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Anti-Drug Antibody Formation Against Biologic Agents in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis

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Abstract

Background and aims: Immunogenicity with formation of anti-drug antibodies (ADA) to biologics is an important reason for treatment failure in inflammatory bowel disease (IBD). Our aim was to assess the rate of ADA, the effect of combination therapy with immunomodulators on ADA and the influence of ADA on efficacy and safety of biologics for IBD treatment.

Methods: MEDLINE, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to April 2020 for trials of biologics that assessed immunogenicity. The overall certainty of evidence was evaluated using Grading of Recommendations, Assessment, Development and Evaluations (GRADE). The primary outcome was rate of ADA. Secondary outcomes included efficacy and safety outcomes among patients with detectable versus undetectable ADA. For dichotomous outcomes, pooled risk ratios (RR) and 95% confidence intervals (CI) were calculated.

Results: Data from 68 studies were analysed and 33 studies (5850 patients) were included in the meta-analysis. Pooled ADA rates for biologic monotherapy were 28.0% for infliximab, 7.5% for adalimumab, 3.8% for golimumab, 10.9% for certolizumab, 6.2% for ustekinumab and 16.0% for natalizumab. Pooled ADA rates were 8.4% for vedolizumab and 5.0% for etrolizumab for combo- and monotherapy combined. In all biologics, ADA rates were underestimated by use

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of drug sensitive ADA assays and higher dose and/or frequency. ADA rate was significantly reduced in patients treated with combination therapy for infliximab (RR 0.52; 95% CI 0.44, 0.62), adalimumab (RR: 0.31; 95% CI 0.14, 0.69), golimumab (RR: 0.29; 95% CI 0.10, 0.83), certolizumab pegol (RR: 0.30; 95% CI 0.14, 0.67) and natalizumab (RR: 0.20; 95% CI 0.11, 0.39). ADA to infliximab were associated with lower clinical response rates (RR: 0.75; 95% CI 0.61, 0.91) and higher rates of infusion reactions (RR: 2.36; 95% CI 1.85, 3.01).

Conclusions: Differences in analytical methods to detect ADA hamper comparison of true ADA rates across biologics in IBD. Use of combination therapy with immunomodulators appeared to reduce ADA positivity for most biologics. For infliximab, ADA were associated with reduced drug efficacy and increased adverse events.

1. Introduction

Although biologics were first introduced for the treatment of inflammatory bowel disease (IBD) in the late nineties guidelines regarding their optimal use are still evolving. Over the last several decades IBD-related healthcare costs have increased significantly due to increased utilization of tumor necrosis factor-alpha (TNF- α) antagonists and other biologics [1, 2]. Accordingly, optimal use of biologics is necessary to enhance efficacy, reduce adverse effects and manage costs.

The TNF- α antagonists infliximab, adalimumab, golimumab and certolizumab pegol act by targeting and inhibiting TNF- α , a pro-inflammatory cytokine that has a central role in mucosal inflammation in IBD [3, 4]. Ustekinumab binds to the common p40 subunit of the pro-inflammatory cytokines interleukin (IL)-12 and IL-23 which are also known to play a role in the pathophysiology of IBD [5]. Natalizumab binds to the α_4 subunit of the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin, thereby blocking the binding to respectively vascular cell adhesion molecule 1 (VCAM-1) and mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) and inhibiting the migration of mononuclear leukocytes to different tissues, predominantly the gut and central nervous system [6]. Vedolizumab recognizes a conformational epitope of the heterodimer $\alpha_4\beta_7$ which blocks binding to MAdCAM-1, thereby inhibiting the migration of gut-selective leukocytes [7]. Etrolizumab targets the β_7 unit of the heterodimeric integrins $\alpha_4\beta_7$ and $\alpha_E\beta_7$, thereby inhibiting migration of gut-selective leukocytes [8].

A major concern when treating patients with biologics is the development of anti-drug antibodies (ADA), since ADA are associated with lower serum drug concentrations, loss of response, and adverse effects such as infusion and injection site reactions [9–11]. Several strategies for prevention of ADAs formation have been investigated. Combination therapy comprised of a biologic with an immunomodulator prevents ADA formation [12, 13]. Higher anti-TNF dosing is associated with less ADA detection [14, 15]. Pre-treatment with hydrocortisone has also been shown to prevent ADA formation and infusion reactions; however, data supporting this strategy are limited [16]. There is also some evidence that a decline in ADA may be achieved by adding or switching immunomodulators [17, 18].

The incidence of immunogenicity varies considerably across studies and biologic agents. A critical factor related to this variability may be the sensitivity of the assay used to detect ADA [19, 20]. Qualitative terms are used to distinguish between drug ‘tolerant’ assays

that are able to measure ADA in the presence of detectable drug concentrations, and drug 'sensitive' assays which are not. Drug tolerant assays are preferred for detecting ADA to assess the true ADA rate.

Strategies for optimal management of ADA formation are still evolving, and the exact influence of concomitant immunomodulator therapy on immunogenicity remains unclear. Therefore, the objectives of this systematic review were to determine the rate of ADA formation in patients on monotherapy or combination therapy, and the impact of ADA formation on the pharmacokinetics, efficacy and safety of biologics in patients with IBD.

2. Methods

This systematic review and meta-analysis was conducted using the methods described in the Cochrane Handbook of Systematic Reviews,[21] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22]. The review protocol was registered in the Cochrane Database of Systematic Reviews [23].

2.1 Eligibility criteria

Any trial of biologics that enrolled adult Crohn's disease (CD) or ulcerative colitis (UC) patients (16 years or older) and assessed immunogenicity was eligible for inclusion. Interventions of interest included adalimumab, certolizumab pegol, golimumab, infliximab, natalizumab, vedolizumab, ustekinumab and etrolizumab administered alone or in combination with another agent (i.e. corticosteroids [including pre-medication], thiopurines, or methotrexate).

2.2 Comparisons and outcomes

The primary outcomes of interest were ADA formation and ADA concentration among patients treated with monotherapy compared to combination therapy. Secondary outcomes included drug serum concentration and rates of response (clinical, endoscopic or biochemical), remission (clinical, endoscopic or biochemical) and adverse events (including acute, delayed or injection site reactions) in patients with detectable versus undetectable ADA. Response and remission rates were pooled for analysis irrespective of the definition employed in the original study.

2.3 Search strategy

MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to April 21, 2020 (Supplementary Appendix 1). No language or date restrictions were applied. The bibliographies of relevant articles and conference proceedings from Digestive Disease Week and United European Gastroenterology Week (2013 to 2020) were hand searched to identify additional studies.

2.4 Screening and data extraction

Two authors (SB and NVC) independently screened search results and extracted information on study design, participants, intervention, comparison, outcomes, and risk of bias using a standardized data collection form. Secondary outcome data were only collected if

immunogenicity data were reported. Disagreements were resolved through discussion with a third author (JFB or CEP). For unclear or missing data, an attempt was made to contact the original study authors for clarification.

2.5 Risk of bias assessment

The Cochrane risk of bias tool was used to assess the methodological quality of randomized controlled trials (RCTs) [24]. The Newcastle-Ottawa Quality Assessment Scale (NOS) was used for quality assessment of the observational studies [25].

2.6 Heterogeneity

Heterogeneity was assessed using the Chi² test ($p < 0.10$ was considered statistically significant) and the I² statistic.[26] I² values of 0%, <50%, 50% and 75% were interpreted as indicating no, low, moderate and high heterogeneity, respectively [26].

2.7 Data synthesis and analysis

Data from individual trials were pooled for meta-analysis if the intervention(s), population, and outcomes were sufficiently similar (determined by consensus). Data were not pooled for analysis if there was a high degree of heterogeneity (I² >75%).

For dichotomous outcomes, the risk ratio (RR) and corresponding 95% confidence interval (CI) were calculated. If outcome data were reported at multiple timepoints, the primary timepoint defined by the original study authors was used. A fixed-effect model was used to pool data, however, we planned to use a random-effects model in the case of significant, unexplained heterogeneity. Review Manager (RevMan 5.4; The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark) was used to perform data analysis according to the intention-to-treat principle.

2.8 Sensitivity and subgroup analyses

Sensitivity analyses were conducted to investigate potential sources of heterogeneity and assess the impact of removing low quality studies from the pooled analyses. Where possible, subgroup analyses were performed to assess the influence of the following factors on the overall RR estimate: study design (randomized versus observational; induction versus maintenance), patient population (CD versus UC versus IBD), combination therapy regimen (combination therapy versus monotherapy) and ADA assay type (drug sensitive versus drug tolerant).

2.9 Quality of the evidence

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was used to assess the overall certainty of the evidence. Results from RCTs were initially considered high-quality, but potentially downgraded due to risk of bias; indirectness of evidence; unexplained heterogeneity; publication bias or sparse data [27]. Observational data were initially considered low quality. Outcomes with less than 35 events were reduced by two GRADE levels; outcomes with less than 300 events were reduced by one GRADE level.

3. Results

3.1 Search results

The search identified 11881 records, from which 3368 duplicates were removed. Of the remaining 8513 records, 7994 were deemed ineligible based on title and abstract. Full-text review was required for 519 records, and 398 records were excluded. Most excluded studies did not report on ADA formation or had no control group. A total of 68 studies met the inclusion criteria (Figure 1). The included studies are described in Supplementary Table 1. ADA formation rates in each study are shown in Supplementary Table 2. Table 1 summarizes the main results and provides an overall assessment of the certainty of the evidence.

3.2 Risk of bias assessment

The risk of bias assessments are reported in Supplementary Tables 3 and 4. The RCTs scored low or unclear risk of bias for most domains. One study was rated as high risk of bias with respect to attrition bias, and seven studies were rated as high risk of bias with respect to blinding. For the observational studies, one study was deemed to be at high risk of bias (NOS *score 6), and 13 studies were deemed to be at low risk of bias (*range 7–9).

3.3 Infliximab

The search identified 26 eligible studies for infliximab, 5 of which were RCTs and 21 were observational. Thirteen studies allowed us to evaluate combination therapy to monotherapy. Eleven studies allowed us to evaluate ADA-positive to ADA-negative or ADA-undetectable patients. Seventeen studies included patients with CD, six studies included patients with UC, and two studies included IBD patients (Supplementary Table 1).

3.3.1 ADA formation—Thirteen studies allowed us to evaluate ADA formation rates among patients treated with infliximab monotherapy versus combination therapy with an immunomodulator (supplementary table 1). Follow-up ranged between 12 weeks and 36 months (median). ADA development occurred in 15.8% (136/863) of patients on combination therapy compared to 28.0% (269/962) of patients on monotherapy. The pooled RR was 0.52 (95% CI 0.44, 0.62, 13 studies, $p < 0.001$; GRADE high; Figure 2.1.1) with low heterogeneity ($I^2 = 40\%$, $p = 0.07$).

The pooled RR for RCT studies was 0.13 (95% CI 0.05, 0.33, 3 studies, $p < 0.001$, GRADE moderate; Figure 2.1.2) with no heterogeneity detected ($I^2 = 0\%$, $p = 0.49$). The pooled RR for observational studies was 0.59 (95% CI 0.49, 0.71, 10 studies, $p < 0.001$, GRADE high; Figure 2.1.3). The RR estimates continued to demonstrate a statistically significant effect in favour of combination therapy when data were pooled based on study design (induction versus maintenance [Figures 2.1.4 and 2.1.5] and CD versus UC [Figures 2.1.6 and 2.1.7]), with between-study heterogeneity remaining low. The RR estimate did not show a statistically significant effect in the mixed population (Figure 2.1.8).

ADA formation resulting from infliximab combination therapy with azathioprine was evaluated in four studies. The pooled RR was 0.50 (95% CI 0.37, 0.67, $p < 0.001$, GRADE

moderate; Figure 2.1.9). The between study heterogeneity was moderate ($I^2=74\%$). When removing the study by Vermeire et al. (a study on episodic infliximab treatment) from the analysis, the pooled RR was 0.15 (95% CI 0.05, 0.41; $p<0.001$, GRADE moderate; Supplementary Figure 1).

Two studies compared the presence of ADA formation among patients treated with infliximab monotherapy relative to infliximab in combination with methotrexate (Figure 2.1.10) with a pooled RR of 0.51 (95% CI 0.36, 0.72, $p<0.001$; GRADE moderate). The between-study heterogeneity was moderate ($I^2=61\%$).

Two studies explored the effect of combined infliximab and corticosteroid therapy on ADA formation, without the use of concomitant immunomodulators (Figure 2.1.11). Sixteen percent (32/200) of patients on combination therapy developed ADAs, compared to 21% (57/277) of patients on monotherapy. This effect was not statistically significant (RR 0.80, 95% CI 0.53, 1.22, $p=0.30$; GRADE moderate), and the between-study heterogeneity was low ($I^2 = 33\%$).

The pooled RR for studies that used a drug sensitive assay was 0.49 (95% CI 0.41, 0.60, 11 studies, $p<0.001$; GRADE high), and the between study heterogeneity was low ($I^2 = 31\%$) (Figure 2.1.12). For two studies that used a drug tolerant assay, ADA development occurred in 19% (24/128) of patients receiving combination therapy versus 29% (39/136) of patients receiving monotherapy. The pooled RR was 0.51 (95% CI 0.13–2.01; $p=0.34$ GRADE low) and the between-study heterogeneity was high ($I^2 = 78\%$) (Figure 2.2). When removing Oh et al. (a prospective observational study) from the analysis, the RR was 0.23 (95% CI 0.07, 0.77; $p=0.02$, GRADE low; Supplementary Figure 2).

3.3.2 ADA concentration—Four infliximab studies reported ADA concentrations.

We did not combine quantitative data for analysis due to the heterogeneous units of measurement used to define ADA concentrations and heterogeneity in statistical reporting.

For the Baert et al. study, the median ADA concentration was higher in patients receiving monotherapy relative to combination therapy [9]. The median concentration of ADAs to infliximab was 13.8 $\mu\text{g/ml}$ (95% CI 7.9–16.2) among patients with luminal disease receiving monotherapy therapy, compared to 1.3 $\mu\text{g/ml}$ (95% CI 0.6–3.2) among patients with luminal disease receiving combination therapy. In patients with fistulizing disease receiving monotherapy, the median concentration of ADAs to IFX was 21.4 $\mu\text{g/ml}$ (95% CI 13.2–24.5) compared to 1.5 $\mu\text{g/ml}$ (95% CI 0.4–8.8) among patients with fistulizing disease receiving combination therapy.

In a study by Farrell et al., ADA concentrations were lower in patients pretreated with hydrocortisone compared to placebo (median 2.9 versus 11.1 $\mu\text{g/ml}$ at week 8 and 1.6 versus 3.4 $\mu\text{g/ml}$ at week 16) [16].

Among 96 patients who developed ADA to infliximab, Vermeire et al. reported 27 (28%), 30 (31%) and 39 (41%) patients with ADA concentrations of below 8, above 8 or above 20 $\mu\text{g/ml}$ respectively [28].

Using a drug tolerant assay, Oh et al. showed a lower median ADA concentration of 8.064 AU/mL (IQR 6.929–9.908) in patients in remission compared to 11.209 AU/mL (IQR 8.008–118.835) in patients with active disease [29].

3.3.3 Serum drug concentrations—Five infliximab studies compared serum drug concentrations among ADA-positive and ADA-negative patients. We did not combine data for analysis due to the heterogeneous cut-off values used to define ADA-positive and ADA-negative patients. A post-hoc analysis of the ACT-1 and ACT-2 trials showed that patients with ADA formation had a higher likelihood of low drug serum concentrations ($p < 0.001$) [30, 31]. Seow et al. showed that of 66/108 patients with undetectable drug serum concentrations, 44 (66.7%) were ADA-positive and 22 (33.3%) were ADA negative [32]. Vermeire et al. showed lower median concentrations of 7.55 $\mu\text{g/mL}$ (IQR 2.65–13.73) after 1 infusion of infliximab in patients who later became ADA-positive, compared with median drug serum concentrations of 11.15 $\mu\text{g/mL}$ [IQR 5.98–18.98] in patients who remained ADA-negative [28]. Oh et al. reported median trough levels of 0.141 $\mu\text{g/mL}$ (IQR 0.002–0.869) in ADA-positive patients versus median trough levels of 1.415 $\mu\text{g/mL}$ (IQR 0.570–2.495) in ADA-negative patients, using a drug tolerant assay [29]. Van Stappen et al. reported an inverse correlation between ADA concentration, as measured with a drug ‘tolerant’ assay, and infliximab trough concentrations in a posthoc analysis of the TAXIT trial [33]. Patients in the highest quadrant of ADA concentrations had lower trough concentrations when compared to the two lowest quadrants and ADA-negative patients ($p < 0.001$). Median trough concentrations were lower in ADA-positive patients when using a drug tolerant and a drug sensitive assay (0.0, IQR 0.0–0.0 $\mu\text{g/mL}$) compared with ADA-negative patients (1.8, IQR 1.4–2.4 $\mu\text{g/mL}$) ($p < 0.001$) and patients who were ADA-positive with a drug tolerant assay only (1.7, IQR 0.7–2.3, $p < 0.001$). There was no difference in trough concentration between ADA-negative patients and patients who were ADA-positive with a drug tolerant assay only ($p = 1.0$). Indicating that low concentration ADA that are undetectable at trough using a drug ‘sensitive’ assay may be pharmacologically less relevant.

3.3.4 Clinical outcomes—A lower overall clinical response to infliximab rate was observed in ADA-positive compared with ADA-undetectable patients (RR 0.75, 95% CI 0.61, 0.91, $p = 0.004$, 7 studies, GRADE high; Figure 3). The heterogeneity was low for this comparison ($I^2 = 0\%$, $p = 0.51$).

3.3.5 Endoscopic outcomes—Two infliximab studies reported on endoscopic outcomes in relation to ADA status. Data were not pooled due to high heterogeneity. Seow et al. showed no difference in endoscopic improvement between ADA-positive and ADA-undetectable patients (25% vs 35%; $p = 0.61$). However, detectable infliximab serum drug concentrations were associated with endoscopic improvement (76% vs 28%; $P < 0.001$) [32]. Reguiero et al. observed a higher endoscopic recurrence rate after ileocecal resection in ADA positive (64.7%, 11/17) vs ADA negative (46.7%, 7/15) or ADA inconclusive (30.1%, 22/73) patients [34].

3.3.6 Biochemical outcomes—No infliximab studies reported on the relationship between biochemical disease activity and ADA formation.

3.3.7 Adverse events—Infliximab infusion reactions occurred in 65/175 (37.1%) of ADA-positive patients versus 165/1067 (15.5%) ADA-undetectable patients (RR 2.36, 95% CI 1.85, 3.01, $p < 0.001$, 5 studies, GRADE moderate; Figure 4). Moderate heterogeneity was detected ($I^2 = 59\%$, $p = 0.04$).

One study reported significantly higher median ADA titers in patients with infusion reactions compared to those without (20.1 vs 3.2 $\mu\text{g/ml}$) [9]. Concentrations of 8 $\mu\text{g/ml}$ or higher predicted a higher risk of infusion reactions (RR 2.40; 95% CI 1.65, 3.66; $P < 0.001$). A single study by Ye et al. reported that 2/2 patients that had an infusion reaction at week 30 were ADA positive. In total, 19/220 infusion reactions were reported but ADA formation was not reported in these cases [35].

3.3.8 Antibody assays—In four infliximab studies, a drug-tolerant assay was used for the assessment of ADA formation. In these studies, the reported ADA formation rates were 47/138 (34.1%), 16/126 (12.7%), 21/122 (17.2%) and 13/42 (31%), respectively.

3.4 Adalimumab

The search identified 10 RCTs of adalimumab treatment that met the eligibility criteria. Seven studies reported data on combination therapy. One study randomized patients to receive adalimumab in combination with immunomodulators or as monotherapy. No studies compared ADA-positive to ADA-negative patients. The majority of studies included patients with CD and two studies included patients with UC (Supplementary Table 1).

3.4.1 ADA formation—ADA formation occurred in 2.2% (6/273) of patients receiving adalimumab combination therapy compared to 7.5% (32/425) of patients treated with monotherapy. The pooled RR was 0.31 (95% CI 0.14, 0.69, 5 studies, $p = 0.004$, GRADE moderate; Figure 5.1.1). No heterogeneity was detected ($I^2 = 0\%$, $P = 0.82$). The RR estimate continued to demonstrate a statistically significant protective effect in favour of combination therapy when data were pooled based on study design (maintenance treatment; Figure 5.1.2). Data on the influence of methotrexate, thiopurines or corticosteroids were unavailable.

3.4.2 Other outcomes—Data on the impact of ADA formation on clinical, biochemical and endoscopic outcomes or serum drug concentrations and adverse events were not available.

3.5 Infliximab and adalimumab

One study by Roblin et al. showed increased incidence of ADA development and undetectable drug concentrations in the monotherapy group after switching TNF antagonist therapy (i.e. from infliximab to adalimumab or from adalimumab to infliximab) because of clinical failure and immunogenicity [36]. Starting the subsequent biologic with combination therapy significantly reduced ADA development and the incidence of undetectable drug concentrations (adalimumab and azathioprine: Hazard ratio [HR] 0.12; 95% CI 0.03, 0.40; $p < 0.001$; infliximab and azathioprine: HR 0.16 95%; CI 0.06, 0.37; $p < 0.001$). This effect was consistent only for infliximab and not for adalimumab when ADA were measured using

a drug tolerant assay (adalimumab and azathioprine: HR 0.61; 95% CI 0.30, 1.24; p=0.17; and infliximab and azathioprine: HR 0.18; 95% CI 0.08, 0.41).

3.6 Golimumab

The search yielded three RCTs of golimumab treatment that met the eligibility criteria. None of the studies randomized patients to monotherapy or combination therapy. No studies compared ADA-positive to ADA-negative patients. All three studies analyzed UC patients (Supplementary Table 1).

3.6.1 ADA formation—Sandborn et al. reported data on the protective effect of combination therapy on ADA formation [37, 38]. ADA formation occurred in 1.1% (4/362) of patients on combination therapy compared to 3.8% (28/741) of patients on monotherapy. The calculated RR was 0.29 (95% CI 0.10, 0.83; p=0.02; GRADE moderate) (Supplementary Figure 3). A post-hoc analysis of PURSUIT-SC, PURSUIT-M and PURSUIT-IV showed much higher ADA detection when using a drug tolerant assay (21.8% versus 2.8%). ADA rates were higher in patients in the PURSUIT-M study who were randomized to placebo after induction treatment (31.6% versus 20.2%). ADA rates were lower in patients receiving immunomodulators (11.8% versus 26.9%; p<0.001) and ADA rates were lower in patients receiving golimumab monotherapy doses of 100mg versus 50mg (22.4% versus 37.1%; p-value unavailable). Additionally, ADA-positive patients with a drug-tolerant assay had lower ADA titers as opposed to ADA-positive patients with a drug-sensitive assay. Trough serum golimumab concentrations were lower in ADA-positive patients 0.51 vs 0.85 µg/mL [50 mg q4w]; 0.85 vs 1.60 µg/mL [100 mg q4w]).

3.6.2 Other outcomes—A post-hoc analysis of Sandborn et al. reported clinical and endoscopic outcomes in relation to ADA status at weeks 6 and 54 and no significant associations were found [39]. However, in the post-hoc analysis by Adedokun et al., clinical response rates were lower at week 54 in ADA-positive versus ADA-negative patients when using a drug-tolerant assay (38.1% versus 52.8%; p=0.047). ADA-formation did not have an impact on injection site reactions. Other data on the effect of ADA formation on biochemical outcomes or adverse events were not available.

3.7 Certolizumab pegol

The search yielded six RCTs that evaluated treatment with certolizumab pegol that met the eligibility criteria. None of the studies randomized patients to monotherapy or combination therapy. Two studies compared ADA-positive to ADA-negative patients. All studies analyzed CD patients (Supplementary Table 1).

3.7.1 ADA formation—Three certolizumab pegol studies provided data on the effect of combination therapy on ADA formation, of which two could be compared. ADA formation occurred in 3.3% (7/213) of patients on combination therapy compared to 10.9% (36/331) of patients on monotherapy (RR 0.30, 95% CI 0.14, 0.67; 2 studies; p=0.003, GRADE moderate; Figure 6). Heterogeneity was low ($I^2 = 0\%$, p=0.43). In all studies, patients received scheduled maintenance treatment for more than 14 weeks. In the PRECiSE 3 study, an extension of PRECiSE 1 and PRECiSE 2, ADA formation occurred in 14.6% (31/213)

of patients on combination therapy compared to 27% (103/382) of patients who received monotherapy (RR 0.54; 95% CI 0.37, 0.78; $p < 0.001$). Data on the effect of methotrexate, thiopurines or corticosteroids on ADA formation were unavailable. In the PRECiSE 2 trial it was shown that immunogenicity rates were higher in patients receiving induction treatment who were then assigned to placebo when compared to patients receiving maintenance treatment (18% versus 8%). This was mainly reflected by patients receiving monotherapy (24% ADA positive).

3.7.2 Serum drug concentrations—An integrated analysis of 5-year follow-up of the PRECiSE trial showed a lower range of mean drug serum concentrations in ADA-positive versus ADA-negative patients (0.88–15.25 vs 8.33–29.89 $\mu\text{g/ml}$) and no influence of ADA-formation on adverse events [40].

3.7.3 Clinical outcomes—Schreiber et al. reported that of the 17 patients with positive tests for ADA against certolizumab pegol, 12 (71%) had a response through week 26, compared with 62% (121/196) of patients with negative antibody tests [41]. In a 7-year analysis of the PRECiSE 3 trial, Sandborn et al. found no difference in clinical disease activity between persistently ADA-positive and ADA-undetectable patients [42].

3.7.4 Biochemical outcomes—Sandborn et al. demonstrated that median CRP and fecal calprotectin concentrations were higher ($p < 0.05$ at some visits) and plasma CZP concentrations were significantly lower ($p < 0.0001$ at all visits) in patients with persistent ADAs when compared to the ADA negative group [42].

3.7.5 Other outcomes—Data on the influence of ADA formation on endoscopic outcomes and antibody assays were not available.

3.8 Vedolizumab

The search yielded nine RCTs that met eligibility criteria. No eligible observational studies were identified. None of the studies randomized patients to vedolizumab with or without an immunomodulator. None of the studies compared ADA-positive to ADA-negative patients. Four studies analyzed CD patients and five studies analyzed UC patients (Supplementary Table 1).

3.8.1 ADA formation—ADA formation occurred in 8.4% of patients treated with vedolizumab. Numerical data on ADA formation in patients treated with monotherapy or concomitant immunomodulator therapy were unavailable. Feagan et al. reported that concomitant immunomodulator therapy was associated with decreased immunogenicity [43]. No other data were available regarding the influence of combination therapy on antibody formation to vedolizumab.

3.8.2 Infusion reactions—Three studies reported on infusion reactions in patients treated with vedolizumab. The number of infusion reactions was very low, however most patients with an infusion reaction were ADA-positive. Wyant et al. reported no relationship between immunogenicity and safety in a long-term safety analysis of the GEMINI studies [44].

3.8.3 Other outcomes—Feagan et al. studied ADA formation against MLN02 (a predecessor compound of vedolizumab which had a modified amino acid sequence and was expressed in a different system) at dosages of 0.5 mg/kg and 2.0 mg/kg, and showed that ADAs were more frequently detected at lower dosages [45]. Additionally, it was reported that patients with clinically significant ADA titers had lower remission rates. Sandborn et al. showed that ADA to subcutaneous or intravenous vedolizumab resulted in lower drug exposure and reduced efficacy, although the number of ADA-positive patients was very low. It was also observed that patients receiving vedolizumab induction treatment who were then randomized to placebo had higher ADA rates (30%). Other relevant data on the influence of ADA formation on clinical, biochemical and endoscopic outcomes or serum drug concentrations and adverse events were not available [46].

3.9 Ustekinumab

The search yielded four RCTs that met the eligibility criteria. No eligible observational studies were identified. None of the studies randomized patients to ustekinumab in combination with immunomodulators or ustekinumab monotherapy. One study compared ADA-positive to ADA-negative patients. All studies analyzed CD patients (Supplementary Table 1).

3.9.1 ADA formation—ADA development occurred in 3.7% (10/273) of patients on combination therapy compared to 6.2% (40/644) of patients treated with monotherapy (RR 0.59; 95% CI 0.30, 1.12; 2 studies; $p=0.13$; GRADE moderate; Supplementary Figure). Low heterogeneity was detected ($I^2=30\%$, $p=0.23$).

3.9.2 Other outcomes—In a post-hoc analysis of UNIFI, Adedokun et al. reported lower serum ustekinumab concentrations in ADA-positive versus ADA-negative patients at week 24 (0.31 $\mu\text{g/ml}$; IQR 0.11–2.14, vs 2.76 $\mu\text{g/ml}$; IQR 1.87–4.18). They also showed that there was no relationship between ADA status and clinical efficacy. Furthermore they reported no difference in endoscopic response between ADA positive and negative patients and no relationship between ADA positivity and injection site reactions or anaphylactic reactions [47, 48]. Other data on the influence of antibody formation on clinical, biochemical and endoscopic outcomes or serum drug concentrations and adverse events were not available.

3.10 Natalizumab

The search yielded six RCTs and one prospective study that met the eligibility criteria. None of the studies randomized patients to natalizumab in combination with immunomodulators or natalizumab monotherapy. None of the studies compared ADA positive to ADA negative patients. All studies analyzed CD patients (Supplementary Table 1).

3.10.1 ADA formation—ADA development occurred in 2.6% (10/389) of patients treated with combination therapy compared to 16.0% (60/374) of patients assigned to monotherapy (RR 0.20; 95% CI 0.11, 0.39; 2 studies, $p<0.001$; GRADE moderate; Supplementary Figure 5). No heterogeneity was detected ($I^2=0\%$, $P=0.48$). Only one study assessed maintenance treatment (>14 weeks), thus no subgroup analysis could be

performed. Data on the effect of methotrexate, thiopurines or corticosteroids on ADA formation were unavailable.

3.10.2 Other outcomes—Data on the influence of ADA formation on clinical, biochemical and endoscopic outcomes or serum drug concentrations and adverse events were not available. None of the studies used drug tolerant assays.

3.11 Etrolizumab

The search yielded two RCTs that met the eligibility criteria. No eligible observational studies were identified. None of the studies randomized patients to etrolizumab in combination with immunomodulators or etrolizumab monotherapy. None of the studies compared ADA-positive to ADA-negative patients. Both studies analyzed UC patients (Supplementary Table 1).

3.11.1 ADA formation—ADAs were measured in 119 patients. Reported ADA formation rates were 4.9% (4/81) (Vermeire et al.) and 5.3% (2/38) (Rutgeerts et al.). ADAs were detected with a drug tolerant assay in both studies. None of the studies reported on the effect of combination therapy on antibody formation. Other data on the influence of ADA formation on clinical, biochemical and endoscopic outcomes or serum drug concentrations and adverse events were not available.

4. Discussion

The results of this systematic review and meta-analysis showed that ADA formation to biologic agents was reduced in patients treated with combination therapy compared to patients treated with monotherapy. Combination therapy has been the preferred strategy for patients starting infliximab treatment, however our findings are consistent with the notion that starting combination therapy with immunomodulators may also be an effective strategy for reducing ADA formation in patients treated with adalimumab, golimumab, certolizumab pegol, and natalizumab. Although comparative evidence is lacking, it is likely that combination therapy reduces ADA formation for other approved biologics agents (i.e., ustekinumab, etrolizumab and vedolizumab). For instance, Feagan et al. noted lower immunogenicity in patients treated with vedolizumab in combination with an immunomodulator, yet quantitative data are lacking [43]. ADA formation with ustekinumab was lower in patients treated with combination therapy compared to monotherapy (4% vs 6%), however this difference was not statistically significant, which may be a consequence of the low number of patients developing ADA.

ADA formation has a negative impact on clinical, biochemical, and endoscopic outcomes. For example, ADA formation to infliximab has usually been associated with lower clinical response rates and Vande Casteele et al. demonstrated higher concentrations of CRP in ADA positive patients [49]. Nonetheless, Seow et al. found that ADA positivity had no influence on endoscopic outcomes in patients treated with infliximab [32]. Sandborn et al. found higher median CRP and fecal calprotectin concentrations in patients persistently positive for ADA to certolizumab pegol, however this was not reflected in clinical outcomes [42]. Based on the available evidence, no robust conclusions can be drawn regarding the effect of

ADA formation on biochemical and endoscopic treatment outcomes. Importantly, none of these studies were powered to assess the influence of ADA formation on these outcomes. Additionally, it is relevant to note that ADA positive patients may have sufficient serum drug concentrations during the majority of the treatment interval, especially for drugs that are more frequently administered (e.g. adalimumab). Lastly, patients who are in remission and develop ADAs are unlikely to immediately lose response due to pharmacodynamic carryover.

Several studies reported on ADA formation and infusion reactions to infliximab or vedolizumab [9, 16, 31, 45, 46, 50, 51]. ADA formation was associated with an increased risk for infusion reactions with infliximab (RR 2.36; 95% CI 1.85, 2.81), however the data regarding vedolizumab were insufficient for meta-analysis.

Rates of ADA formation differed substantially amongst biologics, and across different studies of the same agent. The highest reported incidence of ADA formation in patients receiving scheduled infliximab, adalimumab or golimumab monotherapy was 40.7% (44/108), 16.7% (1/6) and 37.1%, respectively. For scheduled certolizumab pegol and vedolizumab treatment, the highest reported incidence of ADA formation was 24.2% (30/124) and 10.8% (4/37), respectively. Lower rates were reported in patients receiving scheduled natalizumab, ustekinumab and etrolizumab monotherapy (4.1% [5/123], 11.1% [2/18], 4.6% [23/505] and 4.9% [4/81], respectively), despite the use of drug tolerant assays for the newer molecules (ustekinumab and etrolizumab). Higher proportions of ADAs were seen in the older studies where patients were treated episodically, or only received induction treatment with one to three infusions (i.e. phase 2 studies). For instance, the highest reported incidence of ADA formation for episodic infliximab was 60.8% (76/125) [9]. Additionally, ADA rates were higher for episodic vedolizumab, certolizumab pegol and golimumab treatment [14, 45, 52–54]. For the other biologics, the impact of episodic treatment is unknown. Another reason for differences in immunogenicity could be differences in structure of the agent (i.e. infliximab is a chimeric monoclonal antibody). Although the described differences in ADA rates should be interpreted cautiously because of differences between assays it is likely that immunogenicity is of less concern with newer biologics especially given that these agents have been assessed, in the most part, using highly sensitive drug-tolerant assays.

There were several aspects that we could not assess in this review. Only a few studies used drug tolerant assays and a meta-analysis of studies comparing different assays could therefore not be made. However, immunogenicity rates for infliximab, vedolizumab and golimumab are higher when measuring with a drug tolerant assay [14, 33, 53, 55]. Furthermore, we were unable to assess the impact of drug dose on immunogenicity due to lack of sufficient data. Thus it is important to note that higher drug concentrations in patients treated with higher doses may have masked the detection of ADA. Despite those limitations, there are data suggesting that higher doses of infliximab and golimumab result in less immunogenicity [14, 15]. It has been shown that ADA formation results in low serum drug concentrations due to accelerated clearance, which is the main reason for treatment failure due to ADA formation, together with drug neutralization [56, 57]. Some of the included studies showed lower serum drug concentrations in ADA-positive

patients, but we could not perform a meta-analysis due to scarce data and data heterogeneity. We could also not account for the impact of route of administration, which may also be a factor influencing immunogenicity. For instance, there is evidence that subcutaneous infliximab is less immunogenic than intravenous infliximab [58]. Furthermore, we did not assess the difference between neutralizing versus non-neutralizing and transient vs. sustained antibodies, since most studies did not distinguish between the two. Transient ADAs are probably clinically less relevant and sustained ADAs are more likely to result in treatment failure [59, 60]. Additionally, we did not evaluate the risk of developing ADAs when rechallenging with the same biologic agent or when switching to a second biologic. For instance, it has been shown that the risk of ADA formation is higher when switching to a second TNF antagonist [61, 62]. It has also been shown that re-treatment with the same TNF antagonist after stopping maintenance treatment ('drug holiday') is associated with a higher risk of adverse events such as infusion reactions and ADA development, which is also seen with episodic treatment [9, 63, 64]. We did also not assess risk of immunogenicity when switching from originator to biosimilar biologics since this was not within the scope of this review. Nevertheless, it has been shown in previous studies that switching to a biosimilar is safe, effective and not associated with increased immunogenicity [65, 66]. Lastly, there is also some evidence that genetic factors play a role in immunogenicity [67]. Thus, these results should be interpreted with caution and in the context of important aforementioned data gaps. The incidence of ADA for different biologics is likely higher than reported, since most studies used drug sensitive assays. Additionally, there are several important factors impacting ADA formation that could not be properly assessed in this review. However, this does not negate the fact that ADA formation is associated with poorer treatment outcomes and that combination therapy with an immunomodulator results in less immunogenicity, which is mainly of importance for agents with considerable immunogenic potential. Given the fact that immunogenicity is much lower for the newest agents (e.g. anti-integrins and ustekinumab), the benefit of combination therapy for prevention of ADA formation is probably trivial in these agents.

Reduced ADA formation in patients treated with infliximab in combination with an immunomodulator has also been shown in several uncontrolled or retrospective studies [10, 11, 68, 69]. Another systematic review, studying the immunogenicity of TNF antagonists in autoimmune inflammatory diseases found similar results [70]. However, most of the studies in this review were not conducted in patients with IBD. ADA formation was also associated with inferior treatment outcomes. Nevertheless, in other cohort studies it has been shown that immunogenicity increases drug clearance, resulting in lower serum drug concentrations that are, in turn, associated with poorer treatment outcomes for various biologic agents [10, 11].

Despite the available evidence, several knowledge gaps remain. For instance, not much is known on how ADA titers are associated with serum drug concentrations and what ADA titers result in sub-therapeutic serum drug concentrations (i.e. patients could have sub-therapeutic drug concentrations due to ADA formation which is not detected by drug sensitive assays). To evaluate this question, studies with drug tolerant assays should be conducted. Drug sensitive assays only show ADAs when serum drug concentrations are low or undetectable and thus an inverse correlation between both continuous measures is a self-

fulfilling prophecy. Detecting ADAs earlier on, before serum drug concentrations become sub-therapeutic, could be of clinical value and should be evaluated in future studies. In this review, we identified some studies that used a drug tolerant assay. However, the studies did not evaluate this issue. A retrospective study showed that a cut-off in ADA lower than 282 ng/mL was valuable for decision making for interval shortening and dose doubling in infliximab [71]. Controlled prospective studies for different biologics are needed to further assess this phenomenon. These questions also highlight the importance of harmonizing ADA detection methods. Usage of uniform assays and standards would result in more comparable data for meta-analysis and would ultimately lead to improved clinical utility. Additionally, small retrospective cohort studies have suggested that adding an immunomodulator in monotherapy patients who develop ADAs may reverse ADA formation [17, 18]. However, no prospective controlled studies have been conducted.

With respect to combination therapy, the optimal doses of immunomodulators that suffice for prevention of ADA formation are unknown. To our knowledge only one study has addressed this issue [72]. Roblin et al. showed that lower doses of azathioprine worked equally well for ADA prevention with infliximab. More studies on this topic should be conducted in the future. However, it has been shown that lower doses of methotrexate suffice for prevention of immunogenicity in rheumatic diseases [73].

This study has several strengths. To our knowledge this is the first comprehensive systematic review and meta-analysis studying immunogenicity and comparing monotherapy with combination therapy in IBD patients. An extensive literature search was conducted and all available biologics for treatment of IBD were evaluated. In doing so, we highlighted several knowledge gaps that need to be addressed in the future. This review also has some limitations. Firstly, the search was conducted in April 2020. New data may have become available in the meantime, especially regarding newer agents. Given the scale of this project it was not possible to finish the manuscript within one year after the search. Therefore, this review should be updated in the future when more data regarding the newer agents has become available. Furthermore, ADA formation was not the primary outcome in any of the studies. As a result, many studies reported on ADA formation in a smaller subset of patients with available blood samples and not in the entire cohort which could potentially lead to over or underestimation of ADA rates. Additionally, factors such as the amount of blood samples taken, the time-points for measuring, assay types, and treatment duration were not always comparable across studies. Moreover, in the older studies with infliximab, patients were treated episodically, resulting in higher immunogenicity rates which is not applicable to the scheduled treatment regimens used today. Such heterogeneity has likely influenced the results of the meta-analysis. Nevertheless, we believe that most evidence was sufficient to draw reliable conclusions regarding ADA formation and combination therapy with immunomodulators.

In conclusion, our analyses showed that combination therapy reduced ADA formation for most biologics for which data were available. The protective effect of combination therapy on ADA formation may be greater for those biologics with higher immunogenic potential and thus the risks associated with combination therapy may not outweigh the potential benefits for newer, less immunogenic agents. Combination therapy for a subsequent biologic

agent should be considered when switching from a biologic agent in a sensitized patient because of persistent loss of response and presence of ADA. Future studies should focus on harmonizing ADA assays, determining clinically relevant concentration cut-offs for ADA and optimal dosing of immunomodulators to prevent ADA formation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CEP: is an employee of Robarts Clinical Trials, Inc.

JFB: has served as speaker for Abbvie, Merck, Sharp & Dome, Takeda and Tillotts.

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All data will be made available.

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Key findings:

Differences in analytical methods to detect anti-drug antibodies (ADA) hamper comparison of true ADA rates across biologics in IBD.

Use of combination therapy with immunomodulators appeared to reduce ADA positivity for most biologics.

For infliximab, ADA were associated with reduced drug efficacy and increased adverse events. This could not be assessed for other agents due to lack of data.

Future studies should focus on harmonizing ADA assays, determining clinically relevant concentration cut-offs for ADA and optimal dosing of immunomodulators to prevent ADA formation.

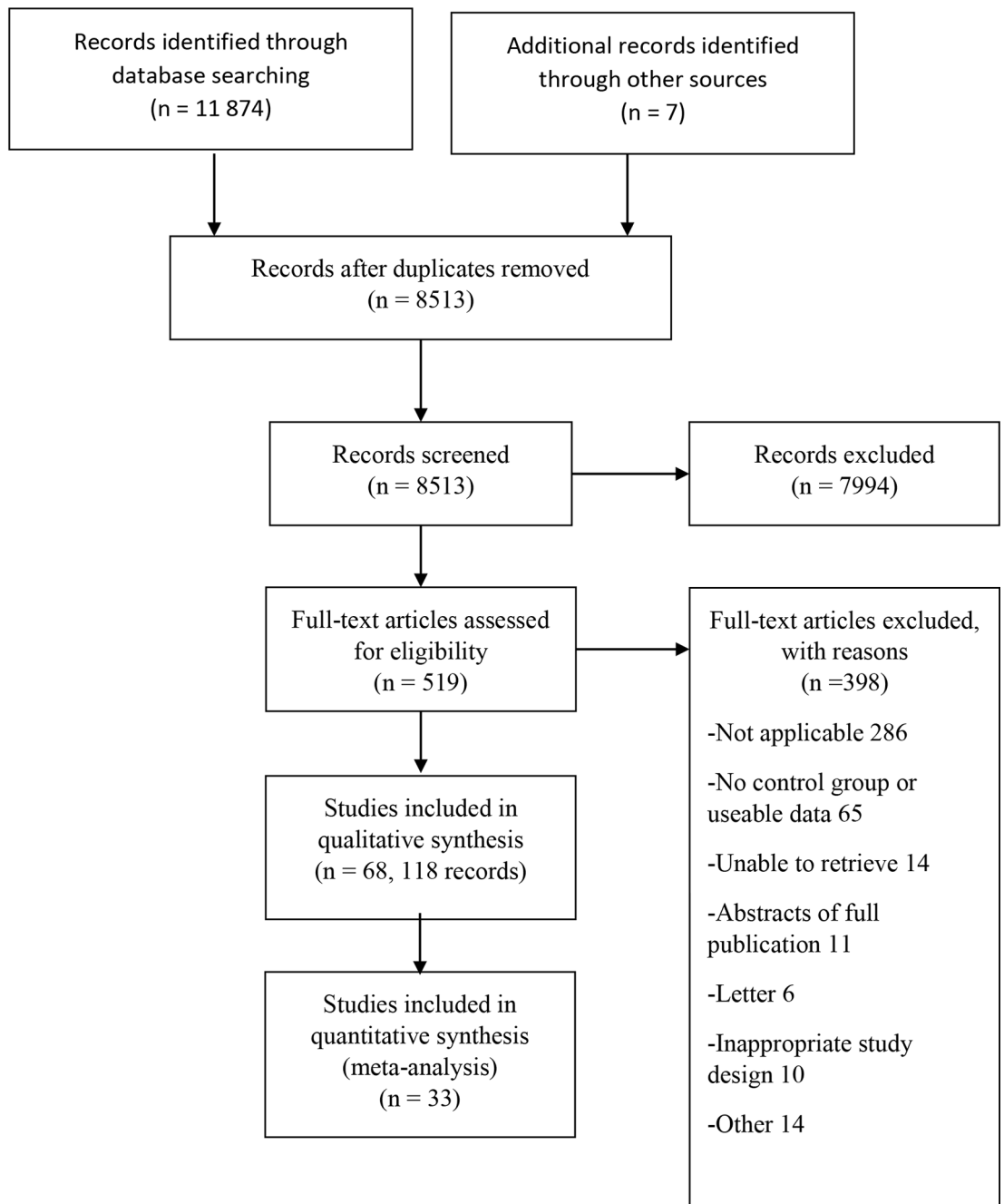


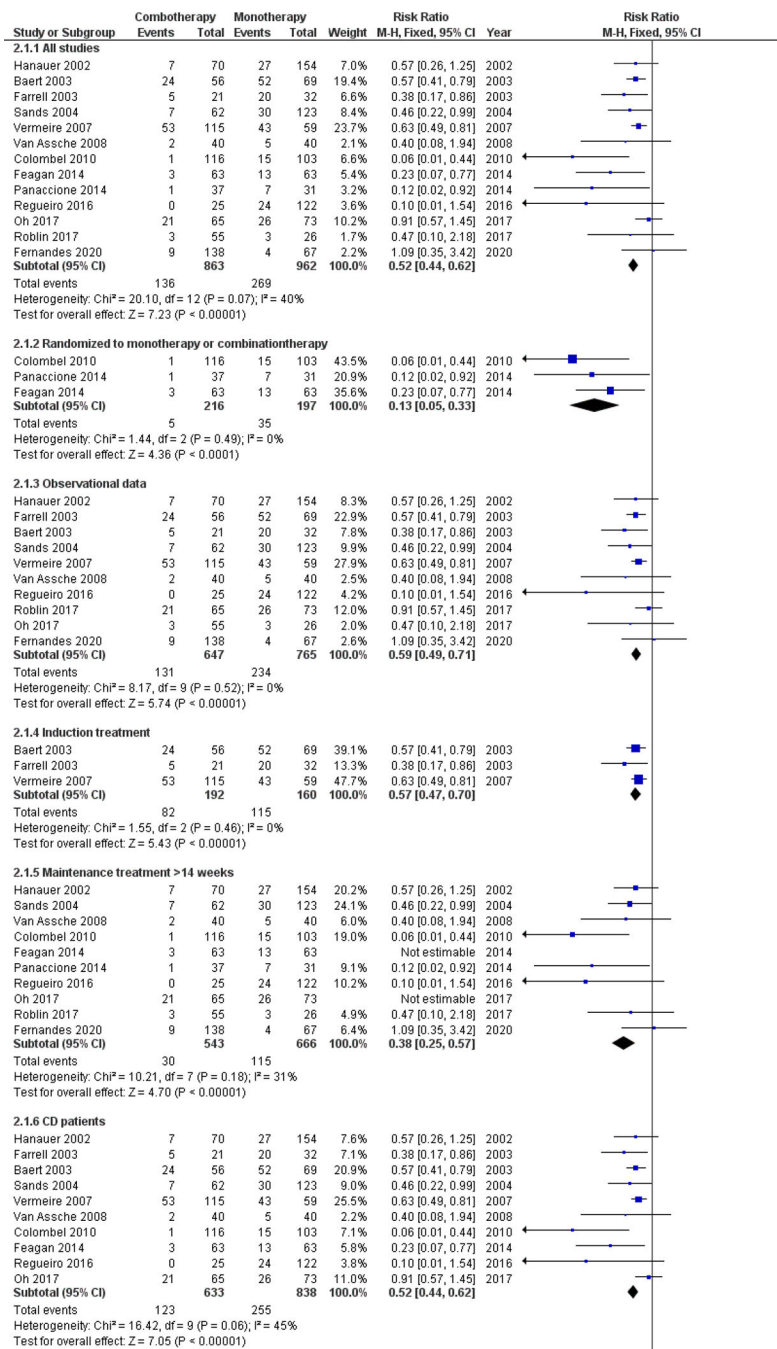
Figure 1:
PRISMA Flow Diagram

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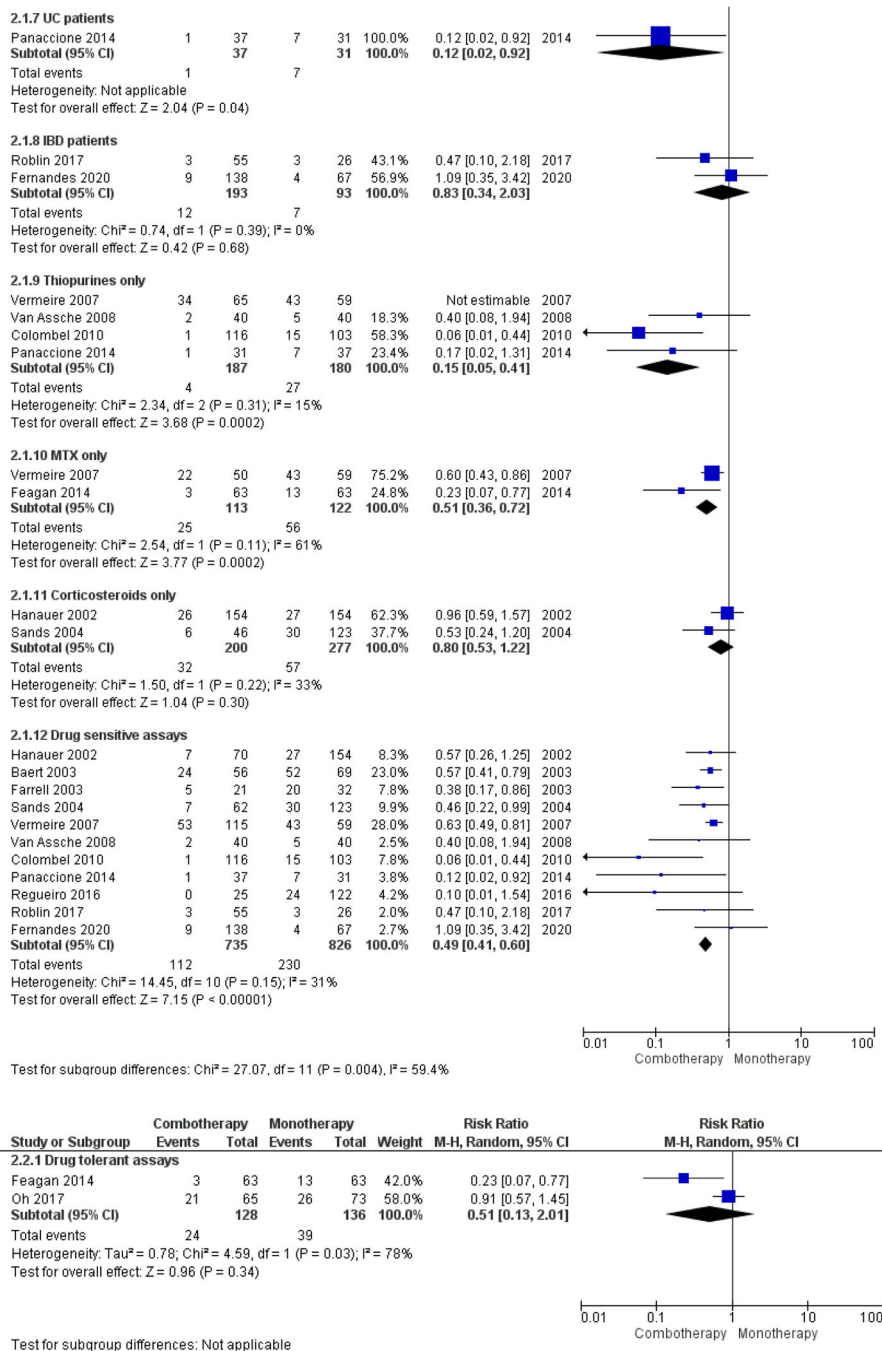


Figure 2:
 ADA formation in infliximab combo- versus monotherapy.
 IBD: inflammatory bowel disease; CD: Crohn’s disease; UC: ulcerative colitis; MTX: methotrexate.

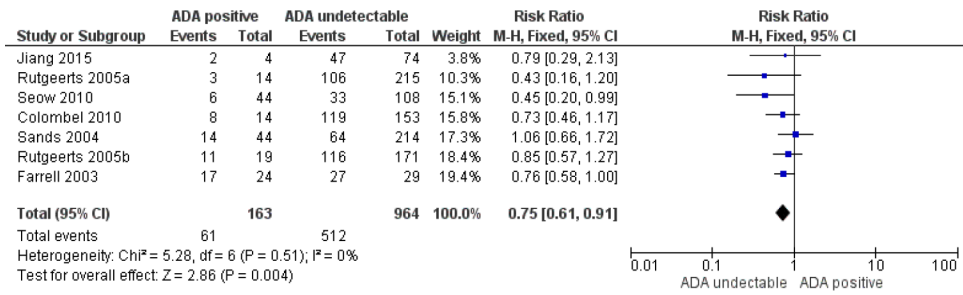


Figure 3:
Clinical response to infliximab in patients with positive versus undetectable ADA.

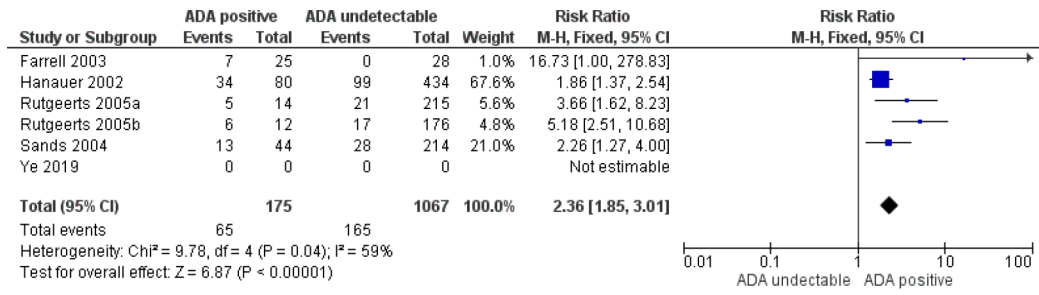


Figure 4:
 Infusions reactions in infliximab treated patients with positive versus undetectable ADA.

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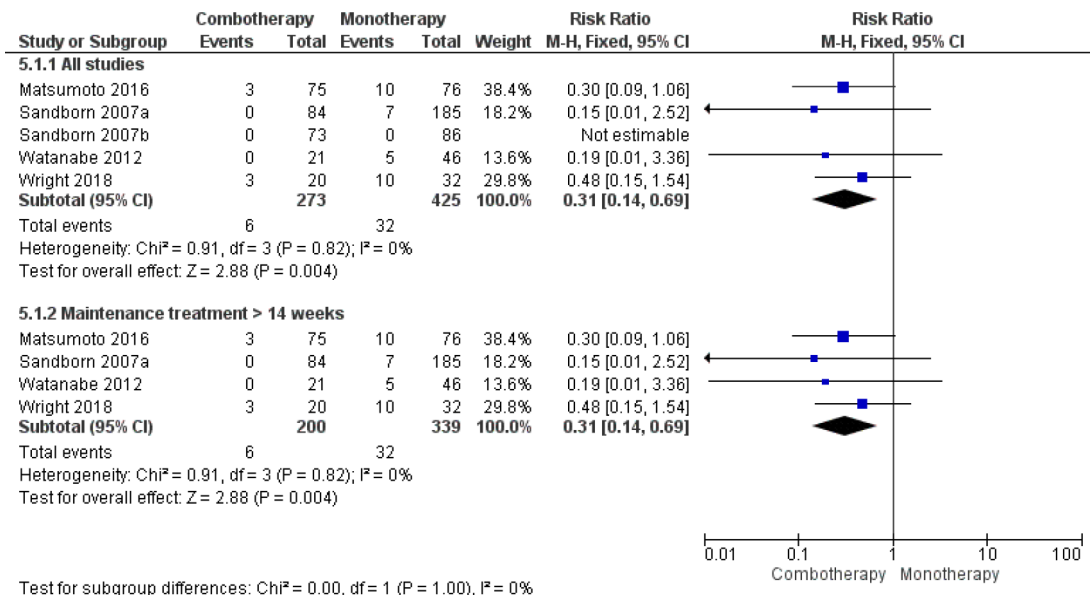


Figure 5:
ADA formation in adalimumab combo- versus monotherapy.

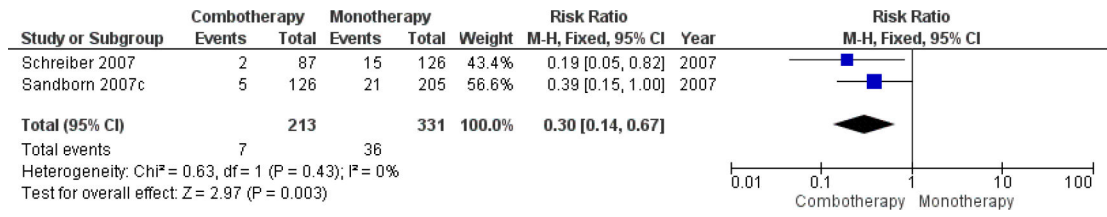


Figure 6:
ADA formation in certolizumab pegol combo- versus monotherapy.

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Table 1:

Summary of findings

Outcome	Studies (N)	Participants (N)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Reporting bias	Pooled RR (95% CI, p)	Quality
Comparison: Infliximab combination therapy vs. infliximab monotherapy									
ADA formation (all studies)	13	1825	High	Low	No indirectness	405 events	None	0.52 (0.44, 0.62; p<0.001)	⊕⊕⊕⊕ High
ADA formation (randomized to monotherapy or combination therapy)	3	413	Low	No	No indirectness	40 events	None	0.13 (0.05, 0.33; p<0.001)	⊕⊕⊕⊕ Moderate ¹
ADA formation (observational data)	10	1412	High	No	No indirectness	365 events	None	0.59 (0.49, 0.71; p<0.001)	⊕⊕⊕⊕ High
ADA formation (induction treatment)	3	352	High	No	No indirectness	197 events	None	0.57 (0.47, 0.70; p<0.001)	⊕⊕⊕⊕ Moderate ¹
ADA formation (maintenance treatment)	10	1473	High	Moderate	No indirectness	208 events	None	0.47 (0.35, 0.63; p<0.001)	⊕⊕⊕⊕ Moderate ¹
ADA formation (CD patients)	10	1471	High	Low	No indirectness	378 events	None	0.52 (0.44, 0.62; p<0.001)	⊕⊕⊕⊕ High
ADA formation (UC patients)	1	68	Low	Not applicable	Not applicable	8 events	None	0.12 (0.02, 0.92; p=0.04)	⊕⊕⊕⊕ Low ²
ADA formation (IBD patients)	2	286	High	No	No indirectness	19 events	None	0.83 (0.34, 2.03; p=0.68)	⊕⊕⊕⊕ Low ²
ADA formation (Thiopurines only)	4	491	High	Moderate	No indirectness	108 events	None	0.50 (0.37, 0.67; p<0.001)	⊕⊕⊕⊕ Moderate ¹
ADA formation (MTX only)	2	235	High	Moderate	No indirectness	81 events	None	0.51 (0.36, 0.72; p<0.001)	⊕⊕⊕⊕ Moderate ¹
ADA formation (Corticosteroids only)	2	477	Low	Low	No indirectness	89 events	None	0.80 (0.53, 1.22; p=0.30)	⊕⊕⊕⊕ Moderate ¹
ADA formation (Drug sensitive assays)	11	1561	High	Low	No indirectness	342 events	None	0.49 (0.41, 0.60; p<0.001)	⊕⊕⊕⊕ High
ADA formation (Drug tolerant assays)	2	264	High	High	No indirectness	63 events	None	0.67 (0.44, 1.04; p=0.07)	⊕⊕⊕⊕ Low ³

Outcome	Studies (N)	Participants (N)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Reporting bias	Pooled RR (95% CI, p)	Quality
Comparison: Infliximab ADA positive vs ADA undetectable									
Clinical response	7	1127	High	No	No indirectness	573 events	None	0.75 (0.61, 0.91; p=0.004)	⊕⊕⊕⊕ High
Infusion reactions	5	1242	Low	Moderate	No indirectness	230 events	None	2.36 (1.85, 3.01; p<0.001)	⊕⊕⊕⊕ Moderate ^I
Comparison: Adalimumab combination therapy vs. adalimumab monotherapy									
ADA formation (all data)	5	698	Low	No	No indirectness	38 events	None	0.34 (0.16, 0.75; p=0.007)	⊕⊕⊕⊕ Moderate ^I
ADA formation (maintenance treatment)	4	539	Low	No	No indirectness	38 events	None	0.31 (0.14, 0.69; p=0.004)	⊕⊕⊕⊕ Moderate ^I
Comparison: Golimumab combination therapy vs. golimumab monotherapy									
ADA formation	1	1103	Low	Not applicable	Not applicable	32 events	None	0.29 (0.10, 0.83; p=0.02)	⊕⊕⊕⊕ Moderate
Comparison: Golimumab ADA positive vs ADA undetectable									
Clinical response (week 6)	1	720	Low	Not applicable	Not applicable	374 events	None	1.26 (0.91, 1.75; p=0.17)	⊕⊕⊕⊕ High
Clinical response (week 54)	1	263	Low	Not applicable	Not applicable	146 events	None	0.51 (0.16, 1.65; p=0.26)	⊕⊕⊕⊕ Moderate ^I
Clinical remission (week 6)	1	720	Low	Not applicable	Not applicable	135 events	None	1.35 (0.62, 2.92; p=0.45)	⊕⊕⊕⊕ Moderate ^I
Clinical remission (week 54)	1	263	Low	Not applicable	Not applicable	77 events	None	0.48 (0.08, 2.98; p=0.43)	⊕⊕⊕⊕ Moderate ^I
Mucosal healing (week 6)	1	720	Low	Not applicable	Not applicable	316 events	None	1.26 (0.84, 1.89; p=0.26)	⊕⊕⊕⊕ High
Mucosal healing (week 54)	1	263	Low	Not applicable	Not applicable	127 events	None	0.59 (0.18, 1.90; p=0.37)	⊕⊕⊕⊕ Moderate ^I
Comparison: Certolizumab pegol combination therapy vs. certolizumab pegol monotherapy									
ADA formation (all data)	2	1139	Low	Low	No indirectness	43 events	None	0.30 (0.14, 0.67; p=0.003)	⊕⊕⊕⊕ Moderate ^I
Comparison: Ustekinumab combination therapy vs. ustekinumab monotherapy									

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Outcome	Studies (N)	Participants (N)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Reporting bias	Pooled RR (95% CI, p)	Quality
ADA formation (all data)	2	917	Low	Low	No indirectness	50 events	None	0.59 (0.30, 1.18; p<0.13)	⊕⊕⊕⊖ ¹ Moderate
Comparison: Natalizumab combination therapy vs. natalizumab monotherapy									
ADA formation (all data)	3	763	Low	No	No indirectness	70 events	None	0.17 (0.08, 0.38; p<0.001)	⊕⊕⊕⊖ ¹ Moderate

¹Downgraded 1 level due to sparse data

²Downgraded 2 levels due to sparse data

³Downgraded 2 levels due to sparse data & high heterogeneity

ADA: anti-drug antibodies; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; MTX: methotrexate.