Adalimumab monotherapy versus combination therapy with immunomodulators in patients with Crohn's disease: A systematic review and meta-analysis

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Abstract

Background and aims: Combination therapy with infliximab and azathioprine has been shown to be superior to either treatment alone in Crohn's disease (CD). However, the benefit of combining adalimumab with an immunomodulator remains controversial. The aim of this study was to compare the efficacy of adalimumab monotherapy with combination therapy for induction and maintenance of response and remission in CD using a meta-analysis of the current literature.

Methods: We performed a systematic literature search using Medline, Embase, Cochrane and several other databases. Prospective randomized controlled trials, retrospective cohort and case-controlled studies were included. The primary outcomes included induction of response and remission (up to week 12), maintenance of clinical response and remission (1 year) and the need for dose escalation. Several subgroup and sensitivity analyses were performed.

Results: Eighteen out of 2743 retrieved studies were included. A meta-analysis of 7 studies assessing induction of remission (n = 1984) showed that ADA monotherapy was inferior to
1. Introduction

Monoclonal anti-TNF antibodies (infliximab, adalimumab, certolizumab) have become a mainstay of inflammatory bowel disease (IBD) therapy since their introduction into clinical practice. These medications are effective for induction and maintenance of remission in Crohn’s disease (CD), with remission rates ranging from 38 to 80% for infliximab. Higher rates are reported for clinical response.1–7 In Crohn’s disease, a combination of infliximab with azathioprine has been shown to be significantly superior to either medication alone, with 56.8% of the patients on combination therapy achieving corticosteroid-free clinical remission at week 26, as compared with 44.4% receiving infliximab alone ($p = 0.02$) and 30.0% receiving azathioprine alone ($p < 0.001$).8 Combination therapy was associated with significantly higher trough infliximab levels and significantly diminished formation of anti-infliximab antibodies.9–13 However, it is still unclear whether such combination therapy with other anti-TNF antibodies has a similar therapeutic benefit. The efficacy of adalimumab monotherapy versus a combination of ADA with an immunomodulator was never examined in a randomized controlled trial. Nevertheless, a significant amount of data on the efficacy of ADA with or without concomitant immunomodulators has accumulated from prospective and retrospective studies and case series. In the present study, we aimed to perform a meta-analysis comparing the efficacy of adalimumab monotherapy with combination therapy using an immunomodulator for induction and maintenance of response and remission in CD.

2. Methods

2.1. Eligibility criteria

Randomized controlled trials, open-label prospective, observational studies, cohort and case–control studies were included. We excluded case reports, studies with less than 30 patients, pediatric studies, studies pertaining exclusively to pregnant or postoperative patients, studies evaluating closure or healing of fistulae as a primary outcome, and studies evaluating a combination therapy of ADA and a surgical or pharmacological intervention other than an immunomodulator. In addition, studies on mixed Crohn’s and ulcerative colitis (UC) or unclassified IBD (UIBD) patients were excluded unless the treatment and outcome data was separately available for CD. Also excluded were studies in which the outcomes could not be stratified by ADA monotherapy and combination therapy, either from publication text or by contacting the authors directly.

2.2. Search strategy

Comprehensive medical literature searches were conducted using Ovid MEDLINE, Medline In-Process, Daily and Old Medline (1946 to Present), EMBASE (1974 to 2013 July 19), Biosis (1969 to 2013 Week 33), Wiley Cochrane Library, Scopus, Web of Science and PubMed (non Medline records). Articles were selected using a highly sensitive search strategy, designed by a librarian (BN) and peer reviewed, to identify reports of RCTs, with a combination of MeSH headings and text words that included 1) adalimumab and synonyms in all fields and 2) inflammatory bowel diseases as a MeSH and in titles, abstracts and journal titles, or Crohn’s disease, pancolitis, proctitis, proctocolitis, ulcerative colitis, gastroenteritis as MeSHs and in titles or abstracts. The two concepts were then combined. The searches were run on July 22nd, 2013 and updated on Nov. 25th. See Appendix A for Ovid Medline search strategy details. Abstracts from major gastroenterology conferences in the past 5 years (including Digestive Disease Week, Canadian Digestive Disease Week, United European Gastroenterology Week, American College of Gastroenterology, European Crohn’s and Colitis annual conference, Crohn’s and Colitis Foundation of America Advances in IBD meeting and the Asia-Pacific Digestive Week) were also searched, as were clinical trials databases [www.clinicaltrials.gov and International Randomised Standard Clinical Trial (IRSC) Register]. Other available sources of unpublished data (gray literature) were also searched, where available through cross-referencing. Recursive searches and cross-referencing were carried out using a “similar articles” function; bibliography of the articles identified after an initial search were also manually reviewed. Articles citing eligible studies were retrieved using Web of Science and Scopus and screened. Data extraction and quality control were done independently by two reviewers (UK and TA). A third reviewer was involved if conflict occurred. When additional data was required, first and last authors of the corresponding manuscript were contacted by email with relevant questions; an additional query was sent if no response was received. Methodological quality of the included studies was evaluated by using the Newcastle–Ottawa scale.14

combination therapy [OR = 0.78 (0.64–0.96), $p = 0.02$]. A meta-analysis of 4 studies revealed that combination therapy was not statistically different from ADA for maintenance of remission [OR = 1.08 (0.79–1.48), $p = 0.48$]. Combination therapy was also not different from ADA monotherapy in terms of requirement for dose escalation [OR = 1.13 (0.69–1.85), $p = 0.62$].

Conclusions: Combination therapy with ADA and immunomodulator was mildly superior to ADA monotherapy for induction of remission in CD. The rate of remission at 1 year and the need for dose escalation were similar in both groups. These findings should be interpreted with caution in view of possible confounders and should be further validated by randomized controlled trials.
2.3. Outcome measures

The efficacy of adalimumab alone as compared to combination therapy was assessed for the following outcomes:

1) Induction of remission defined as clinical remission Crohn’s disease activity index (CDAI) < 150 or Harvey Bradshaw Index (HBI < 4) after ≤ 12 weeks
2) Induction of clinical response (defined as ΔCDAI > 70 or ΔHBI > 2, or by physician’s global assessment (PGA) when clinical scores were unavailable)
3) Maintenance of remission defined as clinical remission after 1 year of therapy
4) Clinical response after ≤ 1 year of therapy
5) Need for dose escalation throughout the duration of follow-up.

2.4. Quality assessment

Quality of studies was assessed using the Newcastle–Ottawa Scale for assessment of quality of studies with the highest obtainable score of 9. A score of equal or more than 6 was defined as high quality.

2.5. Statistical analysis

In randomized placebo controlled studies, only patients in the treatment arm were analyzed. When several treatment arms using different doses of ADA were reported in the study, we have combined the active treatment groups for analysis.

Summary outcomes are described as proportions and 95% CI for categorical and weighted mean difference ± SD for continuous data. A meta-analysis of intention-to-treat data was done using the random model Mantel–Haenszel method. P-values < 0.05 were considered significant. The significance and extent of statistical heterogeneity were calculated using the Q test and I2 index, respectively. Odds ratios (OR) were calculated for each analysis with the corresponding 95% confidence intervals.

Funnel plot was used to detect the possibility of publication bias. We also planned to perform sensitivity analyses based on the quality and weight of the trials, and by excluding each individual trial in turn as recommended by Cochrane Collaboration open learning material for reviewers. Subgroup analyses were also planned based on the follow up period in different studies.

All statistical analyses were done using RevMan 5.0.25, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008 and R version 2.13.0, (R Foundation for Statistical Computing, Vienna, Austria, 2008). The PRISMA statement outline for reporting systematic reviews and meta-analyses was used to report this work.

3. Results

3.1. Characteristics of included trials

A total of 1815,6,17–31 out of 2744 identified studies (N = 4294 patients, including 2280 in the adalimumab group and 2014 in the combination group) were included; all were performed between 2006 and 2013. All studies were published in English. Fig. 1 depicts the PRISMA flow diagram. There was excellent inter-reviewer agreement [Kappa = 0.84 (95% CI: 0.56–1.0)]. All studies were of high quality as defined by a score of 6 or higher in Newcastle–Ottawa Scale. Table 1 shows the methodological and clinical details for each trial. Fig. 2 describes the funnel plot for the analysis of publication bias; no major visual asymmetry in this diagram indicates the low likelihood of major publication bias. The first or last authors of six studies provided further data after being contacted by the authors.19,20,22–24,30

3.2. Analysis of main outcomes

3.2.1. Induction of clinical remission (Fig. 3)

Six studies including 1957 patients were included (960 receiving adalimumab and 997 combination therapy). Combination therapy was superior to adalimumab on random effect meta-analysis [OR: 0.79 (0.65–0.96); p = 0.02]. Heterogeneity was not significant for the analysis [I² = 0%], p = 0.57].

On sensitivity analyses, the result did not remain significant after excluding non-randomized trials [OR: 1.11 (0.72–1.73); p = 0.64] or by excluding the largest included trial [OR: 0.85 (0.63–1.16); p = 0.31] but remained significant after excluding any other individual trial or after excluding the study that reported mucosal healing as the primary outcome (Rutgeerts 2012)18 [OR: 0.78 (0.64–1.96); p = 0.02]. Subgroup analysis of the studies with only 4 weeks of follow up did not show a significant difference between two groups [OR: 0.86 (0.64–1.17), p = 0.35].

3.2.2. Induction of clinical response

Six studies including 833 patients were included (449 receiving adalimumab and 384 combination therapy). There was no significant difference between combination therapy and adalimumab on random effect meta-analysis [OR: 0.68 (0.37–1.25); p = 0.22]. Heterogeneity was significant for the analysis [I² = 63%], p = 0.02]. On sensitivity analysis, after excluding Karmiris et al.23 combination therapy was significantly superior to adalimumab [OR: 0.55 (0.33–0.94), p = 0.03]. On additional subgroup analyses, the result did not remain significant after excluding studies with follow up duration of less than 12 months [OR: 0.71 (0.35–1.46); p = 0.36] or after exclusion of a study published in an abstract form [OR: 0.83 (0.47–1.48); p = 0.51].

3.2.3. Maintenance of remission at 12 months (Fig. 4)

Four studies including 833 patients were included (337 receiving adalimumab and 496 combination therapy). There was no significant difference between combination therapy and adalimumab on random effect meta-analysis [OR: 1.08 (0.79–1.48); p = 0.61]. Heterogeneity was not significant [I² = 0%], p = 0.66]. On sensitivity analyses, the result remained unchanged by excluding any individual trial.

3.2.4. Clinical response at 12 months

Three studies including 446 patients were included (211 receiving adalimumab and 235 combination therapy). There was no significant difference between combination therapy and adalimumab on random effect meta-analysis [OR: 1.21 (0.74–1.99); p = 0.44]. Heterogeneity was not significant for
the analysis \(I^2 = 20\%, \ p = 0.28\). On sensitivity analyses, the result remained unchanged by excluding any individual trial.

3.2.5. Need for dose escalation throughout follow-up (Fig. 5)
Six studies including 1421 patients were included (800 receiving adalimumab and 621 combination therapy). There was no significant difference between combination therapy and adalimumab in random effect meta-analysis [OR: 1.13 (0.69–1.89); \(p = 0.62\)]. Heterogeneity was significant for the analysis \(I^2 = 71\%, \ p = 0.004\). On sensitivity analyses, the result did not remain significant after excluding the only study which was published in abstract [OR: 1.24 (0.70–2.20); \(p = 0.46\)] or by excluding any other individual trial.

3.2.6. Safety
The reported complications were stratified by the use of concomitant immunomodulators in 3 studies only. Karmiris et al.\(^{23}\) reported a similar risk of serious adverse effects in patients on monotherapy and combination therapy; the risk

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**Figure 1** Selection of included studies. *— unavailable outcome data/no stratification by concomitant immunomodulator; the data was not available after contacting the authors.
Table 1  Characteristics of the included studies C – Crohn's disease, IFX – Infliximab, ADA – adalimumab. NA – North America, EU – RCT – randomized controlled studies, OL – open label prospective study; RS – retrospective study; CDAI – Crohn’s disease activity index, HBI – Harvey Bradshaw Index; MH – mucosal healing; and PGA – physician’s global assessment.

| N  | Author     | Year | Type  | Design            | Main inclusion criteria | N   | Definition of remission | Definition of response | Induction of remission-week | Induction of response-week | Maintenance of remission-week | Maintenance of response-week | Dose escalation-week |
|----|------------|------|-------|-------------------|-------------------------|-----|-------------------------|-------------------------|---------------------------|----------------------------|------------------------------|------------------------|
| 1  | Hanauer    | 2006 | Full  | RCT               | CDAI > 220              | 225 | CDAI < 150              | –                        | 4                         | –                         | –                           | –                        | –                      |
| 2  | Sandborn   | 2007 | Full  | RCT               | Anti-TNF naive          | 159 | CDAI < 150              | –                        | 4                         | –                         | –                           | –                        | –                      |
| 3  | Colombel   | 2007 | Full  | RCT               | Active CD with a        | 329 | CDAI < 150              | –                        | –                         | 56                        | –                           | –                      |
| 4  | Sandborn   | 2007 | Full  | RCT               | Active CD, anti-TNF     | 241 | CDAI < 150              | –                        | –                         | 56                        | –                           | –                      |
| 5  | Karmiris   | 2009 | Full  | RS                | Active CD, IFX failures | 158 | –                       | PGA                     | 12                        | –                         | –                           | –                        | 20.4 (11.7–30.0)       |
| 6  | Panaccone  | 2011 | Full  | OL                | CDAI > 220              | 304 | HBI < 4                 | –                        | 8                         | –                         | –                           | –                        | –                      |
| 7  | Fortea-    | 2011 | Full  | RS                | Active CD               | 138 | –                       | PGA                     | 4                         | –                         | 33 (3–120)                   | –                        | –                      |
| 8  | Ormaechea  | 2011 | Full  | RS                | Active CD, IFX failures | 44  | –                       | ΔHBI > 2                | 6                         | –                         | –                           | –                        | –                      |
| 9  | Issa       | 2011 | Abstract | RS      | Active cd           | 310 | –                       | –                       | –                         | –                         | –                           | –                        | 49                     |
| 10 | Loftberg   | 2012 | Full  | OL                | HBI ≥ 7                 | 945 | HBI < 5                 | –                        | 4                         | –                         | –                           | –                        | –                      |
| 11 | Rutseerts  | 2012 | Full  | RCT               | CDAI > 220              | 123 | MH                      | –                        | 12                        | –                         | 52                           | –                        | –                      |
| 12 | Kiss       | 2012 | Full  | RS                | CDAI > 300              | 201 | CDAI < 150              | ΔCDAI > 70              | 12                        | 12                        | 52                          | 52                       | 52                     |
| 13 | Bossa      | 2012 | Abstract | RS      | Active CD           | 75  | –                       | ΔCDAI > 70              | 12                        | 12                        | –                           | –                        | –                      |
| 14 | Reenaers   | 2012 | Full  | RS                | PGA                     | 207 | –                       | PGA                     | 12                        | –                         | –                           | –                        | –                      |
| 15 | Cohen      | 2012 | Full  | RS                | Active CD              | 75  | –                       | –                       | –                         | –                         | –                           | –                        | –                      |
| 16 | Bultman    | 2012 | Full  | RS                | Active CD primary      | 122 | –                       | –                       | –                         | –                         | –                           | –                        | 16 (4–132)             |
| 17 | Kestens    | 2013 | Full  | RS                | Active CD              | 100 | –                       | PGA                     | –                         | –                         | 52                           | –                        | –                      |
| 18 | Baert      | 2013 | Full  | RS                | CD primary responders to ADA | 574 | –                       | –                       | –                         | –                         | –                           | –                        | 14 (mean)              |
of infectious complications was not increased in patients on combination therapy; one patient in each group died of reasons unrelated to therapy. Reenaers et al. reported a single serious adverse effect (pneumonia requiring hospitalization in an intensive care unit) in a cohort of CD patients; the affected patient was treated with monotherapy. Kestens et al. reported a similar rate of opportunistic infections in patients on monotherapy and combination therapy.

We could not perform a meta-analysis of the safety data due to variable definitions of adverse effects, different study designs and small number of patients with reported outcomes.

### 4. Discussion

In this meta-analysis, we have demonstrated that combination therapy with adalimumab is associated with a mildly increased probability to achieve clinical remission by week 12. This superiority was eliminated if only RCTs were included or if the largest available study was excluded. Combination with an immunomodulator did not impact the rate of clinical remission after one year of treatment or the need for dose escalation.

In the SONIC trial, the combination therapy with IFX and azathioprine was significantly superior to either medication alone for induction of clinical response. The difference was significant at week 26, and continued to be significant through week 52 of the study. The main mechanism likely to explain the superiority of combination therapy over monotherapy with IFX is the impact of the concomitant immunomodulator on immunogenicity as manifested by production of anti-infliximab antibodies and the resulting decrease in serum trough levels. Incidence of antibodies to IFX has been reported to be as high as 61% for patients on episodic therapy but also as high as 50% in patients on scheduled treatment. Anti-infliximab antibodies, especially in high titters, are associated with lower serum trough levels of IFX, higher prevalence of loss of response and infusion reactions. In the SONIC trial, patients on IFX monotherapy had median trough levels of serum infliximab of 1.6 μg per milliliter compared to 3.5 μg per milliliter for those in the combination-therapy group (P < 0.001) at week 30; antibodies were detected in 0.9% of the patients on combination therapy and 14.6% of the patients on monotherapy. Similar association of concomitant immunosuppression with reduced...
The immunogenicity of infliximab was also demonstrated in several additional studies.\textsuperscript{35–37} Moreover, addition of an immunomodulator resulted in a disappearance of existing anti-infliximab antibodies that was paralleled by a reemergence of clinical response in a small case series of CD patients.\textsuperscript{38} Adalimumab is also associated with formation of anti-drug antibodies. Initially, the reported rate of antibody formation was 9.2%,\textsuperscript{39} significantly lower than for infliximab. However, later studies utilizing different laboratory techniques (modified enzyme-linked immunosorbent assay (ELISA), radioimmune assay, mobility shift assay) reported rates as high as 44%.\textsuperscript{40} An association of anti-adalimumab antibodies with diminished drug levels and clinical response has been observed in patients with IBD, psoriasis and rheumatoid arthritis.\textsuperscript{40–44} In a large retrospective study from Belgium, concomitant immunomodulator therapy did not impact trough adalimumab levels or the incidence of anti-adalimumab antibodies.\textsuperscript{23} In the CLASSIC I and II studies, patients on concomitant immunosuppression had numerically higher serum trough ADA levels that did not reach statistical significance.\textsuperscript{45}

One of the other possible mechanisms behind the beneficial effect of a combination therapy with IFX is a transient elevation of thiopurine metabolite levels (6-thioguanine (6-TGN)) when IFX is added to maintenance thiopurine therapy.\textsuperscript{46} 6-TGN levels are significantly correlated with clinical response to thiopurines in IBD.\textsuperscript{47} However, no impact on 6-TGN levels was demonstrated for combination of ADA with a thiopurine.\textsuperscript{48}

Our findings demonstrate a mildly increased probability of induction of remission in patients on a combination therapy, but without a long-term impact on either maintenance of remission or need of dose escalation. Interestingly, these results are different from the experience in rheumatoid arthritis, where a superior efficacy of combination therapy (ADA + MTX) in comparison to each therapy alone has been clearly demonstrated in randomized controlled studies; moreover, a clear dose effect of MTX in such combination has been reported.\textsuperscript{49–51}

The optimal duration of concomitant immunosuppression with IFX is debated. In a cohort of CD patients that have achieved clinical remission on combination therapy, discontinuation of AZA did not lead to a higher rate of dose escalation or IFX failure after 2 years of follow-up. However, trough levels of IFX were lower, and CRP levels were higher, in patients who discontinued AZA.\textsuperscript{52} Our findings do not suggest that there is a benefit in combining ADA with an immunomodulator beyond the initial induction phase. A potentially increased risk of infectious and malignant complications...
(lymphoma in particular) with combination therapy needs to be taken into consideration whenever such a treatment is suggested. Short-term safety data available for our analysis was very limited; however, a recent study that analyzed the malignancy-related safety data from a pooled analysis of data from 1594 patients with CD who participated in clinical trials of adalimumab (CLASSIC I and II, CHARMM, GAIN, EXTEND, and ADHERE studies; 3050 patient years of exposure) reported an increased risk of malignancy in patients on combination therapy (malignancies other than non melanoma skin cancer (NMSC) – relative risk, 2.82; 95% CI, 1.07–7.44; and for NMSC – relative risk, 3.46; 95% CI, 1.08–11.06). In our meta-analysis, we have limited our outcomes to one year of follow-up, as longer-term longitudinal data is scarcely available. However, data from the ADHERE cohort, which is an open-label extension study that prospectively follows up the cohort of patients originally enrolled in the CHARMM study, the rates of steroid-free remission were similar in patients with or without concomitant immunosuppression at baseline after 3 years of follow-up. To the best of our knowledge, this work is the first attempt to evaluate the efficacy of a combination of adalimumab with an immunomodulator in CD across a wide range of clinical trials. We have applied a stringent methodology with predefined inclusion criteria and have addressed several of the clinically important outcomes. The included studies were all of high quality and included randomized controlled studies, prospective open-label studies and retrospective reports. We planned and executed several subgroup analyses in order to minimize the impact of a particular study or an inferior study design.

Our meta-analysis has several important limitations. Only one of the included studies was aimed directly at comparison of treatments outcomes between monotherapy and combination therapy. Even though we had included 5 RCTs, the patients included in the patients were not randomized by concomitant immunomodulator treatment, and we could not adequately control for important confounders such as disease phenotype, previous anti-TNF treatment, type of immunomodulator, timing of initiation and duration of concomitant immunomodulation, previous surgery and smoking. Administration of double immunosuppressive treatment to patients who present with a more severe disease is common practice, and it is plausible that stratification by disease severity or other confounders could identify patient groups that may benefit from combination therapy.

In summary, our meta-analysis suggests that a combination of adalimumab with an immunomodulator is potentially mildly more effective than adalimumab monotherapy for induction of clinical remission, however no long-term impact of combination therapy on maintenance of clinical remission, response or need for dose escalation. These findings should be interpreted with caution and validation is needed from a randomized controlled trial.

Conflict of interests

AB: Consultant, Advisory Board: AbbVie, Janssen, Shire, Warner Chilcott, Takeda, Speaker: AbbVie, Janssen, Shire, Warner Chilcott, Aptalis PLL: speaker for AbbVie, MSD and EGIS; consultant for AbbVie, MSD Hungary and EGIS; has received unrestricted research grants from AbbVie and MSD Hungary

WA: Advisory Board Member: Janssen Pharma and Abbott SBH: consultant to Abbott and Schering-Plough and has received unrestricted educational grant from Janssen.

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