SYSTEMATIC REVIEWS AND META-ANALYSES

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Effect of Concomitant Therapy With Steroids and Tumor Necrosis Factor Antagonists for Induction of Remission in Patients With Crohn's Disease: A Systematic Review and Pooled Meta-analysis

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BACKGROUND & AIMS: **It is not clear whether concomitant therapy with corticosteroids and anti-tumor necrosis factor (TNF) agents is more effective at inducing remission in patients with Crohn's disease (CD) than anti-TNF monotherapy. We aimed to determine whether patients with active CD receiving corticosteroids during induction therapy with anti-TNF agents had higher rates of clinical improvement than patients not receiving corticosteroids during induction therapy.**

METHODS: **We systematically searched the MEDLINE, Embase, and CENTRAL databases, through January 20, 2016, for randomized trials of anti-TNF agents approved for treatment of CD and identified 14 trials (5 of adalimumab, 5 of certolizumab, and 4 of infliximab). We conducted a pooled meta-analysis of individual patient and aggregated data from these trials. We compared data from participants who continued oral corticosteroids during induction with anti-TNF therapy to those treated with anti-TNF agents alone. The endpoints were clinical remission (CD activity index [CDAI] scores <150) and clinical response (a decrease in CDAI of 100 points) at the end of induction (weeks 4–14 of treatment).**

RESULTS: **We included 4354 patients who received induction therapy with anti-TNF agents, including 1653 [38.0%] who were receiving corticosteroids. The combination of corticosteroids and an anti-TNF agent induced clinical remission in 32.0% of patients, whereas anti-TNF monotherapy induced clinical remission in 35.5% of patients (odds ratio [OR], 0.93; 95% CI, 0.74–1.17). The combination of corticosteroids and an anti-TNF agent induced a clinical response in 42.7% of patients, whereas anti-TNF monotherapy induced a clinical response in 46.8% (OR 0.84; 95% CI, 0.73–0.96). These findings did not change with adjustment for baseline CDAI scores and concurrent use of immunomodulators.**

CONCLUSIONS: **Based on a meta-analysis of data from randomized trials of anti-TNF therapies in patients with active CD, patients receiving corticosteroids during induction therapy with anti-TNF agents did not have higher rates of clinical improvement compared with patients not receiving corticosteroids during induction therapy. Given these findings and the risks of corticosteroid use, clinicians should consider early weaning of corticosteroids during induction therapy with anti-TNF agents for patients with corticosteroid-refractory CD.**

Keywords: IBD; Biologic; RCT; Inflammatory Bowel Diseases.

[a]Authors share co-first authorship.

Abbreviations used in this paper: CD, Crohn's disease; CDAI, Crohn's disease activity index; CI, confidence interval; IBD, inflammatory bowel disease; IPD, individual participant data; OR, odds ratio; RCT, randomized controlled clinical trial; TNF, tumor necrosis factor.

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Crohn's disease (CD) is an inflammatory bowel disease (IBD) that results in chronic inflammation of the gastrointestinal tract, with periods of remission alternating with relapse.[1] A variety of anti-inflammatory therapies are used in the management of CD, and corticosteroids[2] and biologics targeting tumor necrosis factor-α (anti-TNF agents)[3] are effective at inducing remission in CD. Corticosteroids are among the most commonly used medications in the treatment of CD and are used to induce rapid remission of disease activity.[4,5] In population-based studies, up to 60% of patients with IBD are exposed to corticosteroids within 10 years of diagnosis, without notable decrease since the introduction of biologic therapy.[6–8] However, corticosteroids cause a wide variety of adverse effects,[6,9] and prolonged corticosteroid use in patients with CD has been associated with increased mortality in comparison with patients treated with anti-TNF therapy.[10] Similarly, the combination of corticosteroids with anti-TNF therapy may lead to an increased risk of adverse events. In a pooled analysis of adalimumab studies in CD, concomitant use of corticosteroids was associated with a significantly increased risk of serious infections (hazard ratio, 2.40; 95% confidence interval [CI], 1.33–4.350; $P = .004$).[11] This increased risk from concomitant corticosteroid plus anti-TNF therapy use has been found across different anti-TNF agents and disease processes, including rheumatoid arthritis, psoriasis, and spondyloarthropathies.[12–14]

Whether there is additional symptomatic benefit of continuing corticosteroids in patients starting anti-TNF therapy is an important question that has not been addressed in a prospective trial. Analysis of data from the randomized controlled trial (COMMIT) of infliximab plus prednisone with or without methotrexate in patients with active CD found higher rates of remission in both arms as compared with most prior studies of anti-TNF therapies in CD.[15] The authors hypothesized that using corticosteroids together with infliximab may have resulted in these higher-than-expected remission rates, but this possibility has not been evaluated by a dedicated randomized controlled clinical trial (RCT), and post hoc analyses have been limited and inconsistent.[16,17]

Our objective is to perform a systematic review and meta-analysis of existing induction trials of anti-TNF therapies to assess whether the concomitant use of corticosteroids during induction therapy with anti-TNF results in greater efficacy than anti-TNF monotherapy in patients with active CD. A traditional meta-analysis of RCTs cannot compare the efficacy of concomitant therapy versus monotherapy because published results are in the form of summary estimates, which are not stratified by steroid exposure. Therefore, we requested patient-level data from 3 pharmaceutical companies who served as a sponsor of the eligible RCTs we identified via systematic review. Using these data, we were able to compare clinical outcomes in CD patients treated with anti-TNF therapy plus continued corticosteroids versus anti-TNF monotherapy during induction.

What You Need to Know

Background

Corticosteroids and tumor necrosis factor (TNF) antagonists can induce remission in patients with Crohn's disease (CD). However, it is not clear whether continuing patients on corticosteroids once they begin anti-TNF therapy increases odds of remission.

Findings

A meta-analysis of data from randomized trials showed that the combination of corticosteroids and anti-TNF therapy was no more effective at inducing remission or response than anti-TNF therapy alone. Type of anti-TNF agent, disease activity, and immunomodulator use did not change the study findings.

Implications for patient care

Clinicians should consider early weaning of corticosteroids during induction therapy with anti-TNF agents for patients with active CD despite corticosteroids.

Methods

This study was conducted in accordance with the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[18]

Literature Search

A comprehensive search strategy using both keywords and index terms was executed in the MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases. The search was designed to yield all potential randomized trials related to anti-TNF therapy for CD published between January 1, 1980 and January 20, 2016. The complete search strategy for all databases is available in the Supplementary Appendix. Inclusion criteria included (1) RCTs, (2) studies in the English language, (3) studies that included adults older than 18 years of age, (4) studies with moderate-severe CD patients defined as a Crohn's disease activity index (CDAI) 220–450, (5) studies in which some participants were treated with anti-TNF agents alone and some participants were treated with steroids and anti-TNF concomitant therapy, (6) studies with information on dose and duration of corticosteroid use at induction, and (7) studies with data on clinical remission at weeks 4–14.

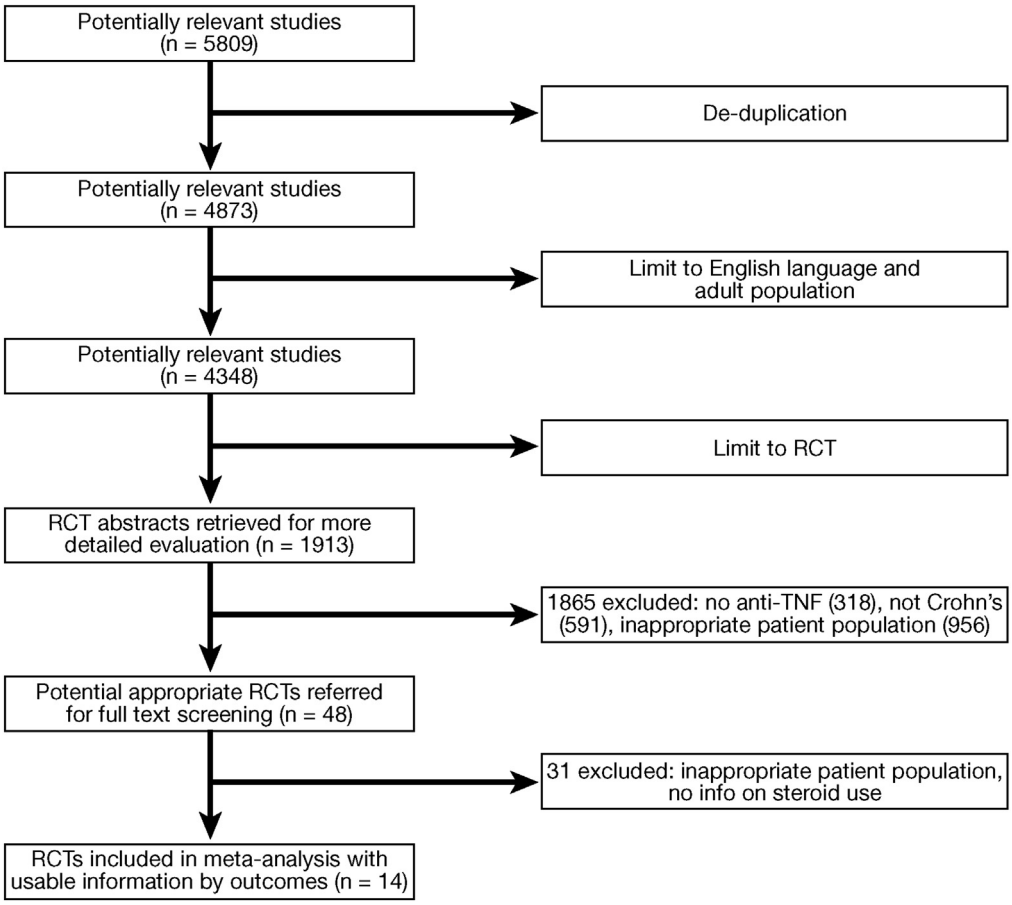


Figure 1. Flow diagram of included studies. RCT, randomized controlled clinical trial; TNF, tumor necrosis factor.

Study Selection and Data Extraction

Study selection was conducted independently by 2 reviewers (E.S., L.K.) in 2 successive rounds. Results were first screened on the basis of their titles and abstracts. All results identified as potentially eligible on the basis of titles and abstracts were advanced to screening on the basis of the full text (Figure 1).

The studies that met the eligibility criteria for inclusion in the analysis are listed in Table 1. Requests were submitted in 2016 to organizations that contained patient-level data for the relevant clinical trials (Yale Open Data Access, UCB, and AbbVie). All relevant data were obtained in 2017.

Individual participant data (IPD) were available for infliximab and adalimumab studies, but only aggregated data could be obtained from the certolizumab studies. To homogenize information across studies with IPD, we accessed the case report forms for each study and extracted steroid medication type, dose and duration of therapy, as well as demographic information. We then calculated average daily dose of steroid treatment throughout induction, according to the tapering schedules of each individual trial. We also calculated CDAI at baseline and at the end of induction, as well as concurrent use of immunomodulator (azathioprine, 6-mercaptopurine, or methotrexate). Studies involving certolizumab were homogeneous in terms of CDAI values, definition of remission/response, and concomitant steroid use.

Outcome Definitions and Statistical Analysis

The primary endpoint, determined a priori, for this meta-analysis was clinical remission, defined as CDAI less than 150 at the end of the induction period, as determined by each individual study (weeks 4–14). The secondary endpoint was clinical response, defined as a decrease in CDAI of 100 points at the end of induction. The odds of remission/response with concomitant steroid use as compared with anti-TNF alone were quantified through the odds ratio (OR) estimated on the intent-to-treat population from each study by using a generalized linear mixed-effect model for binary outcomes. This model used the Mantel-Haenszel method to estimate the overall fixed effects. For each outcome, heterogeneity across studies was quantified by using the Cochran's Q and the I^2 statistic, which summarizes the percentage of variability due to study heterogeneity above chance.[19] A significant Cochran Q test ($P < .05$) with $I^2 > 50\%$ was considered strong evidence of heterogeneity. In the case of significant heterogeneity, the overall pooled summary estimates were obtained by

Table 1. Summary of Studies Included in the Meta-analysis

Author	Study code	Year	Agent	No. of patients	
				Steroids	No steroids
Schreiber et al[23]	C87005	2005	Certolizumab	76	133
Sandborn et al (PRECISE 1)[24]	C87031	2007	Certolizumab	132	199
Schreiber et al (PRECISE 2)[25]	C87032	2007	Certolizumab	251	417
Sandborn et al (WELCOME)[26]	C87042	2010	Certolizumab	235	292
Sandborn et al[27]	C87085	2011	Certolizumab	98	124
Hanauer et al (CLASSIC 1)[28]	M02403	2006	Adalimumab	58	146
Colombel et al (CHARM)[29]	M02404	2007	Adalimumab	279	498
Sandborn et al (GAIN)[16]	M04691	2007	Adalimumab	54	100
Watanabe et al[30]	M04729	2012	Adalimumab	14	50
Rutgeerts et al (EXTEND)[31]	M05769	2012	Adalimumab	31	99
Present et al[32]	C0168T20	1999	Infliximab	21	42
Hanauer et al (ACCENT 1)[33]	C0168T21	2002	Infliximab	201	184
Sands et al (ACCENT 2)[34]	C0168T26	2004	Infliximab	78	204
Colombel et al (SONIC)[35]	C0168T67	2010	Infliximab	125	213
Total n				1653	2701

using a random-effects model; otherwise, a fixed-effects model was used. Forest plots were used to visualize the estimated OR for each study as well as the overall OR. Subgroup analysis for each anti-TNF agent was carried out by using the analysis strategy described above.

The possibility of publication bias was assessed by using a funnel plot.[20] This represents the relationship between treatment effect and study precision, which is quantified by the standard error of the treatment effect in the funnel plot. In the plot, the vertical line represents the estimated common effect. The solid line indicates overall effect from a fixed-effects model, and the dashed line indicates overall effect from a random-effect model. In a funnel plot, a symmetric, inverted funnel shape arises from a "well-behaved" dataset, in which publication bias is unlikely. An asymmetric funnel indicates a relationship between treatment effect estimate and study precision, suggesting the possibility of either publication bias or a systematic difference between studies of higher and lower precision (typically small study effects). Furthermore, a formal statistical test can assess the departure from asymmetry in a funnel plot. Here, we used the Egger test and accepted symmetry when $P > .05$.

To evaluate the impact of steroid dose on outcomes, patients were considered to have high dose steroid exposure if they received the equivalent of $\geq$20 mg daily of prednisone throughout induction; rates of remission and response were compared between low and high exposure groups. Data on steroid dose were only available for adalimumab and certolizumab studies. Stratified analysis was performed to evaluate the effect of steroid adjusted by concurrent immunomodulator use, which was added as a covariate in the generalized linear mixed-effect model. This analysis was only possible for infliximab and adalimumab and required reanalysis from the IPD data. For adalimumab and infliximab studies, meta-regression based on IPD was conducted, adjusting for baseline CDAI score. Statistical analysis was conducted under R environment using packages *meta*[21] and *metafor*[22] among others.

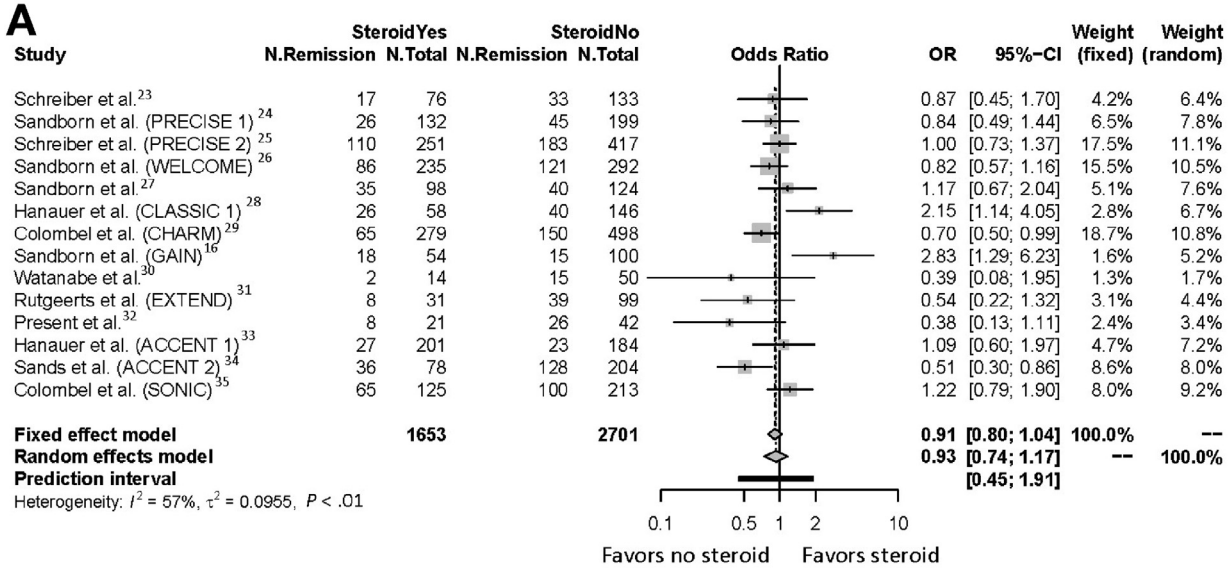
Results

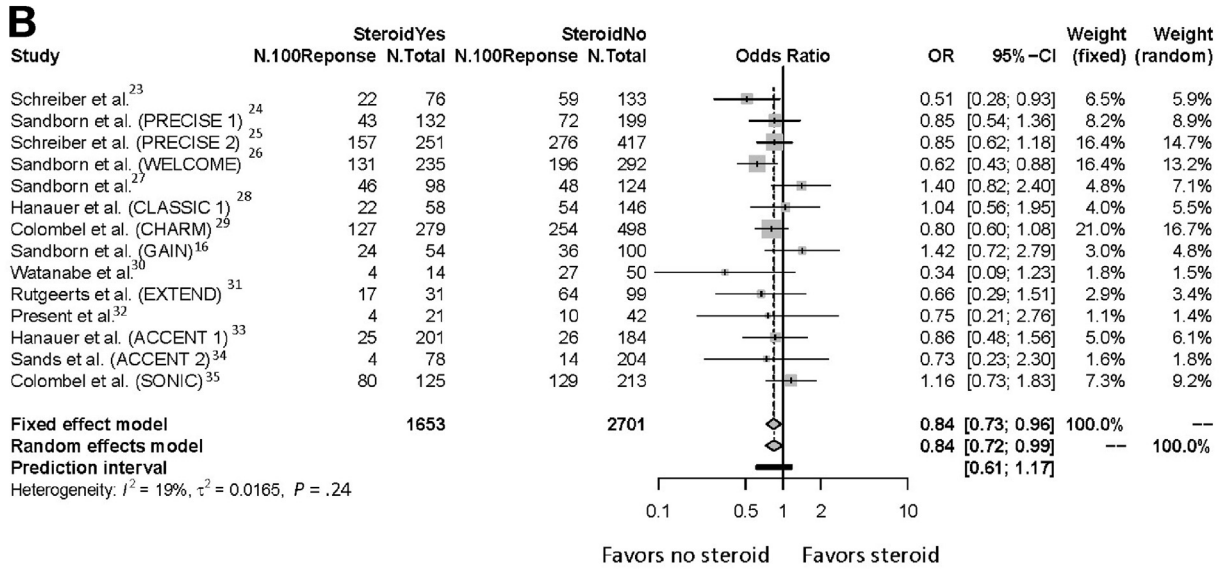
Study Characteristics

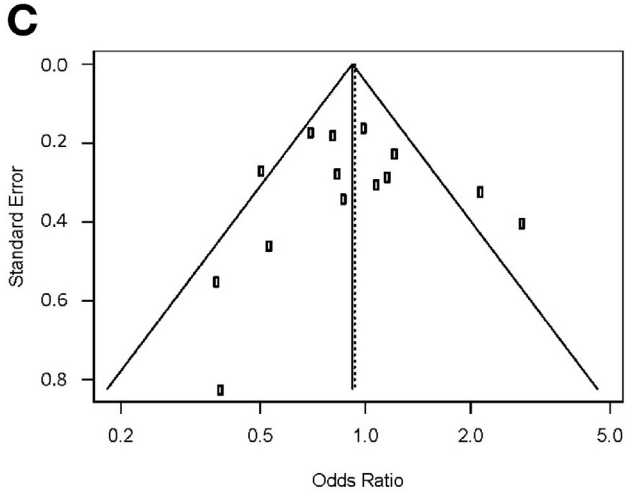
A total of 14 RCTs using anti-TNF agents to treat CD in adults were identified and included in the meta-analysis (Figure 1). Those include 5 studies of certolizumab pegol (Schreiber et al,[23] PRECISE 1[24] and 2,[25] WELCOME,[26] and Sandborn et al[27]), 5 studies of adalimumab (CLASSIC 1,[28] CHARM,[29] GAIN,[16] Watanabe et al,[30] and EXTEND[31]), and 4 studies of infliximab (Present et al,[32] ACCENT 1[33] and 2,[34] and SONIC[35]) (Table 1). Individual participant data were available from the studies with adalimumab and infliximab but not from the 4 studies using certolizumab. The meta-analysis cohort included 2742 patients (62%) treated with anti-TNF therapy alone and 1681 patients (38%) treated with anti-TNF and concomitant corticosteroids.

Clinical Remission

After completion of induction therapy, 32.0% of patients on concomitant steroids plus anti-TNF were in clinical remission versus 35.5% for patients on anti-TNF alone. The overall pooled estimate of the OR of inducing clinical remission between weeks 4–14 in those on concomitant steroids versus those not on steroids was 0.93 (95% confidence interval [CI], 0.74–1.17; $P = .53$) (Figure 2*A*). To address confounding by clinical disease severity at the time of trial entry, data were adjusted for baseline CDAI and confirmed that the odds of inducing clinical remission in patients continued on baseline







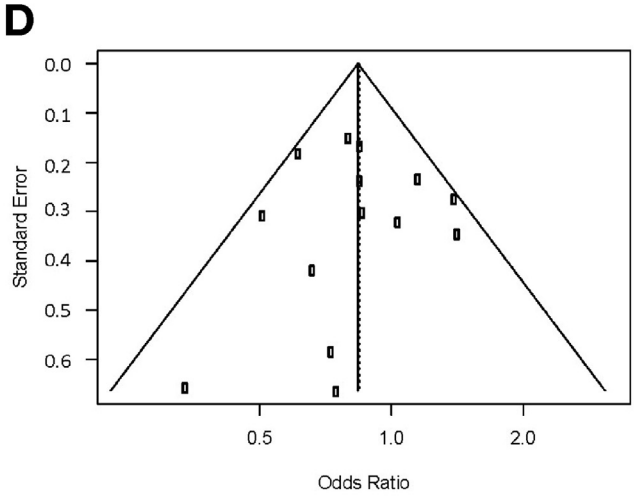


Figure 2. Meta-analysis results. (*A* and *B*) Forest plot quantifying odds ratio of remission (*A*) or clinical response (*B*) of an anti-TNF agent with concomitant use of steroids. (*C* and *D*) Funnel plot evaluating publication bias for remission (*C*) or clinical response (*D*) outcomes. Symmetry of the funnel plot indicated unlikeness of publication bias. CI, confidence interval; OR, odds ratio.

steroids during anti-TNF induction was not higher than in patients treated with anti-TNF therapy alone (OR, 0.96; 95% CI, 0.63–1.48; $P = .86$; available for adalimumab and infliximab studies only, n = 861 for steroid group, n = 1536 for no steroids). The funnel plot showed a nearly symmetric pattern (Figure 2*C*, 6 vs 8 studies on either side), and the Egger test indicated no evidence of asymmetry ($P = .89$). We performed a sensitivity analysis examining the rates of clinical remission only in studies for which we had IPD, ie, infliximab and adalimumab, and the results were unchanged (OR, 0.85; 95% CI, 0.64–1.12; $P = .25$).

Clinical Response

Patients on steroids plus anti-TNF were less likely to achieve clinical response than those on anti-TNF alone (42.7% vs 46.8%, respectively). The overall pooled summary estimate of the OR comparing clinical response between weeks 4–14 in those on concomitant steroids versus those not on steroids was 0.84 (95% CI, 0.73–0.96; $P \leq .01$) (Figure 2*B*). However, after controlling for baseline CDAI, there was no significant difference in odds of clinical response between the 2 groups (OR, 0.91; 95% CI, 0.75–1.11, $P = .36$; available for adalimumab and infliximab studies only, n = 861 for steroid group, n = 1536 for no steroids). No evidence of asymmetry was observed in the funnel plot (Figure 2*D*, 7 studies on each side) or Egger test ($P = .97$).

Concurrent Immunomodulators

Subgroup analyses were performed to assess for the impact of immunomodulator therapy during induction on the relationship between concomitant steroids and efficacy. In patients on baseline immunomodulators, there was no difference in odds of clinical remission or clinical response between those on steroids plus anti-TNF (n = 450) as compared with those on anti-TNF alone (n = 671; OR, 0.85; 95% CI, 0.64–1.12, $P = .25$ and OR, 0.85; 95% CI, 0.67–1.09, $P = .22$, respectively; data available for adalimumab and infliximab studies only). Furthermore, controlling for both baseline CDAI and concurrent immunomodulator use did not change these results.

Steroid Dose

Additional subgroup analyses were performed to assess for the impact of steroid dose on efficacy of concomitant therapy with anti-TNF therapy versus anti-TNF monotherapy. There was no difference in the odds of achieving clinical remission between those on high dose steroids plus anti-TNF (n = 559) as compared with those on low dose steroids + anti-TNF therapy (n= 697; OR, 0.91; 95% CI, 0.63–1.31; $P = .61$) or anti-TNF monotherapy (n = 2099; OR, 0.91; 95% CI, 0.70–1.19; $P = .50$; data available for adalimumab and certolizumab studies only). Similarly, there was no difference in the odds of achieving clinical response between those on high dose steroids plus anti-TNF as compared with those on low dose steroids + anti-TNF or anti-TNF alone (OR, 0.97; 95% CI, 0.75–1.24; $P = .79$ and OR, 0.82; 95% CI, 0.67–1.01; $P = .06$, respectively; steroid dose data available for adalimumab and certolizumab studies only).

Discussion

We performed a meta-analysis of pooled individual patient and aggregated data from pivotal RCTs across the 3 approved anti-TNF therapies for CD to address the question of whether increased rates of clinical remission and response are observed in patients who are or are not on corticosteroids at baseline during induction therapy with an anti-TNF for active CD. We worked with 3 different pharmaceutical companies to obtain original datasets from large RCTs. Across 14 RCTs of anti-TNF therapy in CD included in this meta-analysis, 38% of patients were on baseline corticosteroids during anti-TNF induction. We observed that continued corticosteroid use during induction with anti-TNF therapy did not increase rates of clinical remission and response as compared with the group not receiving corticosteroids. This finding was consistent across all 3 anti-TNF drugs and steroid doses and was unchanged after controlling for disease severity by baseline CDAI scores as well as combination immunomodulator use.

Analysis of several previously published trials suggested that corticosteroids may enhance the rates of remission with anti-TNF induction therapy. Post hoc analysis of the GAIN trial of adalimumab induction in CD patients who had failed or were intolerant to infliximab found numerically higher rates of remission at 4 weeks in patients on concomitant steroids as compared with those not on concomitant steroids during induction (18/55, 33% vs 16/104, 15%), although no statistical comparison was performed.[16] In addition, several studies of triple immunosuppression with anti-TNF therapy combined with an immunomodulator and corticosteroids found numerically higher rates of remission as compared with studies of anti-TNF monotherapy or combination therapy with immunomodulator, which has led to speculation about the additive benefit of corticosteroids during induction. In the COMMIT trial, patients with CD who were on induction courses of prednisone were randomized to infliximab with or without the addition of methotrexate.[15] The study found that the addition of methotrexate was not more effective than prednisone and infliximab alone at achieving remission at week 14 (76% vs 78%, $P = .83$). The authors speculated that the reason for the negative trial may be a synergistic effect of prednisone plus anti-TNF therapy in achieving the highest reported success rates in this patient population. Similarly, results from a GETAID study of adding

infliximab plus azathioprine in steroid-dependent CD patients found a comparably high rate of induction of steroid-free remission, 75% at week 12.[17]

Our results contrast with these prior studies and found no improvement in rates or odds of achieving remission or response among those who were on corticosteroids at baseline versus those who were not and treated with anti-TNF alone. These results were unchanged after controlling for disease severity by CDAI at time of trial enrollment. We also performed subgroup analysis on the group of patients receiving triple immunosuppressive therapy with an immunomodulator, similar to the studies noted above, and found no added benefit of corticosteroids in this subgroup.

Our study is the largest study to date to address the question of whether continued corticosteroid use during induction with anti-TNF leads to higher rates of remission as compared with patients treated with anti-TNF alone in CD. The strength of our study is access to data from pivotal RCTs across 3 anti-TNF therapies in CD, as well as the ability to analyze IPD. The use of data from RCTs, rather than observational cohorts, provides the benefit of rigorously collected prospective data with consistent endpoints. The analyses of IPD enabled us to control for disease activity by using CDAI as well as baseline immunomodulator use, as well as to analyze outcomes on the basis of prednisone dose.

However, our study also has several important limitations. This was a post hoc analysis of RCT data and not a randomized trial comparing anti-TNF monotherapy with anti-TNF plus corticosteroids for induction of remission. As such, this study addresses the clinical question of continuing corticosteroid therapy during induction with anti-TNF therapy but cannot eliminate the possibility that initiation of corticosteroids together with anti-TNF would have some added benefit. In addition, patients meeting trial entry criteria despite baseline corticosteroids may represent a more severe or refractory group of patients who have poorer response to anti-TNF therapy. We attempted to control for disease severity by adjusting for baseline CDAI scores in studies for which we had IPD, and the primary outcomes remain unchanged. However, we do not have CDAI data before initiation of corticosteroids in the corticosteroid group; CDAI is a limited indicator of true disease severity, and there may be other measured (ie, biomarkers, endoscopic severity) or unmeasured confounders still present. Furthermore, IPD was not available for trials of certolizumab, so controlled analyses were not possible for this therapy. No studies of biosimilars were available for inclusion, but our results likely apply to treatment with biosimilars in CD, which is becoming increasingly prevalent as first-line anti-TNF therapy.[36,37] In addition, safety data stratified by steroid exposure were not available for analysis in this study; however, the additive risk of steroid therapy has been reported previously in the literature. Finally, only clinical outcomes but not endoscopic and histologic healing were assessed, on the basis of the data available in these studies.

In conclusion, this meta-analysis using data from pivotal RCTs of anti-TNF therapy in CD found that continuing corticosteroids during induction with anti-TNF therapy was not associated with increased rates or odds of clinical remission or response as compared with the group treated with anti-TNF therapy alone. This finding remained unchanged after controlling for baseline disease activity as well as combination immunomodulator use. These data suggest that a synergistic benefit of corticosteroids plus anti-TNF therapy in patients already dependent on or failing steroids is unlikely. Because of these findings and the known risks of corticosteroid use both alone and in combination, we suggest that clinicians consider early weaning of corticosteroids during induction with anti-TNF therapy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.06.036.

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CRediT Authorship Contributions

David M. Faleck, MD (Conceptualization: Supporting; Data curation: Equal; Formal analysis: Supporting; Writing – original draft: Lead)

Eugenia Shmidt (Conceptualization: Lead; Data curation: Equal; Writing – original draft: Equal)

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Conflicts of interest
These authors disclose the following: Neeraj Narula has received honoraria for speakers bureau or advisory boards from Janssen, AbbVie, Takeda, Pfizer, Merck, and Ferring. Jean-Frederic Colombel reports receiving research grants from AbbVie, Janssen Pharmaceuticals, and Takeda; receiving payment for lectures from AbbVie, Amgen, Allergan, Inc, Ferring Pharmaceuticals, Shire, and Takeda; receiving consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Genentech, Janssen Pharmaceuticals, Landos, Ipsen, Medimmune, Merck, Novartis, Pfizer, Shire, Takeda, and Tigenix; and holding stock options in Intestinal Biotech Development and Genfit. The remaining authors disclose no conflicts.

Supplementary Appendix

Search Strategies

Per the PRISMA checklist, full electronic search strategies are reported below.

MEDLINE (Ovid)

1 Crohn disease/ (30614)

2 crohn* disease.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (37812)

3 regional enteritis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (792)

4 ileitis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (3129)

5 ileitis/ (1703)

6 inflammatory bowel disease/ (13710)

7 inflammatory bowel disease.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (22727)

8 1 or 2 or 3 or 4 or 5 or 6 or 7 (54379)

9 ("anti tumour necrosis factor" or "anti tumor necrosis factor").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2741)

10 ("anti tumour necrosis factor alpha" or "anti tumor necrosis factor alpha").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1218)

11 ("anti tumour necrosis factor alpha antibody" or "anti tumor necrosis factor alpha antibody").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (118)

12 ("anti tumour necrosis factor antibody" or "anti tumor necrosis factor antibody").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (58)

13 ("anti TNF" or "anti TNF alpha").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (6012)

14 ("anti TNF antibody" or "anti TNF alpha antibody").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (870)

15 ("infliximab" or "monoclonal antibody cA2" or "remicade").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (8443)

16 cdp571.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (41)

17 (cdp870 or certolizumab).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (438)

18 (adalimumab or d2e7).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (3356)

19 CNTO 148.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4)

20 golimumab.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (277)

21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (15081)

22 8 and 21 (3735)

23 ("randomized controlled trial" or "randomised controlled trial").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (384473)

24 clinical trial.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (576481)

25 (blind or placebo).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (257955)

26 random allocation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (81915)

27 23 or 24 or 25 or 26 (854335)

28 Controlled Clinical Trial/ (88531)

29 Randomized Controlled Trial/ (376175)

30 Random Allocation/ (80958)

31 Clinical Trial/ (488218)

32 Clinical Protocols/ (19945)

33 Placebos/ (32652)

34 Double-Blind Method/ (126370)

35 Single-Blind Method/ (19229)

36 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (874690)

37 22 and 36 (474)

Embase (Ovid)

1 Crohn disease/ (56008)

2 crohn* disease.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (62423)

3 regional enteritis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (682)

4 ileitis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (5112)

5 ileitis/ (3853)

6 inflammatory bowel disease/ (3095)

7 inflammatory bowel disease.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (38608)

8 1 or 2 or 3 or 4 or 5 or 6 or 7 (83687)

9 ("anti tumour necrosis factor" or "anti tumor necrosis factor").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (4088)

10 ("anti tumour necrosis factor alpha" or "anti tumor necrosis factor alpha").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1650)

11 ("anti tumour necrosis factor alpha antibody" or "anti tumor necrosis factor alpha antibody").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (132)

12 ("anti tumour necrosis factor antibody" or "anti tumor necrosis factor antibody").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (76)

13 ("anti TNF" or "anti TNF alpha").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (11633)

14 ("anti TNF antibody" or "anti TNF alpha antibody").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1048)

15 ("infliximab" or "monoclonal antibody cA2" or "remicade").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (29985)

16 cdp571.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (57)

17 (cdp870 or certolizumab).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (3152)

18 (adalimumab or d2e7).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (15645)

19 CNTO 148.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (55)

20 golimumab.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2168)

21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (41818)

22 8 and 21 (12324)

23 ("randomized controlled trial" or "randomised controlled trial").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (409375)

24 clinical trial.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (986421)

25 (blind or placebo).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (426346)

26 random allocation.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1417)

27 23 or 24 or 25 or 26 (1262214)

28 "controlled clinical trial (topic)"/ (2969)

29 "randomized controlled trial (topic)"/ (53907)

30 randomization/ (62426)

31 "clinical trial (topic)"/ (42830)

32 clinical protocol/ (68111)

33 placebo/ (241541)

34 double blind procedure/ (113934)

35 single blind procedure/ (18431)

36 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (1355517)

37 22 and 36 (3570)

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)

#41 Search #22 AND #40

#40 Search #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR

#36 OR #37 OR #38 OR #39

#39 Search research design [MESH TERMS]

#38 Search single-blind method [MESH TERMS]

#37 Search double-blind method [MESH TERMS]

#36 Search placebos [MESH TERMS]

#35 Search clinical protocols [MESH TERMS]

#34 Search clinical trials [MESH TERMS]

#33 Search random allocation [MESH TERMS]

#32 Search randomized controlled trials [MESH TERMS]

#31 Search Controlled Clinical trials [MESH FORMS]

#30 Search #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR

#29

#29 Search research OR design

#28 Search efficacy OR effective*

#27 Search random allocation

#26 Search blind OR placebo

#25 Search clinical trial

#24 Search random*

#23 Search randomized controlled trial OR randomised controlled

trial

#22 Search #8 AND #21

#21 Search #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #

15 OR #16 OR #17 OR #18 OR #19 OR #20

#20 Search golimumab

#19 Search CNTO 148

#18 Search adalimumab OR d2e7

#17 Search cdp870 OR certolizumab

#16 Search cdp571

#15 Search infliximab OR monoclonal antibody cA2 OR remicade

#14 Search anti TNF antibody OR anti TNF alpha antibody

#13 Search anti TNF OR anti TNF alpha

#12 Search anti tumour necrosis factor antibody OR anti tumor

necrosis factor antibody

#11 Search anti tumour necrosis factor alpha antibody OR anti

tumor necrosis factor alpha antibody

#10 Search anti tumour necrosis factor alphaORanti tumor necrosis

factor alpha

#9 Search anti tumour necrosis factor OR anti tumor necrosis

factor

#8 Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#7 Search inflammatory bowel disease [MESH FORMS]

#6 Search inflammatory bowel disease

#5 Search ileitis [MESH FORMS]

#4 Search ileitis

#3 Search regional enteritis

#2 Search crohn disease [MESH FORMS]

#1 Search crohn* disease