Meta-analysis of: Efficacy and Safety of combined therapy Infliximab (IFX) with Immunosuppressants (IS) vs Infliximab (IFX) alone as Treatment of Moderate – Severe Ulcerative Colitis

Omar Banafea[1*], Haseeb Saattar[1], Yaser Naji[2], Abdullah Fares[3],
Liangru Zhu*, Kaifeng Zou*

* Department of Gastroenterology, Union Hospital, Tongji Medical College,
Huazhong University of Science and Technology, Wuhan 430022, China.

I.   Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) affecting the colon and rectum, with increasing incidence and prevalence.(1–3) The main goal of UC therapy is the induction and maintenance of long-term corticosteroid-free clinical remission.Mucosalhealing is also considered one of the main aims of UC treatment since it has been associated with improved patient outcomes.(4, 5) Aminosalicylates and corticosteroids have shown to beeffective for the induction of clinical remission. However, up to 20% of UC patients become steroid dependent at 1 year.(6, 7)

Azathioprine (AZA) and mercaptopurine (6MP) are immunosuppressants (IS) commonly used for maintenance of long-term steroid-free clinical remission, as recommended by the European Crohn's and Colitis Organizationguidelines.(8–10)

The introduction of anti-TNF-αagents has led to a revolution in the treatment of IBD. Antibodies directed against TNF-α include infliximab (IFX), a monoclonal chimeric antibody, adalimumab (ADA) andgolimumab (GLM), bothhumanized monoclonal antibodies. These treatments have proven to be effective for achieving and maintaining clinical remission in UC. (11–15)In ulcerative colitis, the benefit of the combination of anti-TNF-α agents with an IS (combination therapy) remains debated. In Crohn's disease, the SONIC trial, demonstrated the superiority of combined IFX and AZA therapy over IFX therapy alone for IS naive patients. (16)

Likewise, the SUCCESS trial reported a significantly higher 16 weeks' steroid-free clinical remission rate for the combination therapy compared to IFX alone, for moderate-to-severe active ulcerative colitis.(17) The post hoc analysis of the ACT 1 and 2 trials reported that 6 and 12 month remission rates are not affected by combination therapy.(18) However, a recent prospective cohort from Armuzzi et al. showed that combined IFX-AZA therapy was a predictor of steroid-free clinical remission at 6 and 12 months.(19)

Whether all patients with UC, regardless of their prior IS status, should benefit from combination therapy remains unknown. We therefore conducted this meta-analysis to determine whether the combination of infliximab and immunosuppressants (IS) aresuperior to infliximab alone for achieving and maintaining clinical remission in moderate-to-severe active UC.

II.   Materials and Methods

Trial sources with moderate-to-severe flares (Mayo score 6-12), either treated with infliximab IFX alone or a combination of infliximab (IFX) with an immunosuppressants (IS) were identified. Trials were retrieved using MEDLINE (1990–Dec 2015), EMBASE (1990–2015), Cochrane Central Register of Controlled Trials (up to 2015), and clinicaltrials.gov using the key words ulcerative colitis, infliximab, immunosuppressants (azathioprine, 6-mercaptopurine). The list of published articles or abstracts was verified and completed through an in-depth study of the references quoted in each article. The final search was performed on 23 Dec 2015.

Study Selection:

The studies selected for this meta-analysis met the following criteria: (i) controlled randomized or non-randomized studies, published as peer-reviewed articles or abstracts; (ii) patients with moderate-to-severe active UC (Mayo Score 6–12, with Mayo endoscopic score >2). Patients were included regardless of prior immunosuppressants (IS)use; (iii) interventions: treatment withinfliximab (IFX) alone or combined with immunosuppressants (IS) (iv) main outcome: achievement and maintenance of clinical remission at 12 months. Exclusion criteria were as follows: (i) IFX used only as induction or on-demand treatment; (ii) use of an anti-TNF-α agent other than IFX; (iii) follow-up period less than 16 weeks; (iv) different main outcome without data on clinical remission (clinical response, mucosal healing, IFX discontinuation due to disease relapse, non-primary response).

Data Extraction and Quality Assessment:

All eligible articles were analyzed separately by two reviewers (O.B. and H.S.), who independently performed data extraction and quality assessment. For quality assessment, we took into account the presence and efficacy of randomization, investigator blinding, intention-to-treat analysis, number and reasons of patients lost to follow up and estimation of sample size. Authors were contacted to obtain supplementary data not reported in original articles or abstracts.

Data Synthesis And Analysis:

The main outcome was the achievement and maintenance of clinical remission (total Mayo score <3 with no individual subscore >1,(30) or Powell-Tuck index of 0,(31)as Randomized Controlled Trials (RCTs) and non-Randomized Controlled Studies (nRCSs) including UC patients used in trials) at 4–6 months (16–30 weeks) and at 12 months (48–56 weeks).

We Performed The Following Meta-Analyses:

(i) Meta-analysis including both RCTs and nRCSs, with UC patients treated with IFX or a combination of IFX and an IS, at 4–6 months. (ii) Meta-analysis including both RCTs and nRCSs, with UC patients treated with IFX or a combination of IFX and an IS, at 12 months.

Statistical Methods:

All results were expressed as odds ratios (OR) with a 95% confidence interval (CI). Results were at first calculated using a fixed-effect model (Mantel–Haenszel). (17)Trial heterogeneity was calculated using Breslow-Day's test. When heterogeneity was significant (P-heterogeneity < 0.1) the adjusted OR and P-heterogeneity were calculated by using a random effect model (Der Simonian and Laird), (18) which provides a more conservative estimate of treatment effects with wider confidence intervals to adjust for inter-trial variability. The percentage of inter-trial heterogeneity was estimated using the I² statistic.(19) Publication bias was assessed using the Egger's test (20) and represented graphically using funnel plots.(21)

In case of small study effects, we performed the Harbord test according to the recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomized controlled trials.(22, 23)The Trim and Fill analysis for publication bias was performed using Duvaland Tweedie's methods. (24)Additionally, the fail-safe number according to Orwin's formula was calculated (25, 26) which represents the number of nonsignificant studies which would be necessary to reduce the effect size to a nonsignificant value. Statistical methods were identical to those used in previous meta-analyses published by our group.(27–29)

All analyses were performed using Review Manager (Rev. Man 5.2).

III. Results

Study identification and selection an initial search on MEDLINE identified 432 potentially relevant references. Following the examination of titles and abstracts, 16 studies were considered for detailed analysis. Five retrospective studies using IFX as induction or on-demand treatment were excluded. (32-36)Five studies were excluded as the main outcome was not the clinical remission rate but mucosal healing, (37)diseaserelapse(36–38) and IFX discontinuation.(41)

Six studies were excluded since there were no data available regarding concomitant immunosuppressant(IS) use.(12–15, 42, 43)A total of four studies were included in the meta-analysis (Figure 1).

Study And Patient Characteristics:

Study characteristics are reported in Table 1. Four studies were included 5 trials (44-47) comparing IFX with combination therapy wasincluded with a total of 765 patients. One study was randomized according to the combination of IFX with an IS or not.(44)

Amongst the three remaining studies, two were post hoc analyses of RCTs. (45) Amongst the 765 patients wereanalyzed, 389 were treated with IFX alone, and 376 were treated with a combination therapy. Clinical remission was reported in three studies (four trials) (44–47) where adverse events were reported just in three studies (four trials) (44, 45,47).Detailed patient characteristics were only available for the SUCCESS trial (44).None of the patients included had previously received anti-TNF-αtherapy, whereas both IS naive patients and patients previously treated with IS were included in the meta-analysis.

Amongst the 155 patients of the SUCCESS trial, only 16 (eight in each group) had prior IS therapy. In the study of Armuzzi et al., 69 of 126 patients had prior IS treatment. In the ACT 1 and 2 trials, patients who had no response to azathioprine or mercaptopurine within the preceding 5 years were eligible to be included. Respectively, 125 of 243 and 102 of 241 patients were on IS treatment on inclusion. The exact numbers of

patients having had prior IS treatment in each treatment group (IFX alone or IFX-IS) for the ACT 1 and ACT 2 trials and the Armuzzi cohort were not available. However, taking into account these figures, it appears that a considerable proportion of patients included in the meta-analyses would have had prior IS treatment.

Fig. 10 PRISMA diagram of studies included in this meta-analysis

Quality Assessment:

Variables defining study quality are presented in Table 2. One study was randomized according to the combination of IFX with an IS or not (44) two trials were post hoc analyses of RCTs randomized according to different criteria: IFX (5 or 10 mg/kg every 8 weeks) vs. placebo (45), one study was a prospective cohort with subgroup analysis (46) and one study retrospective study who received combination of IFX with an IS or not (47). Three trials were double blinded (44, 45) whereas two was open (46, 47)Sample size was estimated in only one study (44).
All studies performed intention-to-treat analyses.

Outcome measures:
Clinical Remission:

853 patients analyzed, 131/429patients (30.05%) treated with IFX alone were in clinical remission compared to 175/424patients (41.27%) in the combined IFX-IS group. There was significant difference between the two groups: OR 1.54, 95% CI [1.16–2.05], P = 0.003 where heterogeneity I^2= 42% (P = 0.14) (Table 3). The Forest plot is reported in (Figure 1)
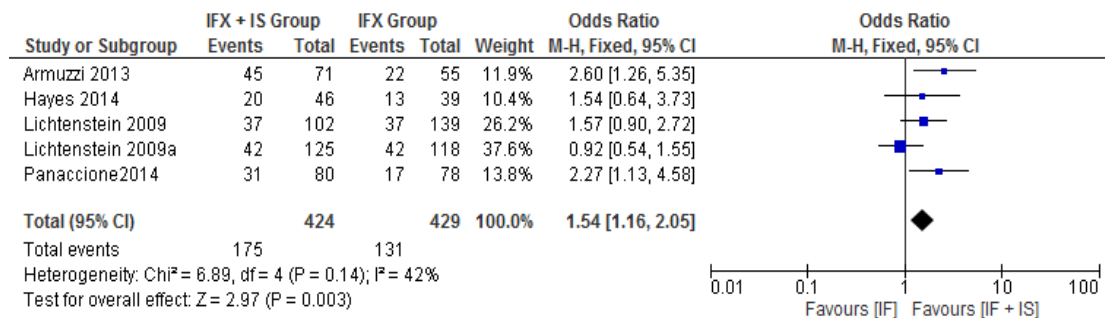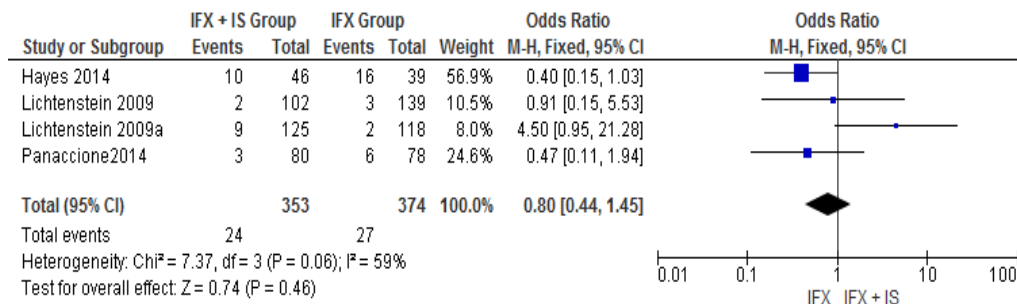

Fig. 1 Outcome of clinical remission rate in pts exposed to IFX + IS vs. IFX.

Adverse Events:

Four trials reported the adverse events of 727 patients were analyzed, 27/374patients (7.2%) treated with IFX alone were in adverse events compared to 24/353 patients (6.8%) in the combined IFX-IS group.

There was no significant difference between the two groups: OR 0.80, 95% CI [0.44–1.45], P = 0.46 where there is heterogeneity I^2= 59% (P = 0.06) (Table 3). The Forest plot is reported in (Figure 2).

Study or Subgroup	IFX + IS Group Events	IFX + IS Group Total	IFX Group Events	IFX Group Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hayes 2014	10	46	16	39	56.9%	0.40 [0.15, 1.03]
Lichtenstein 2009	2	102	3	139	10.5%	0.91 [0.15, 5.53]
Lichtenstein 2009a	9	125	2	118	8.0%	4.50 [0.95, 21.28]
Panaccione2014	3	80	6	78	24.6%	0.47 [0.11, 1.94]
Total (95% CI)		353		374	100.0%	0.80 [0.44, 1.45]
Total events	24		27			

Heterogeneity: Chi² = 7.37, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 0.74 (P = 0.46)

Fig. 2 Forest plot of comparison: IFX + IS vs. IS comparison, outcome: 1.2 Outcome of Serious Adverse effects of pts on Anti TNF-alfa + IS vs. IFX.

IV.   Discussion

The currentmeta-analysis is compared efficacy of combined IFX and IS therapy with IFX alone in moderate-to-severe active UC. In this meta-analysis, the clinical remission rate is higher in the combination therapy group, with significant results (P < 0.003).

In Ulcerative colitis, the benefit of the combination of IFX with an IS isargued. Several studies have been attempted to resolve this issue; although, the results are confounding.The results of post hoc analyses of the ACT 1 and ACT 2 trials, did not find compounded therapy (IFX-AZA) to be higher-up to IFX alone(45).Moreover, Armuzziet al. in their lately published prospective cohort found that combined IFX and AZA therapy was a predictor of steroid-free clinical remission at 6 and 12 months (46) A recent study has compared the compound of IFX with Methotrexate (MTX) to IFX alone and MTX alone to a control group (2 mg/kg prednisone) in patients with severe steroid dependent UC. The current study exhibited that the conjunction of IFX with MTX had not provided any benefit concerning mucosal healing during 16 weeks. However, the results of the SUCCESS trial (Panaccione et al 2014) have provided evidence of the superiority of the combination of IFX with IS compared to IFX alone at 16 weeks for IS naive patients with moderate-to-severe UC (44).

Actually the current meta-analysis establishes a significant difference in clinical remission of moderate to severe UC patientsbetween the two groups therapy. The post hoc analysis of ACT 1 did notdemonstrate difference between combined IFX-IS vs. IFX alone, opposite to the Armuzzi et al. cohort in favour of combined IFX and IS (AZA).

In recentArmuzzi et al. cohort study, patients had a lower mean duration of disease (4 years vs. 6.6 years in the ACT 1 trial), and these patients had significantly higher steroidfree clinical remission rates at 6 and 12 months. On the other hand, in the ACT 1 trial, the absolute majority of patients had formerly been treated with thiopurines over the last 5 years with no response, unlike the Armuzzi et al. cohort where an important proportion of patients were immunosuppressant (IS) naive (45.2%) (42, 43).A subsequent meta-analysis with additional studies would be necessary in order todemonstrate a significant difference between the two treatment groups. Data from the SUCCESS trials demonstrated the superiority of combined IFX-AZA therapy for IS naive UC patients, but the question remains open for all UC patients regardless of their prior IS status. This study population differed somewhat from other trials as patients wereimmunosuppressant (IS) naive and had a relatively short history of UC. Concerning prior IS use, data were clearly available for the two groups (IFX-IS and IFX alone) only in the SUCCESS trial with 8 patients in each group (44). However, in the Armuzzi et al. cohort, 54.8% of patients had prior IS therapy (46) whereas in the ACT1 and ACT2trials, 50.4% and 42.3% of patients were on IS treatment at the time of induction of IFX therapy (45).In addition, patients having had no response to azathioprine or mercaptopurine within the preceding 5 years were eligible for inclusion the ACT1 and ACT 2 trials. We can therefore presume that a considerable number of patients included had prior immunosuppressant (IS) therapy. Therefore, it is likely that our results could be extrapolated to all UC patients regardless of their prior immunosuppressant (IS) use.

Heterogeneity is present in the patient population of our meta-analysis, since we included both trials with IS naive patients and patients previously treated with IS, for which disease duration was variable. In real life practice,both these types of patients are regularly encountered; however it should be noted that in a hospital setting patients with a long disease duration having alreadyreceived several treatments are more frequent, and few of these patients are IS naive. We therefore decided not to limit our analysis to patients with a short disease duration naive of IS.

MJ Hayes et al. demonstrates that concomitant immunosuppressant use with IFX improves outcomes among patients with refractory UC as shown by decreased immunogenicity to IFXand increased duration of therapy however it was an uncontrolled, retrospective chart review andis subject to potential bias (47). As well as there is several studies have shown that concomitant immunosuppressant therapy decreases formation of antibodies to infliximab (ATI) in patients receiving IFX (48-50). The clinical remission rate would be correlated with the trough serum IFX levels and to the absence of ATI formation (34, 43). However, despite the general belief that concomitant IS therapy decreases formation of ATI and leads to a higher IFX trough level in patients with IBD, data are inconsistent (45, 42, 51–53).

We decided to exclude studies using adalimumab or golimumab since there is no trial available comparing ADA or GLM vs. combination therapy in UC patients which would allow us to perform a meta-analysis for each anti-TNFα agent. Data concerning clinical remission rates on golimumab or adalimumab therapy vs. combination therapy (ADA-IS or GLM-IS) are not available neither in manuscript form nor in supplementary appendices of trials evaluating these two anti-TNF-α agents' induction and maintenance efficacy in UC. (12–15)

We chose to include both RCTs randomized according to the combination of IFX with an IS or not, andnRCSs. There is no denying that RCTs are studieswhich are of superior methodological quality with a lower risk of bias, and that post hoc analyses of RCTs are of poorer methodological quality. However, the nRCSs included in our meta-analysis are either studiesrandomized according to different criteria, or cohorts. All these studies are therefore of high methodological quality except MJ Hayes et al. study which was an uncontrolled, retrospective chart review and was subject to potential bias.

On a practical level, prospective cohorts have the advantage of corresponding to real life medical practice than RCTs. Moreover, patients enrolled in RCTs do not always accurately represent the IBD population (54)The frequency of adverse events, including frequency of all and serious infections, all and serious infusion reactions and adverse events leading to discontinuation of study drugs were available in only two studies with separate results at 30 weeks for the ACT 1 trial and at54 weeks for the ACT 2 trial. It was therefore not possible to perform a meta-analysis on these outcomes. (45)

However, in both post hoc analyses there was no significant difference between combination therapy and monotherapy groups concerning infections, serious infections, infusions reactions and adverse events leading to discontinuation of study drugs (45).

V.   Conclusion
our meta-analysis reveals significant superiority for combination IFX and IS therapy (AZA or MP) compared to IFX alone for the achievement and maintenance of clinical remission of UC flares as well as there is no significant difference of adverse events between combinations IFX and IS therapy compare to IFX therapy alone.
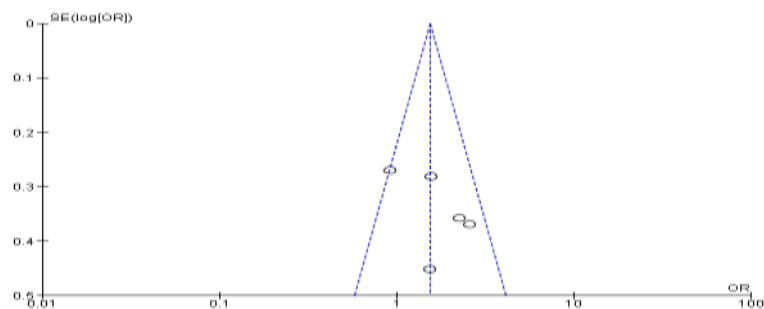
Fig. 3 Funnel plot of comparison: 1 IFX + IS vs. IS comparison, outcome: 1.1 Outcome of clinical remission rate in pts exposed to IFX + IS vs. IS(
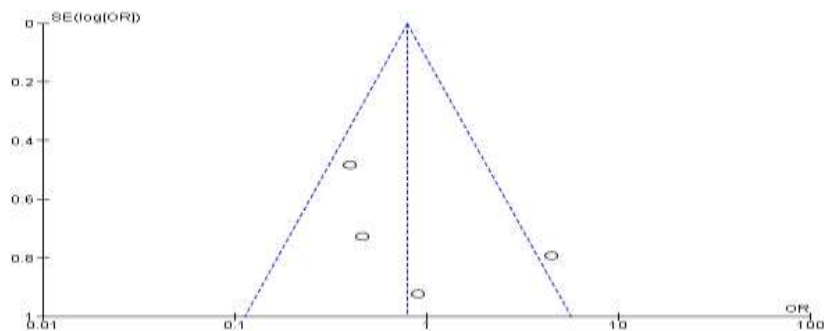
Fig. 4 Funnel plot of comparison: 1 IFX + IS vs. IFX comparison, outcome: 1.2 Outcome of Serious Adverse effects of pts on Anti TNF-alfa + IS vs. IFX.

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