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Systematic review and meta-analysis: evaluating response to empiric anti-TNF dose intensification for secondary loss of response in Crohn's disease

Ashish Srinivasan, Robert Gilmore, Daniel van Langenberg and Peter De Cruz

Abstract

Introduction: Anti-tumor necrosis factor (TNF) dose intensification represents an effective method of overcoming secondary loss of response (LOR); however, a subset of patients may not respond (tertiary non-response), or fail to demonstrate durable response (tertiary LOR) to intensified dosing. This systematic review and meta-analysis aimed to evaluate these outcomes to determine the clinical effectiveness of empiric dose intensification in Crohn's disease.

Methods: Multiple databases including MEDLINE and EMBASE were interrogated to identify studies that reported outcomes following anti-TNF dose intensification to address secondary LOR in Crohn's disease. Studies that used anti-TNF levels as the primary basis for dose intensification were excluded. Studies that reported (1) tertiary response and tertiary non-response within 6 months or (2) tertiary response and tertiary LOR beyond 6 months, were pooled using a random effects model with risk ratio (RR) derived, quantifying the effect of each comparison.

Results: Twenty-six studies reported outcomes following anti-TNF dose intensification to address secondary LOR. Short-term response within 12 weeks of any dose-intensification strategy was 33–90%, while sustained response (⩾48 weeks) was achieved in 25–85%. Tertiary non-response occurred in up to 45% of intensified patients within 6 months of anti-TNF dose intensification, while tertiary LOR beyond 6 months occurred in up to 64% of patients. Tertiary response was more likely than tertiary non-response within 6 months (RR 2.58, 95% CI (1.76, 3.79), $I^2 = 82\%$, 12 studies), while sustained response beyond 6 months compared to tertiary LOR (RR 1.10 (0.75, 1.61) $I^2 = 85\%$, 7 studies) was less convincing.

Conclusion: Although anti-TNF dose intensification is clinically effective in patients with Crohn's disease, particularly within the first 6 months, a proportion of patients will fail to demonstrate short-term and/or sustained clinical response. Hence, clinical reassessment following anti-TNF dose intensification, particularly beyond 6 months, remains important to differentiate between effective and ineffective dose-intensification strategies.

Keywords: adalimumab, anti-TNF, Crohn's disease, dose intensification, infliximab, loss of response

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Introduction

Despite the efficacy of anti-tumor necrosis factor (TNF) agents in Crohn's disease, up to 30% of patients exhibit primary non-response, with a further 46% of anti-TNF responders demonstrating features of secondary loss of response (LOR) within 12 months of anti-TNF initiation.[1–3] Several studies have demonstrated the clinical effectiveness of

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anti-TNF dose intensification to overcome LOR using dosing strategies including one or more of: shortening the interval between anti-TNF doses; increasing the baseline anti-TNF dose while maintaining the dosing interval, and; anti-TNF re-induction.[4–7]

Two recent systematic reviews, one of which also undertook a meta-analysis, evaluated the clinical effectiveness of anti-TNF dose intensification to address LOR across Crohn's disease and ulcerative colitis.[8,9] While comprehensive in their approach, neither review distinguished between anti-TNF dose intensification undertaken to address secondary LOR and anti-TNF dose intensification undertaken to address pooled primary non-response and secondary LOR. It is, however, important to differentiate between both of these entities, given the disparate clinical effectiveness of anti-TNF dose intensification between primary responders and primary non-responders. Thus, targeted evaluation of the clinical effectiveness of anti-TNF dose intensification to address secondary LOR is needed.

Moreover, amid the growing use of intensified anti-TNF dosing to address LOR in Crohn's disease, it remains important that clinicians recognise that a subset of patients may not respond, or fail to demonstrate durable response to intensified anti-TNF dosing. These outcomes, notionally termed, 'tertiary non-response' and 'tertiary LOR', have not previously been well described, nor compared with tertiary response (Figure 1). Hence, in addition to evaluating the clinical effectiveness of anti-TNF dose intensification to address secondary LOR, this review will evaluate outcomes such as 'tertiary non-response' and 'tertiary LOR' reflective of ineffective dose intensification. Factors associated with these outcomes will also be described.

Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines; however, it was not prospectively registered on PROSPERO.[10]

Selection criteria

Studies eligible for inclusion in this systematic review included clinical trials (randomised/non-randomised) and cohort studies (retrospective/prospective) that investigated: (a) Population: adult patients with Crohn's disease who demonstrated primary response to adalimumab, certolizumab, or infliximab; (b) Intervention: empiric adalimumab, certolizumab, or infliximab dose intensification to address secondary LOR following standard induction and maintenance dosing; (c) Outcome: proportion demonstrating clinical response/remission, non-response and LOR following anti-TNF dose intensification. Studies that did not clearly define criteria for secondary LOR prior to dose intensification and/or clinical response/remission following anti-TNF dose intensification, were excluded. Similarly, studies that reported outcomes following anti-TNF dose intensification to address combined primary non-response and secondary LOR were reported separately, unless outcomes specific to secondary LOR were reported or could be imputed.

Definitions

Anti-TNF dose intensification was defined as empiric dose intensification based on clinical symptoms as judged by the treating clinician, with or without objective disease assessment. Studies that used serum anti-TNF trough levels in the absence of clinical symptoms as the primary basis for directing therapeutic intervention following secondary LOR, were excluded. This decision was made to minimise heterogeneity in baseline disease activity and its impact on subsequent assessments of tertiary response, non-response and LOR following anti-TNF dose intensification.

Anti-TNF dose intensification was defined as one or more of: shortening the interval between anti-TNF doses; increasing the baseline anti-TNF dose while maintaining the dosing interval, and; anti-TNF re-induction. Tertiary response was defined as the number of patients demonstrating clinical response following anti-TNF dose intensification undertaken to address secondary LOR relative to all patients who underwent anti-TNF dose intensification. Tertiary non-response was defined as lack of response occurring within 6 months of anti-TNF dose intensification. Tertiary LOR was defined as LOR occurring more than 6 months following anti-TNF dose intensification. Anti-TNF dose intensification following secondary LOR was defined as empiric dose intensification following partial or complete response to standard induction dosing. Studies that included 'non-response' in their criteria for anti-TNF dose

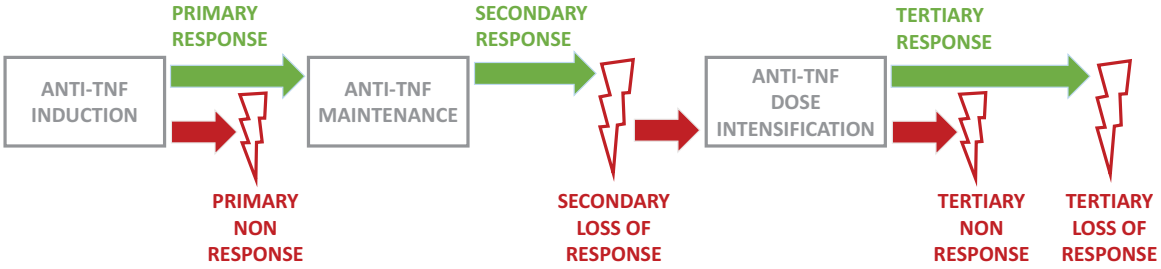

Figure 1. Defining response, non-response, and loss of response to anti-TNF therapy in inflammatory bowel disease.

intensification were deemed to reflect dose intensification undertaken to address primary non-response and were thus reported separately.

Search strategy

A search of the medical literature published in English was conducted, using Ovid MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews through to 30 July 2021. Search algorithms included a combination of terms reflecting the disease of interest (Crohn(s) disease) in combination with treatment (anti-TNF, anti-TNF, TNF-alpha, adalimumab, certolizumab pegol, or infliximab), anti-TNF dosing regimen (intensif*/escalat*) and outcome (response/ LOR) of interest without restriction. Two authors (AS/RG) independently reviewed titles and abstracts of studies identified by the search and excluded those that were clearly unrelated on the basis of pre-specified inclusion and exclusion criteria. This process was undertaken with the assistance of the Covidence software programme.[11] Full-text of selected articles was appraised to determine suitability for inclusion, with conflicts in study selection resolved by consensus and referring back to the original article, in consultation with a senior investigator (PDC). The reference lists of relevant studies were manually searched to identify additional publications of relevance.

Data synthesis and statistical analysis

Systematic review. The primary outcome of interest was tertiary response, that is, the proportion of patients demonstrating clinical response following anti-TNF dose intensification to address secondary LOR. Tertiary non-response, tertiary LOR and clinical remission following anti-TNF dose intensification were also assessed. Factors associated with these outcomes were also evaluated. Where studies reported outcomes following several dose-intensification strategies, outcomes were described collectively, based on anti-TNF, and per dose-intensification strategy, where possible. Studies in which anti-TNF dose intensification was undertaken to address both primary non-response and secondary LOR were reported separately.

Meta-analysis. The purpose of the meta-analysis was to evaluate the clinical effectiveness (tertiary response) of anti-TNF dose intensification against measures of clinical ineffectiveness (tertiary non-response /tertiary LOR). Hence studies that reported (1) tertiary response and tertiary non-response within 6 months or (2) tertiary response and tertiary LOR beyond 6 months, were included in the meta-analysis.

Data were combined to provide risk ratio (RR) with 95% confidence intervals (CIs) to summarise the effect of each comparison using a statistical significance threshold of p value < 0.05. Study heterogeneity was analysed using the I^2 statistic: with heterogeneity thresholds as follows: not important ($I^2 < 40\%$), moderate (40–75%), and considerable (>75%). A Begg's funnel plot was used to estimate the possibility of publication bias.[12] Sensitivity analyses were performed for each meta-analysis subgroup by excluding studies that were identified as potentially introducing a critical risk of bias that could likely modify the outcome. Data were analysed using Review Manager (version 5.4).

Data extraction

The following characteristics were extracted from each eligible study: first author name, year of

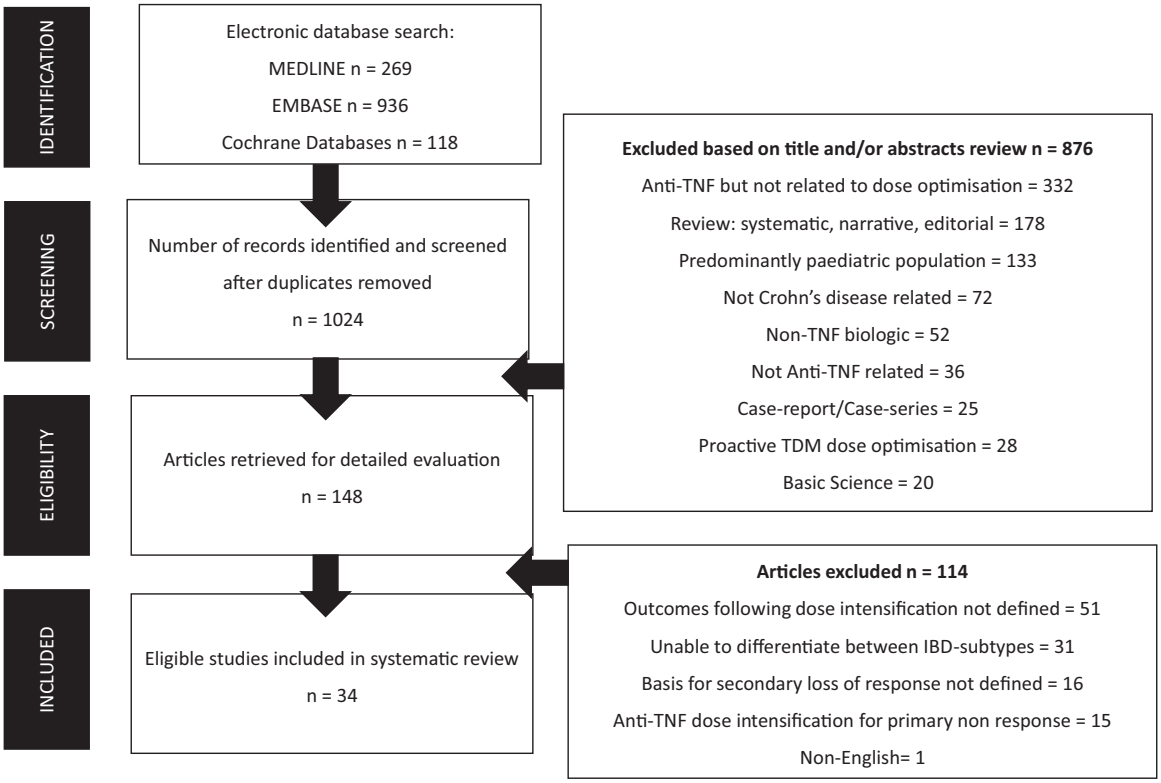

Figure 2. Study selection flowchart as at 30 July 2021.

publication, country where study was undertaken, study design, number of patient who were dose intensified, anti-TNF agent, dose-intensification strategy, duration of anti-TNF therapy prior to dose intensification, proportion on immunomodulator co-therapy at dose intensification, proportion with prior biologic failure at baseline, and proportion with perianal disease at baseline. Key study definitions including the basis for secondary LOR prior to anti-TNF dose intensification, basis for clinical response/remission following anti-TNF dose intensification, and the basis for clinical non-response/LOR following dose intensification were also documented. Finally, outcome measures pertaining to the proportion of patients demonstrating clinical response/remission and clinical non-response/LOR following dose intensification along with corresponding timepoints were recorded.

Risk of bias assessment

The methodological quality of all studies was assessed by two authors (AS and RG) with agreement reached by consensus if discrepancies arose. Each randomised controlled trial (RCT) was assessed using the Cochrane Collaboration tool, evaluating bias across the several domains including selection bias, reporting bias, performance bias, detection bias, attrition bias, and other bias.[13] Similarly, observational studies were evaluated using the Newcastle–Ottawa Scale (NOS), with the quality of each study evaluated independently. Representativeness of the exposed cohorts, ascertainment of exposure, demonstration that the outcome of interest was not present at start of study, assessment of the outcome, and adequacy of the follow-up were assessed for each included study. Two criteria of the NOS,[14] namely selection of the non-exposed cohort and comparability of the cohorts, were not used because cohorts not exposed to intensified anti-TNF therapy were not included.

Results

Search results

Following removal of duplicate records, 1024 articles were identified for assessment (Figure 2). Records deemed irrelevant or not suitable based on predetermined inclusion criteria were

excluded, leaving 148 articles for detailed evaluation. We identified 34 eligible full-text articles of adult patients with Crohn's disease that underwent anti-TNF dose intensification to address secondary LOR, comprising 3 RCTs, 3 *post hoc* analyses of RCTs, 7 prospective observational studies, and 21 retrospective studies (Table 1).[4–7,15–45] Thirteen studies reported outcomes following infliximab dose intensification, 15 studies reported outcomes following adalimumab dose intensification, and six following both adalimumab and infliximab dose intensification. No studies evaluating certolizumab dose intensification met eligibility criteria.

Assessment of bias

The risk of bias assessments for RCTs and observational studies are presented in Supplementary Tables 1 and 2, respectively. Of three included RCTs, the study by Watanabe *et al.*[37] was identified as potentially subject to selection bias owing to insufficient description of the randomisation and allocation concealment processes, while the studies by Steenholdt *et al.*[15,29] were subject to detection bias as outcome assessment was not blinded, thus potentiating a higher risk of bias. Most observational studies exhibited a low to moderate risk of bias when applying the modified NOS scale (out of 6). Notably, observational studies were largely retrospective in design, with study outcomes generally present at study outset, reflecting an obvious source of bias.

Systematic review

Defining LOR prior to anti-TNF dose intensification

Clinical disease assessment. The definition of LOR prior to anti-TNF dose intensification was heterogeneous (Table 2). Several studies incorporated definitions based on validated clinical indices including the Crohn's Disease Activity Index (CDAI) and Harvey–Bradshaw Index (HBI); however, disease activity thresholds associated with clinical LOR prior to dose intensification were variable.[7,15–17,20,22,23,25,27,29,35–39] Eleven studies incorporated assessments of CDAI into the definition of LOR, with four studies documenting absolute CDAI thresholds.[15–17,20,22,25,27,29,35,37,38] Four studies incorporated assessments of HBI into the definition of LOR, each documenting one or both of an absolute HBI threshold and/or change from baseline HBI, reflective of clinical LOR.[7,23,36,39] The remaining studies ostensibly relied on physician-determined clinical deterioration, or definitions of symptomatic disease that did not incorporate validated clinical indices, to define LOR prior to anti-TNF dose intensification.

Objective disease assessment. Six studies required both clinically active disease based on clinical indices (CDAI or HBI) and objective disease activity defined as one or more of elevated C-reactive protein (CRP), faecal calprotectin, evidence of radiologic, and/or endoscopic inflammation.[7,17,20,23,38,39] An additional eight studies required physician-determined symptomatic disease plus objectively assessed disease activity prior to anti-TNF dose intensification.[6,21,26,28,32,41,42,45]

Indication for anti-TNF dose intensification. Outcomes across eight studies did not differentiate between anti-TNF dose intensification undertaken to address primary non-response and secondary LOR.[30,33–37,40,41] The remaining 26 studies reported clinical outcomes following anti-TNF dose intensification specifically undertaken to address secondary LOR.

Anti-TNF dose-intensification strategies

Of 34 eligible studies, clinical outcomes following anti-TNF dose intensification were reported across 45 patient cohorts, comprising 23 infliximab cohorts, 17 adalimumab cohorts, and 5 pooled adalimumab/infliximab cohorts. Thirty-seven cohorts reported outcomes following anti-TNF dose intensification to address secondary LOR, while eight cohorts reported pooled outcomes following anti-TNF intensification for primary non-response and/or secondary LOR, and were thus reported separately.

Infliximab dose intensification

Infliximab dose intensification was undertaken exclusively for secondary LOR across 17 of 19 eligible studies, with all but one study including patients who were anti-TNF experienced. Several studies evaluated more than one dose-intensification regimen, including infliximab 5 mg/kg 4–7 weekly ($n = 10$), infliximab 10 mg/kg 8 weekly or 5 mg/kg 4 weekly ($n = 17$), high-dose infliximab ($\geq$10 mg/kg, 4–7 weekly) ($n = 5$) and infliximab re-induction ($n = 2$).[7,15,17,19,21–30] These regimens

Table 1. Characteristics of all studies included in the systematic review.

Author (year)	Study design (country)	Anti-TNF agent intensified (number intensified)	Anti-TNF duration prior to dose intensification	Immuno modulator co-therapy (%)	Prior biologic failure (%)	Perianal disease (%)
Infliximab						
Rutgeerts *et al.*[25] (2004)	Prospective Multi-centre Randomised control trial (International)	Infliximab (58)	NR	27%[a]	No	NR
Chaparro *et al.*[26] (2011)	Retrospective Multi-centre Observational (Spain)	Infliximab (127)	NR	95%[a]	No	45%[a]
Hibi *et al.*[27] (2012)	Prospective Multi-centre Observational (Japan)	Infliximab (18)	NR	16%[a]	No	NR
Kopylov *et al.*[4] (2011)	Retrospective Multi-centre Observation (Europe)	Infliximab (94)	Median 4 ± 5.7 infusions (range 1–24)	59%	No	39%
Chaparro *et al.*[28] (2012)	Retrospective Multi-centre Observational (Spain)	Infliximab (33)	Median 12 months (IQR = 13.5 months)	76%	No	16%
Katz *et al.*[5] (2012)	Retrospective Multi-centre Observations (Europe, USA, Israel)	Infliximab (168)	Median 6 infusions	71%	3%	49%
Lin *et al.*[21] (2012)	Retrospective Single-centre Observational (USA)	Infliximab (30)	NR	53%	No	30%
Steenholdt *et al.*[15] (2014)	Prospective Multi-centre Randomised Control Trial (Denmark)	Infliximab (36)	Mean 12 infusions (range 4–37)	39%	No	8%
Hendler *et al.*[30] (2015)	Retrospective Single-centre Observation (USA)	Infliximab (86)	NR	49%	31%	48%

(continued)

Table 1. (Continued)

Author (year)	Study design (country)	Anti-TNF agent intensified (number intensified)	Anti-TNF duration prior to dose intensification	Immuno modulator co-therapy (%)	Prior biologic failure (%)	Perianal disease (%)
Nagata *et al.*[20] (2015)	Retrospective Single-centre Observation (Japan)	Infliximab (26)	Mean 32 months (range 8–89)	34%	No	NR
Steenholdt *et al.*[29] (2015)	Prospective Multi-centre Randomised control trial (Denmark)	Infliximab (36)	Mean 12 infusions (range 4–37)	39%	No	8%
Suzuki *et al.*[16] (2015)	Prospective Multi-centre Observational (Japan)	Infliximab (39)	Median 1.7 years (range 0.3–6.0)	33%	No	NR
Dreesen *et al.*[19] (2018)	Retrospective Single-centre Observational (Belgium)	Infliximab (103)	10 mg/kg 8-weekly: median 18 months (range 8–70) 5 mg/kg, interval shortening median 12 months (range 7–19) 10 mg/kg + interval shortening median 17 months (range 9–64)	38%	No	NR
Adalimumab						
Colombel *et al.*[31] (2009)	Prospective Multi-centre Randomised control trial (International)	Adalimumab (40)	NR	43%[a]	51%[a]	11.5%[a]
Karmiris *et al.*[32] (2009)	Retrospective Single-centre Observational (Belgium)	Adalimumab (70)	Median 14 weeks (range 11–24)	37%[a]	100%	11%
Bultman *et al.*[33] (2012)	Retrospective Single-centre Observational (Netherlands)	Adalimumab (46)	Median 21 weeks (range 4–105)	46%	65%	41%
Panaccione *et al.*[34] (2011)	Prospective Multi-centre Observational (Canada)	Adalimumab (40)	NR	46%[a]	53%[a]	22%[a]
Sandborn *et al.*[35] (2011)	Prospective Multi-centre Randomised control trial (International)	Adalimumab (71)	Median 148 days (range 106–338)	NR	52%	NR

(continued)

Table 1. (Continued)

Author (year)	Study design (country)	Anti-TNF agent intensified (number intensified)	Anti-TNF duration prior to dose intensification	Immuno modulator co-therapy (%)	Prior biologic failure (%)	Perianal disease (%)
Löfberg *et al.*[36] (2012)	Prospective Multi-centre Observational (Europe)	Adalimumab (131)	Median 92 days (range 70*–157)	55%[a]	49%[a]	18%[a]
Baert *et al.*[6] (2013)	Retrospective Multi-centre Observational (Belgium)	Adalimumab (208)	Median 7 months (range 0–55)	38%[a]	64%[a]	42%[a]
Ma *et al.*[23] (2014)	Retrospective Single-centre Observational (Canada)	Adalimumab (92)	Median 37 weeks (IQR 20–76)	58%[a]	54%	32%
Watanabe *et al.*[37] (2014)	Prospective Multi-centre Randomised control trial (Japan)	Adalimumab (40)	NR	15%	63%	NR
Bouguen *et al.*[38](2015)	Retrospective Observational Multi-centre France	Adalimumab (42)	Median 1.3 years (IQR75, 0.5–3).	10%	79%	50%
Duveau *et al.*[24] (2017)	Retrospective Single-centre Observational (Canada)	Adalimumab (124)	Median 10 months (range 4–27)	20%	55%	47%
Motoya *et al.*[17] (2017)	Prospective Multi-centre Observational (Japan)	Adalimumab (28)	NR	46%	68%	NR
Restellini *et al.*[39] (2018)	Retrospective Single-centre Observational (Canada)	Adalimumab (48)	Median 22 months (range 6–36)	38%	44%	31%
Verstockt *et al.*[40] (2018)	Retrospective Single-centre Observational (Belgium)	Adalimumab (43)	NR	13%[a]	0%	24%[a]
Suzuki *et al.*[22] (2019)	Retrospective Multi-centre Observational (Japan)	Adalimumab (12)	Median 19 months (range 3–149)[a]	25%	33%	50%

(continued)

Table 1. (Continued)

Author (year)	Study design (country)	Anti-TNF agent intensified (number intensified)	Anti-TNF duration prior to dose intensification	Immuno modulator co-therapy (%)	Prior biologic failure (%)	Perianal disease (%)
Both infliximab and adalimumab						
Ghaly *et al.*[41] (2014)	Retrospective Multi-centre Observational (Australia)	Infliximab (20) Adalimumab (35)	NR	NR	42%	29%
Viazis *et al.*[42] (2015)	Prospective Multi-centre Observational (Greece)	Infliximab (18) Adalimumab (13)	Median 9 months (range 2–22)	100%[a] (at anti-TNF initiation)	No	52%
María Del Carmen *et al.*[45] (2016)	Retrospective Multi-centre Observational (Spain)	Infliximab (24)	Mean 11.9 ± 10.9 months (range 1–40)	46%[a]	100%	45%[a]
Narula *et al.*[43] (2016)	Prospective Multi-centre Observational (Austria)	Infliximab (5) Adalimumab (14)	Median 6 months (infliximab) Median 5 months (adalimumab)	Infliximab 45% Adalimumab 37%	No	Infliximab 5% Adalimumab 0%
Preda *et al.*[44] (2016)	Retrospective Multi-centre Observational (Romania)	Infliximab (26) Adalimumab (19)	Mean 15.5 months (infliximab) Mean 12.7 months (adalimumab)	78%[a]	No	NR
Srinivasan *et al.*[7] (2018)	Retrospective Multi-centre Observational (Australia)	Infliximab (22) Adalimumab (11)	Median 1.8 years	76%	27%	39%
		Infliximab (29) Adalimumab (26)	Median 2.5 years	89%	38%	45%

NR, not reported; immunomodulator: thiopurine or methotrexate.
[a]Across entire study, not just intensified subgroup.

Table 2. Tertiary response and remission following anti-TNF dose intensification.

Author (year)	Anti-TNF dose intensification regimen (number intensified)	Criteria for dose intensification	Definition of tertiary response/ remission following dose intensification	Tertiary response following dose intensification (timepoint)	Tertiary remission following dose intensification (timepoint)	Predictors of tertiary response/remission following dose intensification
Infliximab dose intensification: secondary loss of response						
Rutgeerts *et al.*[25] (2004)	Infliximab 10 mg/kg, 8 weekly (58)	70-point CDAI increase from baseline with total CDAI ⩾ 175 or increase in CDAI by 35% from baseline	Clinical response ⩾70-point reduction in CDAI from baseline and ⩾ 25% from baseline	52/58 (90%) (short-term response)	NR	NR
Chaparro *et al.*[26] (2011)	Infliximab 10 mg/kg, 8 weekly (65) 5 mg/kg, 4–7 weekly (62)	Impairment of symptoms coupled with clinical, endoscopic, radiographic and/or serologic (CRP) evidence of inflammation	Clinical response Decrease in HBI > 3 Clinical remission HBI ⩽ 4 without corticosteroids	51/127 (40%) (clinical response following first intensified infusion)	71/127 (56%) (clinical remission following first intensified infusion)	NR
Hibi *et al.*[27] (2012)	Infliximab 5 mg/kg, 4 weekly (20)	70-point CDAI increase from baseline with total CDAI ⩾ 175 or increase in CDAI by 35% from baseline	Clinical response ⩾70-point reduction in CDAI from baseline or ⩾ 25% from baseline Clinical remission CDAI ⩽ 150	15/18 (83%) (54 weeks)	10/18 (56%) (54 weeks)	NR
Kopylov *et al.*[4] (2011)	Infliximab (94)	Per treating physician's judgement	Immediate response defined as symptom improvement at first clinic visit (4–8 weeks) after dose intensification as per treating physician judgement, coupled with decision to continue intensification without alteration. Sustained response was defined as improvement of symptoms lasting at least 1 year without further alterations in therapeutic regimen	64/94 (68%) (immediate response within 2–8 weeks) 27/76 (36%) (sustained response, ⩾1 year)	NR	↑ normalisation of CRP following dose intensification
	Infliximab 10 mg/kg, 8 weekly 5 mg/kg, 4 weekly (39)	As above	As above	26/39 (67%) (immediate response within 2–8 weeks) 9/31 (29%) (sustained response, ⩾1 year)	NR	
	Infliximab 5 mg/kg, 6 weekly (55)	As above	As above	38/55 (69%) (immediate response within 2–8 weeks) 18/45 (40%) (sustained response, ⩾1 year)	NR	
Chaparro *et al.*[28] (2012)	Infliximab 10 mg/kg, 8 weekly (25) 5 mg/kg, 4–7 weekly (7) 10 mg/kg, 6 weekly (1)	Worsening of symptoms together with endoscopic, radiographic and/ or serologic (CRP) inflammation	Clinical response Decrease in HBI by >3; OR ⩾ 50% reduction in draining fistula Clinical remission HBI ⩽ 4 without corticosteroids; OR closure of all fistulas	26/33 (79%) (4 weeks)	11/33 (33%) (4 weeks)	No predictors found

(continued)

Table 2. (Continued)

Author (year)	Anti-TNF dose intensification regimen (number intensified)	Criteria for dose intensification	Definition of tertiary response/ remission following dose intensification	Tertiary response following dose intensification (timepoint)	Tertiary remission following dose intensification (timepoint)	Predictors of tertiary response/remission following dose intensification
	Infliximab 10 mg/kg, 8 weekly (25)	As above	As above	13/25 (52%) (4 weeks)	7/25 (28%) (4 weeks)	
	Infliximab 5 mg/kg, 4–7 weekly (7)	As above	As above	1/7 (15%) (4 weeks)	4/7 (57%) (4 weeks)	
Katz *et al.*[5] (2012)	Infliximab (168)	Per treating physician's judgement	Immediate response defined as symptom improvement at first clinic visit (4–8 weeks) after dose intensification as per treating physician judgement, coupled with decision to continue intensification without alteration. Sustained response was defined as improvement of symptoms lasting at least 1 year without further alterations in therapeutic regimen	123/168 (73%) (immediate response within 4–8 weeks) 78/166 (47%) (sustained response, ⩾1-year)	NR	↑ baseline CRP normal ↑ stricturing and penetrating phenotype ↑ non-smoking status ↑ age of diagnosis between 16–40
	Infliximab 10 mg/kg, 8 weekly (112)	As above	As above	86/112 (77%) (immediate response) 56/111 (50%) (sustained response, ⩾1 year)	NR	
	Infliximab 5 mg/kg, 4 weekly (56)	As above	As above	37/56 (66%) (immediate response) 22/55 (39%) (sustained response, ⩾1 year)	NR	
Lin *et al.*[21] (2012)	Infliximab (30)	Per treating physician's judgement based on disease-related symptoms in the context of objective data including inflammatory markers, endoscopic activity and radiologic imaging	Clinical response Symptomatic improvement with ongoing dose intensified infliximab for ⩾3 infusions	24/30 (80%) (after 3 intensified infliximab infusions) 10/30 (33%) (sustained, ⩾1 year)	NR	None
	Infliximab,10 mg/ kg,8 weekly (17)	As above	As above	13/17 (76%) (after 3 intensified infusions) 7/17 (41%) (sustained, ⩾1 year)	NR	
	Infliximab 5 mg/kg, 4–6 weekly (8)	As above	As above	7/8 (88%) (after 3 intensified infusions) 1/8 (13%) (sustained, ⩾1 year)	NR	

(continued)

Table 2. (Continued)

Author (year)	Anti-TNF dose intensification regimen (number intensified)	Criteria for dose intensification	Definition of tertiary response/ remission following dose intensification	Tertiary response following dose intensification (timepoint)	Tertiary remission following dose intensification (timepoint)	Predictors of tertiary response/remission following dose intensification
	Infliximab 10 mg/kg, 4–6 weekly (5)	As above	As above	4/5 (80%) (after 3 intensified infusions) 2/5 (40%) (sustained, ⩾1 year)	NR	
Steenholdt *et al.*[15] (2014)	Infliximab 5 mg/kg, 4 weekly (36)	CDAI ⩾ 220 and/or ⩾1 draining perianal fistula	Clinical response ⩾70-point reduction in CDAI from baseline, or ⩾50% reduction active fistulas Clinical remission CDAI ⩽ 150 and complete closure of all fistulas despite gentle pressure	19/36 (53%) (12 weeks)	14/36 (39%) (12 weeks)	NR
Steenholdt *et al.*[29] (2015)	Infliximab 5 mg/kg, 4 weekly (36)	CDAI ⩾ 220 and/or ⩾ 1 draining perianal fistula	Clinical response ⩾70-point reduction in CDAI from baseline, or ⩾50% reduction active fistulas Clinical remission CDAI ⩽ 150 and complete closure of all fistulas despite gentle pressure	10/36 (28%) (20 weeks)	7/36 (19%) (12 weeks)	NR
Suzuki *et al.*[16] (2015)	Infliximab 10 mg/kg, 8 weekly (39)	CDAI ⩾ 175 at 8-weeks or CDAI ⩾ 50 points from 4-weeks	Clinical response Reduction in median CDAI of ⩾50 points in 8-weeks Clinical remission CDAI ⩽ 150	26/39 (67%) (4 weeks) 23/39 (59%) (8 weeks)	13/39 (39%) (8 weeks) 16/39 (41%) (40 weeks)	↑ baseline serum infliximab trough level ⩾ 1 mg/mL ↑ baseline plasma IL-6 levels ⩽ 2.41 pg/mL ↑ baseline serum albumin level ⩾ 3.8 g/dL
Nagata *et al.*[20] (2015)	Infliximab (26)	Deterioration in CDAI and CRP within an 8-week interval after administration of 5 mg/kg, 8 weekly infliximab	Clinical response ⩾25% or 70-point reduction in CDAI Clinical remission CDAI < 150	18/26 (69%) (week 4)	15/26 (58%) (week 4) 11/22 (50%) (week 48)	NR
	Infliximab 10 mg/kg, 8 weekly (13)	As above	As above	8/13 (62%) (week 4)	7/13 (54%) (week 4) 4/9 (44%) (week 48)	
	Infliximab 5 mg/kg, 4–7 weekly (13)	As above	As above	10/13 (77%) (week 4)	8/13 (62%) (week 4) 7/13 (54%) (week 48)	
Dreesen *et al.*[19] (2018)	Infliximab (103)	No longer being in remission based on physicians' global assessment of signs and symptoms	Clinical response Marked decrease or disappearance of symptoms (physicians' global assessment)	65/103 (63%) (second infusion) 51/103(50%) (1-year persistence)	NR	Biologic response ↑ magnitude of increase in adalimumab trough concentration following dose intensification ↑ achieving therapeutic trough concentrations

(continued)

Table 2. (Continued)

Author (year)	Anti-TNF dose intensification regimen (number intensified)	Criteria for dose intensification	Definition of tertiary response/ remission following dose intensification	Tertiary response following dose intensification (timepoint)	Tertiary remission following dose intensification (timepoint)	Predictors of tertiary response/remission following dose intensification
	Infliximab 10 mg/kg, 8 weekly (45)	As above	As above	24/45 (53%) (second infusion) 21/45 (47%) (1-year persistence)	NR	
	5 mg/kg dose interval shortened (45)	As above	As above	33/45 (73%) (second infusion) 23/45 (51%) (1-year persistence)	NR	
	10 mg/kg dose interval shortened (13)	As above	As above	8/13 (62%) (second infusion) 7/13 (54%) (1-year persistence)	NR	
Infliximab dose intensification: primary non-response or secondary loss of response						
Hendler *et al.*[30] (2015)	Infliximab >10 mg/kg, 8 weekly (86)	Treating physician's clinical judgement	Clinical response Incomplete resolution of symptoms Clinical remission Complete resolution of symptoms	31/66 (47%) (within 16 weeks)[a] 21/61 (34%) (within 100 weeks)[a]	17/66 (25%) (within 16 weeks)[b] 17/61 (28%) (within 100 weeks)[b]	NR
Adalimumab dose intensifiction: secondary loss of response						
Colombel *et al.*[31] (2009)	Adalimumab 40 mg weekly (40)	Disease Flare: increase in CDAI of ⩾70 points vs. week 4 and an absolute CDAI score >220	Clinical response Decrease in CDAI of ⩾70 points	34/40 (85%) (56 weeks)	NR	NR
Karmiris *et al.*[32] (2009)	Adalimumab 40 mg, weekly (70)	Recurrent symptoms of active luminal disease and were accompanied by an increase in CRP or endoscopic lesions	Clinical response Lasting control of disease activity by end of follow-up	53/70 (78%) (long-term)	NR	↑ adalimumab trough concentration post dose intensification
Baert *et al.*[6] (2013)	Adalimumab 40 mg, weekly (208)	Reappearance of symptoms and CRP re-elevation (if applicable) judged by treating investigator	Clinical response durable response for ⩾6 months or successful de-escalation within 6 months	139/208 (67%) (6 months)	NR	NR
Ma *et al.*[23] (2014)	Adalimumab 40 mg, weekly or 80 mg, 2 weekly (92)	HBI >5 AND >3 points from post-induction baseline AND elevated inflammatory markers (CRP >10, FCP >50) or evidence of activity on endoscopy or CT enterography	Clinical response Decrease in HBI of >3 points	74/92 (80%) (within 24 weeks)	NR	NR

(continued)

Table 2. (Continued)

Author (year)	Anti-TNF dose intensification regimen (number intensified)	Criteria for dose intensification	Definition of tertiary response/ remission following dose intensification	Tertiary response following dose intensification (timepoint)	Tertiary remission following dose intensification (timepoint)	Predictors of tertiary response/remission following dose intensification
Bouguen *et al.*[38] (2015)	Adalimumab 80 mg, 2 weekly (42)	CDAI > 150 and 1 objective sign of inflammation (elevated C-reactive protein (CRP) .5 mg/L and/ or faecal calprotectin level .300 ug/g and/or radiologic and/or endoscopic evidence of disease activity),	Clinical response 70 point decrease in CDAI from baseline Clinical remission CDAI < 150 without steroids	23/42 (55%) (short-term, median 4.9 weeks) 12/42 (29%) (6 months)	14/42 (33%) (short-term median 4.9 weeks) 10/42 (24%) (6 months)	Baseline CDAI < 260
Duveau *et al.*[24] (2017)	Adalimumab 40 mg, weekly (100) 80 mg, 2 weekly (24)	Physician-determined increase in clinical Crohn's disease activity	Clinical response Significant improvement in Crohn's disease–related clinical symptoms and laboratory tests assessed by treating physician, leading to continued adalimumab treatment, associated with complete weaning from steroids, without luminal or anal surgery, or introduction of immunosuppressants	99/124 (79%) (3 months) 62/124 (58%) (12 months)	NR	↑ secondary loss of response ⩾10 months after adalimumab initiation ↑ stricturing phenotype ↑ adalimumab 40 mg weekly *vs* adalimumab 80 mg 2 weekly ↑ baseline CRP ⩽ 5 mg/L
Motoya *et al.*[17] (2017)	Adalimumab 80 mg, 2 weekly (28)	CDAI ⩾ 200 including CDAI ⩾ 50-points from lowest CDAI AND CRP ⩾ 1 mg/dL	Clinical response Reduction in CDAI of ⩾50 points in 8 weeks Clinical remission CDAI < 150	21/28 (75%) (8 weeks) 20/28 (71%) (24 weeks) 16/28 (57%) (52 weeks)	7/28 (25%) (8 weeks) 12/28 (43%) (24 weeks) 10/28 (36%) (52 weeks)	↑ lower baseline CDAI ↑ lower week-4 CDAI
Restellini *et al.*[39] (2018)	Adalimumab 40 mg, weekly (48)	HBI > 5 and/or biochemical evidence of disease (CRP/ faecal calprotectin) and/ or endoscopic findings confirming active disease in patients who were in remission before	Clinical remission HBI < 5, with CRP < 5 mg/L, faecal calprotectin < 250 ug/g, and SES-CD score < 3	NR	4/25 (16%) (3 months) 8/26 (31%) (6-months) 6/22 (27%) (12-months)	NR

(continued)

Table 2. (Continued)

Author (year)	Anti-TNF dose intensification regimen (number intensified)	Criteria for dose intensification	Definition of tertiary response/ remission following dose intensification	Tertiary response following dose intensification (timepoint)	Tertiary remission following dose intensification (timepoint)	Predictors of tertiary response/remission following dose intensification
Suzuki *et al.*[22] (2019)	Adalimumab 80 mg, 2 weekly (12)	CDAI ⩾ 150 or elevated CRP	Clinical response ⩾70-point reduction Clinical remission CDAI < 150-points	4/12 (33%) (CDAI-70, 12 weeks) 3/9 (33%) (CDAI-70, 52 weeks)	8/12 (67%) (12 weeks) 6/12 (50%) (52 weeks)	NR
Adalimumab dose intensification: primary non-response or secondary loss of response						
Bultman *et al.*[33] (2012)	Adalimumab 40 mg, weekly (46)	Physician determined need to decrease the dosing interval in patients that failed to respond or lost response, where loss of response was defined as increase in CDAI > 50 points from baseline	Clinical response Treating physician-determined response	20/46 (43%)[a] (3 months)	NR	NR
Panaccione *et al.*[34] (2011)	Adalimumab 40 mg, weekly (120)	Physician-determined flare or non-response	Clinical response Decrease in HBI by ⩾3 from baseline Clinical remission HBI ⩽ 4	85/120 (71%)[b] (24 weeks)	36/120 (30%)[b] (24 weeks)	NR
Sandborn *et al.*[35] (2011)	Adalimumab 40 mg, weekly (71)	Not achieving CDAI reduction of ⩾70 points from baseline	Clinical response Reduction in CDAI ⩾ 70-points (CR-70) Clinical remission CDAI < 150	45/71 (63%)[a] (CR-70, within 56 weeks)	26/71 (37%)[b] (within 56 weeks)	NR
Löfberg *et al.*[36] (2012)	Adalimumab 40 mg, weekly (131)	Disease flare characterised by increase in HBI ⩾ 3 and total HBI ⩾ 7; OR Non-response defined as drop in HBI < 3 from baseline	Clinical response Decrease in HBI by ⩾3 Clinical remission HBI < 5	76/131 (58%)[a] (20 weeks)	46/131 (35%)[b] (20 weeks)	NR
Watanabe *et al.*[37] (2014)	Adalimumab 80 mg, 2 weekly (40)	Flare defined as recurrence of active disease (i.e. CDAI ⩾ 220 including an increase of ⩾70 points from baseline)	Clinical response Decrease in CDAI by ⩾70-points from baseline Clinical remission CDAI < 150	8/40 (20%)[a] (48 weeks)	6/40 (15%)[b] (48 weeks)	NR
Verstockt *et al.*[40] (2018)	Adalimumab 40 mg, weekly (43)	Physician initiated dose intensification ⩾4 weeks following adalimumab initiation	Clinical response Global physician assessment	31/43 (72%)[a] (median 88.7 weeks)	NR	NR

(continued)

Table 2. (Continued)

Author (year)	Anti-TNF dose intensification regimen (number intensified)	Criteria for dose intensification	Definition of tertiary response/ remission following dose intensification	Tertiary response following dose intensification (timepoint)	Tertiary remission following dose intensification (timepoint)	Predictors of tertiary response/remission following dose intensification
Both infliximab and adalimumab dose intensification: secondary loss of response						
Viazis *et al.*[42] (2015)	Infliximab 10 mg/kg, 4–8 weekly (18) Adalimumab 40 mg, weekly (13)	Recurrence of clinical symptoms with elevated CRP or endoscopic activity in patients that initially responded to anti-TNF	Clinical remission Absence of symptoms and normal CRP	NR	25/31 (81%) (⩾12 months)	NR
María Del Carmen *et al.*[45] (2016)	Infliximab Dose increase and/ or dose interval shortening Adalimumab 40 mg, weekly (24)	Worsening of symptoms associated with endoscopic, radiographic and/or serological evidence of inflammation	Clinical response Decrease in HBI by ⩾3 from baseline; OR ⩾50% reduction in draining fistulas Clinical remission HBI⩽4 without steroids; OR Closure of all fistula	11/24 (46%) (short-term follow-up)	8/24 (33%) (short-term follow-up)	NR
Narula *et al.*[43] (2016)	Infliximab (22) Adalimumab (14)	Physician-determined flare following primary response to anti-TNF therapy	Clinical response Decrease in HBI by ⩾3 from baseline; OR ⩾50% reduction in baseline number of draining fistula Clinical remission HBI<5; OR Complete cessation of drainage from perianal fistulas	6/21 (29%) (12 months)	9/21 (43%) (12 months)	NR
	Infliximab 10 mg/kg, 8 weekly (17) 5 mg/kg, 4–7 weekly (5)	As above	As above	Infliximab 4/16 (25%) (12 months)	Infliximab 8/16 (50%) (12 months)	
	Adalimumab 40 mg, weekly (14)	As above	As above	Adalimumab 2/5 (40%) (12 months)	Adalimumab 1/5 (20%) (12 months)	
Preda *et al.*[44] (2016)	Infliximab (26) Adalimumab (19)	Physician-determined clinical loss of response	Clinical response Decrease in CDAI by >70 points Clinical remission CDAI<150 at last evaluation	NR	NR	NR
	Infliximab 10 mg/kg, 8 weekly (13) 5 mg/kg, 4–7 weekly (13)	As above	As above		Infliximab 11/26 (42%) (after mean 36 months))	

(continued)

Table 2. (Continued)

Author (year)	Anti-TNF dose intensification regimen (number intensified)	Criteria for dose intensification	Definition of tertiary response/ remission following dose intensification	Tertiary response following dose intensification (timepoint)	Tertiary remission following dose intensification (timepoint)	Predictors of tertiary response/remission following dose intensification
	Adalimumab 40 mg, weekly (19)	As above	As above		Adalimumab 16/19 (84%) (after mean 20 months)	
Srinivasan *et al.*[7] (2018)	Infliximab (51) Adalimumab (37)	HBI ⩾ 5 and objective evidence of disease (CRP ⩾ 5 mg/L, FCP ⩾ 100 ug/mL)	Clinical remission HBI < 5	NR	36/59 (61%) (last clinical review)	NR
	Infliximab 5 mg/kg, 0, 2, 6 re-induction (22) Adalimumab 160 mg/80 mg 0, 2 re-induction (11)	As above	As Above	NR	11/17 (65%) (last clinical review, median 3.5 years)	
	Infliximab 5 mg/kg, 6 weekly (29) Adalimumab 40 mg, weekly (26)	As above	As above	NR	25/42 (60%) (last clinical review, median 1.5 years)	
Both infliximab and adalimumab dose intensification: primary non-response or secondary loss of response						
Ghaly *et al.*[41] (2014)	Infliximab 5 mg/kg, 0, 2, 6 re-induction (8) 5 or 10 mg/kg, 6 weekly (11) 5 mg/kg, 4 weekly (1) Adalimumab 40 mg, weekly (35)	Clinically active Crohn's disease supported by laboratory parameter, imaging or endoscopy	Good response physician and patient satisfied by clinical response Partial response guarded comments regarding clinical response	50/55 (91%) (any response, 3 months)[a] 40/55 (73%) (good response, 3 months)[a] 10/55 (18%) (partial response, 3 months)[a]	NR	↑ absence of continuous corticosteroids for ⩾6 months in preceding 5 years

CDAI, Crohn's disease activity index; CRP, C-reactive protein; HBI, Harvey–Bradshaw Index; NR, not reported.
[a]Pooled outcomes following anti-TNF dose intensification for primary non-response and secondary loss of response.

were evaluated across 19 studies, 13 of which evaluated outcomes following infliximab dose intensification alone, with the remaining six studies evaluating outcomes across mixed adalimumab and infliximab cohorts.

Clinical outcomes following infliximab dose intensification. Clinical response and remission across all infliximab dose-intensification studies, strategies and timepoints ranged from 25% to 90% and 19% to 58%, respectively. Short- to medium-term clinical response following infliximab dose intensification undertaken to address secondary LOR using any dose-intensification strategy ranged from 40% to 90% at 4–8 weeks to 28–80% at 12–24 weeks; with longer-term response after at least 1 year sustained in 25–83% of patie nts.[4,5,15,16,19–21,25–29,43] The proportion of patients who achieved short-term clinical remission using any infliximab dose-intensification strategy to address secondary LOR at 4–12 weeks was 19–58%, while long-term clinical remission was reported in 41–56%.[15,16,20,26–29,43,44] Only one study adopted infliximab dose intensification to address both non-response and secondary LOR, and despite the use of high-dose infliximab intensification (⩾ 10 mg/kg 4–7 weekly), reported short-term and sustained clinical response in 47% and 34% of patients, respectively.[30]

Infliximab 10 mg/kg 8 weekly. Eleven studies included patients who underwent infliximab 10 mg/kg 8 weekly dose intensification, of which seven studies reported clinical response and three studies reported clinical remission outcomes specific to this dosing strategy. Seven studies reported short-term clinical response in 52–90% of patients within 12 weeks.[5,16,19–21,25,28] Three studies reported sustained clinical response in 41–50% of patients following at least 12 months of intensification.[5,19,21] Three studies reported clinical remission in 28–54% of patients within 4–8 weeks of intensification.[16,20,28] Two studies reported sustained clinical remission after 40–48 weeks of intensification in 41–44% of patients.[16,20]

Infliximab 5 mg/kg 4 weekly. Six studies included patients who underwent infliximab 5 mg/kg 4 weekly dose intensification, of which four studies reported clinical response and three studies reported clinical remission outcomes specific to this dose-intensification strategy. Three studies reported clinical response in 28–66% of patients within 20 weeks of intensification.[5,15,29] Two studies reported sustained clinical response in 39–83% of patients following at least 12 months of intensification.[5,27] Two studies reported clinical remission in 19–39% of patients after 12-weeks of intensification.[15,29] Only one study reported sustained clinical remission following 54-weeks of intensification in 56% of patients.[27]

Infliximab 5 mg/kg 4–7 weekly. Six studies included patients who underwent infliximab 5 mg/kg 4 weekly dose intensification, of which five studies reported clinical response and two studies reported clinical remission outcomes specific to these dose-intensification strategies. Five studies reported clinical response in 15–88% of patients within 18 weeks of intensification.[4,19–21,28] Three studies reported sustained clinical response in 13–51% of patients following at least 12 months of intensification.[4,19,21] Two studies reported clinical remission in 57–62% of patients 4 weeks following intensification.[20,28] Only one study reported sustained clinical remission following 48 weeks of intensification in 54% of patients.[20]

High dose infliximab ⩾10 mg/kg 4–7 weekly. Five studies included patients who underwent high-dose infliximab dose intensification, of which three studies reported clinical response and one study reported clinical remission outcomes specific to this dose-intensification strategy. Three studies reported short-term clinical response in 47–80% of patients after 2–3 intensified infusions, and sustained clinical response in 34–54% of patients following at least 12-months of intensification.[19,21,30] One study reported short-term clinical remission within 16-weeks in 25% of patients and sustained clinical remission within 100 weeks in 34% of patients.[30]

Factors associated with response and/or remission following infliximab dose-intensification. Several factors have been associated with favourable clinical outcomes following infliximab dose intensification. Katz *et al.*[5] found that immediate clinical response was associated with a stricturing (OR 4.1, 95% CI (1.8–9.1)) or penetrating (OR 4.1 (1.8–9.1)) phenotype and normal baseline CRP (OR 3.2, (1.2–9.4)) *via* multivariate analysis. Similarly, Kopylov *et al.*[4] reported that normalisation of CRP following infliximab dose intensification was associated with immediate clinical response (OR 4.2 (1.2–15.2)), relative to persistent CRP elevation.

Katz *et al.*[5] also documented that sustained response at 1 year was associated with younger age (16–40 years) at disease diagnosis (OR 2.7 (1.1–7.7)), and normal CRP (OR 4.0 (1.5–10.3)) at LOR. The proportion of patients achieving clinical remission at week 40 was found to be higher in patients with serum infliximab trough levels ⩾1 mg/mL, plasma interleukin (IL)-6 levels ⩽2.41 pg/mL and/or serum albumin level ⩾3.8 g/dL at baseline by Suzuki *et al.*[16] Dreesen *et al.* also noted that patients who achieved biologic response (defined by reduction in CRP by 50% or CRP ⩽ 5 mg/L from baseline CRP > 5 mg/L) and remission (CRP ⩽ 5 mg/L from baseline CRP > 5mg/L) following infliximab dose intensification were more likely to have higher infliximab trough levels.[19] Moreover, a therapeutic (>3.0 ug/mL) infliximab trough concentration was also positively associated with biologic response.[19]

Adalimumab dose intensification

Adalimumab dose intensification was undertaken exclusively for secondary LOR in 14 of 21 studies. Unlike infliximab, the majority ($n=17$) of adalimumab studies included patients who were anti-TNF naïve. Adalimumab dose-intensification strategies evaluated included adalimumab 40 mg weekly ($n=17$), adalimumab 80 mg 2 weekly ($n=6$), and adalimumab re-induction ($n=1$).[6,7,17,22–24,31–45] These regimens were evaluated in 21 studies, 15 of which evaluated outcomes following adalimumab dose intensification alone, with the remaining six studies evaluating outcomes across mixed adalimumab and infliximab cohorts.

Clinical outcomes following adalimumab dose intensification. Clinical response and remission across all adalimumab dose-intensification studies, strategies, and timepoints ranged from 20% to 85% and 15% to 84%, respectively. Short-term clinical response within 12 weeks of adalimumab dose intensification undertaken to address secondary LOR across all dose-intensification strategies ranged from 33% to 79%, while clinical response within 24 weeks ranged from 29% to 80%, and sustained clinical response following at least 1 year of intensified adalimumab therapy ranged from 33% to 85%.[6,17,22–24,31,32,38,43] Short-term clinical remission following adalimumab dose intensification to address secondary LOR was achieved at 8–12 weeks in 16–67% of patients, while medium-term (12–24 weeks) and sustained (⩾52 weeks) clinical remission was reported in 24–43% and 20–84% of patients, respectively.[17,22,38,39,43,44]

Comparatively, six studies used adalimumab dose intensification to address both non-response and secondary LOR, with overall adalimumab response ranging from 20% to 72%.[31,33–37,40] Of these six studies, three reported short-term (⩽24 weeks) response in 58–72% of patients, while three studies reported sustained response (⩾52 weeks) in 20–72% of patients.[33–37,40]

Adalimumab 40 mg weekly. Seventeen studies included patients who underwent adalimumab 40 mg weekly dose intensification, of which nine studies reported clinical response and six studies reported clinical remission outcomes specific to this dose-intensification strategy. Four studies reported clinical response in 35–71% of patients following 3–6 months of intensification.[6,33,34,36] Five studies reported sustained clinical response in 40–85% of patients following at least 12 months of intensification.[31,32,35,40,43] Three studies reported clinical remission in 16–35% of patients following 3–6 months of intensification.[34,36,39] Three studies reported sustained clinical remission following at least 12 months of intensification in 20–84% of patients.[35,43,44]

Adalimumab 80 mg 2 weekly. Six studies included patients who underwent adalimumab 80 mg 2 weekly dose intensification, of which four studies reported clinical response and four studies reported clinical remission outcomes specific to this dose-intensification strategy. Three studies reported short- to medium-term clinical response in 39–75% of patients within 6 months of intensification.[17,22,38] Three studies also reported sustained clinical response in 20–57% of patients following at least 12 months of intensification.[16,17,37] Similarly, three studies reported clinical remission in 24–67% of patients within 6-months of intensification and sustained clinical remission following at least 48-weeks of intensification in 15–50% of patients.[17,22,37]

Adalimumab 40 mg weekly or adalimumab 80 mg 2 weekly. Two studies reported pooled outcomes following adalimumab 40 mg weekly and 80 mg 2 weekly. Short-term clinical response was achieved in 79–80% of intensified patients between 3 and 6 months, while sustained clinical response at 12 months was achieved in 60%.[23,24]

Factors associated with response and/or remission following adalimumab dose intensification. Duveau *et al.*[24] found that adalimumab 40 mg weekly rather than 80 mg 2 weekly (OR 3.6, 95% CI (1.3–10.4)) and CRP ⩽ 5 mg/L at dose intensification (OR 6.6 (1.4–27.5)) were associated with 12 month clinical response to adalimumab dose intensification. Secondary LOR that developed 10 months or more (OR 2.6 (1.0–6.5)) after adalimumab initiation and stricturing disease (OR 4.4 (1.4–14.0)) were also found to be associated with clinical response at 3 months.[24] Motoya *et al.*[17] also noted that CDAI at baseline and at 4 weeks were each lower in patients that achieved 24-week clinical remission.

Pooled infliximab and adalimumab dose intensification

Clinical outcomes following pooled infliximab and adalimumab dose intensification. Six studies reported outcomes across cohorts that underwent both infliximab and adalimumab dose intensification, including two studies that reported outcomes across infliximab and adalimumab subgroups.[7,41–45] The remaining four studies only reported pooled outcomes following infliximab and adalimumab dose intensification, including one study by Ghaly *et al.*[41] which included patients that underwent dose intensification for primary non-response.[7,42,45] Pooled outcomes across these four studies using any infliximab or adalimumab dose-intensification strategy, reported clinical response in 46–91% (⩽3 months) and sustained clinical remission in 61–81% of patients.[7,41,42,45]

Factors associated with response and/or remission following pooled infliximab and adalimumab dose intensification. Ghaly *et al.*[41] reported that the absence of continuous corticosteroids for ⩾6 months in the 5 years preceding anti-TNF dose intensification was the sole predictor of durable steroid-free remission over the 12 months following dose intensification (OR 3.5, 95% CI 1.05–12.05).

Non-response and LOR following anti-TNF dose intensification

Nineteen studies reported or allowed imputation of clinical outcomes pertaining to tertiary non-response and tertiary LOR following infliximab and/or adalimumab dose intensification (Table 3).[4–7,16,17,21,23–25,28–30,33,35,38,41,44,45]

Tertiary non-response. Tertiary non-response within 6 months of anti-TNF dose intensification undertaken to address secondary LOR was reported in 10–45% of patients across 10 studies, including two studies that reported outcomes following both infliximab and adalimumab dose intensification.[6,16,17,21,24,28,29,38,44,45] When outcomes were analysed by anti-TNF agent, tertiary non-response occurred in 10-58% and 14-45% of patients following infliximab and adalimumab dose intensification, respectively. Comparatively, three studies included patients who underwent anti-TNF dose intensification for both primary non-response and secondary LOR, reporting tertiary non-response in 7–37% of patients.[30,33,41]

Tertiary LOR. Tertiary LOR following at least 6 months of anti-TNF dose intensification to address secondary LOR was reported in 7–64% of patients across 10 studies; including 16–64% and 7–57% of patients following infliximab and adalimumab dose intensification, respectively.[4,5,7,16,17,21,23–25,28] Comparatively, two studies included patients who underwent anti-TNF dose intensification for both primary non-response and secondary LOR, reporting tertiary LOR in 30–38% of patients.[30,35]

Predictors of tertiary non-response and tertiary LOR following anti-TNF dose intensification. Baert *et al.*[6] reported that failure of dose intensification was associated with elevated CRP at baseline, while Ma *et al.*[23] ascribed the need for concurrent corticosteroid therapy at initial adalimumab induction to a reduced likelihood of response to adalimumab dose intensification following secondary LOR. Duveau *et al.*[24] reported that tertiary LOR occurred less frequently over time with adalimumab 40 mg weekly than 80 mg 2-weekly and with a CRP ⩽ 5 mg/L compared with a CRP > 5 mg/L prior to dose intensification. Ma *et al.* also reported that factors including CRP > 10 mg/L and prior anti-TNF exposure were associated with an increased risk of tertiary LOR on univariate analysis, while elevated CRP was predictive of shorter time to tertiary LOR on Kaplan–Meier analysis[23]. In a pooled cohort who underwent anti-TNF re-induction and/or dose interval shortening with infliximab and adalimumab, longer time to treatment failure was associated with higher baseline serum albumin, male sex, and thiopurine co-therapy on multiple regression analyses.[7]

Table 3. Tertiary non-response and loss of response following anti-TNF dose intensification.

Author (year)	Anti-TNF dose intensification regimen (number intensified)	Definition of tertiary non-response/ loss of response following dose intensification	Tertiary non-response following dose intensification (timepoint)	Tertiary loss of response following dose intensification (timepoint)	Predictors of tertiary non-response/ loss of response following dose intensification
Infliximab dose intensification: secondary loss of response					
Rutgeerts *et al.*[25] (2004)	Infliximab (58)	Discontinuation of intensified infliximab due to lack of efficacy	NR	9/58 (16%) (within 54 weeks)	NR
Kopylov *et al.*[4] (2011)	Infliximab (94)	Absence of symptomatic improvement and a decision to further dose increase or dose interval shorten, add immunomodulator or corticosteroids, switch anti-TNF medications or Crohn's disease-related surgery	NR	49/76 (64%) (1 year)	NR
Chaparro *et al.*[28] (2012)	Infliximab (33)	Loss of response following infliximab dose intensification	7/33 (21%) (4 weeks)	13/26 (50%) (median 33 months)	NR
Katz *et al.*[5] (2012)	Infliximab (168)	Absence of symptomatic improvement and a decision to further dose increase or dose interval shorten, add immunomodulator or corticosteroids, switch anti-TNF medications or Crohn's disease-related surgery	NR	88/166 (53%) (1 year)	NR
Lin *et al.*[21] (2012)	Infliximab (30)	Tertiary non-response to initial dose intensification, and tertiary loss of response following initial response to dose intensification, were defined as persistent disease-related symptoms followed by (1) resumption of steroids, (2) Crohn's disease-related hospitalisation or surgery, or (3) discontinuation of infliximab in favour of another biologic	6/30 (20%) (after three intensified infusions)	14/30 (47%) (median 9 months	NR
Steenholdt *et al.*[29] (2015)	Infliximab (36)	Lack of effect to 4-weekly infliximab dose intensification	12/36 (33%) (20 weeks)	NR	NR
Suzuki *et al.*[16] (2015)	Infliximab (39)	Discontinuation attributable to lack of efficacy to intensified dosing	4/39 (10%) (8 weeks)	7/39 (18%) (40 weeks)	NR
Infliximab dose intensification: primary non-response and secondary loss of response					
Hendler *et al.*[30] (2015)	Infliximab (86)	Lack of improvement in symptoms	10/66 (15%)[a] (within 16 weeks)	23/61 (38%)[a] (within 100 weeks)	NR
Adalimumab dose intensification: secondary loss of response					
Baert *et al.*[6] (2013)	Adalimumab (208)	Did not re-induce clinical response for at least 6-months	49/208 (24%) (6 months)	NR	↑ baseline CRP elevated

(continued)

Table 3. (Continued)

Author (year)	Anti-TNF dose intensification regimen (number intensified)	Definition of tertiary non-response/ loss of response following dose intensification	Tertiary non-response following dose intensification (timepoint)	Tertiary loss of response following dose intensification (timepoint)	Predictors of tertiary non-response/ loss of response following dose intensification
Ma *et al.*[23] (2014)	Adalimumab (92)	HBI > 5 and >3 points from post-induction baseline AND elevated inflammatory markers (CRP > 10, faecal calprotectin > 50) or evidence of activity on endoscopy or CT enterography following initial response to adalimumab dose intensification	NR	42/74 (57%) (median 48 weeks)	↑ baseline CRP > 10.0 mg/L ↑ prior anti-TNF exposure ↑ need for corticosteroid therapy at initial adalimumab induction
Bouguen *et al.*[38] (2015)	Adalimumab (42)	did not achieve a 70 point drop in CDAI	19/42 (45%) (<14 weeks)	NR	NR
Motoya *et al.*[17] (2017)	Adalimumab (28)	Did not achieve a ⩾50 point reduction in CDAI at week 8, or across two consecutive CDAI evaluations after week 8	4/28 (14%) (8 weeks)	2/28 (7%) (52 weeks)	NR
Duveau *et al.*[24] (2017)	Adalimumab (124)	Adalimumab discontinuation, or introduction/continuation of corticosteroids, or luminal or anal surgery, or introduction of immunomodulators	21%, (3 months) 29%, (6 months)	40%, (12 months)	↓ adalimumab 40 mg weekly *vs* 80 mg 2-weekly ↑ baseline CRP > 5 mg/L
Adalimumab dose intensifcation: primary non-response and secondary loss of response					
Sandborn *et al.*[35] (2011)	Adalimumab (71)	Discontinuation attributable to lack of efficacy to intensified dosing	NR	21/71(30%)[a] (⩽56 weeks)	NR
Bultman *et al.*[33] (2012)	Adalimumab (46)	Treating physician determined that dose intensification was not effective	17/46 (37%)[a] (3 months)	NR	NR
Both infliximab and adalimumab dose intensification: secondary loss of response					
María Del Carmen *et al.*[45] (2016)	Infliximab Adalimumab (24)	Did not achieve drop in HBI by ⩾3; OR Did not achieve closure of at least 50% fistulas	5/24 (21%) (short-term follow-up)	NR	NR
Preda *et al.*[44] (2016)	Infliximab (26) Adalimumab (19)	No response Drop in CDAI < 70 points	Infliximab 15/26 (58%) (short-term follow-up) Adalimumab 3/19 (16%) (short-term follow-up)	NR	NR

(continued)

Table 3. (Continued)

Author (year)	Anti-TNF dose intensification regimen (number intensified)	Definition of tertiary non-response/ loss of response following dose intensification	Tertiary non-response following dose intensification (timepoint)	Tertiary loss of response following dose intensification (timepoint)	Predictors of tertiary non-response/ loss of response following dose intensification
Srinivasan *et al.*[7] (2018)	Infliximab (51) Adalimumab (37)	Treatment failure refers to any of: (1) Crohn's disease-related abdominal surgery, (2) anti-TNF cessation, or (3) switching to another biologic agent	NR	Infliximab 9/51 (18%) (12 months) Adalimumab 7/37 (19%) (12 months)	↓ baseline thiopurine co-therapy ↓ higher baseline serum albumin ↓ male sex
Both infliximab and adalimumab dose intensification: primary non-response and secondary loss of response					
Ghaly *et al.*[41] (2014)	Infliximab (20) Adalimumab (35)	No real improvement in clinical symptoms	4/55 (7%) (3 months)[a]	NR	NR

NR: not reported; CRP C-reactive protein; CDAI: Crohn's disease activity index; HBI: Harvey–Bradshaw Index
[a]Pooled outcomes following anti-TNF dose intensification for primary non-response and secondary loss of response.

Meta-analysis

Differentiating between effective and ineffective dose intensification

Studies evaluated as part of each meta-analysis below, that is, (1) tertiary response *versus* tertiary non-response and (2) tertiary response *versus* tertiary LOR, were assessed across comparable timepoints.

Evaluating tertiary response and tertiary non-response. Twelve studies reported both tertiary response and tertiary non-response within 6 months of infliximab ($n=5$), adalimumab ($n=5$) or co-reported infliximab/adalimumab ($n=2$) dose intensification, including nine studies that used dose intensification to address secondary LOR alone.[6,16,17,21,24,28–30,33,38,41,45] Clinical assessment of tertiary response and tertiary non-response was undertaken after a median of 14 weeks (range 4–24 weeks). Anti-TNF dose intensification using any strategy was more likely to result in tertiary response than tertiary non-response within the first 6 months (RR 2.58 [95% CI 1.76, 3.79, $I^2=82\%$], Figure 3(a)).

Evaluating tertiary response and tertiary LOR. Seven studies reported both tertiary response and tertiary LOR beyond 6 months of infliximab ($n=4$) or adalimumab ($n=3$) dose intensification, including five studies that used dose intensification to address secondary LOR alone.[4,5,17,21,24,30,35] Sustained tertiary response to anti-TNF dose intensification beyond 6 months (RR 1.10 (95% CI 0.75, 1.61, $I^2=85\%$), Figure 3(b)) was comparable to tertiary LOR after a median of 12 months (range 9–23 months).

Potential sources of heterogeneity were evaluated by subgroup analysis, including by anti-TNF (infliximab. adalimumab or pooled infliximab/adalimumab) or indication for dose intensification (secondary LOR *versus* pooled primary non-response/secondary LOR). The results remained similar in all cases with no variations of significance, although heterogeneity remained high.

Discussion

This systematic review affirms that empiric anti-TNF dose intensification represents a clinically effective strategy to address secondary LOR to adalimumab and infliximab therapy in patients with Crohn's disease. Short-term clinical response

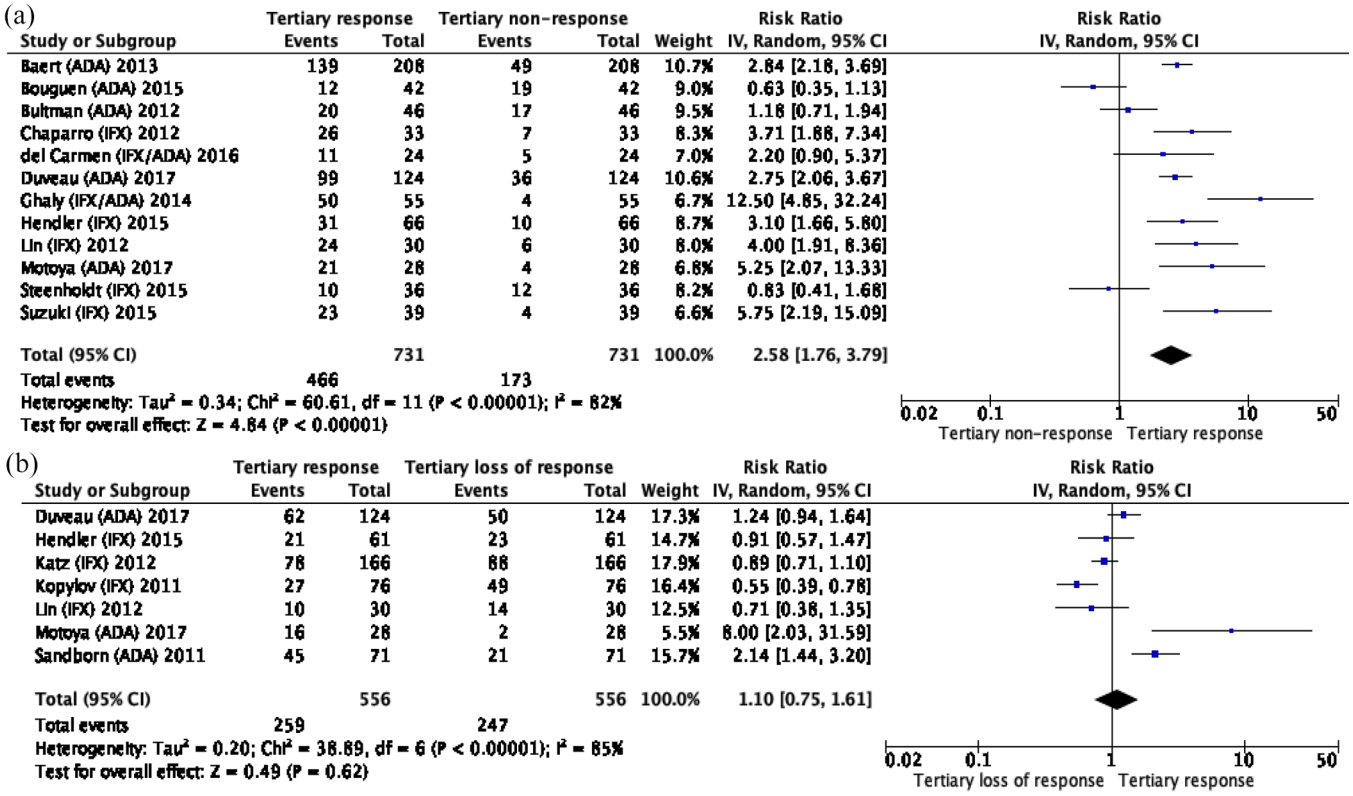

Figure 3. Forest plot comparison of: (a) tertiary response *versus* tertiary non-response within 6 months of anti-TNF dose intensification (b) tertiary response *versus* tertiary loss of response beyond 6 months of anti-TNF dose intensification.

following any anti-TNF dose-intensification strategy to address secondary LOR within 12 weeks ranged from 33% to 90%, while sustained clinical response lasting at least 48 weeks ranged from 25% to 85%.[4–6,15–17,19–29,31,32,38,43,45] Similarly, short-term clinical remission following any anti-TNF dose-intensification strategy to address secondary LOR was 16–67% within 12 weeks, while longer-term clinical remission was reported in 20–84%.[7,15–17,20,22,26–29,38,39,42–45]

Nevertheless, empiric anti-TNF dose intensification is not always effective, and even when effective, may not provide a durable clinical response. Hence, the current systematic review also evaluated tertiary non-response and tertiary LOR following anti-TNF dose intensification. Tertiary non-response within 6 months of any anti-TNF dose-intensification strategy occurred in 10–45% of patients, while tertiary LOR following at least 6 months of intensified therapy occurred in 7–64% of patients. Hence, despite the clinical effectiveness of anti-TNF dose intensification in addressing LOR, clinicians must remain cognisant that a proportion of patients may not respond, or fail to demonstrate durable response to anti-TNF dose intensification. This highlights the need to differentiate between effective and ineffective dose intensification. Our meta-analysis demonstrated that patients are more than twice as likely to achieve tertiary response then experience tertiary non-response within the first 6 months following anti-TNF dose intensification; however, on the basis of currently available data, the clinical effectiveness of longer-term anti-TNF dose intensification remains to be clarified. These findings reflect real-world data wherein the likelihood of response is highest immediately following anti-TNF initiation, with diminishing response over time.

Given that some patients will respond to empiric anti-TNF dose intensification, while others may not, it remains important to identify factors associated with response, non-response and LOR following anti-TNF dose intensification. Baseline characteristics associated with favourable clinical response following either adalimumab or infliximab dose intensification included younger age at

diagnosis (16–40 years),[5] stricturing/penetrating phenotype,[5,24] absence of continuous (⩾6 months) corticosteroid use within 5 years of dose intensification,[41] LOR after ⩾10 months of adalimumab,[24] non-smoking status,[5] lower baseline CDAI,[17] lower baseline CRP,[5,24] baseline albumin ⩾3.8 g/dL,[16] baseline serum infliximab trough levels ⩾1 mg/mL,[16] and plasma IL-6 levels ⩽2.41 pg/mL.[16] Other factors associated with clinical response included dose intensification using adalimumab 40 mg weekly rather than 80 mg 2-weekly,[24] lower CDAI 4 weeks following dose intensification,[17] and normalisation of CRP following dose intensification.[4] Similarly, characteristics associated with tertiary non-response and tertiary LOR-included corticosteroid use at adalimumab induction,[23] higher baseline CRP,[6,23,24] and prior anti-TNF exposure,[23] while adalimumab 40 mg weekly (*versus* adalimumab 80 mg 2 weekly),[24] male sex,[7] higher baseline albumin,[7] and thiopurine co-therapy[7] were all associated with more favourable outcomes.

This systematic review and meta-analysis is, to the best of our knowledge, the first to evaluate tertiary response, tertiary non-response, and tertiary LOR following empiric anti-TNF dose intensification undertaken specifically to address secondary LOR in patients with Crohn's disease. Strengths of our study include the rigorous and extensive literature search, evaluation of both favourable and unfavourable post-intensification clinical outcomes, patient, disease and treatment characteristics associated with these outcomes, and evaluating post-intensification outcomes specific to secondary LOR; however, we also acknowledge several limitations. Methodological heterogeneity impacts the interpretation of the studied outcomes, including differences between studies relating to study design, study population, and analytical approaches. Moreover, while current treatment algorithms advocate that secondary LOR be defined by the presence of both clinical and objective disease activity prior to anti-TNF dose intensification, only 15 of 34 eligible studies included validated clinical indices in their definition of LOR, of which six studies also required objective disease activity prior to anti-TNF dose intensification. Hence, a lack of standardisation between definitions of secondary LOR and clinical outcomes following dose intensification, likely reduces the reliability of direct comparison between studies. This also highlights the current unmet need for a more standardised approach to clinical assessment of secondary LOR and/or clinical response following anti-TNF dose intensification.

There is accumulating evidence to suggest that the first biologic agent may offer the most favourable response; reflected by studies documenting that a greater proportion of patients require adalimumab and infliximab dose escalation with second and third-line therapy.[46] This review noted that studies that reported outcomes following infliximab dose intensification were more likely to have included patients who were biologic experienced relative to studies that reported outcomes following adalimumab dose intensification across largely biologic naïve cohorts. However, the impact of prior biologic exposure on clinical outcomes, particularly tertiary response and tertiary non-response, following anti-TNF dose intensification was difficult to ascertain owing to incomplete reporting of prior biologic exposure across patient subsets who were dose intensified. For similar reasons, it was difficult to ascertain the comparative effectiveness of empiric anti-TNF dose intensification undertaken for primary non-response and secondary LOR across studies that reported pooled clinical outcomes.

Despite the clinical effectiveness of anti-TNF dose intensification based on clinical and/or objective disease assessment alone, strategies that incorporate anti-TNF drug levels at the time of secondary LOR have been purported to increase the likelihood of therapeutic success.[2,47,48] This implies that the optimal clinical approach to secondary LOR involves assessment of clinical and objective disease activity in conjunction with anti-TNF trough levels; highlighting the need to update existing model of care to facilitate this approach. Our group has demonstrated the utility of a virtual biologic clinic-led approach in executing such a strategy; showcasing that a virtual clinic led model-of-care is supported by processes that promote more appropriate dose intensification and more frequent treatment success than standard outpatient care alone.[18]

In conclusion, although empiric anti-TNF dose intensification is clinically effective in patients with Crohn's disease, particularly within the first 6 months, a proportion of patients will fail to demonstrate short-term and/or sustained clinical response. This highlights the need for clinical reassessment following anti-TNF dose intensification, particularly beyond 6 months, to differentiate

between effective and ineffective dose-intensification strategies. The ideal paradigm for disease reassessment following dose intensification is yet to be fully elucidated in Crohn's disease, but should accommodate early recognition of response and non-response to facilitate discontinuation of ineffective therapy in cases of tertiary non-response, and consideration of further therapeutic optimisation or switching in cases of partial or incomplete tertiary response, respectively. Such an approach embodies many of the principles central to the modern-day treat-to-target paradigm.

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Ashish Srinivasan: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.
Robert Gilmore: ata curation; Formal analysis; Methodology; Writing – review & editing.
Daniel van Langenberg: onceptualization; Supervision; Writing – review & editing.
Peter De Cruz: onceptualization; Methodology; Supervision; Writing – review & editing.

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Supplemental material

Supplemental material for this article is available online.

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