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REVIEW

Systematic review with meta-analysis: loss of response and requirement of anti-TNFα dose intensification in Crohn's disease

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Abstract

Background To review the frequency with which anti-TNF-α loses its effect and dose "intensification" is required for Crohn's disease (CD) treatment.

Methods Electronic databases were searched for eligible studies. Raw data from studies meeting inclusion criteria were pooled for effect estimates. Subgroup analyses were performed for exploration of heterogeneity regarding all outcomes.

Results Eighty-six eligible studies were included. Estimates of loss of response (LOR) incidence ranged from 8 to 71%. The random effects pooled incidence of LOR with a median follow-up of 1-year was 33% (95% CI 29–38, 55 studies, n = 6135). The effect estimate based on data from patients with infliximab was 33% (95% CI 27-40), 30% (95% CI 22–39) for adalimumab, and 41% (95% CI 30–53) for certolizumab-pegol. Overall, the mean percentage of patients' LOR to anti-TNFs was 38.5%. The annual risk for LOR was 20.9% per patient-year. The random-effects pooled rate of need for dose intensification with a median follow-up of 1 year was 34% (95% CI 28–41, 38 studies, n = 10,690). The effect estimate for infliximab was 38% (95% CI 28–50), 36% (95% CI 30–43) for adalimumab, and 2% (95% CI 2–3) for certolizumab-pegol. The mean percentage of patients who needed an anti-TNF dose escalation was 23% with an annual risk of 18.5% per patient-year. There was no evidence of publication bias for incidence of LOR but not for the dose intensification (p = 0.001).

Conclusions Overall, around one-third of CD patients experience a LOR and required dose intensification in primary anti-TNF-α responders.

Keywords Loss of response · Anti-TNFα · Dose intensification · Crohn's disease

Introduction

The use of drugs targeting tumour necrosis factor-α (anti-TNF) has greatly advanced the therapeutic armamentarium for the treatment of inflammatory bowel diseases (IBD) [1–3]. Infliximab (IFX), followed by adalimumab (ADA), certolizumab-pegol (CZP), and golimumab have shown significant efficacy in Crohn's disease (CD) and ulcerative colitis (UC) refractory to conventional treatments, including immunosuppressive drugs [1–4]. This clinical efficacy is associated with mucosal healing and fewer hospitalizations and surgical procedures [5]. However, approximately one-third of the IBD patients receiving anti-TNF agents do not respond to treatment (primary failure), and a significant proportion experience a loss of response (LOR) (secondary failure) or intolerance to treatment. These scenarios pose a therapeutic challenge to gastroenterologists [6].

For patients who lose their initial response, consideration can be given to dose "intensification" to regain therapeutic benefit. Dose intensification is defined either as an increase

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of the anti-TNF dose (e.g., generally from 5 to 10 mg/kg for IFX), or as a decrease in the frequency of infusion (to as often as every 4 weeks for IFX). The strategies of dose escalation have been very different in clinical trials conducted with different anti-TNF agents IFX, ADA, and CZP. Therefore, the incidence of dose intensification, both in the short and long term, has been poorly studied.

The aims of this article were therefore to review LOR to anti-TNFα therapy and requirement for dose intensification in adult and pediatric CD patients.

Methods

The study was performed following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [7].

Literature search

Studies that investigated (a) Patients: adults OR pediatric with established CD; (b) Intervention: anti-TNF-α agents (mainly IFX, ADA, CZP or golimumab etc.); and (c) Outcome: patients developed LOR and/or with the need for dose intensification on anti-TNF-α therapy were considered.

We identified relevant literature (published articles and abstracts) by performing a systematic search of three databases: PubMed, Cochrane Library CENTRAL, and Embase (initial search February 4–5, 2015; updated May 5, 2015). Keywords used were (all fields): (anti-TNF OR TNF-alpha OR TNF-α OR OR "human anti-chimeric antibodies (HACAs)", infliximab OR adalimumab OR certolizumab pegol OR golimumab) AND ('Inflammatory bowel disease' and 'Crohn*.af.'), and any appropriate abbreviations. The terms "ADA", "IFX", "CZP", and "GOL" were used as alternative keywords to find additional relevant articles. For PubMed, all relevant MeSH terms were used. The final queries were validated by manual review and matching results.

The conference proceeding abstracts for annual meetings of European (European Crohn's and Colitis Organization (ECCO) congress, United European Gastroenterology Week) and American (Digestive Disease Week) Congresses were searched between 2002 and 2015.

The reference lists of eligible studies and review articles were hand-searched to identify further relevant publications. The primary authors of abstracts and studies without sufficient data were contacted for additional information.

Study selection

Two coauthors independently checked the retrieved articles according to a standardized data extraction form. All abstracts were screened to eliminate duplicates, reviews, case studies. In duplicated reports, the most comprehensive article was chosen.

Studies were included if they met the following criteria: We finally performed a manual selection of studies which satisfied the following criteria: (a) RCTs, non-randomized controlled trials and observational studies (including cohort, case control studies); (b) established diagnosis of CD by accepted criteria; (c) with a minimal follow-up of 14 or 12 or 4 weeks for IFX, ADA, or CZP, respectively, when the anti-TNFs achieving maximal response according to the guideline by ECCO [6]. For golimumab, steady-state was reached approximately 8 weeks after patients receiving golimumab maintenance doses [8]. So, a minimal follow-up of >8 weeks was required for golimumab; and (d) clear definition of LOR to anti-TNFα therapy.

We excluded (a) trials in which the incidence of LOR and/or the need for anti-TNF-α dose intensification not systematically documented or the crude rates of LOR or requirement of dose intensification could not retrieved; (b) trials studied patients with reinitiation of the same anti-TNFs; (c) review articles; (d) trials with exclusively a diagnosis of ulcerative colitis, indeterminate colitis, or an unclear diagnosis of CD were also excluded.

Eligibility assessment and data extraction were carried out by Y.Q. and B.L.C., with discrepancies resolved by consensus with M.H.C. and B.H.S.

Data extraction and quality assessment

Eligible articles were reviewed in a blind manner by two different investigators (Y.Q. and B.L.C.), and the results of the primary research studies were abstracted onto specially designed data extraction forms. Agreement between investigators was >95% and disagreement in data extraction was resolved by consensus.

The variables recorded were year of publication, first- and second-line anti-TNF treatments, patients' characteristics, therapeutic regimens, sample size, trial duration, and outcome measures.

Assessment of quality of randomized controlled trials and observational studies was performed using Cochrane risk of bias tool [9] and Newcastle Ottawa Quality Assessment Scale (NOS) [10], respectively. For the NOS, studies scoring ≥7 (of 9) were considered high quality.

Data synthesis and analysis

We calculated incidence estimates with the variance-stabilizing double arcsine transformation [11] because the inverse variance weight in fixed-effects meta-analyses is suboptimum when dealing with binary data with low incidences. Additionally, the transformed incidences are

weighted very slightly towards 50%, and studies with incidences of zero can thus be included in the analysis. We used the Wilson method [12] to calculate 95% CIs around these estimates because the asymptotic method produces intervals that can extend below zero.

We estimated heterogeneity between studies with Cochran's Q (reported as χ^2 and p values) and the I^2 statistic, which describes the percentage of variation between studies that is due to heterogeneity rather than chance [13, 14]. The random-effects model was chosen a priori for all analyses. These models (in which the individual study weight is the sum of the weight used in a fixed-effects model and between-study variability) produce study weights that mainly show between-study variation and thus provide close to equal weighting.

In our analyses, LOR and the need for dose intensification were analyzed separately. We also split study populations into IFX, ADA, CZP, and golimumab groups as appropriate. We defined studies as mixed when only overall estimates of the incidences of LOR were reported and we could not obtain further information from the authors to stratify results by types of anti-TNFs.

For each study, the incidence of LOR was calculated by using the reported numbers of subjects losing clinical response per study definition, divided by the total number of primary responders. Proportions were transformed with the logit transformation and pooled using a random-effects model to account for the expected high heterogeneity between studies [15]. The logit-transformed proportions were back-transformed and results were presented as percentages. The logit transformation was used to avoid studies with few events from being weighted too heavily in the random-effects model and because the multivariate analysis, which used a random-effects logistic regression model, is also based on the logit transformation. The extent of heterogeneity across studies was quantified by calculating the I^2 statistic [21].

Heterogeneity exploring

Subgroup analysis

We pre-identified several potential sources of heterogeneity: (a) types of diseases (pediatric versus adults); (b) types of anti-TNFs (IFX, ADA, CZP versus golimumab); (c) anti-TNFs schedule (episodic versus scheduled); (d) quality of study (high quality only); (e) concomitant IMMs; (f) type of IMMs (i.e., MTX versus purines etc.); (g) prior anti-TNFs exposure (naive versus prior user); (h) anti-TNFs concentration and antibodies (i) design of study, i.e., clinical trial versus observational as well as prospective observational compared to point-incidence studies; and (j) length of follow-up as these variables were believed a priori to be important predictors of LOR or dose escalation.

Meta-regression analysis

We further investigated the above-mentioned potential sources of heterogeneity by arranging groups of studies according to potentially relevant characteristics and by meta-regression analysis, which attempts to relate differences in effect sizes to study characteristics [16]. We entered only factors that we deemed significant individually ($p < 0.05$) into a multiple regression model to avoid model instability. The regression coefficients for each study characteristic in individual analysis were provided to enable comparison across diagnoses.

Meta-regression analysis to investigate the sources of heterogeneity was only performed if there were ≥10 trials available for each analysis.

Publication bias

Funnel-plot asymmetry as proposed by Begg and Mazumdar and Egger et al. [17] was used to investigate the possibility of publication bias. The meta-analysis was performed using the metaprop command of the meta package in R (version 3.2.0) [18] and Stata (version 12.1) with the commands metareg (for meta-regression). All statistical tests were two-sided, and statistical significance was defined as a p value <0.05.

Results

Study characteristics

Figure 1 illustrates the study selection process. Initial search of online databases yielded 7825 papers and was supplemented with conference abstracts. From these, only 86 articles [1–4, 19–93] were deemed suitable and met the pre-specified inclusion criteria. Seventy-one of them included adult or mixed-age (adult and pediatric) CD patients and six studies [25, 27, 35, 57, 58, 94] included exclusively pediatric CD patients. Only one study [95] in the form of abstract included patients receiving golimumab, thus a meta-analysis was not performed. Table 1 summarizes the main characteristics of the included studies. The quality assessment and risk of bias score for each study is detailed in Supp. Table 1. All the included 14 RCT studies were rating low risk per each quality domain except for one study [38]. Fifty-five of 73 observational studies were considered as high quality (scoring ≥7) using the NOS scale. Detailed quality assessments are provided in Supp. Figure 1 and Supp. Tables 1.

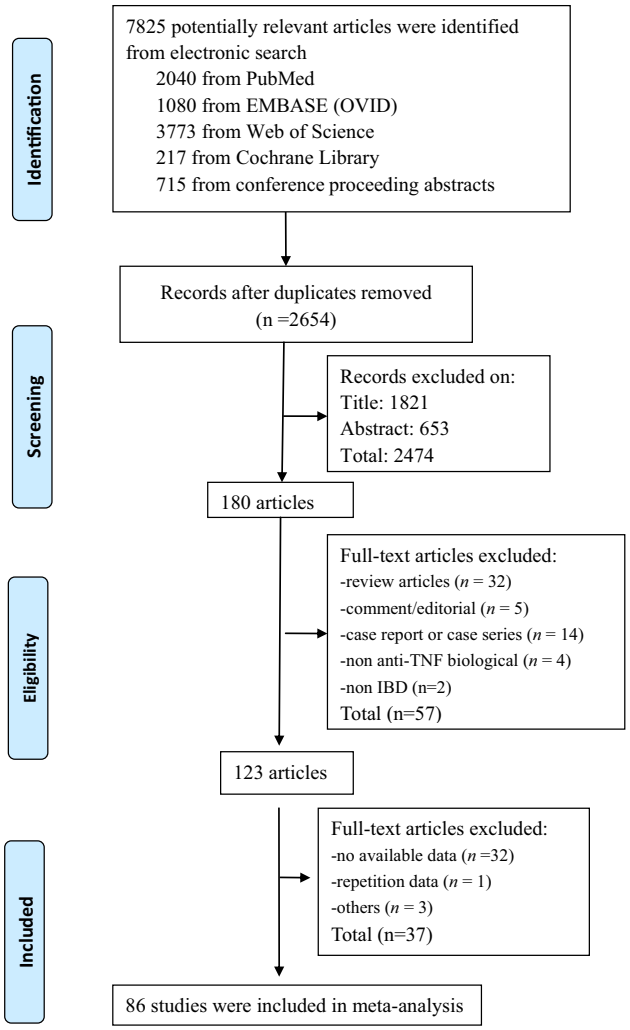

Fig. 1 Study selection

Anti-TNFs loss of response among primary responders

Description of studies A total of 55 studies involving 6135 patients were included, that is, 13 [1–4, 19, 21, 22, 25, 34, 38, 59, 61, 63] multicenter randomized, placebo-controlled trials (RCTs), seven studies of follow-up of RCTs, ten prospective open-label observational trials, and 26 retrospective studies (five multicenter and 16 single-center) (Table 1).

Risk for loss of response Estimates of LOR incidence ranged from 8 to 71% (Fig. 2). The random effects pooled incidence of LOR with a median follow-up of 1-year (IQR 1–2.33) was 33% (95% CI 29–38); heterogeneity was substantial ($\chi^2 = 1220$, $p < 0.001$; $I^2 = 92.4\%$).

Comparison between types of anti-TNFs When subgrouping the studies by type of anti-TNFs, 24 studies [1, 4, 19–38, 40, 41] included patients receiving IFX ($n = 2356$), 19 studies [2, 38, 42–58] included patients received ADA ($n = 2112$), nine studies [3, 59–66] included patients receiving CZP ($n = 1667$), two studies [39, 96] included patients receiving both IFX and ADA, and another study [97] included patients receiving both CZP and ADA. For the Christopher Ma 2014 study [96], data were further stratified by either naïve to anti-TNF therapy or with prior anti-TNF exposure among patients received ADA. For study that reported data for two anti-TNFs, the study was put under the anti-TNF subgroup with the most number of patients.

For IFX, incidence of LOR ranged from 11 to 71%, the pooled incidence of LOR in patients treated with IFX was 33% (95% CI 27–40, random effect model). The heterogeneity was substantial ($p < 0.001$; $I^2 = 90\%$). For ADA, incidence of LOR ranged from 8 to 65%, the random-effects pooled incidence was 30% (95% CI 22–39) with substantial heterogeneity ($\chi^2 = 451$, $p < 0.001$; $I^2 = 93.2\%$). For CZP, incidence of LOR ranged from 18 to 67%. The random-effects pooled incidence was 41% (95% CI 30–53) with substantial heterogeneity ($\chi^2 = 451$, $p < 0.001$; $I^2 = 94.8\%$).

Use of arcsine-transformed estimates of incidence made little difference to the overall random-effects estimates, which were themselves shown to be notably different (closer to 50%) from the fixed-effects estimates (in which smaller incidences have smaller SEs and thus greater weight than they would have in random-effects estimates).

Percentage and annual risk for LOR A total of 6135 primary responders were included in these studies, providing an 11,294 patient-years follow-up (excluding four studies [26, 36, 37, 55] with no available follow-up). The mean percentage of patients who lost response to anti-TNFs was 38.5% (2364/6135). The annual risk for LOR was calculated to be 20.9% (2306/11,294) per patient-year.

When subgrouped by type of anti-TNFs, the mean percentage of patients who lost response to IFX was 37.8% (892/2356). The annual risk for LOR was calculated to be 18% (840/4583) per patient-year (excluding three studies [26, 36, 37] with no available follow-up). The mean percentage of patients who lost response to adalimumab was 35.4% (749/2112) with an annual risk for LOR of 22.7% (744/3300) per patient-year. Similarly, the mean percentage of patients' LOR to CZP was 43.3% (722/1667) with an annual risk for LOR of 21.2% (722/3411) per patient-year.

Anti-TNFs dose escalation among primary responders

Description of studies A total of 38 studies [42, 43, 49, 50, 53, 54, 67–93] included data for need for dose intensification were included, that is, four reports [67–70] of IFX ($n = 1397$), 28 studies [42, 43, 49, 50, 53, 54, 71–87, 89–93] of ADA ($n = 5457$), one study [98] of

Table 1 Anti-TNFs loss of response among initial responders with CD

Study	Adult	Prior IFX	Anti-TNFs	Design	Center	F/U	LOR	Definition	Concomitant therapies (%)	Predictors for LOR
Rutgeerts [19]	Y	Y	IFX	Double-blind RCT	M	Week 44	4/37 (10.8)	PCDAI	Y	NA
Present [4]	Y	N	IFX	Double-blind RCT	M	Week 54	40/63 (64)	↓No. fistulas	29/63TP	NA
Hanauer [1]	Y	N	IFX	Double-blind RCT	M	Week 54	109/385 (28.3)	CDAI	81 (24%) TP, 10 (3%) MTX	NA
Hommes [20]	Y	N	IFX	NRPC	S	1 year	11/73 (15.1)	PGA	Aza 5 (7%) Aza + steroids 10 (14%) MTX 17 (24%) MTX + steroids 8 (11%)	Concomitant MTX↑
Farrell [21]	Y	N	IFX	Double-blind RCT	S	20 weeks	15/36 (41.7)	CDAI	3 (20) AZA, 1 (6.6) MTX	ATI↑
Sands [22]	Y	Y	IFX	Double-blind RCT	M	Week 54	40/96 (41.7)	Physician	29 (30)TP 1 (1)MTX	Base-line characteristics→
Candon [23]	N	N	IFX	RS	S	144 weeks	8/17 (47.1)	HBI	MTX 18 Aza 16 others 11	NA
Corman [24]	Y	Y	IFX	NA	NA	>1 year	42/125 (33.6)	NA	NA	NA
Hyams [25]	N	N	IFX	Open-label RCT	M	Week 54	19/52 (36.5)	PCDAI	93 (90.3%) TP, 9 (8.7%) MTX	Scheduled maintenance therapy↓
Ainsworth [26]	Y	N	IFX	RS	S	NA	8/31 (25.8)	Physician	14 TP, 3 MTX	ATI↑, TNF-α-BC↓
De Ridder [27]	N	N	IFX	NRPC	M	41.3 months	19/66 (28.8)	Physician	TP 42 (63.6) MTX 15 (22.7)	Fistulizing disease↓, disease duration→
Gonzaga [28]	Y	N	IFX	RS	S	≥1 year	58/153 (37.9)	Physician	0.838	Prior episodic dosing↑, gender/smoking/disease duration→
González-Lama [29]	Y	N	IFX	RS	M	≥14 weeks	24/114 (21.1)	CDAI	NA	IMM + ↓
Milestone [30]	Y	N	IFX	RS	S	28 months	10/69 (14.5)	Surgical resection	82% (57/69)	NA
Rudolph [31]	Y	N	IFX	RS	S	≥30 months	95/198 (48)	Physician	127/198	IMM + ↓, Smoker↑
Teshima [32]	Y	N	IFX	RS	S	Week 104	41/133 (30.8)	Physician	TP 81/105 (69%); MTX 24/105 (21%)	IMM + ↓
Vera [33]	Y	N	IFX	RS	S	≥1 year	5/44 (11.4)	Physician	Y	Disease duration ≥10 years↑, colectomy↑
Colombel [34]	Y	N	IFX	Double-blind RCT	M	50 weeks	11/31 (35.5)	CDAI	NA	NA
Goldner [35]	N	Y	IFX	RS	S	≥30 months	1/4 (25)	MRI evaluation	NA	NA

Table 1 continued

Study	Adult	Prior IFX	Anti-TNFs	Design	Center	F/U	LOR	Definition	Concomitant therapies (%)	Predictors for LOR
Steenholdt [36]	Y	mixed[a]	IFX	RS	S	NA	27/85 (31.8)	Physician	12 (46)TP, 2 (8)MTX	IFX + ATI + status↑
Imaeda [37]	Y	N	IFX	RS	S	NA	17/58(29.3)	CDAI	Aza 2 (11.8%) 9 (22.0%)	ATI levels↑
Van Assche [38]	Y	N	IFX	Open-label RCT	M	1 year	6/37 (16)	CDAI	0 (AZA), 2 (MTX)	Adherence to IFX + ↓, switch to ADL↑
Brandse [39]	Y	N	IFX/ ADL	RS	M	18 months	7/29 (24)	HBI	IM, 20 (69) Aza 8 (28) 6-Mercaptopurine 4 (14) MTX 8 (28)	Induction schedule, IMs→
Cornillie [40]	Y	N	IFX	RS	M	Week 54	207/291 (71.1)	CDAI		NA
Hibi [41]	Y	N	IFX	RS	S	Week 54	8/12 (67)	CDAI	IM 8 (14.0)	IFX level↓, CRP↑
Colombel [2]	Y	N	ADL	Double-blind RCT	M	Week 56	151/329 (46)	CDAI	47% IMM	ADL Maintenance↓
Peyrin-Biroulet [42]	Y	N	ADL	NRPC	S	Week 52	5/16 (31.3)	Physician	TP 16 (66.6) MTX 1 (4.1)	NA
Sandborn [43]	Y	Y	ADL	Follow-on CLASSIC II	M	Week 56	6/37 (16.2)	CDAI	33 (16) AZA, 25 (12) 6-MP, 6 (3)MTX	
Seiderer [44]	Y	N	ADL	NRPC	S	Week 24	4/10 (40)	CDAI	7 TP, 1 MTX	NA
Karmiris [45]	Y	Y	ADL	NRPC	S	Week 24	17/55 (31)	Physician	Y	TR at week 12↓
Lopez Palacios [46]	Y	N	ADL	RS	S	48 months	5/22 (22.7)	HBI	18 (81.8%)	NA
Panaccione [47]	Y	Y	ADL	Follow-up of Gain Trial(RCT)	M	1 years	74/156 (47.4)	CR70	NA	NA
Bortlik [48]	Y	Y	ADL	RS	S	21 weeks	8/47 (17)	NA	NA	NA
Karmiris [49]	Y	Y	ADL	NRPC	S	20.4 months	41/116 (35.3)	Physician	TP 41 (24.4) MTX21 (12.5)	ADL TR↓
Oussalah [50]	Y	N	ADL	RS	S	130 week	17/53 (32.2)	Physician	TP 17 (32.1) MTX 1 (1.9)	NA
Chaparro [51]	Y	Mixed[a]	ADL	RS	M	8 months	42/380 (11.1)	NA	NA	EIM↑ (OR = 1.7), prior anti-TNF↑(OR = 2.5)
Russo [52]	Y	Y	ADL	RS	M	22 months	5/56 (8.9)	HBI or PGA	NA	NA
Russo [53]	Y	N	ADL	RS	M	8 months	5/59 (8.5)	NA	NA	NA
Swoger [54]	Y	Y	ADL	RS	S	1 year	18/55 (32.7)	Physician	S (60); T/MTX (59)	NA
Sprakes [55]	Y	N	ADL	NRPC	S	NA	6/34 (17.6)	PGA	NA	NA

Table 1 continued

Study	Adult	Prior IFX	Anti-TNFs	Design	Center	F/U	LOR	Definition	Concomitant therapies (%)	Predictors for LOR
Molnar [56]	Y	Mixed[a]	ADL	RS	S	1 year	22/61 (36.1)	Physician	42.1%TP	IM + ↓, ADL-naive ↑
Van Assche [38]	Y	N	ADL	Open-label RCT	S	1 year	17/36 (47)	CDAI	6 (AZA), 0 (MTX)	Adherence to first anti-TNF↓
Assa [57]	N	N	ADL	RS	M	Week 52	18/107 (17)	Physician	NA	NA
Panaccione [109]	Y	N	ADL	F/U of CHARM and ADHERE	M	Year 4	213/329 (64.7)	CDAI	S (42); T (40); MTX (10); 5-ASA (41)	NA
Christopher Ma [96]	Y	N	IFX	RS	S	170 weeks	60/117 (51.3)	HBI + CRP ± CTE or endoscopy	AZA or MTX (%): 100 (85.5)	Prior anti-TNF exposure↓
		N	ADL			122 weeks	23/38 (60.5)	HBI + CRP ± CTE or endoscopy	31 (81.6)	
		Y	ADL			122 weeks	41/63 (65.1)	HBI + CRP ± CTE or endoscopy	60 (95.2)	
Cozijnsen [58]	N	Y	ADL	RS	M	12 m	11/53 (20.8)	wPCDAI, PGA	21 TP, 11 MTX	IFX nonresponder, ATI↑, IMM→
Sandborn [59]	Y	Mixed[a]	CZP	Double-blind RCT	M	Week 26	44/115 (38)	CDAI	Y	IMM + ↓
Schreiber [3]	Y	Mixed[a]	CZP	Double-blind RCT	M	Week 26	163/428 (38)	CDAI	Y	Previously received IFX↓, IMM→
D'Haens [60]	Y	Y	CZP	F/U of PRECISE 2/3	M	18 months	86/215 (40)	CDAI, HBI	Y	Rapidity or magnitude of CR following induction→
Sandborn [61]	Y	Y	CZP	Double-blind RCT	M	Week 26	203/329 (62)	CDAI	NA	NA
Allez [97]	Y	Y	CZP/ ADL	RS	M	44 weeks	15/41 (36.6)	HBI	Aza /MP13 (19%) MTX 13 (19%)	NA
Lichtenstein [62]	Y	N	CZP	NRPC	M	Week 80	41/121 (33.9)	HBI		
Sandborn [64]	Y	N	CZP	Double-blind RCT	M	Week 26	203/329 (61.7)	HBI	239/329IM	ATI↑
Sandborn [63]	Y	Y	CZP	F/U of PRECiSE 4	M	Week 52	11/31 (35.5)	HBI	3 (6.1)	NA
Mocciaro [65]	Y	Y	CZP	NRPC	S	30 months	4/6 (67)	HBI ≥3	NA	NA

Table 1 continued

Study	Adult	Prior IFX	Anti-TNFs	Design		Center	F/U	LOR	Definition	Concomitant therapies (%)	Predictors for LOR
Sandborn [66]	Y	N	CZP	F/U of PRECiSE 3		M	7 year	58/329 (17.6)	HBI	124 (37.7)	NA

IFX infliximab, *ADA* adalimumab, *CZP* certolizumab-pegol, *CDAI* Crohn's disease activity index, *EOW* every other week, *EW* every week, *CD* Crohn's disease, *RS* retrospective, *NRPC* non-randomized, prospective cohort, *HBI* Harvey–Bradshaw index, *CAI* ulcerative colitis clinical activity index, *PDAI* perianal disease activity index, *PGA* Physician Global Assessment, *pro* prospective, *retro* retrospective, *WELCOME* certolizumab in Crohn's disease patients with loss of response or intolerance to infliximab, *CHARM* Crohn's trial of the fully human antibody adalimumab for remission maintenance, *ADHERE* additional long-term dosing with HUMIRA to evaluate sustained remission and efficacy in CD, *CLASSIC II* clinical assessment of adalimumab safety and efficacy studied as induction therapy in Crohn's disease, *ACCENT I* the A Crohn's disease clinical trial evaluating infliximab in a new long-term treatment regimen, *PRECiSE* PEGylated antibody fragment evaluation in Crohn's disease safety and efficacy, *IM* immunomodulator, *Y* yes, *N* no, *NA* not available

↓ Predicting decreased risk of LOR

↑ Predicting increased risk of LOR

→ No significant correlation were found

[a] Study that include patients either failed IFX or naive to IFX

CZP ($n = 2647$), and four studies [88, 99–101] with use of both IFX and ADA, with pooled data on 10,690 patients (Table 2). Two studies' [88, 99] according data were drawn separately. Seventeen studies included patients with previous IFX treatment, ten studies with the data of the "real world", and 17 studies had a follow-up of at least 52 weeks.

Anti-TNFs dose intensification Rates of the need for dose intensification ranged from 2 to 82% (Fig. 3). The random-effects pooled rate of need for dose intensification with a median follow-up of 1 year (IQR 0.8–1.2) was 34% (95% CI 28–41); heterogeneity was pronounced ($\chi^2 = 541$, $p < 0.001$; $I^2 = 96.9\%$).

Comparison between types of anti-TNFs For IFX, estimates ranged from 14 to 54%. The random-effects pooled incidence of dose intensification was 38% (95% CI 28–50) with substantial heterogeneity ($\chi^2 = 67$, $p < 0.001$; $I^2 = 93.7\%$). For ADA, estimates ranged from 11 to 82%. The random-effects pooled incidence of dose escalation was 36% (95% CI 30–43) with substantial heterogeneity ($\chi^2 = 451$, $p < 0.001$; $I^2 = 93.7\%$). The pooled incidence of dose intensification was 2% (95% CI 2–3) for CZP.

As in the analysis for LOR, use of arcsine-transformed estimates of incidence made little difference to the overall random-effects estimates.

Percentage and annual risk for dose intensification among the overall population

A total of 10,690 primary responders were included in these studies providing 12,908 patient-years follow-up (excluding two studies [81, 92] with no available follow-up). The mean percentage of patients who needed an anti-TNF dose escalation was 23% (2489/10,690). The annual risk was calculated to be 18.5% (2383/12,908) per patient-year.

When subgrouped by type of anti-TNFs, the mean percentage of patients on IFX who needed an dose escalation was 41.8% (585/1397). The annual risk was calculated to be 14.9% (585/3918) per patient-year. The mean percentage of patients on adalimumab who needed a dose escalation was 29% (1576/5457). The annual risk was 26.3% (1531/5815) per patient-year. Only one "real-world" study reported data on CZP, and the mean percentage of patients who needed an CZP dose escalation was 2% (53/2647) with an annual risk of 2.7% (53/1985) per patient-year.

Pediatric CD

A total of six studies [23, 25, 27, 35, 57, 58] reported data of LOR to anti-TNFs, that is, one single-center prospective open-label trial, one multicenter retrospective study, and two single-center retrospective studies (Table 1). The random-effects pooled incidence of LOR was 35% (95%

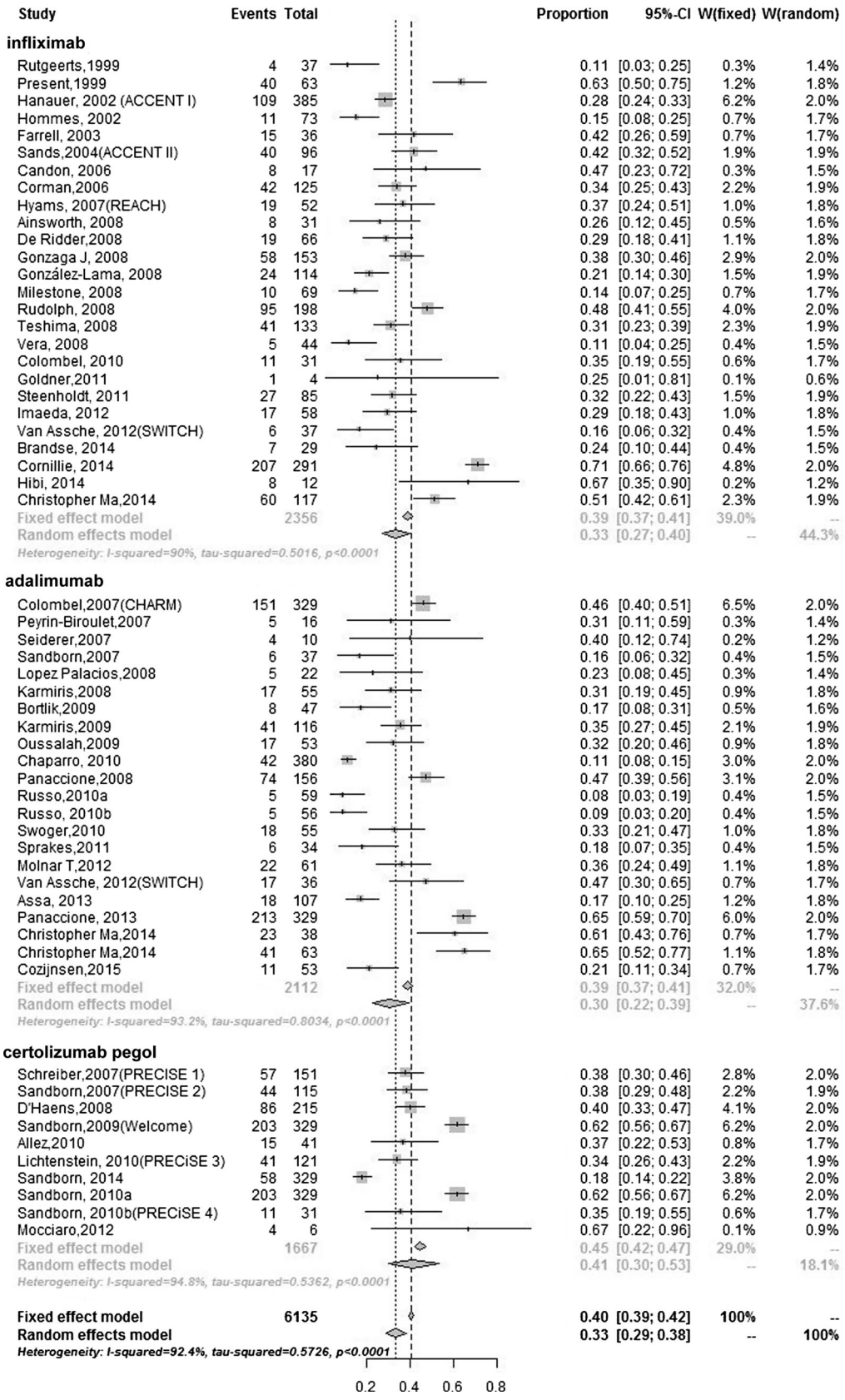

Fig. 2 Estimated incidence of anti-TNFs LOR among primary responders

Table 2 The need for dose escalation among primary responders with CD on anti-TNF agents

Study	Anti-TNFs	Prior IFX	Design	Real-world	F/U median	Concomitant IM (%)	Dose escalation				
							Rate (%)	Modality, mg (%)	Interval	Regain response	Predictors
Regueiro [67]	IFX	Y	RS	N	30-months	78.7	54/108(50)	↑dose or ↓dosing interval or both	NA	75.9	Prior IFX use, lapse > 6 m between infusions, concomitant IM→
Schnitzler [68]	IFX	N	NRPC (Leuven)	N	55 months	6-MP/AZA 305 (49.7) MTX 58 (9.4)	273/547(49.9)	↑dose or ↓dosing interval or both	NA	NA	Indication for IFX, concomitant IM, disease duration, prior history of MAS or CRP level →
Issa [88]	IFX	Y	RS	N	>2 years	NA	176/416(42.3)	NA	21.6 ± 1.6 m	NA	IM + ↓
Lam [69]	IFX	N	RS (Hungary)	Y	10 months	34 (51)	34/68(50)	NA	10.0 (5.3-4.8) m		Disease duration, concurrent IM↑
Taxonera [70]	IFX	N	NRPC	N	10.7 months	45 (76.3)	16/59(27)	↑dose or ↓dosing interval	10.7 (8.9-15.7) m		IM, the need for steroids at baseline, steroid-refractory disease→
Sandborn [71]	ADA	Y	NRPC	N	12 weeks	6-MP/AZA 7 (29) MTX 3 (13)	19/24	40 ew(79)	NA	NA	None
Papadakis [72]	ADA	Y	RS	N	>6 months	8/15(53.3)	6/15 (40)	80 eow (20) 80 ew (13.3) 120 eow (6.7)	NA	NA	NA
Peyrin-Biroulet [42]	ADA	Y	NRPC	N	52 weeks	6-MP/AZA 16 (66.6) MTX 1 (4.1)	6/24 (25)	40 ew (25)	NA	NA	NA
Sandborn [43]	ADA	Mixed	NRPC	N	56 weeks	Aza 33 (16) 6-MP 25 (12) MTX 6 (3)	89/204 (43.6)	40 ew (43.6)	NA	67/89 (75)	None
Karmiris [49]	ADA	Y	NRPC	N	16 weeks	Y	66/105(62.9)	40 ew	16 [11–32] weeks	NA	TR at week 12↓; smoking, concomitant IM, time to first intervention→
Ho [73]	ADA	Mixed	RS	Y	> 3 years	15 (68%)	13/22 (59.1)	40 ew (59.1)	28.6 weeks (median)	NA	NA
Sheridan [74]	ADA	Y	RS	N	NA	NA	20/51 (39.2)	40 ew (39.1)	Week 52	NA	NA
West [75]	ADA	Y	RS	N	45.4 weeks	Aza/MP/MTX 9	8/30 (26.6)	40 ew (26.6)	NA	6/8 (75)	ATAs→
Cohen [76]	ADA	Mixed	RS	N	NA	NA	31/75 (41.3)	40 ew (41.3)	53 weeks (median)	21/31 (67.7)	Family history, males, isolated colonic disease, smokers↑; Prior INF→

Table 2 continued

Study	Anti-TNFs	Prior IFX	Design	Real-world	F/U median	Concomitant IM (%)	Dose escalation				
							Rate (%)	Modality, mg (%)	Interval	Regain response	Predictors
Ho [77]	ADA	Y	RS	Y	30.1 weeks	60 (61.2)	54/98 (55.1)	40 ew (55.1)	At week 114	NA	Concomitant IM/IFX primary nonresponders→
Karmiris [49]	ADA	Mixed	NRPC	N	20.4 months	6-MP/AZA 41 (24.4) MTX 21 (12.5)	102/156 (65)	40 ew	14 (10.7–24) weeks	73 (71.6%)	Ada TR↑; Concomitant IM therapy → , ATI before initiation of ADA→
Kemp [78]	ADA	Mixed	NRPC	N	2 years	1/25(4)	5/25 (20)	40 ew (20)	40 weeks (median)	NA	Smoker, primary or secondary IFX non-responders→
Lees [79]	ADA	Y	RS	N	2.4 years	102/157 (65.0%) 6-MP/AZA/MTX	16/30 (53.3)	40 ew (53.3)	28.6 weeks (median)	NA	NA
Loftus [80]	ADA	N	RS	Y	12 months	NA	151/1335 (11.3)	40 ew (11.3)	NA	NA	Geographic region, not starting on 160/80 mg for induction therapy (HR = 0.48)
Naik [99]	ADA	NA	RS	N	52 weeks	93.00%	44/136 (32.4)	NA	NA	NA	Stricturing phenotype (OR 0.18); prior anti-TNF exposure(OR 2.59)
	IFX	NA	RS	N	52 weeks	64.00%	28/199(14%)	NA	NA	NA	Longer disease duration (OR 0.91)↓
Oussalah [50]	ADA	Y	RS	N	3-year	6-MP/AZA 17 (32.1) MTX 1 (1.9)	7/53 (13.2)	40 ew (13.2)	NA	6/7 (85.7)	Loading dose→
Plevy [101]	ADA	Y	RS	Y	52 weeks	NA	170/701 (24.3)	NA	NA	NA	NA
Swaminath [81]	ADA	Mixed	RS	N	≥6 weeks	IM 21	14/48(29)	NA	2.2 ± 1.5 m	5/14 (36%)	NA
Bultman [82]	ADA	Y	NRPC	N	≥12 weeks	Y	34/108 (31.5)	NA	16 weeks (Median)	NA	Previous nonresponse to IFX↑
Nichita [83]	ADA	Y	RS	N	52 weeks	Aza 5 (9%)	13/55 (23.6)	40 ew (16.4)	NA	8/13 (61.5)	NA
Panaccione [84]	ADA	Mixed	NRPC	N	60 weeks	NA MTX 3 (5.4%)	82/349 (23.5)	40 ew (23.5) 40 every 10 d (3.6) 80 eow (1.8) 80ew (1.8)	NA	NA	NA
Russo [53]	ADA	Y	RS	Y	32 weeks (mean)	96.70%	10/61 (16.4)	40 ew (13) 80 ew (3)	At week 24	NA	NA

Table 2 continued

Study	Anti-TNFs	Prior IFX	Design	Real-world	F/U median	Concomitant IM (%)	Dose escalation				
							Rate (%)	Modality, mg (%)	Interval	Regain response	Predictors
Swoger [54]	ADA	Y	RS	N	54.8 weeks	AZA/6-MP/ MTX 70 (59%)	59/118 (50)	40 ew (42) 80 ew (3)	16.8 weeks (Median)	NA	NA
Sandborn [90]	ADA	NA	Data from EXTEND	N	52 weeks	NA	16/64 (25)	40 ew (25)	NA	NA	NA
Wolf [85]	ADA	NA	RS	N	72 weeks	NA	35/106 (33)	40 ew (33)	NA	NA	NA
Cordero [86]	ADA	Y	NRPC	N	48 weeks	NA	18/25(72)	40 ew	NA	NA	NA
Fortea-Ormaechea [87]	ADA	Mixed	RS	Y	40 weeks	Y	58/174 (33.3)	NA	33 weeks (median)	NA	NA
Issa [88]	ADA	Y	RS	N	>2 years	NA	119/310 (38.4)	NA	11.3 ± 0.8 m	NA	IMM + ↓
Kiss [89]	ADA	Mixed	NRPC	N	12-months	AZA 53 (26.4%)	32/201 (16)	40 ew	NA	NA	Early CR and normalization of CRP
Bultman [91]	ADA	Mixed	RS	N	21 weeks	50 (41)	46/122 (37.7)	40 ew	NA	NA	BMI, secondary non-response to IFX↑
Cohen [92]	ADA	Mixed	RS	N	20 weeks	IM 30 (40%)	31/75 (41.3)	40 ew	NA	NA	Male gender, isolated colonic disease, smoking history↑
Bart [93]	ADA	Mixed	RS	Y	14 months	Aza 31% MTX 10%	202/574 (35.2)	40 ew(34)	7 (Median) (0–55 m)	0.7	Prior anti-TNF use, no concomitant Aza or < 3 m, abnormal CRP↑
Rubin [98]	CZP	NA	RS	Y	9 months	Y	53/2.647 (2)	400 mg <16 d apart	NA	NA	Step Up↑ versus Early Bio
Rubin [100]	IFX/ ADA	N	RS	Y	12 months	Y	459/2.717 (16.9)	>2 × recommended maintenance dose	NA	NA	Step Up↑versus Early Bio

IFX infliximab, *ADA* adalimumab, *CZP* certolizumab-pegol, *CDAI* Crohn's disease activity index, *EOW* every other week, *EW* every week, *CD* Crohn's disease, *HBI* Harvey–Bradshaw index, *CAI* ulcerative colitis clinical activity index, *PDAI* perianal disease activity index, *PGA* physician global assessment, *RS* retrospective, *NRPC* nonrandomized, prospective cohort, *IM* immunomodulator, *Y* yes, *N* no, *NA* not available

↓ Predicting decreased risk of LOR

↑ Predicting increased risk of LOR

→ No significant correlation were found

[a] Study that include patients either failed IFX or naive to IFX

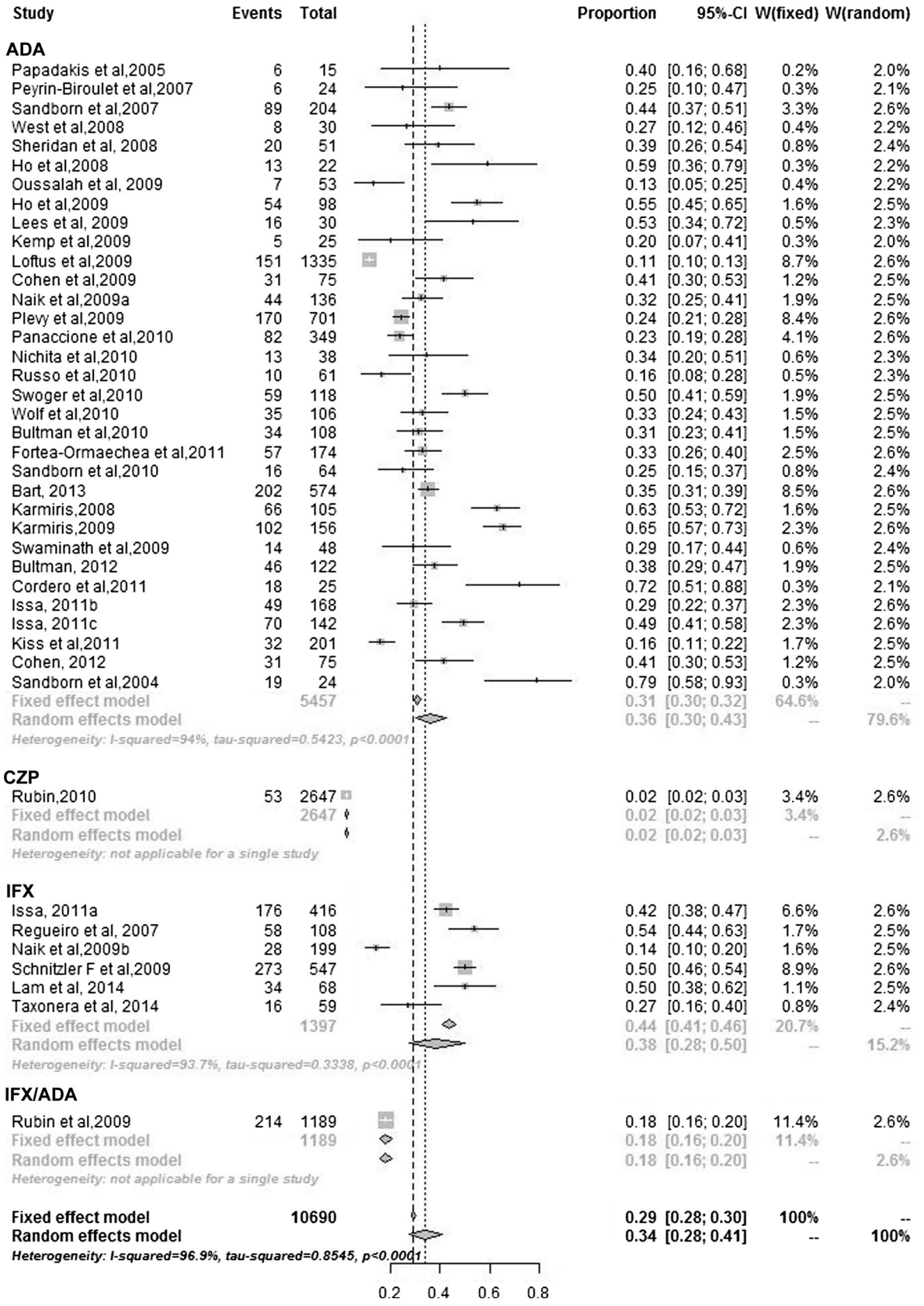

Fig. 3 Estimated incidence of anti-TNFs dose intensification among primary responders

Table 3 Summary of subgroup analysis of anti-TNFs loss of response among primary responder

Items	*n*	Heterogeneity		Overall effect		ES	95% CI
		I^2	*p*	z	*p*		
Overall	58[a]	95%	<0.001	11.380	<0.001	0.33	[0.29, 0.38]
Anti-TNFs							
IFX	26	94.50%	<0.001	9.12	<0.001	0.33	[0.266, 0.403]
ADA	22	95.80%	<0.001	6.87	<0.001	0.30	[0.220, 0.39]
CZP	10	97.00%	<0.001	6.58	<0.001	0.41	[0.301, 0.53]
F/U							
<52 week	14	97.60%	<0.001	5.09	<0.001	0.32	[0.22, 0.45]
>52 week	41	94.60%	<0.001	11.87	<0.001	0.30	[0.25, 0.36]
NA	3	0	0.809	8.60	<0.001	0.30	[0.23, 0.366]
Prior IFX user							
Yes	18	93.20%	<0.001	7.57	<0.001	0.34	[0.254, 0.431]
No	34	95.80%	<0.001	9.79	<0.001	0.35	[0.283, 0.424]
Mixed[b]	6	98.80%	<0.001	4.78	<0.001	0.31	[0.184, 0.440]
Study designs							
RCT	13	94.60%	<0.001	43.8	<0.001	0.43	[0.408, 0.446]
NRPC	14	77.30%	<0.001	14.44	<0.001	0.23	[0.202, 0.265]
RS	19	89.40%	<0.001	20.82	<0.001	0.19	[0.176, 0.212]
F/U of RCT	8	98.10%	<0.001	36.47	<0.001	0.42	[0.401, 0.446]
Definition of LOR							
CDAI or PCDAI	24	93.20%	<0.001	7.74	<0.001	0.37	[0.282, 0.458]
HBI	13	98.00%	<0.001	4.31	<0.001	0.37	[0.243, 0.503
Physician	14	92.30%	<0.001	6.42	<0.001	0.30	[0.236, 0.362]
Others	7	96.80%	<0.001	4.39	<0.001	0.37	[0.202, 0.528]
Patients							
Adult	52	95.80%	<0.001	10.77	<0.001	0.35	[0.296, 0.407]
Pediatric	6	58.10%	0.036	7.48	<0.001	0.35	[0.293, 0.398]

IFX infliximab, *ADA* adalimumab, *CZP* certolizumab-pegol, *CDAI* Crohn's disease activity index, *HBI* Harvey–Bradshaw index, *CAI* ulcerative colitis clinical activity index, *PDAI* perianal disease activity index, *PGA* physician global assessment, *RS* retrospective, *NRPC* nonrandomized, prospective cohort, *NA* not available

[a] Christopher Ma study [96] included patients with use of both IFX and ADA, according data were draw separately. Among the patients receiving ADA, data were further stratified by either naïve to anti-TNF therapy or with prior anti-TNF exposure

[b] Study including patients that either failed IFX or were naive to IFX

CI 29–40) with modest heterogeneity ($p = 0.03$; $I^2 = 58.9\%$) (see Table 3). The mean percentage of patients who lost response to anti-TNFs was 25.5% (76/299). The annual risk for LOR was calculated to be 15.3% (76/498) per patient-year.

Exploring sources of heterogeneity

Subgroup analysis

Subgroup analyses based on prior anti-TNFs exposure (naive versus prior user), type of anti-TNFs (IFX, ADA versus CZP), concomitant IMMs (monotherapy versus combined therapy), study design (prospectively versus retrospectively, RCTs versus non-randomized), definition of LOR (CDAI, HBI, PGA, Mayo score, versus physician's assessment) and length of follow-up (≥52 weeks versus <52 weeks) did not significantly change the effect estimate (see Table 3).

As part of our sensitivity analyses, when six pediatric studies [25, 27, 35, 57, 58, 94] were excluded, the random-effects pooled incidence of LOR rose to 35% (95% CI 29–41). The random-effects pooled prevalence for LOR among primary responders was 23 and 41% for retrospective and prospective studies, respectively. The according prevalences were 32% (95% CI 22–45) and 30% (95% CI 25–36) for studies with a follow-up <52 weeks or ≥52 weeks, respectively (see Table 3).

For dose intensification, we excluded three large "real-world" studies using Health Claims Data, [80, 98, 100] the random-effects pooled incidence rose slightly to 37% (95% CI 32–43). On contrary, the random-effects pooled prevalence for dose intensification using data from "real-world" studies was 26% (95% CI 17–34), which is relatively lower. Accordingly, the random-effects pooled prevalence for dose intensification was 31.7 and 34.1% for retrospective and prospective studies, respectively. The according prevalences were 39.6% (95% CI 26–53) and 31.6% (95% CI 25.4–37.9) for studies with a follow-up <52 or ≥ 52 weeks, respectively (see Supp. Table 2).

Meta-regression analyses

In meta-regression analyses, the associations between anti-TNFs and LOR were not substantially altered by prior IFX user ($p = 0.54$), types of ant-TNFs ($p = 0.85$), length of follow-up ($p = 0.58$) or definition for LOR ($p = 0.35$). Similarly, we found no evidence of interactions with the above variables when the meta-regression analyses were repeated for dose intensification.

Test for publication bias

Begg's funnel plot and Egger's test were performed, both indicated no publication bias for the incidence of LOR ($p = 0.65$, Fig. 4), but a tendency toward publication bias for the need for dose intensification ($p = 0.001$).

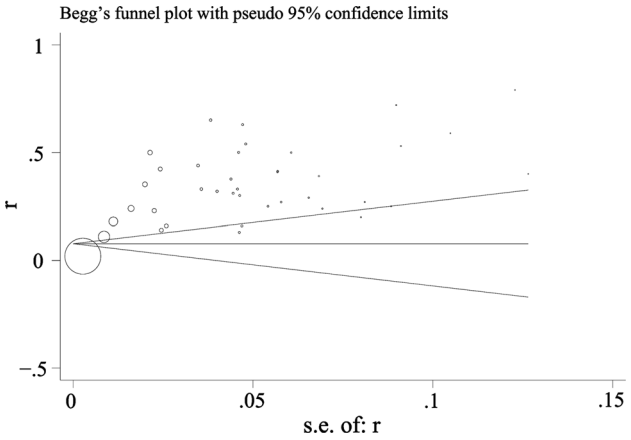

Fig. 4 Begg's funnel plot for publication bias for incidence of LOR. Studies (*circles*) within the projected 95% CI (*diagonal lines*) should have complementary areas on the opposite side of the *dashed line* (estimated risk ratio). *Gaps* in the *funnel patterns* indicate possible areas of publication bias

Discussion

Anti-TNF therapy has changed the treatment of CD that is refractory to standard medications [102]. However, as only four anti-TNF agents (IFX, ADA, CZP and golimumab) have shown their efficacy in treating CD, LOR is a major concern in clinical practice. The durability of anti-TNFs especially CZP response over years and the need for dose escalation remain poorly studied. Our study is the first meta-analysis to investigate the pooled incidence of LOR or need for dose escalation in patients with CD on anti-TNF-α therapy. In the present study, we predefined LOR in the primary responders rather than the overall population (primary and non-primary responders). Estimates of LOR incidence ranged from 8.5 to 71.7%. The random effects pooled incidence was 33% (95% CI 29–38). Similarly, estimates of the need for dose intensification ranged from 2 to 82% with a random-effects pooled rate of need for dose intensification of 34% (95% CI 28–41).

Overall, the mean percentage of patients who lost response to anti-TNFs was 38.5%. The annual risk for LOR was calculated to be 20.9% per patient-year. Specifically, the mean percentage of patients who lost response to IFX was 37.8%. The annual risk for LOR was calculated to be 18% per patient-year, and the according data for adalimumab was 35.4 and 22.7%, respectively. Both rates were relatively similar to previous studies [103, 104]. The mean percentage of patients with loss of IFX response was 37% in a systematic review by Gisbert et al. [103], with the annual risk for loss of IFX response of 13% per patient-year [103]. Billioud et al. [104] later demonstrated the mean percentage of LOR to ADA among primary responders was 18.2% with the annual risk was 20.3% per patient-year. However, as already pointed out by Chao et al., derived from the ratio of total number of patients with lost response (827) to total follow-up time (6284 patient-years), the calculation of 13.1% per patient-year rate was flawed. The follow-up time reviewed was a mix of mean, median, minimum, and maximum values. In addition, most follow-up times included periods after LOR or discontinuation, when patients were no longer at risk for LOR [105]. In these settings, pooling these studies with a random-effect seems more reasonable.

According to our meta-analysis, the pooled incidence of LOR in patients treated with IFX was 33% (95% CI 27–40). For ADA, the random-effects pooled incidence of LOR was 30% (95% CI 22–39). Hence, rates of LOR to IFX and ADA are broadly similar. Both estimates were higher than the previous studies [103, 104], probably due to the different definition for LOR. In contrast, the durability of CZP, which serves as a third-line, response over years, and the need for dose escalation remain poorly studied. According to our meta-analysis, estimates of LOR to CZP ranged from 4.3 to 36.2%, with the random-effects pooled incidence of 41% (95% CI 30–53).

LOR rates should be interpreted with caution as studies differed in population characteristics, study design and LOR definition. Importantly, definition of LOR also differed within anti-TNFs studies. For example, a LOR was defined as an increase in CDAI score of >70 points and a CDAI score of >220 points in ACCENT I trial [1] or with CDAI, HBI in an analysis of PRECISE 2/3 [60] or as 'a return in symptoms consistent with a flare' in a chart-review study. When subgrouped by criteria of LOR, the random-effects pooled incidence of LOR varied among 29.9–37.3% (see Table 3). Thus, the need for dose escalation is a more objective and reliable measure. According to our meta-analysis, the random-effects pooled incidence of dose escalation for ADA was 36% (95% CI 30–43) which was higher than 21.4% reported in the ADA study [104]. Dose escalation over the global study population (initial responders and primary non-responders) underestimated LOR rates by including patients with primary failure to ADA therapy who stopped the drug before dose intensification. Consistently, when considering dose intensification only over primary responders, the mean percentage of patients who needed a dose escalation for LOR was higher (35.5%) [104].

The mean intervals of IFX exposure to lose response or to need dose intensification ranged from 25 weeks to 7 years have been reported [103]. According to studies we reviewed, the intervals of anti-TNFs exposure to LOR or to need dose intensification ranged from 4 weeks to 7 years. The efficacy of anti-TNF may be lost as early as a few months after starting treatment. In fact, in the ACCENT I trial, 40% of patients lost response between weeks 2 and 30, whereas among those with a sustained response up to week 30, 80% maintained the response at week 54. Similarly, 81% of patients in remission at week 30 were still in remission at week 54. Interestingly, an effect of very similar magnitude has been observed for ADA in the CHARM trial [2]. Nevertheless, durability of anti-TNFs maintenance therapy over multiple years has not been defined, and consequently, the true frequency of loss of efficacy and requirement of anti-TNFs dose intensification in the long term is not well known. In the present study, subgrouped by length of follow-up (≥52 or <52 weeks) did not significantly change the effect estimate. However, the risks for LOR (32 versus 30%) or dose intensification (39.6 versus 31.6%) tended to be higher when considering studies with a follow-up of <52 weeks. These data potentially indicate that such events occur preferentially within the first year of therapy. Regarding the study design, prospective studies showed a higher risk for LOR. Indeed, prospective trials are more efficient in detecting loss or primary non-response in clinical practice. Both of trends consisted with the previous ADA study [104].

Factors supposed to be predictors for LOR or dose escalation based on previous studies included previous infliximab therapy, anti-TNFs induction and maintenance regimen, anti-TNFs serum concentration and antibodies and concomitant therapy (see Tables 1, 2). However, a meta-analysis revealed that combination therapy was not statistically different from ADA monotherapy in terms of for maintenance of remission ($p = 0.48$) or requirement for dose escalation ($p = 0.62$) [106]. Whether patients will benefit from combined therapy warrants further study. On the contrary, according to a recent meta-analysis, during maintenance therapy, patients in clinical remission had significantly higher mean trough IFX levels than patients LOR: 3.1 versus 0.9 μg/ml [107]. These data support therapeutic drug monitoring (TDM) in order to optimize serum drug levels, especially in patients with LOR to these agents. Moreover, optimization of anti-TNF therapy by applying TDM enables clinicians to regain response to anti-TNFs in a significant proportion of patients [108]. Further prospective studies evaluating proactive TDM are strongly expected.

This meta-analysis is potentially limited in some ways. First, assessment of the methodological quality determined that there were deficiencies in all studies evaluated, 18 of 73 observational studies were considered as low quality (scoring <7) using the NOS Scale (Supp. Table 1). In addition, the Begg's funnel plot suggested a publication bias existed toward the need for dose intensification. We used a random effects model to conservatively account for the clinical and statistical heterogeneity in pooled studies. Second, the I^2 statistics indicated that there was significant heterogeneity among included studies, and we could not identify the main determinants of the statistical heterogeneity seen in the overall effect estimate and the main subgroup analysis in meta-regression. To incorporate for statistical heterogeneity in the meta-analysis, we used a random-effects model to analyze all outcomes. We also performed sensitivity analyses to examine differences in the overall effect estimate. Third, some of the predefined subgroup aimed to evaluate the possible predictors for LOR or dose escalation that were not performed, e.g., anti-TNFs schedule, concomitant IMMs, type of IMMs and anti-TNFs concentration and antibodies due to the lack of required original data.

In conclusion, the present meta-analysis quantifies the incidence of LOR in patients with CD on anti-TNFs therapy. Overall, around a third of adult patients requires dose intensification and experience a LOR after initiation of anti-TNFα therapy.

Author contributions Acquisition of data, analysis and interpretation of data, and wrote the manuscript: Yun Qiu, Bai-li Chen; critical revision of the manuscript for important intellectual content: Ren

Mao, Sheng-hong Zhang, Yao He, Zhi-rong Zeng, and Shomron Ben-Horin; study concept and design, critical revision of the manuscript for important intellectual content, statistical analysis, and study supervision: Min-hu Chen. All authors discussed the results and implications and commented on the manuscript at all stages.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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