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# Has the therapeutical ceiling been reached in Crohn's disease randomized controlled trials? A systematic review and meta-analysis

Fernando Magro[1,2,3,4,5,6] | Paula Leão Moreira[2] | Gaia Catalano[7] | Catarina Alves[8] | Joana Roseira[9,10] | Maria Manuela Estevinho[11] | Isabel Silva[2] | Axel Dignass[12] | Laurent Peyrin-Biroulet[13] | Silvio Danese[14] | Vipul Jairath[15,16,17] | Claudia Camila Dias[4,18] | Mafalda Santiago[4,6]

[1]Department of Gastroenterology, São João University Hospital Center, Porto, Portugal

[2]Clinical Pharmacology Unit, São João University Hospital Center, Porto, Portugal

[3]Department of Biomedicine, Unit of Pharmacology and Therapeutics, Faculty of Medicine, University of Porto, Porto, Portugal

[4]CINTESIS—Center for Health Technology and Services Research, Porto, Portugal

[5]RISE—Health Research Network, Porto, Portugal

[6]GEDII—Portuguese Inflammatory Bowel Disease Study Group, Porto, Portugal

[7]Università Vita-Salute San Raffaele, Milan, Italy

[8]Faculty of Medicine, University of Porto, Porto, Portugal

[9]Gastroenterology Department, Algarve University Hospital Center, Faro, Portugal

[10]ABC—Algarve Biomedical Center, Loulé, Portugal

[11]Department of Gastroenterology, Centro Hospitalar de Vila Nova de Gaia/Espinho EPE, Vila Nova de Gaia, Portugal

[12]Department of Medicine I, Agaplesion Markus Hospital, Goethe-University, Frankfurt Am Main, Germany

[13]Department of Gastroenterology and Inserm NGERE U1256, University Hospital of Nancy, University of Lorraine, Nancy, France

[14]Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milan, Italy

[15]Department of Medicine, Division of Gastroenterology, Western University, London, Ontario, Canada

[16]Lawson Health Research Institute, Western University, London, Ontario, Canada

[17]Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada

[18]MEDCIDS - Department of Community Medicine, Information and Health Decision Sciences, Faculty of Medicine, University of Porto, Porto, Portugal

**Correspondence**
Fernando Magro, Department of Biomedicine, Unit of Pharmacology and Therapeutics, Faculty of Medicine, University of Porto, Rua Plácido Costa, 4200-450, Porto, Portugal.
Email: fm@med.up.pt

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GEDII - Portuguese Inflammatory Bowel Disease Study Group, Portugal

## Abstract

**Background and Aims:** The availability of biological agents for inflammatory bowel disease has increased over the past years. In this systematic review and meta-analysis, we aimed to explore time trends in clinical response and clinical remission rates in Crohn's disease (CD) patients treated with biologics while discussing the need for new strategies.

Fernando Magro and Paula Leão Moreira share first co-authorship.

**Methods:** MEDLINE, Cochrane, and ISI Web of Science databases were searched for randomized placebo-controlled trials with biological agents in moderate-to-severe CD patients. Sub-group and meta-regression analyses compared treatment and placebo by calculating the pooled odds ratios of clinical remission and clinical response, across time categories and publication year. We also estimated the proportion of patients achieving clinical remission and clinical response by comparing both groups according to the publication year.

**Results:** Twenty-five trials were included in the systematic review, which enrolled 8879 patients between 1997 and 2022. The clinical remission and clinical response odds, in induction and maintenance, have been constant over time, as no statistically significant differences were found between time categories (interaction *p*-values: clinical remission [induction, $p = 0.19$; maintenance, $p = 0.24$]; clinical response [induction, $p = 0.43$; maintenance, $p = 0.59$]). In meta-regression analyses, publication year did not influence these outcomes (clinical remission [induction, OR 1.01 {95% CI 0.97–1.05}, $p = 0.72$; clinical response [induction, OR 1.01{95% CI 0.97–1.04]; $p = 0.63$; maintenance, OR 1.03{95% CI 0.98–1.07}; $p = 0.21$]), with the exception of clinical remission in maintenance studies, which presented a decreased effect (odds ratio 0.97{95% CI 0.94–1.00}, $p = 0.03$]).

**Conclusions:** Our review highlights that the odds of clinical outcomes in CD patients receiving biological treatment relative to placebo have been stable in the last decades.

**KEYWORDS**
biologics, clinical remission, clinical response, Crohn's disease, meta-analysis, randomized controlled trial, RCT, systematic review, therapeutical ceiling, therapy

## INTRODUCTION

Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and Ulcerative Colitis (UC), have been treated with biologics for more than 20 years.[1] The first biological agent tested and approved for IBD treatment was infliximab, an anti-tumor necrosis factor (anti-TNF) compound.[2] At that time, clinical response and remission results were substantially better than those of conventional therapies, hailing a new era of improved outcomes for patients with IBD.[3] Over the last decade, the number of biological agents with alternative mechanisms of action has gradually increased, resulting in considerable number of therapeutic options for patients with IBD.[3,4] For CD, these include anti-TNF agents (infliximab, adalimumab, and certolizumab pegol), anti-integrin agents (vedolizumab), and, most recently, selective monoclonal antibodies for different interleukins, such as ustekinumab (IL-12/23), risankizumab (IL-23), guselkumab and mirikizumab (IL-23).[5,6] The latter three are still under development for the adult IBD population. In addition, some biosimilar agents are now also available.[5–7]

The relatively recent advent of new biological drugs and biosimilars has revolutionized IBD treatment, allowing for a treat-to-target approach made possible by more effective treatments. However, some authors[8–10] have proposed that current therapies for IBD are suboptimal as the rates of clinical remission (particularly with anti-TNF agents) have shown a ceiling effect.

We conducted a systematic review and meta-analysis to assess time trends in clinical response and remission in CD patients treated with biologics and to evaluate the evidence supporting the need for new treatment strategies.

**Key summary**

**Summarise the established knowledge on this subject**

- The availability of biological agents for Crohn's disease patients has increased over the past years and this study aims to explore time trends in clinical response and remission rates.

**What are the significant and/or new findings of this study?**

- Our review highlights that the odds of clinical outcomes in CD patients receiving biological treatment relative to placebo have been stable in the last decades.
- It remains to be determined the specific reasons leading to the therapeutic ceiling.

## METHODS

### Search strategy

This systematic review and meta-analysis was registered with PROSPERO (CRD42022292527) and designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[11] MEDLINE (via PubMed), Cochrane, and ISI Web of Science databases were searched from inception to 15 March 2022, with the following keywords or medical subject heading (MeSH) terms (Crohn's disease [MeSH Terms] odds ratio (OR) Crohn's disease OR IBD [MeSH Terms]) AND (randomized controlled trial OR trial OR randomized clinical trial (RCT)) AND (biologics OR biological therapy OR infliximab OR anti-TNF OR vedolizumab OR adalimumab OR certolizumab OR ustekinumab OR risankizumab) AND (clinical remission OR clinical response OR endoscopic remission OR biomarkers OR mucosal healing OR histologic remission). No publication date or language restrictions were applied at this stage. We manually searched reference lists to ensure that all relevant articles were identified and included those pertaining to guselkumab, mirikizumab, and upadacitinib.

### Eligibility criteria

Using the PICO (P: Population; I: Intervention; C: Comparison; O: Outcome) model, we searched for phase II or phase III RCTs addressing the induction and maintenance phases of biological treatments (infliximab, adalimumab, certolizumab, vedolizumab, risankizumab, ustekinumab, guselkumab, and mirikizumab) in patients with moderate to severe active Crohn' disease. All studies including biological therapies as a first- or second-line treatment and that achieved positive outcomes (defined as being statistically superior to those observed in the placebo group) were included.

### The selected outcomes were clinical remission and clinical response

The exclusion criteria were (i) systematic reviews, review articles, animal and in vitro studies, guidelines, and editorials; (ii) studies enrolling patients with diseases other than CD; (iii) studies that did not differentiate between CD and UC, in the results; (iv) RCTs that did not test biological treatments; (v) RCTs with active comparator group; (vi) RCTs enrolling pediatric patients; (vii) studies that did not assess the outcomes of interest; and (viii) study reports not written in the English language.

### Study selection and data collection

To begin, titles and abstracts were analyzed, and studies that did not fulfill the eligibility criteria were excluded. Afterwards, the full texts of the remaining studies were evaluated to determine their inclusion or exclusion. Each evaluator (PM and CA) compiled a separate list of articles to be included according to the eligibility criteria. The lists were then compared and disagreements were solved by dialogue and consensus. From each selected study, the following information was collected: authors; trial name; phase of the study (induction or maintenance); period of data collection; publication year; cohort's region/country of origin; the type of treatment (identity of the biologic agent); placebo only; duration of the study; disease duration; number of patients enrolled in the intervention and the placebo groups; definition of clinical remission; clinical remission results at the prefixed timepoints; percentage of patients achieving clinical remission per study group; definition of clinical response; clinical response results at the prefixed timepoints; and percentage of patients achieving a clinical response per study group.

### Outcomes and summary measures

The outcomes were the proportions of clinical remission and clinical response observed in the group treated with the biological drugs compared with those of the placebo group. Clinical remission and clinical response definitions were used as reported in the individual studies. In the event of multiple treatment groups, data were synthesized by combining groups to create a single pair-wise comparison as recommended by Cochrane.[12] This same rule was applied whenever studies did not report global values regarding disease duration; thus, medians were used as a summary measure. In addition, we performed a sub-analysis of the maintenance studies by identifying which presented a funnel approach to the trial design, that is, by not allowing patients who did not achieve the outcomes to continue the study (Supplementary Figure 1). We also performed a sensitivity analysis to check whether prior exposure to biologics (bio-naïve and bio-experienced) affected the overall results.

### Quality assessment

The methodological quality of the studies was determined using the Critical Appraisal Skills Programme checklist.[13] The authors assigned a global quality score based on 11 questions that assessed the validity, results, and applicability of each RCT.

### Statistical analysis

Data were extracted or calculated and the two groups (intervention and placebo) were compared to estimate absolute proportions, OR, and 95% confidence interval (CI) for clinical remission or response. The Mantel–Haenszel random-effect method, which considers variance as a summary of the study-level heterogeneity, was used. Statistical heterogeneity was assessed using the Cochran $\chi 2$ method and the $I^2$ statistic (substantial heterogeneity was assumed if $I^2 > 50\%$). Subgroup analyses were conducted to evaluate time trends according to the following categories: before 2005, between 2005 and 2010, between 2011 and 2015, and after 2015. The category assigned to

each study was based on the time period in which they were conducted. Moreover, by using meta-regression analysis, we tested the effect of the publication year, disease duration, prior anti-TNF exposure, and prior immunomodulator (IM) exposure on the odds of achieving the relevant clinical outcomes. Both the Harbord test and visual analysis of funnel plots were used to detect potential publication bias.[12] A sensitivity analysis was performed to assess the influence of any particular study on the overall results.

In addition, the proportions of outcomes, according to the publication year, were presented graphically using a local regression smoothing technique and 95% confidence intervals. All analyses and charts were made using *R* software (version 4.1.0).

# RESULTS

## Literature search and study selection

The electronic database search yielded 5654 records (2580 records in MEDLINE-Pubmed, 1155 in Cochrane Library, and 1919 in ISI Web of Science); the manual search did not identify any additional studies. After removing duplicates ($n = 998$), 4656 records remained, of which 3316 were excluded. The remaining 106 were assessed for eligibility. Eighty-two studies were excluded following the eligibility assessment, resulting in a total of 25 trials selected for inclusion in the systematic review (Supplementary Figure 2).

## Characteristics of the included studies

The clinical and demographic characteristics of each study are shown in Table 1. Trials' specific findings such as the total number of selected patients, the weeks considered by each study to define the main outcomes, and the final number of patients reaching clinical remission and/or clinical response are reported in Table 2. Like-wise, patients' disease duration is reported in Supplementary Table 1.

Except for two studies,[14,15] all studies were full-text. Although all studies were published from 1997 onwards, the study period ranged from 1995 to 2022. Most were conducted in Europe,[16–27] 12 in the USA,[16–18,20–24,26–29] four in Africa,[16,23–25] five in Asia[17,23,24,30,31] and four in Oceania,[16,22–24] being the majority intercontinental.[16–18,20–27,29,32–38] Overall, the studies enrolled 8879 CD patients, varying from 42[38] to 778[16] patients. When assessing the outcomes, clinical remission was estimated in 25[14–38] studies, while clinical response was assessed in 17[16,17,20,21,23,24,26,28–31,33–38] studies.

## Clinical remission

### Induction

The proportion of patients achieving clinical remission at the end of the induction phase was available in 18[14,15,17,21–23,25,26,28–36,38] studies (Table 2). The pooled OR for achieving clinical remission in induction studies for patients receiving intervention versus placebo was 2.18 (95% CI 1.73–2.74, $I^2 = 46\%$, $p < 0.01$; Figure 1). The odds of achieving clinical remission were constant over time, as we did not observe statistically significant differences across time categories ($p = 0.19$; Figure 1). Additionally, on meta-regression, the year of publication was not a statistically significant covariate for the odds of achieving remission ($p = 0.73$); Figure 2a). Other factors, such as disease duration, prior anti-TNF exposure, and prior IM exposure, were considered in the meta-regression models and none were associated with significant changes in clinical remission during induction. Also, meta-regression performed on bio-naïve or bio-experienced patients separately indicated that the year of publication was not a statistically significant covariate for the odds of achieving remission.

### Maintenance

On the other hand, the pooled OR for clinical remission in maintenance studies (13[16–21,24,27,30,31,33,34,37] studies) was 2.31 (95% CI 1.90–2.82, $I^2 = 40\%$, $p < 0.01$; Figure 3). As in the induction studies, no differences among time categories were observed ($p = 0.24$; Figure 3). However, meta-regression showed a significant impact of the year of publication on the odds of achieving clinical remission ($p = 0.049$), meaning that for every additional year, the effect size of the study is expected to decrease by 0.049 (Figure 2b).

Considering only maintenance studies presenting a funnel approach to the trial design (nine[14,18,20,24,30,31,33,34,37] studies), the pooled OR was 2.11 (95% CI 1.75–2.54, $I^2 = 25\%$, $p < 0.01$, Supplementary Figure 3). Again, no differences between time categories were observed ($p = 0.29$; Supplementary Figure 3). However, the heterogeneity level improved in this group. Focusing on the studies without funneling,[16,19,21,27] the pooled OR was 2.65 (95% CI 1.79–3.93, $I^2 = 60\%$, $p < 0.01$; Supplementary Figure 3). Overall, we did not observe statistically significant differences over time while analyzing each drug individually (Supplementary Figure 4).

The sensitivity analysis approach summarized in Supplementary Table 3 was conducted for clinical remission in both treatment phases (induction and maintenance): five[22,26,28,30,31] and six[16,18,19,30,33,37] bio-naïve studies and eight[21,23,29–31,33,35,36] and five[16,20,30,33,37] bio-experienced studies, respectively. As in the global analyses, there were no differences among time categories according to prior patient experience with biologics. In addition, leave-one-out analyses did not modify global results (Supplementary Figure 5A).

Finally, we plotted OR values across the publication year and observed a consistent decline regardless of the treatment phase (Supplementary Figure 6).

### Intervention versus placebo effect

We also analyzed the proportion of patients achieving clinical remission by comparing the intervention and placebo groups

**TABLE 1** Characteristics of the included studies.

| Author, publication year, trial name, *n.* patients ($n = x$) | Study type | Agent (Intervention vs. Comparator) | Treatment phase | Maintenance funnel | Location of centers | Age (mean ± SD) | Duration of follow-up (weeks) | Definition of clinical remission | Definition of clinical response |
|---|---|---|---|---|---|---|---|---|---|
| RCT studies | | | | | | | | | |
| Targan et al. (1997), NA, (107) | Multicenter, double-blind, placebo-controlled trial | Infliximab versus Placebo | Induction | | North America and Europe | I: 37.0 ± 11.8, 39.3 ± 10.6, 36.0 ± 9.7<br>P: 38.5 ± 11.0 | 12 | CDAI < 150 | CDAI reduction ≥70-point from baseline |
| Rutgeerts et al. (1999), NA, (73) | Randomized, double-blind, placebo-controlled, parallel group clinical trial | Infliximab versus Placebo | Maintenance | ✓ | North America and Europe | 35 (20–65)[a] | 44 | CDAI < 150 | CDAI reduction ≥70-point from baseline |
| Hanauer et al. (2002), ACCENT I, (335) | Multicentre, randomised, double-blind trial | Infliximab versus Placebo | Maintenance | ✓ | North America, Europe, and Israel | 35 (28–46)[a] | 30 | CDAI < 150 | NA |
| Winter et al. (2004), NA, (50) | Phase II, single-dose, randomized, double-blind, placebo-controlled, parallel-group, multicentre study | Certolizumab pegol versus Placebo | Induction | | Six countries | I: 36.5 (31–42), 36.4 (21–61), 40.3 (18–64), 33.3 (19–60)<br>P: 32.2 (18–56)[b] | 12 | CDAI ≤ 150 | CDAI score of ≥100 points |
| Schreiber et al. (2005), NA, (291) | Phase II, multicenter, randomized, double- blind, placebo-controlled, parallel-group, dose-response study | Certolizumab pegol versus Placebo | Induction | | Belgium, Canada, Denmark, Germany, Ireland, Russia, Serbia, South Africa, Sweden, and the United Kingdom | I: 33.5 (18–56), 40.1 (19–71), 35.9 (18–67)<br>P: 35.8 (19–64)[b] | 12 | CDAI ≤ 150 | NA |
| Hanauer et al. (2006), CLASSIC I—(299) | Multicenter, randomized, double-blind, placebo-controlled trial | Adalimumab versus Placebo | Induction | | USA | I: 39 ± 13, 38 ± 12, 39 ± 11<br>P: 37 ± 13 | 4 | CDAI ≤ 150 | CDAI reduction ≥100 points from week 0 |
| Lémann M et al. (2006), NA, (110) | Randomized, multicenter, double-blind, placebo-controlled trial | Infliximab + Azathioprine versus Placebo | Maintenance | | France | I: 26 (22–37), 27 (22–38)<br>P: 29 (23–33), 26 (22–36)[a] | 52 | CDAI ≤ 150 off steroids at week 24 | NA |
| Colombel et al. (2007), CHARM, (778) | Randomized, double-blind, placebo- controlled, multicenter | Adalimumab versus Placebo | Maintenance | | Europe, USA, Canada, Australia, and South Africa | All patients: 37.1 (11.9) | 56 | CDAI ≤ 150 | CDAI reduction ≥100 points from week 0 or CDAI reduction ≥70-point from baseline |
| Schreiber et al. (2007), PRECISE2, (425) | Multicenter, randomized, double-blind, placebo-controlled trial | Certolizumab versus Placebo | Maintenance | ✓ | Worldwide | I: 38 ± 11<br>P: 38 ± 12 | 26 | CDAI ≤ 150 | CDAI score of ≥100 points from baseline |
| Sandborn et al. (2007), NA, (660) | Certolizumab versus Placebo | Certolizumab versus Placebo | Induction + Maintenance | | Worldwide | I: 37 ± 12<br>P: 38 ± 12 | 26 | CDAI ≤ 150 | CDAI score of ≥100 points from baseline |
| Sandborn et al. (2007), NA, (325) | Randomized, double-blind, placebo-controlled trial | Adalimumab versus placebo | Induction | | United States, Canada and Europe | I: 39 ± 12<br>P: 37 ± 12 | 4 | CDAI ≤ 150 | CDAI reduction ≥100 points at week 4 or CDAI reduction ≥70-point from baseline |

**TABLE 1** (Continued)

| Author, publication year, trial name, *n*. patients (*n* = x) | Study type | Agent (Intervention vs. Comparator) | Treatment phase | Maintenance funnel | Location of centers | Age (mean ± SD) | Duration of follow-up (weeks) | Definition of clinical remission | Definition of clinical response |
|---|---|---|---|---|---|---|---|---|---|
| Sandborn et al. (2011), NA, (424) | Multicenter, randomized, double-blind, placebo-controlled trial | Certolizumab versus Placebo | Induction | | Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Re- public, Republic of Estonia, Finland, Germany, Hungary, Israel, Italy, Latvia, New Zealand, Poland, Romania, Russia, Ukraine, and the United States | I: 36.3 ± 12.6<br>P: 38.8 ± 12.8 | 6 | CDAI ≤ 150 | NA |
| Watanabe et al. (2012), NA, (90 I, 50 M) | Randomized, double-blind clinical trials | Adalimumab versus Placebo | Induction + Maintenance | ✓ | Japan | Induction<br>31.1 ± 8.8<br>Maintenance<br>31.2 ± 9.2 | 4 (I), 52 (M) | CDAI < 150 | CDAI decrease of ≥100 from baseline (induction only) |
| Rutgeerts et al. (2012), EXTEND, (129) | Randomized, double-blind, placebo-controlled, maintenance/withdrawal study | Adalimumab versus Placebo | Maintenance | | Europe, USA, and Canada | I: 37.2 (12.6)<br>P: 37.1 (11.1) | 52 | CDAI < 150 | NA |
| Sandborn et al. (2012), NA, (526) | Randomized, double-blind, placebo-controlled phase | Ustekinumab versus Placebo | Induction | | 12 countries | I: 38.8 ± 12.6<br>P: 39.5 ± 13.1 | 8 | CDAI < 150 | CDAI decrease of ≥100 from baseline |
| Sandborn et al. (2013), GEMINI 2, (368 I, 461 M) | Phase 3, randomized, parallel-group, double- blind, placebo-controlled study | Vedolizumab versus Placebo | Induction + Maintenance | ✓ | 39 countries | I: 35.7 ± 11.9<br>P: 38.6 ± 13.2 | 6 (I), 52 (M) | CDAI ≤ 150 | CDAI decrease of ≥100 from baseline |
| Sands et al. (2014), GEMINI 3, (315) | Phase 3, randomized, placebo-controlled, double-blind, multinational, multicenter trial | Vedolizumab versus Placebo | Induction | | North America, Europe, Asia, Africa, and Australia | I: 37.5 (20–69)<br>P: 36.6 (19–77) | 10 | CDAI ≤ 150 | CDAI decrease of ≥100 from baseline |
| Feagan et al. (2016), UNITI-1, 2, IM-UNITI, (741 UNITI-1, 628 UNITI-2, 397 IM-UNITI) | Double-blind, placebo-controlled trials | Ustekinumab versus Placebo | Induction + Maintenance | ✓ | UNITI-1 (23 countries) UNITI-2 (23 countries), IM-UNITI (27 countries) | UNITI-1<br>I: 37.3 ± 12.5, 37.4 ± 11.8<br>P: 37.3 ± 11.8<br>UNITI-2 I: 38.4 ± 13.1, 39.1 ± 13.8 P: 40.2 ± 13.1<br>IM- UNITI<br>I: 37.9 ± 13.2, 38.6 ± 13.7<br>P: 39.5 ± 12.7 | | CDAI < 150 | CDAI decrease of ≥100 from baseline or a CDAI score <150, (induction only) |
| Feagan et al. (2017), NA, (121) | Multicentre, randomised, placebo-controlled, phase 2 study | Rizankizumab versus Placebo | Induction | | 36 referral sites in North America, Europe, and southeast Asia | I: 39 (13)<br>P: 36 (14) | 50 | CDAI ≤ 150 | CDAI <150 or drop >100 |
| Feagan et al. (2017), NA, (62) | Double-blind, open label study | Rizankizumab versus Placebo | Maintenance | ✓ | Not reported | NA | 52 | CDAI < 150 | NA |
| Feagan et al. (2019), NA, (80) | Randomized, double-blind, placebo-controlled induction phase of the trial. | Risankizumab versus Placebo | Induction | | Not reported | NA | 12 | Stool frequency (SF) ≤2.8 and abdominal pain (AP) ≤1 | NA |

(Continues)

**TABLE 1** (Continued)

| Author, publication year, trial name, n. patients (n = x) | Study type | Agent (Intervention vs. Comparator) | Treatment phase | Maintenance funnel | Location of centers | Age (mean ± SD) | Duration of follow-up (weeks) | Definition of clinical remission | Definition of clinical response |
|---|---|---|---|---|---|---|---|---|---|
| Watanabe et al. (2020), NA, (157 I, 24 M) | Phase 3 randomized, double-blind, placebo-con- trolled, parallel group study | Vedolizumab versus. Placebo | Induction + Maintenance | ✓ | Japan | Induction I: 33.9 (12.3) P: 32.6 (10.9)<br>Maintenance I: 36.7 (16.8) P: 35.2 (13.0) | 60 | CDAI ≤ 150 | CDAI decrease of ≥ 100 from baseline |
| Vermeire et al. (2022), VISIBLE 2, (410) | Randomized, double-blind, placebo- controlled, phase 3 trial | Vedolizumab versus Placebo | Maintenance | ✓ | 30 countries | I: 38.2 (13.9)<br>P: 36.1 (12.9) | 50 | CDAI ≤ 150 | CDAI decrease of ≥100 from baseline |
| Sandborn et al. (2022), GALAXI-1, (494) | Phase 2, randomized, double-blind, placebo- and active-controlled, multicenter study | Guselkumab versus Placebo | Induction | | 32 countries | I: 40.3 (13.67)<br>P: 38.9 (12.95) | 12 | CDAI < 150 | CDAI decrease of ≥100 from baseline or CDAI score <150 |
| Sands et al. (2022), NA, (191) | Multicenter, randomized, parallel-arm, double-blind, placebo (PBO)-controlled trial | Mirikizumab versus Placebo | Induction | | 14 countries | I: 38.1 (11.8), 40.4 (13.3), 37.7 (13.1)<br>P: 39.0 (13.0) | 52 | CDAI < 150 | CDAI decrease of ≥100 from baseline or CDAI score <150 |

Abbreviations: CDAI, Crohn's disease activity index; I, Intervention; NA, Not applicable; P, Placebo; SD, Standard deviation.

[a]Results expressed in median (25%–75% interquartile range).

[b]Mean (range).

according to the publication year. The resulted evidenced contrasting behaviors in induction and maintenance studies. The intervention groups presented slightly downward and upward trends in induction and maintenance studies, respectively, while in the placebo groups, we observed an increasing proportion in both phases (Supplementary Figure 7).

Moreover, we displayed proportion values by publication year and disease duration and found mostly constant levels (horizontal sheet), regardless of the administration group and study phase (Supplementary Figure 8).

## Clinical response

### Induction

The proportion of patients achieving a clinical response at the end of the induction phase was available in 16[14,17,20,21,23,26,28–36,38] studies (Supplementary Table 2). The pooled OR for clinical response in patients receiving intervention versus those under placebo was 2.27 (95% CI 1.83–2.81, $I^2 = 54\%$, $p < 0.01$, Figure 4). The odds of response in induction studies were constant over time as no statistically significant differences were observed across time categories ($p = 0.43$; Figure 4). Accordingly, meta-regression analysis showed no effect of publication year on the results ($p = 0.52$; Figure 5a).

### Maintenance

Regarding maintenance studies (seven[16,20,21,24,30,34,37] studies), the pooled OR for clinical response was 2.18 (95% CI 1.59–2.99, $I^2 = 70\%$, $p < 0.01$, Figure 6). As in the induction studies, there were no differences among time categories ($p = 0.59$, Figure 6). Additionally, meta-regression was not statistically significant for publication year ($p = 0.32$; Figure 5b).

Focusing only on maintenance studies showing a funnel strategy (five[20,24,30,34,37] studies), the pooled OR was 2.18 (95% CI 1.46–3.28, $I^2 = 63\%$, $p < 0.01$, Supplementary Figure 9). Likewise, no differences between time categories were observed ($p = 0.24$; Supplementary Figure 9). However, the heterogeneity level decreased in this group compared with Figure 6. Overall, we did not observe significant differences between time categories while analyzing each drug separately (Supplementary Figure 10).

The same sensitivity analyses reported above for clinical remission (Supplementary Table 3) were performed also for clinical response induction (bio-naïve six[21,26,28,30,31,33] studies; bio-experienced nine[21,23,29–33,35,36] studies) and maintenance (bio-naïve three[21,24,30] studies; bio-experienced six[16,20,24,30,32,37] studies). As for clinical remission, there were no differences among time categories according to prior patient experience with biologics.

In addition, leave-one-out analyses did not affect the overall results (Supplementary Figure 5B).

**TABLE 2** Results and number of patients

| Author, publication year, trial name, *n.* patients ($n = x$) | Agent (Treatment vs. Comparator) | Treatment phase (Funnel:✓) | Total number of patients (T vs. C) | Week | Number of patients achieving clinical remission (T vs. C) | Number of patients achieving clinical response (T vs. C) |
|---|---|---|---|---|---|---|
| Targan et al., 1997, NA, (107) | Infliximab versus placebo | Induction | T: 83<br>C: 24 | Crem: w4<br>Cresp: w4 | T: 27<br>C: 1 | T: 54<br>C: 4 |
| Rutgeerts et al.,1999, NA, (73) | Infliximab versus placebo | Maintenance (✓) | T: 37<br>C: 36 | Crem: w44<br>Cresp: w44 | T: 19<br>C: 7 | T: 22<br>C: 13 |
| Hanauer et al., 2002, ACCENT I, (335) | Infliximab versus placebo | Maintenance (✓) | T: 225<br>C: 110 | Crem: w30<br>Cresp: NA | T: 94<br>C: 23 | NA |
| Winter et al., 2004, NA, (50) | Certolizumab pegol | Induction | T: 17<br>C: 25 | Crem: w2<br>Cresp: w4 | T: 8<br>C: 4 | T: 39<br>C: 11 |
| Schreiber et al., 2005, NA, (291) | Certolizumab pegol versus placebo | Induction | T: 218<br>C: 73 | Crem: w2<br>Cresp: NA | T: 68<br>C: 11 | NA |
| Hanauer et al, 2006, CLASSIC I—(299) | Adalimumab versus placebo | Induction | T: 225<br>C: 74 | Crem: w4<br>Cresp: w4 | T: 58<br>C: 9 | T: 93<br>C: 19 |
| Lémann M et al., 2006, NA, (110) | Infliximab + Azathioprine versus placebo | Maintenance | T: 57<br>C: 56 | Crem: w24<br>Cresp: NA | T: 31<br>C: 15 | NA |
| Sandborn et al., 2007, NA, (660) | Certolizumab versus placebo | Induction | T: 331<br>C: 329 | Crem: w6<br>Cresp: w6 | T: 71<br>C: 57 | T: 112<br>C: 89 |
| Sandborn et al., 2007, NA, (660) | Certolizumab versus placebo | Maintenance | T: 331<br>C: 329 | Crem: w26<br>Cresp: NA | T: 96<br>C: 59 | NA |
| Colombel et al., 2007, CHARM, (778) | Adalimumab versus placebo | Maintenance | T: 517<br>C: 261 | Crem: w26<br>Cresp: w26 | T: 224<br>P: 44 | T: 273<br>C: 69 |
| Schreiber et al., 2007, PRECISE2, (425) | Certolizumab versus placebo | Maintenanance (✓) | T: 215<br>C: 210 | Crem: w26<br>Cresp: w26 | T: 103<br>C: 61 | T: 135<br>C: 76 |
| Sandborn et al., 2007, NA, (325) | Adalimumab versus placebo | Induction | T: 159<br>C: 166 | Crem: w4<br>Cresp: w4 | T: 34<br>C: 12 | T: 61<br>C: 41 |
| Sandborn et al., 2011, NA, (424) | Certolizumab versus placebo | Induction | T: 215<br>C: 209 | Crem: w6<br>Cresp: NA | T: 68<br>C: 53 | NA |

(Continues)

**TABLE 2** (Continued)

| Author, publication year, trial name, *n.* patients (*n* = *x*) | Agent (Treatment vs. Comparator) | Treatment phase (Funnel:✓) | Total number of patients (T vs. C) | Week | Number of patients achieving clinical remission (T vs. C) | Number of patients achieving clinical response (T vs. C) |
|---|---|---|---|---|---|---|
| Watanabe et al., 2011, NA, (90 I) | Adalimumab versus placebo | Induction | T: 67<br>C: 23 | Crem: w4<br>Cresp: w4 | T: 17<br>C: 3 | T: 32<br>C: 4 |
| Watanabe et al., 2011, NA, (50 M) | Adalimumab versus placebo | Maintenance (✓) | T: 25<br>C: 25 | Crem: w52<br>Cresp: NA | T: 10<br>C: 2 | NA |
| Rutgeerts et al., 2012, EXTEND, (129) | Adalimumab versus placebo | Maintenance | T: 65<br>C: 64 | Crem: w12<br>Cresp: NA | T: 30<br>C: 18 | NA |
| Sandborn et al., 2012, NA, (526) | Ustekinumab versus placebo | Induction | T: 394<br>C: 132 | Crem: w6<br>Cresp: w6 | T: 58<br>C: 14 | T: 145<br>C: 31 |
| Sandborn W et al., 2013, GEMINI 2, (368 I) | Vedolizumab versus placebo | Induction | T: 220<br>C: 148 | Crem: w6<br>Cresp: w6 | T: 32<br>C: 10 | T: 69<br>C: 38 |
| Sandborn W et al., 2013, GEMINI 2, (461 M) | Vedolizumab versus placebo | Maintenance (✓) | T: 308<br>C: 153 | Crem: w52<br>Cresp: w52 | T: 116<br>C: 33 | T: 137<br>C: 46 |
| Sands et al., 2014, GEMINI 3, (315) | Vedolizumab versus placebo | Induction | T: 158<br>C: 157 | Crem: w6<br>Cresp: w6 | T: 24<br>C: 19 | T: 62<br>C: 35 |
| Feagan BG et al., 2016, UNITI-1, (741 UNITI-1) | Ustekinumab versus placebo | Induction | T: 494<br>C: 247 | Crem: w8<br>Cresp: w6 | T: 85<br>C: 22 | T: 168<br>C: 53 |
| Feagan BG et al., 2016, UNITI-2, (628 UNITI-2) | Ustekinumab versus placebo | Induction | T: 418<br>C: 210 | Crem: w8<br>Cresp: w6 | T: 148<br>C: 41 | T: 224<br>C: 60 |
| Feagan BG et al., 2016, IM-UNITI, (397 IM-UNITI) | Ustekinumab versus placebo | Maintenance (✓) | T: 264<br>C: 133 | Crem: w44<br>Cresp: NA | T: 134<br>C: 48 | NA |
| Feagan BG et al., 2017, NA, (121) | Rizankizumab versus placebo | Induction | T: 82<br>C: 39 | Crem: w12<br>Cresp: w50 | T: 23<br>C: 6 | T: 32<br>C: 8 |
| Feagan BG et al., 2017, NA, (62) | Rizankizumab versus placebo | Maintenance | T: 68<br>C: 33 | Crem: w52<br>Cresp: NA | T: 29<br>C: 15 | NA |
| Feagan BG et al., 2019, NA, (80) | Risankizumab versus placebo | Induction | T: 40<br>C: 40 | Crem: w12<br>Cresp: NA | T: 10<br>C: 2 | NA |

TABLE 2 (Continued)

| Author, publication year, trial name, *n*. patients (*n* = *x*) | Agent (Treatment vs. Comparator) | Treatment phase (Funnel:✓) | Total number of patients (T vs. C) | Week | Number of patients achieving clinical remission (T vs. C) | Number of patients achieving clinical response (T vs. C) |
|---|---|---|---|---|---|---|
| Watanabe et al., 2020, NA, (157) | Vedolizumab versus placebo | Induction | T: 79<br>C: 78 | Crem: w6<br>Cresp: w6 | T: 11<br>C: 10 | T: 19<br>C: 10 |
| Watanabe et al., 2020, NA, (24) | Vedolizumab versus placebo | Maintenance (✓) | T: 12<br>C: 12 | Crem: w60<br>Cresp: w60 | T: 5<br>C: 2 | T: 7<br>C: 1 |
| Vermeire et al., 2021, VISIBLE 2, (410) | Vedolizumab versus placebo | Maintenance (✓) | T: 275<br>C: 135 | Crem: w52<br>Cresp: w52 | T: 132<br>C: 46 | T: 143<br>C: 60 |
| Sandborn et al., 2022, GALAXI-1, (494) | Gulsekumab versus Gulsekumab | Induction | T: 185<br>C: 61 | Crem: w12<br>Cresp: w12 | T: 98<br>C: 10 | T: 122<br>C: 15 |
| Sands et al, 2022, NA, (191 I) | Mirikizumab versus placebo | Induction | T: 127<br>C: 64 | Crem: w12<br>Cresp: w12 | T: 35<br>C: 6 | T: 60<br>C: 15 |

Abbreviations: C, Comparator; Crem, Clinical Remssion; CResp, Clinical Response; I, Induction; M, Maintenance; NA, Not available; T, Treatment.

Finally, we plotted OR values throughout publication years, showing distinct trends in both treatment phases (Supplementary Figure 11). However, the increasing slope observed in the maintenance group is driven solely by the Targan *et al.* 1997 trial.[26]

### Intervention versus placebo effect

As for clinical remission, we also looked at the proportion of patients achieving a clinical response by comparing intervention and placebo groups across publication years and found comparable trends in induction and maintenance studies. Both intervention and placebo groups presented downward slopes regardless of the study phase (Supplementary Figure 12).

In addition, we plotted proportion values according to publication year and disease duration and observed mostly constant levels (horizontal sheet) despite the administration group or study phase (Supplementary Figure 13).

## Quality of studies and publication bias

The risk of bias assessment was low (green dots) for most studies. Overall, the reporting quality was adequate. Nevertheless, some doubts persisted regarding the identification and control of confounding factors, as portrayed by the yellow dots. Also, the extrapolation to the general population was limited (Supplementary Table 2).

Regarding the meta-analyses, the funnel plot suggested a low risk of publication bias for both clinical outcomes (Harbord test not significant and even scattering to both sides; Supplementary Figure 14).

## DISCUSSION

This systematic review and meta-analysis reviewed RCT presenting results for clinical remission and response of moderate-to-severe CD patients treated with biological agents. The primary aim of the study was to determine whether there was a relative difference between active drugs and placebo over time. In addition, we included disease duration in the analysis to assess how this variable affected clinical outcomes after an increasing course of biological treatment administration.

No differences in terms of clinical outcomes (response or remission) were identified across temporal categories in both induction and maintenance phases.

Moreover, the comparison between the intervention and the placebo groups does not appear to be affected by the publication year. However, a progressive narrowing of the difference between active treatment and placebo can be observed, especially in clinical remission in maintenance studies, which aligns with our meta-regression results. A sensitivity analysis clarified that different covariates, such as bio-naïve patients or bio-experienced patients, do

| Study or sub group | Intervention Events | Intervention Total | Placebo Events | Placebo Total | Weight | Odds Ratio MH, Random, 95% CI |
|---|---|---|---|---|---|---|
| Years = <2005 | | | | | | |
| Hanauer et al., 2006 | 58 | 225 | 9 | 74 | 5.5% | 2.51 [1.17; 5.35] |
| Schreiber et al; 2005 | 68 | 218 | 11 | 73 | 6.0% | 2.56 [1.27; 5.16] |
| Targan et al., 1997 | 27 | 83 | 1 | 24 | 1.2% | 11.09 [1.42; 86.49] |
| Winter et al., 2004 | 8 | 17 | 4 | 25 | 2.2% | 4.67 [1.11; 19.54] |
| Total (95% CI) | | | | | | |
| Heterogeneity: $Tau^2 = 0.0001$; $Chi^2 = 2.33$, df = 3 (P = 0.51); $I^2 = 0\%$ | | | | | | |
| Years = 2005-2010 | | | | | | |
| Sandborn et al., 2007 | 71 | 331 | 57 | 329 | 9.9% | 1.30 [0.88; 1.92] |
| Sandborn et al., 2007 | 34 | 159 | 12 | 166 | 6.1% | 3.49 [1.73; 7.02] |
| Sandborn et al., 2011 | 68 | 215 | 53 | 209 | 9.4% | 1.36 [0.89; 2.08] |
| Sandborn et al., 2012 | 58 | 394 | 14 | 132 | 6.9% | 1.45 [0.78; 2.71] |
| Sandborn et al., 2013 | 32 | 220 | 10 | 148 | 5.7% | 2.35 [1.12; 4.94] |
| Watanabe et al., 2012 | 17 | 67 | 3 | 23 | 2.5% | 2.27 [0.60; 8.59] |
| Total (95% CI) | | 1386 | | 1007 | 40.4% | 1.71 [1.24; 2.35] |
| Heterogeneity: $Tau^2 = 0.0601$; $Chi^2 = 7.79$, df = 5 (P = 0.17); $I^2 = 36\%$ | | | | | | |
| Years = 2011-2015 | | | | | | |
| Feagan et al., 2016 | 85 | 494 | 22 | 247 | 8.4% | 2.13 [1.29; 3.49] |
| Feagan et al., 2016 | 148 | 418 | 41 | 210 | 9.8% | 2.26 [1.52; 3.36] |
| Feagan et al., 2017 | 23 | 82 | 6 | 39 | 3.9% | 2.14 [0.79; 5.80] |
| Sands et al., 2014 | 24 | 158 | 19 | 157 | 6.6% | 1.30 0.68; 2.48] |
| Total (95% CI) | | 1152 | | 653 | 28.6% | 2.01 [1.54; 2.63] |
| Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.14$, df = 3 (P = 0.54); $I^2 = 0\%$ | | | | | | |
| Years = 2015 | | | | | | |
| Feagan et al., 2019 | 10 | 40 | 2 | 40 | 1.8% | 6.33 [1.29; 31.11] |
| Sands et al., 2014 | 35 | 127 | 6 | 64 | 4.3% | 3.68 [1.46; 9.29] |
| Watanabe et al., 2020 | 11 | 79 | 10 | 78 | 4.3% | 1.10 [0.44; 2.76] |
| Sandborn et al., 2022 | 98 | 185 | 10 | 61 | 5.7% | 5.74 [2.75; 12.00] |
| Total (95% CI) | | 431 | | 243 | 16.1% | 3.33 [1.47; 7.50] |
| Heterogeneity: $Tau^2 = 0.4223$; $Chi^2 = 8.34$, df = 3 (P = 0.04); $I^2 = 64\%$ | | | | | | |
| **Total (95% CI)** | | **3512** | | **2099** | **100.0%** | **2.18 [1.73; 2.74]** |
| Heterogeneity: $Tau^2 = 0.1007$; $chi^2 = 31.65$, df = 17 (P < 0.02); $I^2 = 46\%$ | | | | | | |
| Test for overall effect: Z = 6.61 (P < 0.01) | | | | | | |
| Test for subgroup differences: $Chi^2 = 4.79$, df = 3 (P = 0.19) | | | | | | |

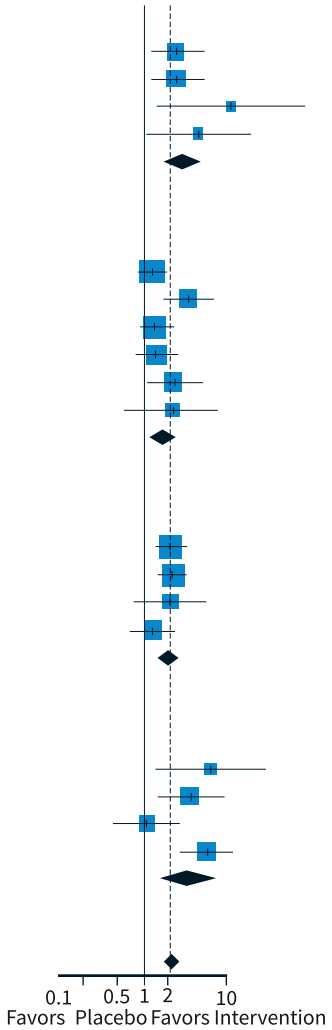


**FIGURE 1** Pooled odds ratio (OR) for clinical remission across time categories in induction studies. CI: Confidence interval; MH: Mantel–Haenszel.

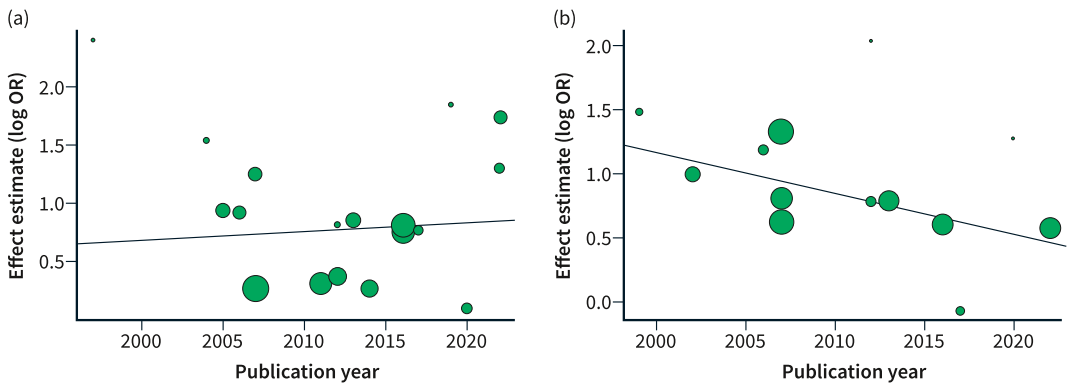


**FIGURE 2** Impact of publication year on effect estimates for the odds of achieving clinical remission in: (a) Induction studies; (b) Maintenance studies. The size of the circles is proportional to the weight of the individual publication. OR, Odds Ratio.

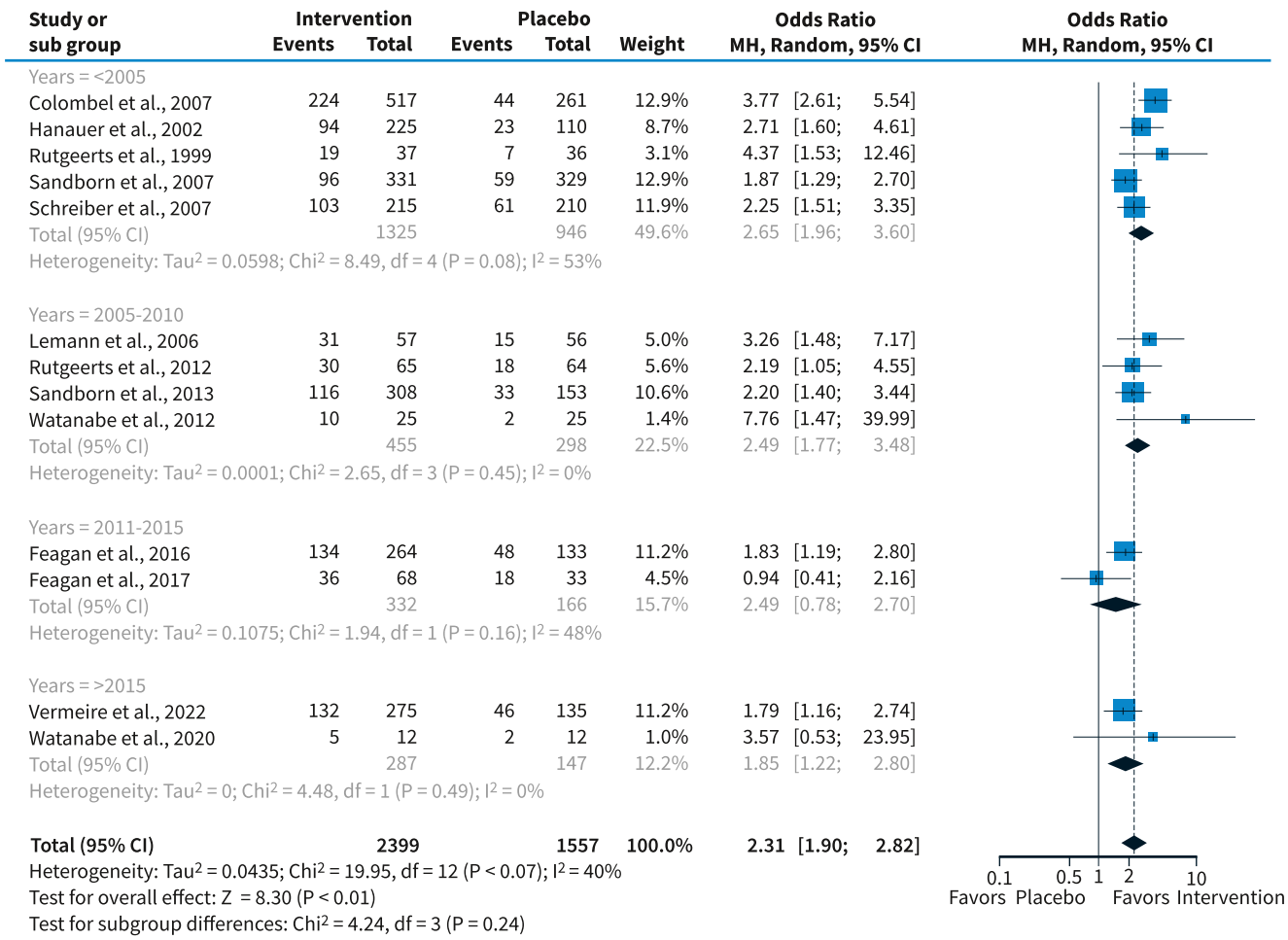


**FIGURE 3** Pooled odds ratio (OR) for clinical remission across time categories in maintenance studies. CI, Confidence interval; MH, Mantel–Haenszel.

not have a relative influence on the effect estimates of the study. Even though the findings are consistent with the primary analysis, a careful interpretation is warranted as not all studies included information about the outcomes in this subgroup of patients.

As mentioned before, these results compared with placebo in the ideal, not real-world, setting of an RCT have not changed over time. These results shall be confirmed through future studies in a real-world setting. Even though the results are in agreement with previous reports,[10] they may be explained by the following considerations: (i) despite the recent enrichment of the therapeutic armamentarium, CD remains a progressive, long-standing disease; (ii) patients are known to become refractory to different lines of treatment over time, both in monotherapy or in combination with immunomodulators. A recent study by Ben-Horin and colleagues[10] linked longer disease durations (above 18 months) with lower rates of induction of remission in CD patients receiving either biologics or placebo therapy.

In addition, despite the recent trend to favor a treat-to-target approach, in which a specific effort is made to change the natural history of the disease via a step-by-step achievement of previously defined clinical outcomes, the outcomes reported in clinical trials are still outdated and based mainly on subjective measurements such as the Crohn's Disease Activity Index (CDAI) score. These measurements are prone to bias from patients reporting their own symptoms and likely to be influenced by their expectations regarding the progress of the disease.[39] Nevertheless, since these outcomes have been consistently used in the literature, their inclusion enables longitudinal analyses, consequently increasing the study's statistical power. Additional factors may have influenced the result of this review and meta-analysis: (i) the differences in assessing clinical remission and response in CD patients over time; (ii) even though the design of clinical trials has evolved over time to overcome the heterogeneity of patients' characteristics, study populations may remain non-comparable, for example, due to the inclusion of patients pre-treated with several medications such as distinct biologics; and (iii) the inclusion of patients with different disease duration and with mostly active IBD due to strict inclusion parameters with objective validation of active inflammation, in recent years. All these issues may have resulted in lower response or remission rates over time. More sub-analyses could have been relevant for the overall analysis, but this was not possible as only global baseline characteristics of each study patient population

| Study or sub group | Intervention Events | Total | Placebo Events | Total | Weight | Odds Ratio MH, Random, 95% CI |
|---|---|---|---|---|---|---|
| Years = <2005 | | | | | | |
| Hanauer et al., 2006 | 93 | 225 | 19 | 74 | 6.6% | 2.04 [1.14; 3.66] |
| Rutgeerts et al., 1999 | 22 | 36 | 13 | 37 | 3.6% | 2.90 [1.12; 7.51] |
| Sandborn et al., 2007 | 112 | 331 | 89 | 328 | 9.9% | 1.37 [0.98; 1.92] |
| Targan et al., 1997 | 54 | 83 | 4 | 24 | 2.7% | 9.31 [2.91; 29.83] |
| Winter et al., 2004 | 39 | 66 | 11 | 24 | 3.7% | 1.71 [0.67; 4.37] |
| Total (95% CI) | | 741 | | 487 | 26.5% | 2.29 [1.32; 3.98] |
| Heterogeneity: $Tau^2 = 0.2419$; $Chi^2 = 11.3$, df = 4 (P = 0.02); $I^2 = 65\%$ | | | | | | |
| Years = 2005-2010 | | | | | | |
| Sandborn et al., 2012 | 145 | 394 | 31 | 132 | 8.3% | 1.90 [1.21; 2.98] |
| Watanabe et al., 2012 | 32 | 67 | 4 | 23 | 2.6% | 4.34 [1.33; 14.13] |
| Sandborn et al., 2007 | 61 | 159 | 41 | 166 | 7.9% | 1.90 [0.18; 3.05] |
| Total (95% CI) | | 620 | | 321 | 18.8% | 2.01 [1.47; 2.76] |
| Heterogeneity: $Tau^2 = 0.0001$; $Chi^2 = 1.76$, df = 2 (P = 0.42); $I^2 = 0\%$ | | | | | | |
| Years = 2011-2015 | | | | | | |
| Feagan et al., 2016 | 168 | 494 | 53 | 247 | 9.6% | 1.89 [1.32; 2.68] |
| Feagan et al., 2016 | 224 | 418 | 60 | 210 | 9.6% | 2.89 [2.02; 4.12] |
| Feagan et al., 2017 | 32 | 82 | 8 | 39 | 4.0% | 2.48 [1.01; 6.07] |
| Sandborn et al., 2013 | 69 | 220 | 38 | 148 | 8.1% | 1.32 [0.83; 2.11] |
| Sands et al., 2014 | 62 | 158 | 35 | 157 | 7.7% | 2.25 [1.37; 3.69] |
| Total (95% CI) | | 1372 | | 801 | 38.9% | 2.08 [1.56; 2.77] |
| Heterogeneity: $Tau^2 = 0.0501$; $Chi^2 = 7.41$, df = 4 (P = 0.12); $I^2 = 46\%$ | | | | | | |
| Years = >2015 | | | | | | |
| Sands et al., 2022 | 60 | 127 | 15 | 64 | 5.7% | 2.93 [1.49; 5.75] |
| Watanabe et al., 2020 | 19 | 79 | 10 | 78 | 4.3% | 2.15 [0.93; 4.99] |
| Sandborn et al., 2022 | 122 | 185 | 15 | 61 | 5.8% | 5.94 [3.08; 11.46] |
| Total (95% CI) | | 391 | | 203 | 15.8% | 3.47 [1.93; 6.26] |
| Heterogeneity: $Tau^2 = 0.1363$; $Chi^2 = 4.03$, df = 2 (P = 0.13); $I^2 = 50\%$ | | | | | | |
| **Total (95% CI)** | | **3124** | | **1812** | **100.0%** | **2.27 [1.83; 2.81]** |
| Heterogeneity: $Tau^2 = 0.0901$; $Chi^2 = 32.93$, df = 15 (P < 0.01); $I^2 = 54\%$ | | | | | | |
| Test for overall effect: Z = 7.54 (P < 0.01) | | | | | | |
| Test for subgroup differences: $Chi^2 = 2.77$, df = 3 (P = 0.43) | | | | | | |

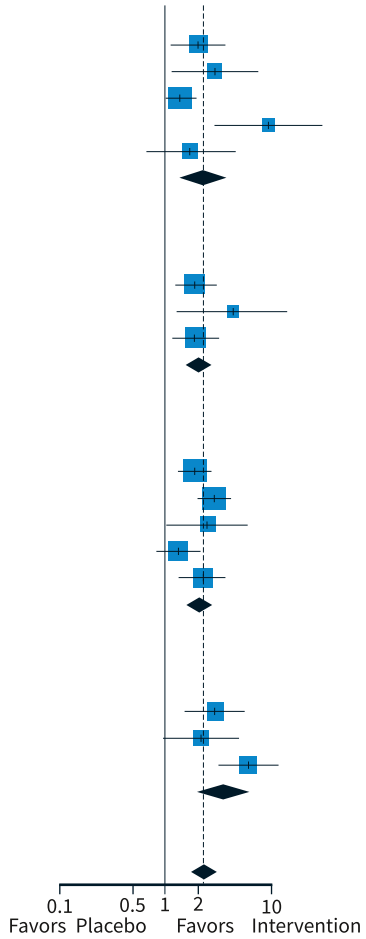


**FIGURE 4** Pooled odds ratio (OR) for clinical response across time categories in induction studies. CI, confidence interval; MH, Mantel–Haenszel.

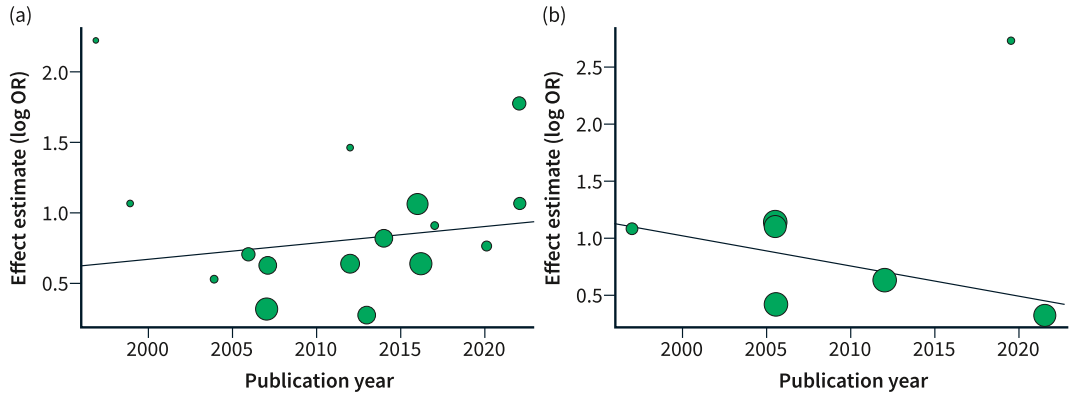


**FIGURE 5** Impact of publication year on effect estimates for the odds of achieving clinical response in: (a) Induction studies; (b) Maintenance studies. The size of the circles is proportional to the weight of the individual publication. OR, Odds Ratio.

were available. Comparing bio-naïve patients with short disease duration and using standard definitions for response and remission would provide more reliable results, but these data are also unavailable.

This study may also be limited by the disadvantages of most systematic reviews, as the selected search expressions might have missed some studies. In addition, the time categories selected for the meta-analysis could have affected the results; however, we tested

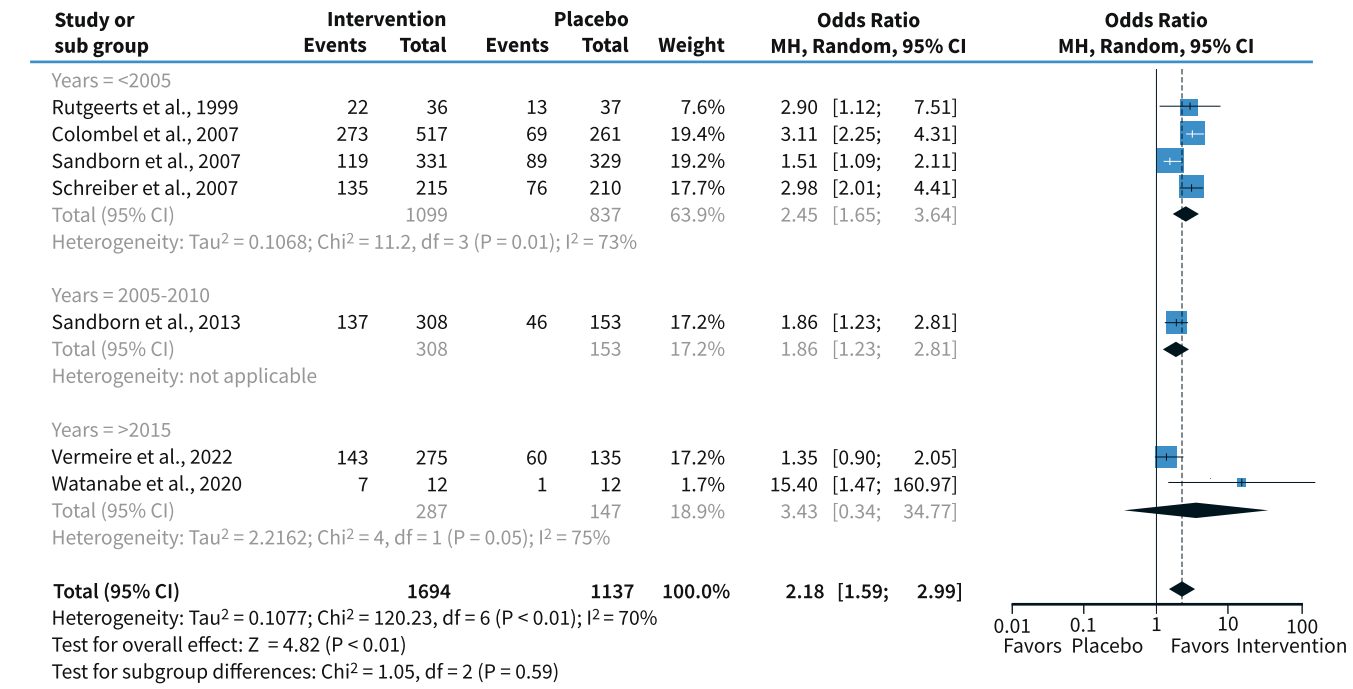


**FIGURE 6** Pooled odds ratio (OR) for clinical response across time categories in maintenance studies. CI, Confidence interval; MH, Mantel–Haenszel.

other pairings, and the results remained similar. It is worth mentioning that in the present analysis, we grouped therapeutic agents with different mechanisms of action within the same category to increase the statistical power. Although we are aware that this could have obscured a potential effect restricted to a specific subcategory of therapeutic agents, adopting such a strategy became unavoidable considering the relative scarcity of relevant studies in the literature. As additional primary studies become available in the future, a more detailed analysis that could potentially uncover such effects may be possible.

In conclusion, the present systematic review highlighted that the achievement of clinical outcomes in CD patients receiving biological treatment has not shown any clear pattern of change over the years. Moreover, specific characteristics, such as disease duration, may not have any noticeable effect. As mentioned before, these results must be interpreted carefully as they were derived only from RCTs, and real-world studies could have provided different results. If the therapeutical ceiling is a reality, it remains to be determined whether it is (i) due to the inability of novel biologic agents to further improve the performance of older drugs; (ii) the result of substandard reporting of clinical outcomes in clinical trials designed to test effectiveness; or (ii) the result of a wrong strategy when compared to treat-to-target or tight control.

To break the therapeutical ceiling in the future, some strategies may be considered: (i) using different outcomes (based on patient-reported outcome and selected composite outcomes) to assess treatment success; (ii) combining biologics/small molecules; (iii) focusing on other treatment targets; (iv) combining drugs and nutrition; and (v) modulating gut microbiota, among others.

## AUTHOR CONTRIBUTIONS

Paula Leão Moreira was involved in data acquisition, analysis, interpretation, and manuscript drafting; Gaia Catalano was involved in data acquisition, interpretation, and manuscript drafting; Catarina Alves, Joana Roseira, and Isabel Silva were involved in data and data acquisition; Mafalda Santiago was involved in data analysis and manuscript drafting; FM coordinated the study's conception and design and was involved in data interpretation, manuscript revision. Laurent Peyrin-Biroulet, Silvio Danese, Vipul Jairath, and Claudia Camila Dias were involved in data interpretation and manuscript revision. All authors approved the final version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

Fernando Magro served as a speaker and received honoraria from Merck Sharp & Dohme, Abbvie, Vifor, Falk, Laboratórios Vitória, Ferring, Hospira, and Biogen; Laurent Peyrin-Biroulet reports personal fees from Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, For-ward Pharma GmbH, Celgene, Biogen, Lycera, and Samsung Biosepsis; Silvio Danese served as a speaker, consultant and advisory board member for Schering-Plough, Abbott (AbbVie)

Laboratories, Merck, UCB Pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alfa Wasserman, Genentech, Grunenthal, Pfizer, AstraZeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor and Johnson and Johnson; Vipul Jairath has received consulting/advisory board fees from AbbVie, Alimentiv Inc (formerly Robarts Clinical Trials), Arena pharmaceuticals, Asahi Kasei Pharma, Asieris, Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring, Flagship Pioneering, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead, Janssen, Merck, Mylan, Pandion, Pendopharm, Pfzer, Protagonist, Reistone Biopharma, Roche, Sandoz, Second Genome, Takeda, Teva, Topivert, and Vividion; speaker's fees from, Abbvie, Ferring, Galapagos, Janssen Pfzer Shire, Takeda, and Fresenius Kabi; Axel Dignass has received has received research support or acted as a principal investigator for Abbvie, Celgene/BMS, Dr Falk Pharma, Gilead/Galapagos, Janssen, Pfizer and Takeda; has acted as a consultant for AbbVie, Amgen, Boehringer Ingelheim, Celgene/BMS, Celltrion, Dr Falk Pharma, Ferring, Fresenius Kabi, Janssen, MSD, Pharmacosmos, Pfizer, Roche, Takeda, Tillotts, and Vifor; and has participated in speaker bureaus for AbbVie, Eli Lilly, Falk Foundation, Ferring, Janssen, MSD, Pharmacosmos, Pfizer, Roche, Takeda, Tillotts, and Vifor; the other authors have no conflict of interests to disclose.

## DATA AVAILABILITY STATEMENT

The data underlying this article will be shared at reasonable request to the corresponding author.

## PROSPERO REGISTRATION

CRD42022292527.

## ORCID

*Fernando Magro* https://orcid.org/0000-0003-2634-9668
*Joana Roseira* https://orcid.org/0000-0002-5098-8729
*Maria Manuela Estevinho* https://orcid.org/0000-0001-7171-0139
*Axel Dignass* https://orcid.org/0000-0002-9724-054X
*Laurent Peyrin-Biroulet* https://orcid.org/0000-0003-2536-6618

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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