For infliximab, dose escalation was defined as a shortening of treatment interval to 4-7 weeks (n= 7), an increase in dose up to or exceeding 10mg/kg (n=9), or a combination of both (n=21). Across included studies, secondary loss of response to standard dosing was defined by global physician assessment and/or objective evidence of increased disease activity in patients with previous response to therapy. Clinical response and remission

were generally reported using standardised clinical indices (Crohn's Disease Activity Index [CDAI] or Harvey Bradshaw Index [HBI]). Across the included studies, clinical response was defined as a decrease in CDAI score of 50-70 points or more, or a decrease in HBI score of 3 or more points. A CDAI score less than 150 or a HBI score below five indicated clinical remission.

3.2 Risk of bias assessment

The risk of bias assessment for RCTs is presented in Figure S6. All but one study[23] described the randomisation process and allocation concealment sufficiently. None of the studies were assessed to be at risk of attrition bias due to incomplete outcome data. The CALM trial[3] and the PRECISION trial[12] were at a high risk of bias due to lack of participant or investigator blinding. The outcome assessors were not blinded to TDM data in the Steenholdt RCT[20] leading to a high risk of bias. Overall, five of the RCTs were found to be at low risk of bias,[9-11] three studies were at a high risk of bias,[3,12,20,21] and one study[23] was rated as having some concerns around risk of bias.

The majority of observational studies (n=34) received 4-6 stars out of 9 on the NOS scale indicating a moderate risk of bias, the remainder of the studies (n=23) were at a low risk of bias (Table S7). As data from observational studies was largely retrospective, outcomes of interest were often present at the outset increasing the potential for bias. Important confounders were uncontrolled in some cases with differences in care delivery and non-standardised protocols for anti-TNF optimisation.

3.3 Standard maintenance dosing of infliximab and adalimumab

Our literature search identified three RCTs that validated anti-TNF dosing schedules in large prospective cohorts.[9-11] The Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM)[10] was a double-blind maintenance study in patients with moderately to severely active CD (n=854). All patients received open-label induction with adalimumab 80mg at week 0 and 40mg at week 2. Following this, patients were randomised to one of three

maintenance arms: adalimumab 40mg every other week, 40mg weekly or placebo. The coprimary endpoints were clinical remission (CDAI<150) at weeks 26 and 56. Both adalimumab dosing regimens were found to be superior to placebo, and equally effective in maintaining remission at both week 26 (39.5% 40mg every other week *vs* 46.5% 40mg weekly, *P*=0.22) and week 56 (36% *vs* 41.4%, *P*=0.34).[10]

In ACCENT I,[11] all patients received a 5mg/kg infliximab infusion at baseline (n=580). Patients were then randomised to receive placebo (group I), infliximab 5mg/kg (group II) or infliximab 10mg/kg (group III) with infusions at week 2, week 6 and every eight weeks thereafter. Infliximab maintenance treatment was superior to placebo, with infliximab-treated patients more likely to be in clinical remission (CDAI<150) at week 30 compared to patients receiving placebo (OR 2.7, 95% CI 1.6-4.6). However, there was no clinically significant difference in remission rates between the two infliximab dosing strategies at week 30 (OR 1.3, 95% CI 0.74-2.20) or week 54 (OR 1.58, 95% CI 0.90-2.80).[11]

3.4 Efficacy of anti-TNF dose escalation

3.4.1 Clinical response and remission

Clinical outcomes following anti-TNF dose escalation are shown in Tables 1-2. The majority of clinical efficacy data were from retrospective studies with subcohorts that underwent empiric dose escalation (without the use of TDM) for loss of response to standard treatment. Twenty studies reported clinical outcomes following empiric escalation of maintenance adalimumab.[10,23-41] Response rates ranged from 33 to 100% (Figure 2), and remission was achieved in 15 to 83% of patients at any point after treatment escalation.[10,23-41] In 15 of these studies, more than half of the patients regained clinical response after dose escalation.[23-25,27-32,35-39,42] In the study by Narula *et al*,[31] only one (7.1%) of the 14 anti-TNF naïve patients escalated to 40mg weekly achieved clinical remission at the end of follow-up. For infliximab, rates of clinical response and remission following empiric escalation for treatment failure ranged from 34 to 90% and 26 to 81%, respectively, across

12 studies (Figure 3).[28,31-33,43-50] In eight of these studies, intensified therapy recaptured response in over 50% of the patients.[28,36,45-50] In one retrospective study (n=265), a switch to adalimumab achieved numerically higher rates of clinical response (83.3%) than infliximab dose escalation (42.3%).[32]

Sustained clinical response and remission beyond 12 months from the time of dose escalation were reported in 14 studies and ranged from 33 to 90% for response and 28 to 81% for remission.[27,31,33-36,41,42,45-48,50,51] Similar rates of loss of response to dose-escalated treatment (tertiary loss of response) were reported across five studies.[27,30,44,45,52] In the study by Ma *et al*,[30] over half (56.8%) of those that responded clinically to escalated adalimumab subsequently lost response (median time to tertiary loss of response 47.9 weeks [IQR 24.7-80.3]). In another study[45] of 82 patients receiving high dose infliximab therapy, 33% discontinued treatment after a median of 31.3 weeks.

3.4.2 Biochemical response and remission

Twelve studies analysed the biomarker response to anti-TNF dose escalation.[3,25,27,34,39,45,49,51,53-56] Of these, six showed a significant reduction in CRP with anti-TNF dose escalation.[45,49,51,54-56] A post-hoc analysis[53] of the TAILORIX trial showed a significant decrease in faecal calprotectin (P=0.049) but not in CRP (P=0.193) following escalation of infliximab dosing.

3.5 Optimisation strategies for anti-TNF therapy

3.5.1 Interval shortening versus dose doubling

In five retrospective studies comparing dose escalation strategies, doubling the infliximab dose versus shortening the treatment interval led to similar clinical and biochemical outcomes.[47,48,51,53,54] In the study by Dreesen *et al*,[54] dose escalation failed to achieve therapeutic infliximab levels (≥3µg/mL) when high titre antidrug antibodies (>282 ng/L) were present, regardless of dosing strategy. However, when antibodies were quantifiable but low (<282 ng/mL), a combination of

increased dose and reduced interval was most effective at restoring drug levels, followed by dose doubling alone, which was superior to interval shortening alone *(P*=0.0005). In the absence of anti-infliximab antibodies, all three strategies were equally effective at restoring serum drug levels in patients with loss of response.[54] For adalimumab, Duveau *et al*[27] showed that 40mg weekly dosing was associated with higher rates of clinical response at 12 months (*P*=0.03) and lower rates of tertiary loss of response (*P*=0.01) compared to 80mg every other week.

3.5.2 Dose escalation versus anti-TNF re-induction

One retrospective study[57] (n=80) compared anti-TNF re-induction to shortening the dosing interval in a cohort with complex CD (91% stricturing or penetrating) and secondary loss of response. There was no significant difference in the rates of treatment failure within 12 months of re-induction compared to dose escalation (24% *vs* 15%, *P*=0.27).[57] However, beyond 24 months, rates of treatment failure were higher in the re-induction group compared to the dose escalation group, leading to a higher overall rate of treatment failure after re-induction over the course of the study (48% vs 24%, *P*=0.02).[57]

3.5.3 Therapeutic drug monitoring

Three RCTs compared TDM-guided dosing to empiric dose escalation.[20,21,58,59] In a single-blind non-inferiority trial, 69 CD patients with loss of response to standard infliximab therapy were randomised to empiric escalation (5mg/kg every four weeks) or optimised using a TDM algorithm.[20,21] The primary objective of this study was to demonstrate that the use of reactive TDM had comparable clinical efficacy to empiric dose escalation, but was significantly more cost effective. Clinical response rates were similar between the two groups at 12 weeks (57.6% TDM group *vs* 52.8% empiric group, *P*=0.810) [20] and 20 weeks of follow-up (75.8% *vs* 55.6%, *P*=0.128).[21] This was also observed for perianal disease, with a similar decrease in Perianal Disease Activity Index (PDAI) scores for patients in the reactive TDM group versus the empiric treatment group at 12 weeks (*P*=0.421) [20] and 20 weeks (*P*=0.495).[21]

Restellini *et al*[60] compared reactive TDM to empiric dosing in a retrospective cohort of CD patients with loss of response to adalimumab (n=104). The primary outcome was the rate of composite remission, defined as HBI<5 with biomarker normalisation and Simple Endoscopic Activity Score (SES-CD) <3. Similar proportions of patients achieved the primary endpoint in the TDM group versus the empiric escalation group at 3 months (42.3% *vs* 16%, *P*=0.619), 6 months (30.8% *vs* 45.5%, *P*=0.328) and 12 months (39.4% *vs* 27.3%, *P*=0.978).[60] Conversely, Kelly *et al*[61] compared endoscopic outcomes after TDM based dose adjustment versus standard clinical management in CD and UC patients with documented endoscopic disease at baseline. While the baseline SES-CD was comparable between the two groups, the TDM group had lower SES-CD scores compared to the clinically dosed group at median 6 months after dose optimisation (*P*=0.054).[61]

In the TAXIT trial,[58] all patients were initially dose adjusted to achieve therapeutic infliximab trough levels between 3-7 µg/mL. Following this proactive optimisation phase, the proportion of CD patients in clinical remission increased significantly compared to baseline (88.4% *vs* 65.1%, *P*=0.020). However, at 12 months after randomisation, there was no significant difference in clinical remission rates between the proactive TDM group versus patients dosed on symptoms alone (62.6% *vs* 54.9%, *P*=0.353). In terms of secondary endpoints, the proactive TDM group had fewer relapses (7% *vs* 17%, *P*=0.018) and longer times to relapse (*P*=0.017) compared to those who received standard care based on clinical symptoms. Pouillon *et al*[22] conducted a retrospective follow-up study of the TAXIT cohort examining mucosal healing and the durability of infliximab treatment. The rates of mucosal healing were high at the conclusion of TAXIT, and similar between the proactive TDM group and the standard care group (91% *vs* 90%, *P*=1). Overall, the rate of infliximab discontinuation was similar, however, within one year, more patients in the clinically-based dosing group discontinued treatment compared to the proactive TDM group (37% *vs* 9.5%, *P*=0.04). Similarly, a multicenter retrospective study of 264 IBD patients demonstrated a significantly lower cumulative probability of treatment failure in infliximab-treated CD patients

where dosing was optimised by proactive versus reactive TDM over a median follow-up of 2.4 years (log-rank *P*<0.001).[62]

More recently, the TAILORIX trial[59] evaluated proactive TDM in a cohort of biologic naïve patients with active luminal CD (n=122). The primary endpoint was corticosteroid-free remission (CDAI<150) at all visits between week 22 and week 52 of the study, with no ulcers at week 54, no surgery for bowel resection or abscess, and no new fistula. Again, incorporating proactive TDM data into clinical decision-making showed no significant benefit, with comparable proportions of patients achieving the primary endpoint across two dosing arms that utilised infliximab trough levels and one dosing arm that relied on symptoms and biomarkers alone (*P*=0.50).

Fernandes *et al* conducted a prospective study of proactive TDM, with a historical control group that received conventional treatment.[63] IBD patients completing infliximab induction were prospectively enrolled in the proactive TDM group (n=135) and were subsequently optimised to maintain infliximab trough levels between 5 – 10 µg/mL, with the primary outcome of faecal calprotectin remission (<250 µg/g) at two years of follow-up. The majority of patients were biologic naïve (85.6%) and were receiving concomitant immunomodulators (82.3%). At the end of follow-up, rates of faecal calprotectin remission were higher in the proactive TDM group compared to the control group (72.0% *vs* 53.8%, *P*=0.018). Proactive TDM was also associated with higher rates of clinical remission (87.8% *vs* 72.5%, *P*=0.014).[63] In an earlier study of the same cohort, CD patients (n=153) that were optimised by proactive TDM had higher rates of endoscopic remission (75.8% *vs* 41.7%, *P*<0.001) and fewer adverse disease outcomes (48.5% *vs* 70.0%, *P*=0.019) when compared to the historical control group that received standard care.[64]

3.5.4 Individualised Bayes-based dosing

The literature search identified two studies of Bayesian-based anti-TNF dosing in prospective cohorts of IBD patients receiving maintenance infliximab therapy.[12,65] The PRECISION trial (n=80)

evaluated proactive dashboard dosing for adult IBD patients in stable clinical remission.[12] Patients were randomised to either a 'precision dosing' group where infliximab maintenance doses were individualised to achieve and maintain trough levels at a target of 3 µg/mL using a dashboard system or a control group without dose adjustments. The dashboard system utilised Bayesian software and individual patient data, including drug levels, antidrug antibody titres, inflammatory markers, and other patient-specific variables such as body weight and gender, to proactively determine the optimal dose and infusion interval. A higher proportion of patients optimised by dashboard dosing remained in clinical remission, with fewer relapses, during 12 months of treatment compared to those who received standard care (90.9%% *vs* 63.6%, *P*=0.008). Patients in the precision dosing group also had lower faecal calprotectin levels (47 µg/g [IQR 6-120] *vs* 144 µg/g [IQR 59-666], *P*=0.031) but this was not observed for CRP levels. Similarly, Juncosa *et al* found that clinical remission rates increased significantly from baseline in the 34 CD patients where treatment was proactively intensified with guidance from a dashboard system to maintain infliximab trough levels >3 µg/mL (23.5% to 38.2%, *P*=0.007).[65]

3.5.5 Tight control

The CALM trial[3] compared early treatment escalation using a tight control strategy to standard clinical management in a prospective cohort of 244 adult patients with moderate to severe CD. The tight control group had treatment escalations according to strict clinical and biochemical criteria (CDAI≥150, CRP≥5mg/L, faecal calprotectin ≥250 µg/g or prednisolone use). The standard care group was escalated based on clinical disease activity alone (CDAI decrease of <100 points compared with baseline or CDAI≥200 or prednisolone use). The primary endpoint of mucosal healing (CDEIS<4) with the absence of deep ulcers at 48 weeks was achieved by 46% of the tight control group compared to 30% of the clinical management group (*P*=0.010). Overall, more patients in the tight control group were escalated to adalimumab 40mg weekly compared to those in the standard care group. A retrospective follow-up study of the CALM cohort found that patients who achieved endoscopic or deep remission after one year of intensified treatment were

significantly less likely to have disease progression, including new fistulas, strictures and hospitalisation or surgery for CD, over a median of three years.[4] In a 'real world' context, a retrospective study of dose-escalated CD patients (n=149) found that management via a virtual clinic, where there is a tendency towards a 'tight control' approach with regular biomarker analysis, is associated with higher rates of treatment escalation success compared to standard outpatient care (*P*<0.001).[66]

3.6 Relationship between anti-TNF dosing schedule and serum drug level

Thirteen studies reported on serum drug levels following dose escalation.[22,23,29,45,53,54,67-74] Of these, seven showed significantly higher drug levels in patients on escalated anti-TNF therapy compared to standard dosing.[29,45,53,54,68-70] In a prospective study[29] of 168 CD patients on maintenance adalimumab therapy, over half (65.4%) required escalation to weekly dosing. Adalimumab trough levels increased after dose escalation compared to baseline (4.8 µg/mL [2.3-8.9] to 9.4 µg/mL [1.2-16.4], *P*=0.001). The increase in drug level was significantly higher for those that responded clinically to dose-escalated therapy versus non-responders (5.9 µg/mL [1.9-7.3] *vs* 0.0 µg/mL [0.0-1.7], *P*<0.0001). In a post hoc analysis[69] of the Steenholdt RCT, infliximab trough levels were found to be increased across all patients after the treatment interval was shortened to four weeks. However, the increase in drug level from the point of standard treatment failure was significantly higher in those that regained clinical response during the 12 week follow-up after dose escalation compared to non-responders (9.9 µg/mL [7.4-12.9] *vs* 4.7 µg/mL [1.7-10.6), *P*=0.040). These findings are supported by the Paul *et al* study,[71] where an increase in infliximab trough level >0.5µg/mL after dose escalation was strongly associated with clinical remission (*P*=0.044) and mucosal healing (*P*=0.048). In a post-hoc analysis of the TAILORIX study by Dreesen *et al,*[53] infliximab trough levels after dose escalation were found to be significantly higher in patients without endoscopic ulceration at 54 weeks compared to those with endoscopic ulceration (8.0 µg/mL[6.7-9.3] *vs* 5.1 µg/mL [4.5-5.8], *P*=0.002). Similarly, an infliximab trough level >7 µg/mL at all time points following dose escalation was associated with radiologic response (*P*=0.039) and

remission (*P*=0.019) in a sub-group analysis of the TAILORIX cohort.[75] In five studies, however, an exposure-response relationship following treatment intensification was not observed.[23,68,72-74,76]

3.7 Factors affecting response to dose escalation

Twenty-two studies analysed factors which affect response to escalated anti-TNF therapy.

Clinical disease activity: In a small prospective study (n=42) examining the efficacy of adalimumab 80mg weekly in patients with active luminal CD, CDAI<260 at baseline predicted short term clinical remission following dose escalation (*P*=0.0016).[25] Motoya *et al*[39] found that baseline CDAI was significantly lower in patients who achieved clinical remission at week 24 after escalation to adalimumab 80mg every other week compared to those not achieving remission (OR 0.961, 95% CI 0.9307-0.9920). In the Suzuki *et al* trial,[49] baseline CDAI <220 did not predict clinical remission at 40 weeks after dose escalation (*P*=0.116). The absence of prolonged steroid use was associated with sustained steroid-free remission after dose escalation in one study,[28] while the need for concurrent steroids at anti-TNF induction predicted nonresponse to dose escalation in another study.[30]

Disease phenotype: In the majority of literature reviewed, disease phenotype did not predict clinical response to dose escalation.[25,30,39,45,51,56,59] In two retrospective studies, patients with complicated disease were more likely to respond to escalated therapy than patients with an inflammatory phenotype.[27,47] However, in two other retrospective studies, nonstricturing nonpenetrating disease was associated with successful dose escalation.[66,77]

Disease duration: Disease duration did not affect clinical response to escalated anti-TNF treatment in most cases.[25,27,39,45] Older age at diagnosis was associated with a better response to dose escalation in a small number of studies.[47,60,66]

Prior anti-TNF exposure: Of ten studies, six showed no difference in response to escalated therapy according to previous anti-TNF exposure.[15,25,27,45,47,57] In the Restellini *et* al study,[60] patients without prior infliximab exposure were more likely to achieve composite remission at 12 months following adalimumab escalation compared to anti-TNF experienced patients (41.7% *vs* 20%, *P*=0.025). Ma *et al*[30] found that previous anti-TNF exposure predicted earlier time to tertiary loss of response (*P*=0.048).

Concomitant immunomodulators: Of eleven studies evaluating the role of combination therapy in patients with loss of response to anti-TNF agents,[27,30,39,44,45,47-49,51,57,60] only one study[57] showed a therapeutic benefit. Srinivasan *et al*[57] found that immunomodulator co-therapy was associated with a significantly longer time to treatment failure following dose escalation compared to anti-TNF monotherapy (*P*<0.03).

Inflammatory biomarkers: There were conflicting data about the effect of biochemical inflammation at baseline on the response to dose escalation. In five retrospective studies, lower CRP and faecal calprotectin at standard treatment failure were associated with a durable clinical response to dose escalation.[16,27,47,57,60] However, five other studies did not find any association between biomarker levels at loss of response to standard dosing and the success of treatment escalation.[25,30,39,51,54] Higher serum albumin,[49,57,60,71] lower platelet count,[60] and higher haemoglobin levels[60] at baseline predicted a better response to anti-TNF escalation.

Serum drug level and antidrug antibodies at baseline: In three retrospective studies, serum drug levels at the time of treatment failure did not distinguish responders to dose escalation from nonresponders.[45,57,60] However, in a prospective single-arm trial[49] (n=39) of intensified infliximab therapy, clinical remission rates at 40 weeks after dose escalation were higher in patients with a trough infliximab level ≥1μg/mL at baseline compared to those with a level <1μg/mL (*P*=0.033). In a prospective study of therapeutic drug monitoring, Paul *et al*[71] showed that an infliximab trough

level <2μg/mL along with an antidrug antibody titre <200ng/mL at baseline were strongly predictive of subsequent mucosal healing after dose escalation (*P*=0.004). Dreesen *et al*[54] found that an antibody titre <282ng/mL at baseline independently predicted therapeutic drug levels (*P*=0.003) and clinical response (*P*=0.034) after dose intensification compared to patients with an antibody titre >282ng/mL.

3.8 Efficacy of escalated anti-TNF dosing for perianal Crohn's disease

Four studies reported perianal disease outcomes in dose-escalated patients.[12,20,21,78,79] In a cross-sectional study of 117 CD patients with fistulising perianal disease, patients that achieved the primary outcome of fistula healing were more likely to be on escalated dosing regimens when compared to those who did not (OR 8.3, 95% CI 3.5-19.9).[78] Serum infliximab levels were also higher in patients that achieved fistula healing compared to those with active fistulas (15.8 μg/mL [IQR 9.9-27] *vs* 4.4 μg/mL [IQR 0-9.8], *P*<0.0001). Similarly, in a retrospective study by Strik *et al*, patients on intensified infliximab dosing tended to have higher rates of fistula closure (80%) compared to those on standard dosing (59%).[79] Infliximab trough levels were again higher amongst those that achieved fistula closure (6.0μg/mL [IQR 5.4-6.9] *vs* 2.3μg/mL [IQR 1.1-4.0], *P*<0.001) compared to those who did not. This was also seen in the adalimumab-treated patients, with higher drug levels in patients with fistula closure compared to active fistulising disease (7.4μg/mL [IQR 6.5-10.8] *vs* 4.8μg/mL [IQR 1.7-6.2], *P*=0.003). However, the rate of fistula closure was numerically higher in the standard dosing group (81.8%) compared to the dose intensified group (50%).[79] In the PRECISION trial, treatment was de-escalated for three patients with infliximab trough levels above 3μg/mL, which was the set therapeutic target.[12] However, this resulted in a flare of perianal disease, with re-opening of a previously closed perianal fistula in the three patients.[12]

4. Discussion

Implementing a 'treat-to-target' strategy in Crohn's disease, which may have the potential to prevent disease progression, requires the optimal use of anti-TNF therapies. Loss of response to anti-TNF agents is a common therapeutic challenge,[5] but dose escalation can re-capture response in a majority of patients without an increased risk of toxicity,[9-11] and is likely to be an important strategy in prolonging the life of these treatments.

We considered a number of factors that may affect patient response to intensified therapy. Prior anti-TNF exposure predicts the need for dose escalation in population based cohorts,[24] however, outcomes following treatment escalation were generally comparable between anti-TNF naïve and anti-TNF experienced patients.[16,25,27,45,47,57] This likely reflects the efficacy of dose escalation in overcoming low levels of immunogenicity.[54] Thiopurine co-therapy reduces immunogenicity and the risk of loss of response in anti-TNF treated patients,[80-82] but did not appear to improve the clinical response to dose escalation, with only one retrospective study[57] showing an additional therapeutic benefit of combination therapy compared to escalated monotherapy.

Anti-TNF treatment failure is predicted by low serum drug levels.[80] A significant increase in drug level after dose escalation was an important predictor of clinical, biochemical and endoscopic response in observational studies.[29,69,71] However, antidrug antibody titre remains important with dose escalation restoring therapeutic drug levels most reliably when antibodies are absent or present in low-titres.[54,71] Therapeutic drug monitoring may prevent futile treatment escalation by identifying patients with high-titre antidrug antibodies, and has been found to be a cost-effective strategy in the 'reactive' setting.[20,21]

However, the clinical utility and longitudinal benefits of regular or proactive TDM remain uncertain. Randomised controlled trials comparing TDM-based strategies to empiric escalation for infliximab have failed to reach their primary end-points.[58,59] Similarly, preliminary data from the recent

Serene-CD Maintenance Study showed comparable clinical and endoscopic outcomes in adalimumab-treated patients who underwent proactive TDM compared to clinically adjusted dosing.[83] One reason for this may be the lack of long term follow-up in many of these studies. In the TAXIT trial,[58] all patients were initially optimised to achieve therapeutic trough levels prior to randomisation, which may have obscured potential benefits of proactive dosing in comparison to standard treatment. However, some recent data do indicate that proactively dosed patients have fewer flares and lower rates of treatment discontinuation compared to those receiving standard care.[58,63-64]

The pharmacokinetics of anti-TNF agents have significant inter-individual variability.[84] Moreover, optimal drug levels may vary according to therapeutic target, disease phenotype or complexity.[85] In perianal fistulising disease, for instance, the need for more aggressive drug level targets, to achieve endpoints such as fistula healing, is well established.[78,79] Intensified maintenance doses are likely required to achieve adequate drug levels in this group of patients.[78] In most studies, patients with complex disease phenotypes, including those with perianal involvement, had similar clinical and biochemical response rates to treatment escalation compared to patients with predominantly inflammatory luminal disease.[25,27,30,39,45,47,51,57,60] In an era moving increasingly towards personalised treatments, dashboard systems that incorporate individual patient data,[12] including disease severity and phenotype, to determine the optimal anti-TNF dose are a novel therapeutic strategy, requiring further validation in 'real world' settings.

The control of biomarkers, such as faecal calprotectin and C-reactive protein, may be an alternative therapeutic target to guide the escalation of maintenance treatment in CD. The CALM trial[3] provides compelling evidence for this 'tight-control' approach. Early treatment escalation in response to biomarker elevation, which may indicate residual intestinal inflammation, was associated with superior clinical and endoscopic outcomes in this study.[3] However, further data

are required to determine the efficacy of such tight control algorithms in clinical practice, where it may be more challenging to apply stringent clinical and biochemical treatment escalation criteria.

The potential for bias in the included literature must be considered. While rates of clinical and biomarker response to dose escalation were high in randomised trials, patients were generally dose escalated on an 'open-label' basis and assessments of response to escalated therapy were subject to investigator bias.[3,9-11] In addition, much of the evidence to support anti-TNF escalation in the setting of treatment failure comes from non-randomised uncontrolled assessments, with largely retrospective data. The majority of these studies did not follow a standardised protocol for treatment optimisation and, definitions of secondary loss of response and dose escalation were often applied retrospectively.

Moreover, this review has several limitations. We have qualitatively summarised the relevant literature, but did not perform a meta-analysis of the evidence supporting each dose escalation strategy. Our focus was on anti-TNF maintenance therapy, emerging data comparing standard and high induction dosing regimens were not reviewed.[86] The pharmacoeconomic implications of each therapeutic strategy were not evaluated in this review, although optimising the cost efficacy of anti-TNF agents remains an important consideration.

We have identified some knowledge gaps. In clinical practice, treatment de-escalation is often unsuccessful,[24,87] however, data evaluating effective step-down strategies for anti-TNF therapy are lacking. Moreover, the optimal duration of intensified anti-TNF treatment following secondary loss of response is not yet established. While empiric escalation may be adequate initially to re-establish clinical response, further prospective data are needed to determine the utility of regular TDM for maintaining remission in patients receiving intensified therapy.

In this systematic review, we have summarised the controlled trial and 'real world' experience with escalated maintenance anti-TNF dosing. We have examined the exposure-response relationship following dose escalation, and the comparative efficacy of intensification strategies, including for perianal fistulising disease, which has not been done elsewhere. Our findings have implications for clinical practice. In the setting of secondary anti-TNF loss of response, empiric dose escalation was found to be an effective therapeutic strategy. The evidence to support the use of proactive TDM in guiding treatment escalation is limited. Biomarker normalisation may be a helpful target in driving anti-TNF dose escalation, however, the efficacy of such tight-control strategies in prospective 'real world' settings remains to be seen.

References

1. Peyrin-Biroulet L, Loftus EV, Jr., Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol. 2010;105(2):289-97.
2. Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis. 2010;4(1):28-62.
3. Colombel JF, Panaccione R, Bossuyt P, Lukas M, Baert F, Vanasek T, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet. 2017;390(10114):2779-89.
4. Ungaro RC, Yzet C, Bossuyt P, Baert FJ, Vanasek T, D'Haens GR, et al. Deep Remission at 1 Year Prevents Progression of Early Crohn's Disease. Gastroenterology. 2020;159(1):139-47.
5. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. Clin Transl Gastroenterol. 2016;7(1):e135.
6. Ding NS, Hart A, De Cruz P. Systematic review: predicting and optimising response to anti-TNF therapy in Crohn's disease - algorithm for practical management. Aliment Pharmacol Ther. 2016;43(1):30-51.
7. Mitrev N, Vande Casteele N, Seow CH, Andrews JM, Connor SJ, Moore GT, et al. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. Aliment Pharmacol Ther. 2017;46(11-12):1037-53.
8. Niewiadomski O, Studd C, Hair C, Wilson J, McNeill J, Knight R, et al. Health Care Cost Analysis in a Population-based Inception Cohort of Inflammatory Bowel Disease Patients in the First Year of Diagnosis. Journal of Crohn's and Colitis. 2015;9(11):988-96.
9. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007;56(9):1232-9.
10. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: The CHARM trial. Gastroenterology. 2007;132(1):52-65.
11. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359(9317):1541-9.
12. Strik AS, Löwenberg M, Mould DR, Berends SE, Ponsioen CI, van den Brande JMH, et al. Efficacy of dashboard driven dosing of infliximab in inflammatory bowel disease patients; a randomized controlled trial. Scand J Gastroenterol. 2021;56(2):145-54.
13. Brandse JF, Strik AS, Mould D, Ashruf Y, Smeekes OS, Kuin S, et al. 695 Insufficient Infliximab Exposure Predisposes to Immunogenicity and Enhanced Clearance of Infliximab in IBD. Gastroenterology. 2016;150(4, Supplement 1):S144.
14. Zittan E, Kabakchiev B, Milgrom R, Nguyen GC, Croitoru K, Steinhart AH, et al. Higher Adalimumab Drug Levels are Associated with Mucosal Healing in Patients with Crohn's Disease. J Crohns Colitis. 2016;10(5):510-5.
15. Cornillie F, Hanauer SB, Diamond RH, Wang J, Tang KL, Xu Z, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut. 2014;63(11):1721-7.
16. Baert F, Noman M, Vermeire S, Van Assche G, D' Haens G, Carbonez A, et al. Influence of Immunogenicity on the Long-Term Efficacy of Infliximab in Crohn's Disease. New England Journal of Medicine. 2003;348(7):601-8.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
18. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

19. Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. 2000. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed December 10, 2017.
20. Steenholdt C, Brynskov J, Thomsen OO, Munck LK, Fallingborg J, Christensen LA, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: A randomised, controlled trial. Gut. 2014;63(6):919-27.
21. Steenholdt C, Brynskov J, Thomsen OO, Munck L, Fallingborg J, Christensen L, et al. Individualized Therapy Is a Long-Term Cost-Effective Method Compared to Dose Intensification in Crohn's Disease Patients Failing Infliximab. Digestive Diseases and Sciences. 2015;60(9):2762-70.
22. Pouillon L, Ferrante M, Van Assche G, Rutgeerts P, Noman M, Sabino J, et al. Mucosal Healing and Long-term Outcomes of Patients With Inflammatory Bowel Diseases Receiving Clinic-Based vs Trough Concentration-Based Dosing of Infliximab. Clin Gastroenterol Hepatol. 2018;16(8):1276-83.e1.
23. Watanabe M, Hibi T, Mostafa NM, Chao J, Arora V, Camez A, et al. Long-term safety and efficacy of adalimumab in Japanese patients with moderate to severe Crohn's disease. Journal of Crohn's and Colitis. 2014;8(11):1407-16.
24. Baert F, Glorieus E, Reenaers C, D'Haens G, Peeters H, Franchimont D, et al. Adalimumab dose escalation and dose de-escalation success rate and predictors in a large national cohort of Crohn's patients. Journal of Crohns & Colitis. 2013;7(2):154-60.
25. Bouguen G, Laharie D, Nancey S, Hebuterne X, Flourie B, Filippi J, et al. Efficacy and safety of adalimumab 80 mg weekly in luminal Crohn's disease. Inflammatory Bowel Diseases. 2015;21(5):1047-53.
26. Bultman E, de Haar C, van Liere-Baron A, Verhoog H, West RL, Kuipers EJ, et al. Predictors of dose escalation of adalimumab in a prospective cohort of Crohn's disease patients. Alimentary Pharmacology & Therapeutics. 2012;35(3):335-41.
27. Duveau N, Nachury M, Gerard R, Branche J, Maunoury V, Boualit M, et al. Adalimumab dose escalation is effective and well tolerated in Crohn's disease patients with secondary loss of response to adalimumab. Digestive & Liver Disease. 2017;49(2):163-9.
28. Ghaly S, Costello S, Beswick L, Pudipeddi A, Agarwal A, Sechi A, et al. Dose tailoring of anti-tumour necrosis factor-alpha therapy delivers useful clinical efficacy in Crohn disease patients experiencing loss of response. Internal Medicine Journal. 2015;45(2):170-7.
29. Karmiris K, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D, et al. Influence of Trough Serum Levels and Immunogenicity on Long-term Outcome of Adalimumab Therapy in Crohn's Disease. Gastroenterology. 2009;137(5):1628-40.
30. Ma C, Huang V, Fedorak DK, Kroeker KI, Dieleman LA, Halloran BP, et al. Adalimumab dose escalation is effective for managing secondary loss of response in Crohn's disease. Alimentary Pharmacology and Therapeutics. 2014;40(9):1044-55.
31. Narula N, Kainz S, Petritsch W, Haas T, Feichtenschlager T, Novacek G, et al. The efficacy and safety of either infliximab or adalimumab in 362 patients with anti-TNF-alpha naive Crohn's disease. Alimentary Pharmacology and Therapeutics. 2016;44(2):170-80.
32. Preda C, Fulger L, Gheorghe L, Gheorghe C, Goldis A, Trifan A, et al. Adalimumab and Infliximab in Crohn's disease - real life data from a national retrospective cohort study. Current Health Sciences Journal. 2016;42(2):115-24.
33. R-Grau M, Chaparro M, Mesonero F, Barreiro-de Acosta M, Castro L, Castro M, et al. Effectiveness of anti-TNFalpha drugs in patients with Crohn's disease who do not achieve remission with their first anti-TNFalpha agent. Digestive & Liver Disease. 2016;48(6):613-9.
34. Suzuki T, Mizoshita T, Sugiyama T, Hirata Y, Kimura Y, Suzuki Y, et al. Adalimumab Dose-Escalation Therapy Is Effective in Refractory Crohn's Disease Patients with Loss of Response to Adalimumab, Especially in Cases without Previous Infliximab Treatment. Case Reports in Gastroenterology. 2019:37-49.

35. Verstockt B, Moors G, Bian S, Van Stappen T, Assche G, Vermeire S, et al. Influence of early adalimumab serum levels on immunogenicity and long-term outcome of anti-TNF naive Crohn's disease patients: the usefulness of rapid testing. Alimentary Pharmacology & Therapeutics. 2018;48(7):731-9.
36. Viazis N, Koukouratos T, Anastasiou J, Giakoumis M, Triantos C, Tsolias C, et al. Azathioprine discontinuation earlier than 6 months in Crohn's disease patients started on anti-TNF therapy is associated with loss of response and the need for anti-TNF dose escalation. European Journal of Gastroenterology and Hepatology. 2015;27(4):436-41.
37. Lichtiger S, Binion DG, Wolf DC, Present DH, Bensimon AG, Wu E, et al. The CHOICE trial: Adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohns disease who failed prior infliximab therapy. Alimentary Pharmacology and Therapeutics. 2010;32(10):1228-39.
38. Lofberg R, Louis EV, Reinisch W, Robinson AM, Kron M, Camez A, et al. Adalimumab produces clinical remission and reduces extraintestinal manifestations in Crohn's disease: Results from CARE. Inflammatory Bowel Diseases. 2012;18(1):1-9.
39. Motoya S, Watanabe M, Wallace K, Lazar A, Nishimura Y, Ozawa M, et al. Efficacy and Safety of Dose Escalation to Adalimumab 80 mg Every Other Week in Japanese Patients with Crohn's Disease Who Lost Response to Maintenance Therapy. Inflammatory Intestinal Diseases. 2018;2(4):228-35.
40. Panaccione R, Loftus EV, Jr., Binion D, McHugh K, Alam S, Chen N, et al. Efficacy and safety of adalimumab in Canadian patients with moderate to severe Crohn's disease: results of the Adalimumab in Canadian SubjeCts with ModErate to Severe Crohn's DiseaSe (ACCESS) trial. Canadian Journal of Gastroenterology. 2011;25(8):419-25.
41. Sandborn WJ, Colombel JF, Schreiber S, Plevy SE, Pollack PF, Robinson AM, et al. Dosage adjustment during long-term adalimumab treatment for Crohn's disease: Clinical efficacy and pharmacoeconomics. Inflammatory Bowel Diseases. 2011;17(1):141-51.
42. Colombel JF, Sandborn WJ, Rutgeerts P, Kamm MA, Yu AP, Wu EQ, et al. Comparison of two adalimumab treatment schedule strategies for moderate-to-severe crohn's disease: Results from the CHARM trial. American Journal of Gastroenterology. 2009;104(5):1170-9.
43. Chaparro M, Panes J, Garcia V, Manosa M, Esteve M, Merino O, et al. Long-term durability of infliximab treatment in Crohn's disease and efficacy of dose "escalation" in patients losing response. Journal of Clinical Gastroenterology. 2011;45(2):113-8.
44. Chaparro M, Martinez-Montiel P, Van Domselaar M, Bermejo F, Perez-Calle JL, Casis B, et al. Intensification of infliximab therapy in Crohn's disease: Efficacy and safety. Journal of Crohn's and Colitis. 2012;6(1):62-7.
45. Hendler SA, Cohen BL, Colombel JF, Sands BE, Mayer L, Agarwal S. High-dose infliximab therapy in Crohn's disease: clinical experience, safety, and efficacy. Journal of Crohn's & colitis. 2015;9(3):266-75.
46. Hibi T, Sakuraba A, Watanabe M, Motoya S, Ito H, Motegi K, et al. Retrieval of serum infliximab level by shortening the maintenance infusion interval is correlated with clinical efficacy in Crohn's disease. Inflammatory Bowel Diseases. 2012;18(8):1480-7.
47. Katz L, Gisbert JP, Manoogian B, Lin K, Steenholdt C, Mantzaris GJ, et al. Doubling the infliximab dose versus halving the infusion intervals in Crohn's disease patients with loss of response. Inflammatory Bowel Diseases. 2012;18(11):2026-33.
48. Lin KK, Velayos F, Fisher E, Terdiman JP. Durability of infliximab dose intensification in crohn's disease. Digestive Diseases and Sciences. 2012;57(4):1013-9.
49. Suzuki Y, Matsui T, Ito H, Ashida T, Nakamura S, Motoya S, et al. Circulating interleukin 6 and albumin, and infliximab levels are good predictors of recovering efficacy after dose escalation infliximab therapy in patients with loss of response to treatment for Crohn's disease: A Prospective Clinical Trial. Inflammatory Bowel Diseases. 2015;21(9):2114-22.
50. Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Comparison of Scheduled and Episodic Treatment Strategies of Infliximab in Crohn's Disease. Gastroenterology. 2004;126(2):402-13.

51. Kopylov U, Mantzaris GJ, Katsanos KH, Reenaers C, Ellul P, Rahier JF, et al. The efficacy of shortening the dosing interval to once every six weeks in Crohn's patients losing response to maintenance dose of infliximab. Alimentary Pharmacology and Therapeutics. 2011;33(3):349-57.
52. Osamura A, Suzuki Y. Fourteen-Year Anti-TNF Therapy in Crohn's Disease Patients: Clinical Characteristics and Predictive Factors. Digestive Diseases and Sciences. 2018;63(1):204-8.
53. Dreesen E, Baert F, Laharie D, Bossuyt P, Bouhnik Y, Buisson A, et al. Monitoring a Combination of Calprotectin and Infliximab Identifies Patients With Mucosal Healing of Crohn's Disease. Clinical Gastroenterology & Hepatology. 2020;18(3):637-46.e11.
54. Dreesen E, Van Stappen T, Ballet V, Peeters M, Compernolle G, Tops S, et al. Anti-infliximab antibody concentrations can guide treatment intensification in patients with Crohn's disease who lose clinical response. Alimentary Pharmacology & Therapeutics. 2018;47(3):346-55.
55. Nagata Y, Esaki M, Umeno J, Fuyuno Y, Ikegami K, Maehata Y, et al. Therapeutic Strategy for Crohn's Disease with a Loss of Response to Infliximab: A Single-Center Retrospective Study. Digestion. 2015;91(1):50-6.
56. Papamichael K, Rakowsky S, Rivera C, Cheifetz AS, Osterman MT. Association between serum infliximab trough concentrations during maintenance therapy and biochemical, endoscopic, and histologic remission in Crohn's disease. Inflammatory Bowel Diseases. 2018;24(10):2266-71.
57. Srinivasan A, Vasudevan A, McFarlane A, Sparrow MP, Gibson PR, Van Langenberg DR. Anti-TNF re-induction is as effective, simpler, and cheaper compared with dose interval shortening for secondary loss of response in Crohn's disease. Journal of Crohn's and Colitis. 2018;12(3):280-8.
58. Vande Casteele N, Ferrante M, Van Assche G, Ballet V, Compernolle G, Van Steen K, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology. 2015;148(7):1320-9.e3.
59. D'Haens G, Vermeire S, Lambrecht G, Baert F, Bossuyt P, Pariente B, et al. Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease. Gastroenterology. 2018;154(5):1343-51.e1.
60. Restellini S, Chao CY, Lakatos PL, Aruljothy A, Aziz H, Kherad O, et al. Therapeutic Drug Monitoring Guides the Management of Crohn's Patients with Secondary Loss of Response to Adalimumab. Inflamm Bowel Dis. 2018;24(7):1531-8.
61. Kelly OB, Donnell SO, Stempak JM, Steinhart AH, Silverberg MS. Therapeutic Drug Monitoring to Guide Infliximab Dose Adjustment is Associated with Better Endoscopic Outcomes than Clinical Decision Making Alone in Active Inflammatory Bowel Disease. Inflammatory Bowel Diseases. 2017;23(7):1202-9.
62. Papamichael K, Chachu KA, Vajravelu RK, Vaughn BP, Ni J, Osterman MT, et al. Improved Long-term Outcomes of Patients With Inflammatory Bowel Disease Receiving Proactive Compared With Reactive Monitoring of Serum Concentrations of Infliximab. Clinical Gastroenterology and Hepatology. 2017;15(10):1580-8.e3.
63. Fernandes SR, Serrazina J, Rodrigues IC, Bernardo S, Rita Gonçalves A, Valente A, et al. Proactive therapeutic drug monitoring is more effective than conventional management in inducing fecal calprotectin remission in inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2021.
64. Fernandes SR, Bernardo S, Simoes C, Goncalves AR, Valente A, Baldaia C, et al. Proactive Infliximab Drug Monitoring Is Superior to Conventional Management in Inflammatory Bowel Disease. Inflammatory Bowel Diseases. 2020;26(2):263-70.
65. Juncosa ES, Rodriguez-Alonso L, Padulles Zamora A, Guardiola J, Rodriguez-Moranta F, Serra Nilsson K, et al. Bayes-based dosing of infliximab in inflammatory bowel diseases: Short-term efficacy. British Journal of Clinical Pharmacology. 2020.

66. Srinivasan A, van Langenberg DR, Little RD, Sparrow MP, De Cruz P, Ward MG. A virtual clinic increases anti-TNF dose intensification success via a treat-to-target approach compared with standard outpatient care in Crohn's disease. Alimentary Pharmacology and Therapeutics. 2020;51(12):1342-52.
67. Chiu YL, Rubin DT, Vermeire S, Louis E, Robinson AM, Lomax KG, et al. Serum adalimumab concentration and clinical remission in patients with Crohn's disease. Inflammatory Bowel Diseases. 2013;19(6):1112-22.
68. Edlund H, Grisic AM, Steenholdt C, Ainsworth MA, Brynskov J, Huisinga W, et al. Absence of Relationship Between Crohn's Disease Activity Index or C-Reactive Protein and Infliximab Exposure Calls for Objective Crohn's Disease Activity Measures for the Evaluation of Treatment Effects at Treatment Failure. Therapeutic Drug Monitoring. 2019;41(2):235-42.
69. Steenholdt C, Bendtzen K, Brynskov J, Thomsen OO, Munck LK, Christensen LA, et al. Changes in serum trough levels of infliximab during treatment intensification but not in anti-infliximab antibody detection are associated with clinical outcomes after therapeutic failure in Crohn's disease. Journal of Crohn's & colitis. 2015;9(3):238-45.
70. Plevris N, Lyons M, Jenkinson PW, Chuah CS, Merchant LM, Pattenden RJ, et al. Higher Adalimumab Drug Levels during Maintenance Therapy for Crohn's Disease Are Associated with Biologic Remission. Inflammatory Bowel Diseases. 2019;25(6):1036-43.
71. Paul S, Del Tedesco E, Marotte H, Rinaudo-Gaujous M, Moreau A, Phelip JM, et al. Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. Inflamm Bowel Dis. 2013;19(12):2568-76.
72. Mazor Y, Almog R, Kopylov U, Ben Hur D, Blatt A, Dahan A, et al. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. Alimentary Pharmacology and Therapeutics. 2014;40(6):620-8.
73. Ward MG, Warner B, Unsworth N, Chuah SW, Brownclarke C, Shieh S, et al. Infliximab and adalimumab drug levels in Crohn's disease: contrasting associations with disease activity and influencing factors. Alimentary Pharmacology and Therapeutics. 2017;46(2):150-61.
74. Zapater P, Almenara S, Gutierrez A, Sempere L, Garcia M, Laveda R, et al. Actual anti-TNF trough levels relate to serum IL-10 in drug-responding patients with Crohn's disease. Inflammatory Bowel Diseases. 2019;25(8):1357-66.
75. Bossuyt P, Dreesen E, Rimola J, Devuysere S, De Bruecker Y, Vanslembrouck R, et al. Infliximab Exposure Associates With Radiologic Evidence of Healing in Patients With Crohn's Disease. Clinical Gastroenterology & Hepatology. 2020;28:28.
76. Sono K, Yamada A, Yoshimatsu Y, Takada N, Suzuki Y. Factors associated with the loss of response to infliximab in patients with Crohn's disease. Cytokine. 2012;59(2):410-6.
77. Menachem Y, Avidan B, Lavy A, Lang A, Bardan E, Fidder H, et al. Increasing the infliximab dose is beneficial in Crohn's disease patients who responded to a lower dose and relapsed. Digestion. 2005;72(2-3):124-8.
78. Yarur AJ, Kanagala V, Stein DJ, Czul F, Quintero MA, Agrawal D, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. Alimentary Pharmacology and Therapeutics. 2017;45(7):933-40.
79. Strik AS, Löwenberg M, Buskens CJ, K BG, C IP, Bemelman WA, et al. Higher anti-TNF serum levels are associated with perianal fistula closure in Crohn's disease patients. Scand J Gastroenterol. 2019;54(4):453-8.
80. Kennedy NA, Heap GA, Green HD, Hamilton B, Bewshea C, Walker GJ, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol. 2019;4(5):341-53.
81. Hanauer SB, Wagner CL, Bala M, Mayer L, Travers S, Diamond RH, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clinical Gastroenterology and Hepatology. 2004;2(7):542-53.
82. Kosa F, Kunovszki P, Borsi A, Ilias A, Palatka K, Szamosi T, et al. Anti-TNF dose escalation and drug sustainability in Crohn's disease: Data from the nationwide administrative database in Hungary. Digestive and Liver Disease. 2020;52(3):274-80.

83. Danese S, Sandborn WJ, Loftus Jr EV, Hanauer S, Schreiber S, Peyrin-Biroulet L, et al. Clinically Adjusted vs Therapeutic Drug Monitoring Dosing Regimens With Adalimumab in Patients With Moderately to Severely Active Crohn's Disease: Results From the SERENE-CD Maintenance Study. American Journal of Gastroenterology. 2020; 115:S326.
84. Eser A, Primas C, Reinisch S, Vogelsang H, Novacek G, Mould DR, et al. Prediction of Individual Serum Infliximab Concentrations in Inflammatory Bowel Disease by a Bayesian Dashboard System. J Clin Pharmacol. 2018;58(6):790-802.
85. Colombel JF, D'Haens G, Lee WJ, Petersson J, Panaccione R. Outcomes and Strategies to Support a Treat-to-target Approach in Inflammatory Bowel Disease: A Systematic Review. J Crohns Colitis. 2020;14(2):254-66.
86. D'Haens G, Sandborn W.J, Loftus E, Hanauer S.B, Schreiber S, Peyrin-Biroulet L et al. High versus standard adalimumab induction dosing regimens in patients with moderately to severely active Crohn's disease: Results from the Serene-CD induction study. United European Gastroenterology Journal. 2019; 7(10)S-1411-1425.
87. Torres J, Boyapati RK, Kennedy NA, Louis E, Colombel JF, Satsangi J. Systematic Review of Effects of Withdrawal of Immunomodulators or Biologic Agents From Patients With Inflammatory Bowel Disease. Gastroenterology. 2015;149(7):1716-30.

Table 1 Study characteristics and clinical outcomes after dose escalation (randomised and nonrandomised interventional studies and post hoc analyses)

Study	Study design	*N*	Anti-TNF agent	Concomitant immunomodulators *N* (%) [AZA, MP, MTX]	Patients on escalated dosing *N* (%)	Escalated dosing schedule	Empiric or TDM-guided dose escalation	Clinical outcomes after anti-TNF dose escalation
Colombel, 2007[10]	RCT (CHARM)	854	Adalimumab	446 (52.2%)	157 (18.4%)	40mg weekly	NA	Clinical remission (CDAI<150) 40mg EOW *vs* 40mg weekly: 68/172 (39.5%) *vs* 73/157 (46.5%) at 26w, *P*=0.22; 62/172 (36%) *vs* 65/157 (41.4%) at 56w, *P*=0.34
Colombel, 2009[42]	Post hoc analysis	854	Adalimumab	446 (52.2%)	40 (15.4%)	40mg weekly	Empiric for LOR	Clinical response (CDAI ↓ ≥70) in patients escalated to 40mg weekly from standard dosing: 34/40 (85%) at w56
Colombel, 2017[3]	RCT (CALM)	244	Adalimumab	0 (0%) at baseline	Tight control group: 41 (47%) Clinical management group: 17 (22%)	40mg weekly	NA	Steroid-free clinical remission (CDAI<150, steroid-free ≥8w) in tight control *vs* clinical management: 73/112 (59.8%) *vs* 48/112 (39.3%) at 48w, *P*<0.001
D'Haens, 2018[59]	RCT (TAILORIX)	122	Infliximab	122 (100%)	Dosing strategy 1 (DIS1): 20 (44.4%) Dosing strategy 2 (DIS2): 23 (62.2%) Control: 16 (40%)	Incremental escalation by 2.5mg/kg (DIS1) or 5mg/kg (DIS2) from 5mg/kg to a maximum of 10mg/kg q8w; or dose increase to 10mg/kg q8w based on symptoms alone (control)	Proactive TDM vs empiric	Steroid-free remission (CDAI<150) at all visits 22-54w without ulcers at 54w in DIS1 *vs* DIS2 *vs* control: 15/45 (33.3%) *vs* 10/37 (27.0%) *vs* 16/40 (40.0%), *P*=0.50
Hanauer, 2002[11]	RCT (ACCENT I)	580	Infliximab	168 (30%)	193 (33.7%)	10mg/kg q8w	NA	Clinical remission (CDAI<150) 5mg/kg q8w *vs* 10mg/kg q8w: 44/90 (48.9%) *vs* 50/111 (45%) at 30w, *P*=0.386
Lofberg, 2012[38]	Single-arm trial	945	Adalimumab	517 (54.7%)	131 (13.9%)	40mg weekly	Empiric for LOR	Clinical response (HBI ↓ ≥3): 76/131 (58%) at 20w Clinical remission (HBI<5): 46/131 (35.1%) at 20w
Motoya, 2018[39]	Single-arm trial	28	Adalimumab	13 (46.4%)	28 (100%)	80mg EOW	Empiric for LOR	Clinical response (CDAI ↓ ≥50): 21/28 (75%) at 8w

Study	Study design	*N*	Anti-TNF agent	Concomitant immunomodulators *N* (%) [AZA, MP, MTX]	Patients on escalated dosing *N* (%)	Escalated dosing schedule	Empiric or TDM-guided dose escalation	Clinical outcomes after anti-TNF dose escalation
Panaccione, 2011[40]	Single-arm trial	304	Adalimumab	141 (46.4%)	120 (39.5%)	40mg weekly	Empiric for nonresponse or LOR	Clinical response (HBI ↓ ≥3): 69/120 (57.5%) at 4w and 85/120 (70.8%) at 24w Clinical remission (HBI ≤4): 18/120 (15%) at 4w and 36/120 (30%) at 24w
Rutgeerts, 2004[50]	Post hoc analysis	580	Infliximab	167 (30%)	193 (33.7%)	10mg/kg q8w	Empiric for LOR	Clinical response (CDAI ↓ ≥70) in patients escalated to 10mg/kg q8w from 5mg/kg q8w: 51/57 (90%) by 54w
Sandborn, 2007[9]	RCT (CLASSIC II)	276	Adalimumab	12/55 (21.8%) of randomised cohort	18/55 (32.7%) of randomised cohort	40mg weekly	NA	Clinical remission (CDAI <150) 40mg EOW *vs* 40mg weekly: 15/19 (78.9%) *vs* 15/18 (83.3%) at 56w, *NS*
Sandborn, 2011[41]	Post hoc analysis	260	Adalimumab	67/204 (32.8%) of open-label cohort	71 (27.3%)	40mg weekly	Empiric for inadequate response or LOR	Clinical remission (CDAI<150): 26/71 (36.6%) at any point after dose escalation, 17/36 (47.2%) at 56w
Steenholdt, 2014[20]	RCT	69	Infliximab	27 (39.1%)	NR	5mg/kg q4w	Reactive TDM vs empiric	Clinical response (CDAI ↓ ≥70 or ≥50% ↓ in active fistulas) reactive TDM *vs* empiric dosing: 19/33 (57.6%) *vs* 19/36 (52.8%) at 12w (RR 1.091, 95% CI 0.713-1.673, *P*=0.810) Clinical remission (CDAI ≤ 150 and complete closure of all fistulas) reactive TDM *vs* empiric dosing: 10/33 (30.3%) *vs* 14/36 (38.9%) at 12w (RR 0.779, 95% CI 0.403-1.507, *P*=0.613)
Steenholdt, 2015[21]	Follow up study of RCT	69	Infliximab	27 (39.1%)	NR	5mg/kg q4w	Reactive TDM vs empiric	Clinical response (CDAI ↓ ≥70 or ↓ ≥50% in active fistulas) reactive TDM *vs* empiric dosing: 25/33 (75.8%) *vs* 20/36 (55.6%) at 20w, *P*=0.128 Clinical remission (CDAI ≤ 150 and complete closure of all fistulas) reactive TDM *vs* empiric dosing: 18/33 (54.5%) *vs* 14/36 (38.9%) at 20w, *P*=0.232
Strik, 2021[12]	RCT	80	Infliximab	32 (40%)	NR	>5mg/kg &/or infusion interval ≤ 7w	Proactive TDM vs empiric	Sustained clinical remission (HBI ≤ 4 at 1y) precision dosing *vs* control: 30/33 (90.9%) *vs* 21/33 (63.6%), *P*=0.008
Suzuki, 2015[49]	Single-arm trial	39	Infliximab	13 (33%)	39 (100%)	10mg/kg q8w	Empiric for LOR	Clinical response (CDAI ↓ ≥50): 23/33 (69.7%) at 8w

Study	Study design	*N*	Anti-TNF agent	Concomitant immunomodulators *N* (%) [AZA, MP, MTX]	Patients on escalated dosing *N* (%)	Escalated dosing schedule	Empiric or TDM-guided dose escalation	Clinical outcomes after anti-TNF dose escalation
Vande Casteele, 2015[58]	RCT (TAXIT)	263	Infliximab	9 (5.1%)	76 (51.4%) in optimisation phase	Interval shortening by 2w to minimum of 4w, followed by dose ↑ by 2.5mg/kg from 5mg/kg to a maximum of 10mg/kg	Proactive TDM vs empiric	Clinical remission (HBI≤4) baseline *vs* after dose escalation in optimisation phase: 28/43 (65.1%) *vs* 38/43 (88.4%) (OR 4.1, 95% CI 1.2-12.5, *P*=0.020) Durable clinical remission (HBI≤4 at 1y) proactive TDM *vs* empiric dosing: 57/91 (62.6%) *vs* 45/82 (54.9%), *P*=0.353
Watanabe, 2014[23]	RCT	79	Adalimumab	20 (25.3%)	40 (50.6%)	80mg EOW	Empiric for LOR	Clinical remission (CDAI<150) baseline *vs* 48 w after dose-escalation : 0/42 (0%) *vs* 6/8 (75%) Clinical response (CDAI ↓ ≥70) baseline *vs* 48w after dose-escalation: 3/40 (7.5%) *vs* 8/8 (100%) Clinical response (CDAI ↓ ≥100) baseline *vs* 48w after dose-escalation: 1/40 (2.5%) *vs* 7/8 (87.5%)

Abbreviations: ADA, adalimumab; AZA, azathioprine; CDAI, Crohn's Disease Activity Index; EOW, every other week; HBI, Harvey Bradshaw Index; IFX, infliximab; LOR, Loss of response; **MP, mercaptopurine**; MTX, methotrexate; mo, months; NA, not applicable; NR, no record; RCT, randomised controlled trial; TDM, therapeutic drug monitoring; w,week; q4w, every four weeks; q6w, every six weeks; q8w, every eight weeks; y, years

Table 2 Study characteristics and clinical outcomes after dose escalation (observational studies)

Study	Study design	*N*	Anti-TNF agent	Concomitant immunomodulators *N* (%) [AZA, MP, MTX]	Patients on escalated dosing *N* (%)	Escalated dosing schedule	Empiric or TDM-guided dose escalation	Clinical outcomes after anti-TNF dose escalation
Baert, 2013[24]	Retrospective	720	Adalimumab	273 (37.9%)	208 (34.4%)	40mg weekly	Empiric for LOR	Clinical response (standard clinical evaluation & CRP): 139/208 (66.8%) at ≥26w
Bouguen, 2015[25]	Prospective	42	Adalimumab	4 (9.5%)	42 (100%)	80mg weekly	Empiric for LOR	Clinical response (CDAI ↓ 70): 23/42 (54.8%) within 14w and 12/14 (85.7%) at 26w Steroid free clinical remission (CDAI<150): 14/42 (33.3%) within 14w and 10/12 (83.3%) at 26w
Bultman, 2011[26]	Prospective	122	Adalimumab	50 (41%)	46 (37.7%)	40mg weekly	Empiric for LOR	Clinical response: 20/46 (43.5%) at 13w
Chaparro, 2011[43]	Retrospective	309	Infliximab	294 (95.1%)	NR	10mg/kg q8w (51%), 5mg/kg q4w (49%)	Empiric for LOR	Partial clinical response (HBI ↓ >3 or ≥50% ↓ in no. of draining fistulas): 40% at 4w Clinical remission (HBI ≤4 or closure of all fistulas): 56% at 4w
Chaparro, 2012[44]	Retrospective	33	Infliximab	25 (75.8%)	33 (100%)	10mg/kg q8w (75.8%), 10mg/kg q6w (3%), 5mg/kg q4-7w (21.2%)	Empiric for LOR	Partial clinical response (HBI ↓ >3 or ≥50% ↓ in no. of draining fistulas): 15/33 (45.5%) at 4w Clinical remission (HBI ≤4 or closure of all fistulas): 11/33 (33.5%) at 4w
Dreesen, 2018[54]	Retrospective	103	Infliximab	40 (38.8%)	103 (100%)	Dose doubling group: 10mg/kg q8w (44%) Interval shortening group: 5mg/kg q2-7w (44%)	Empiric for LOR	Short-term clinical response (physician assessment): 65/103 (63.1%) at T+1 (just after treatment escalation) Dose doubling *vs* interval shortening *vs* combined dose doubling and interval shortening: 24/45 (53.3%) *vs* 33/45 (73.3%) *vs* 8/13 (61.5%), *P*=0.144
Duveau, 2016[27]	Retrospective	124	Adalimumab	26 (21%)	124 (100%)	80mg EOW (80%), 40mg weekly (20%)	Empiric for LOR	Clinical response (steroid-free improvement in symptoms): 99/124 (79.8%) at 13w and 62/107 (57.9%) at 52w
Fernandes, 2021[63]	Prospective	243	Infliximab	200 (82.3%)	103 (76.3%) in proactive TDM *vs* 28 (25.9%) in empiric	>5mg/kg or infusion interval ≤7 weeks	Proactive TDM vs empiric	Clinical remission (HBI <5) proactive TDM *vs* empiric: 72/82 (87.8%) *vs* 66/91 (72.5%), *P*=0.014

Study	Study design	*N*	Anti-TNF agent	Concomitant immunomodulators *N* (%) [AZA, MP, MTX]	Patients on escalated dosing *N* (%)	Escalated dosing schedule	Empiric or TDM-guided dose escalation	Clinical outcomes after anti-TNF dose escalation
Ghaly, 2014[28]	Retrospective	55	Infliximab Adalimumab	NR	47 (85.5%)	IFX: 5mg/kg q6w (16.4%), 10mg/kg q6w (3.6%), 5mg/kg q4w (1.8%) ADA: 40mg weekly (63.6%)	Empiric for LOR	Clinical response (physician assessment): 40/55 (72.7%) 'good' response, 10/55 (18.2%) 'partial' response at 13w
Hendler, 2015[45]	Retrospective	86	Infliximab	42 (48.8%)	86 (100%)	10mg/kg every 4-7w, 15mg/kg every 4-8w, 20mg/kg every 4-8w, 22.5mg/kg every 4w	Empiric for LOR	Early clinical response: 17/66 (25.8%) complete, 39/66 (59.1%) partial at 1-16w Late clinical response: 17/61 (27.9%) complete, 21/61 (34.4%) partial at 38-100w
Hibi, 2012[46]	Prospective	64	Infliximab	10 (15.6%)	20 (31.3%)	5mg/kg q4w	Empiric for LOR	Clinical response (CDAI ↓ ≥25% or ↓ ≥70 points): 15/18 (83.3%) at 54w Clinical remission (CDAI<150): 10/18 (55.6%) at 54w
Juncosa, 2020[65]	Prospective	108	Infliximab	75 (69.4%)	34 (31.5%)	Ranging from 5mg/kg q8w to 10mg/kg q4w	Proactive TDM	Clinical remission (HBI<5) before *vs* after dose escalation: 8/72 (11.1%) *vs* 13/72 (18.1%) at least 98d after dose escalation, *P*=0.007
Katz, 2012[47]	Retrospective	168	Infliximab	121 (72%)	168 (100%)	Dose doubling group:10mg/kg q8w (67%) Interval shortening group: 5mg/kg q4w (33%)	Empiric for LOR	Clinical response (physician assessment) dose doubling *vs* interval shortening: 86/112 (76.8%) *vs* 37/56 (66.1%) within 4-8w (OR 1.7, 95% CI 0.8-3.4, *P*=0.14) Long term sustained response (physician assessment) dose doubling *vs* interval shortening: 56/111 (50.5%) *vs* 22/55 (40%) for ≥12mo (OR 1.5, 95% CI 0.8-2.9, *P*=0.2)
Karmiris, 2009[29]	Prospective	168	Adalimumab	62 (36.9%)	102 (65.4%)	40mg weekly	Empiric for inadequate response or LOR	Clinical response (physician assessment): 73/102 (71.6%) at any point after treatment escalation

Study	Study design	*N*	Anti-TNF agent	Concomitant immunomodulators *N* (%) [AZA, MP, MTX]	Patients on escalated dosing *N* (%)	Escalated dosing schedule	Empiric or TDM-guided dose escalation	Clinical outcomes after anti-TNF dose escalation
Kopylov, 2010[51]	Retrospective	94	Infliximab	56 (59.6%)	94 (100%)	Group I 5mg/kg q6w (58.5%) Group II 10mg/kg q8w or 5mg/kg q4w (41.5%)	Empiric for LOR	Immediate clinical response (physician assessment and continuation of escalated dosing): 64/94 (68.1%) at 1st clinic visit after treatment escalation Group I *vs* Group II: 38/55 (69.1%) *vs* 26/39 (66.7%), *P*>0.9 Long term sustained response (physician assessment and continuation of escalated dosing): 27/76 (35.5%) for ≥12mo Group I *vs* Group II: 18/45 (40%) *vs* 9/31 (29%), *P*=0.65
Lin, 2012[48]	Retrospective	30	Infliximab	16 (53.3%)	30 (100%)	10mg/kg q8w, 5mg/kg every ≤6w	Empiric for LOR	Clinical response (symptom improvement and continuation of escalated dosing): 24/30 (80%) at any point after dose escalation, 15/23 (65.2%) for ≥52w
Ma, 2014[30]	Retrospective	92	Adalimumab	91 (98.9%)	92 (100%)	40mg weekly (99%), 80mg EOW (1%)	Empiric for LOR	Clinical response (HBI ↓ >3): 74/92 (80.4%) within 24w
Nagata, 2015[55]	Retrospective	33	Infliximab	14 (42.4%)	26 (78.8%)	10mg/kg q8w (39.4%), 5mg/kg q7w (9%), 5mg/kg q6w (27.3%), 5mg/kg q4w (3%)	Empiric for LOR	Clinical response (CDAI ↓ ≥70 or ≥25%): 18/26 (69.2%) at 4w Dose doubling *vs* interval shortening *vs* ADA switch: 8/13 (61.5%) *vs* 10/13 (76.9%) *vs* 4/7 (57.1%), *NS* Clinical remission (CDAI<150): 15/33 (45.5%) at 4w Dose doubling *vs* interval shortening *vs* ADA switch: 7/13 (53.8%) *vs* 8/13 (61.5%) *vs* 3/7 (42.9%), *NS*
Narula, 2016[31]	Retrospective	362	Infliximab Adalimumab	IFX: 114 (45.4%) ADA: 41 (36.9%)	IFX: 22 (11.6%) ADA: 14 (16.3%)	IFX: 10mg/kg q8w (9%), interval shortening (2.6%) ADA: 40mg weekly	Empiric for LOR	Clinical remission (HBI <5) ADA-treated patients: 1/14 (7.1%) at end of follow up (20.7 ± 16.0 mo) IFX-treated patients: 8/22 (36.4%) at end of follow up (18 ± 18.0 mo)

Study	Study design	*N*	Anti-TNF agent	Concomitant immunomodulators *N* (%) [AZA, MP, MTX]	Patients on escalated dosing *N* (%)	Escalated dosing schedule	Empiric or TDM-guided dose escalation	Clinical outcomes after anti-TNF dose escalation
Preda, 2016[32]	Retrospective	265	Infliximab Adalimumab	IFX: 96 (74.4%) ADA: 112 (82.4%)	NR	IFX: 10mg/kg q8w, 5mg/kg q6w ADA: 40mg weekly	Empiric for LOR	Clinical response (CDAI ↓ ≥ 70) ADA-treated patients dose escalation *vs* IFX switch: 16/19 (84.2%) *vs* 1/3 (33.3%) IFX-treated patients dose escalation *vs* ADA switch: 11/26 (42.3%) *vs* 10/12 (83.3%)
Restellini, 2018[60]	Retrospective	104	Adalimumab	28 (26.9%)	66 (63.5%)	40mg weekly	Reactive TDM vs empiric	Composite remission (HBI<5 with CRP <5, FCP<250, SES-CD score<3) reactive TDM *vs* empiric: 11/26 (42.3%) *vs* 4/25 (16%) at 13w (*P*=0.619), 15/33 (45.5%) *vs* 8/26 (30.8%) at 26w (*P*=0.328), 13/33 (39.4%) *vs* 6/22 (27.3%) at 52w (*P*=0.978)
R-Grau, 2016[33]	Retrospective	118	Infliximab Adalimumab	51 (45.9%)	39 (33.1%)	IFX: dose increase, interval reduction or both ADA: 40mg weekly	Empiric for LOR	Clinical response (HBI ↓ ≥3 points or ↓ ≥50% in number of draining fistulas): 16/38 (42.1%) at end of follow-up (26 ± 21mo) Clinical remission (HBI ≤ 4 points without steroids or closure of all fistulas): 14/38 (36.8%) at end of follow-up (26 ± 21mo)
Srinivasan, 2018[57]	Retrospective	88	Infliximab Adalimumab	74 (84%)	55 (62.5%)	IFX: 5mg/kg q6w ADA: 40mg weekly	Reactive TDM	Clinical remission (HBI<5) re-induction *vs* interval shortening: 11/17 (64.7%) *vs* 25/42 (59.5%) at end of follow up (median 1.8y), *P*=0.78
Suzuki, 2019[34]	Retrospective	14	Adalimumab	3 (21.4%)	14 (100%)	80mg EOW	Empiric for LOR	Clinical response (CDAI ↓ ≥70): 4/12 (33.3%) at 12w and 3/9 (33.3%) at 52w Clinical remission (CDAI<150): 8/12 (66.7%) at 12w and 5/8 (62.5%) at 52w
Verstockt, 2018[35]	Retrospective	116	Adalimumab	15 (12.9%)	43 (37.1%)	40mg weekly	Empiric for LOR	Clinical response (physician assessment): 31/43 (72.1%) at 26w
Viazis, 2015[36]	Prospective	132	Infliximab Adalimumab	132 (100%)	31 (23.5%)	IFX: 10mg/kg q8w (9.8%), 10mg/kg q6w,10mg/kg q4w (3.8%) ADA: 40mg weekly	Empiric LOR	Clinical remission (absence of symptoms & normal CRP): 25/31 (80.6%) at end of follow up (median 28mo)

Abbreviations: ADA, adalimumab; AZA, azathioprine; CDAI, Crohn's Disease Activity Index; EOW, every other week; HBI, Harvey Bradshaw Index; IFX, infliximab; LOR, Loss of response; **MP, mercaptopurine**; MTX, methotrexate; mo, months; NA, not applicable; NR, no record; RCT, randomised controlled trial; TDM, therapeutic drug monitoring; w,week; q4w, every four weeks; q6w, every six weeks; q8w, every eight weeks; y, years

Figure legends

Figure 1 PRISMA flow diagram of study selection

Figures 2 The rate of clinical response (%) following empiric dose escalation for patients with secondary loss of response to standard maintenance adalimumab in the included studies. Bubble size is proportional to the number of dose-escalated patients in each study. The number within each bubble corresponds to the study reference.

Figure 3 The rate of clinical response (%) following empiric dose escalation for patients with secondary loss of response to standard maintenance infliximab in the included studies. Bubble size is proportional to the number of dose-escalated patients in each study. The number within each bubble corresponds to the study reference.

Supplementary Table 1 PRISMA Checklist for Preferred Reporting Items for Systematic Reviews and Meta-Analyses

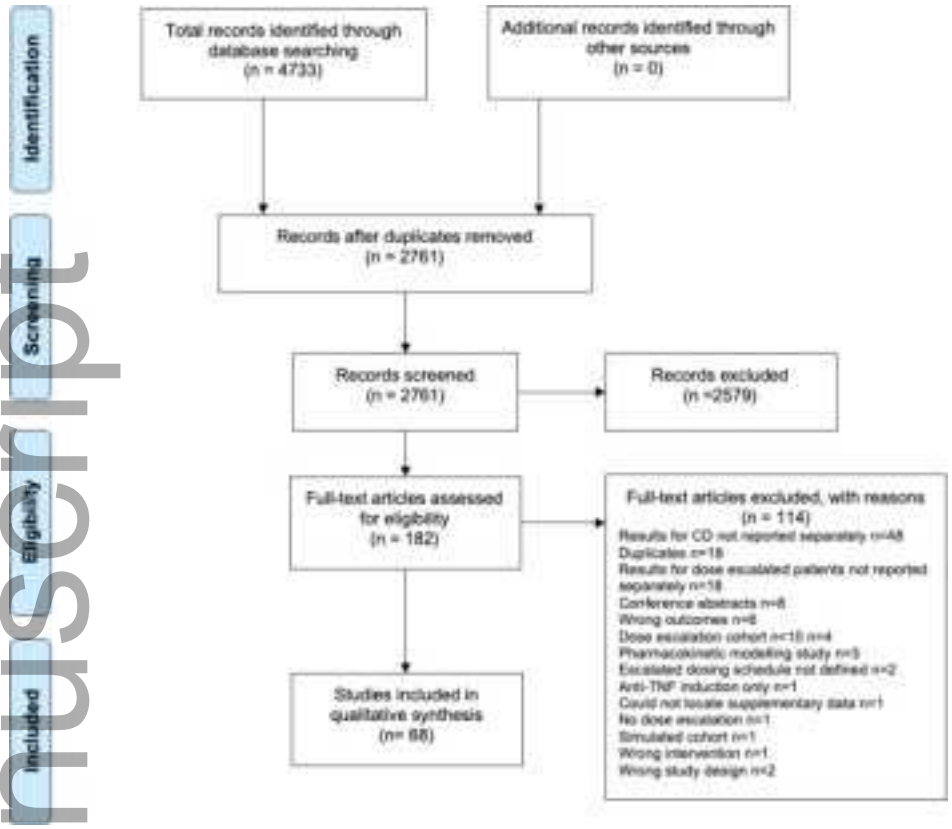
PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Tables S2-5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA



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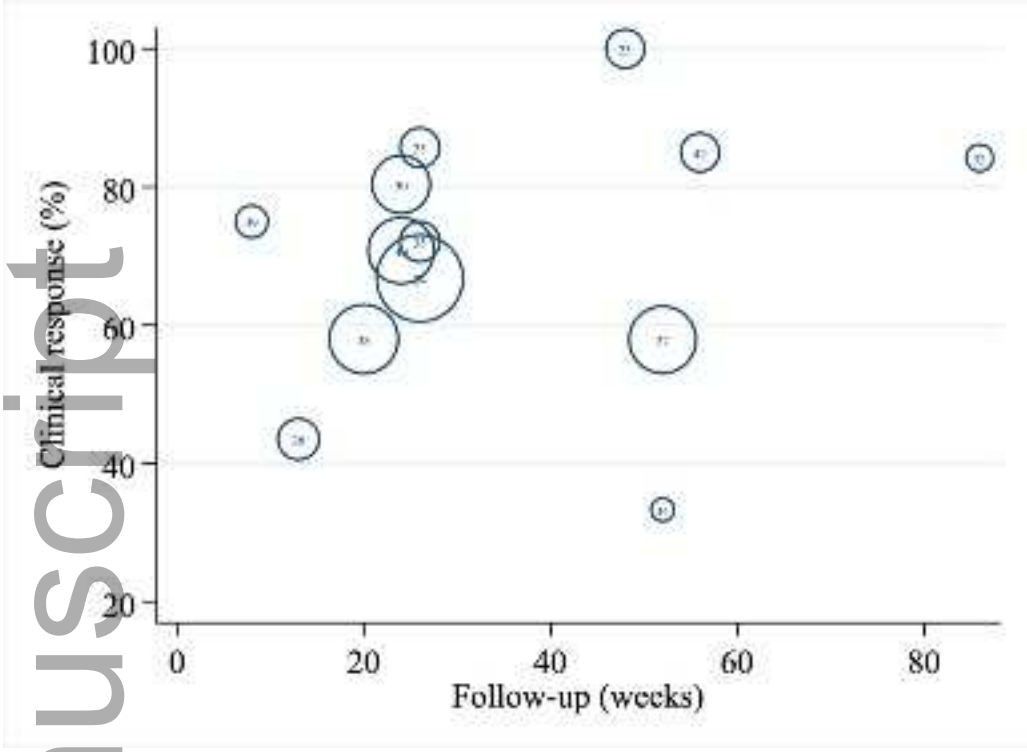

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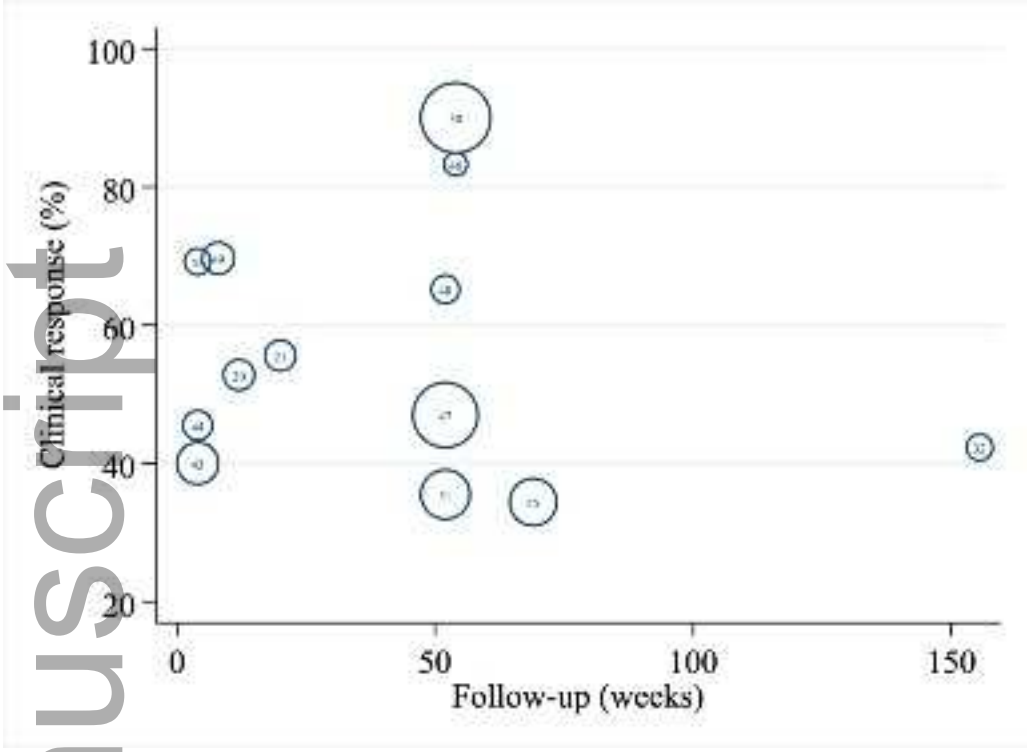

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