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Review

Induction and maintenance treatment of inflammatory bowel disease: A comprehensive review

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ABSTRACT

Ulcerative colitis (UC) and Crohn's disease (CD) are the two major types of inflammatory bowel disease (IBD). We conducted a comprehensive review of meta-analyses to summarize the reported effectiveness of different drugs for IBD. We performed a literature search and a total of 110 meta-analyses from 66 articles were summarized and re-analyzed (62 in UC and 48 in CD). In summary, 5-ASA was more effective than placebo in both induction and maintenance treatment of UC, but there were conflicting results on the effect of 5-ASA on the induction treatment or relapse of CD. The use of immunomodulatory agents in the induction or maintenance phase of UC and CD using immunomodulators appeared to be more effective than placebo, but the results were impacted by small number of patients, discordant results with the largest study and risk of biases. Anti-TNF-α and anti-integrin therapeutic antibodies in both, induction and maintenance, showed a better efficacy than placebo in a large proportion of patients analyzed. Other agents, such as probiotics, antibiotics, omega-3, were shown to be more effective than placebo, but the same issues arose as stated above with the use of immunomodulatory agents. In conclusion, we performed a comprehensive review of meta-analysis on comparative efficacy of pharmacotherapy used in the management of IBD. Our review will augment our understanding of the treatment of UC and CD by providing a guideline for interpreting the statistically significant findings and discusses the optimal choice for IBD treatment.

1. Introduction

Inflammatory bowel disease (IBD) is regarded as a worldwide healthcare issue, with its steady increase in prevalence [1]. Two major types of IBD, Crohn's disease (CD) and ulcerative colitis (UC) [2], are chronic relapsing immunologic disorders of the intestine and they are considered to result from dysregulated expressions of molecules engaged in pro-inflammatory and anti-inflammatory processes [2–5]. They are frequently associated with other autoimmune diseases such systemic lupus erythematosus (SLE) [3]. Although the pathogenesis of an epithelial injury via aberrant inflammatory response is not clearly identified [6,7], it has been presumed that a combination of genetic susceptibility, external environment and intestinal commensal flora is involved in the etiology [8–10]. Both UC and CD are reported to be highly prevalent especially in westernized areas [11]. However, the incidence and prevalence of IBD is on the rise globally, and a recent increase particularly in Asian and Hispanic populations [12] should not be overlooked.

Recently, the treatment for IBD has made progress from simply controlling symptoms to modifying the course of the disease by achieving and maintaining remission which is defined as complete mucosal healing and normalization of blood markers as well as disappearance of symptoms [13,14]. However, heterogeneity in clinical presentation of UC and CD makes it difficult to find an optimal therapy which satisfies all patients [13]. In addition, though UC can be diagnosed in a way similar to CD, the approach to medical treatment of UC and CD varies substantially [14].

Although the efficacy of different pharmacotherapies has been

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assessed in a large number of randomized controlled trials (RCTs) and recently published guidelines based on those studies provide instructions for clinicians to treat IBD [15,16], there has not been a comprehensive review of meta-analysis on comparative effectiveness of pharmacotherapy of IBD (for UC and CD). This review aims to augment our understanding of the treatment of UC and CD by providing a guideline for interpreting the statistically significant findings and discusses the optimal choice for IBD treatment.

2. Methods

2.1. Inclusion and exclusion criteria

Studies were eligible for our re-analysis if they met all the following conditions: (1) they estimated the efficacy of individual treatment for induction or maintenance of IBD (for UC and CD) using odds ratio (OR), relative risk (RR), risk difference (RD), or mean difference (MD), and 95% confidence interval (CI); (2) they were written in English; (3) they were a systematic review and meta-analysis.

Articles were excluded if they met at least one of the following criteria: (1) they were irrelevant to pharmacotherapy for IBD; (2) they did not report individual results for UC or CD; (3) they were not meta-analyses such as a narrative review; (4) participants/patients were not human.

2.2. Search strategy and data extraction

Two of the authors (DYJ, SK) performed a literature search in PubMed/Medline to find meta-analyses evaluating the efficacy of various induction or maintenance therapies for IBD from their inception to March 31st, 2018, using the search term “inflammatory bowel disease” OR “ulcerative colitis” OR “Crohn's disease” AND “meta-analysis” (Fig. 1). A manual search was also conducted to identify and include any relevant studies that could have been missed out during the literature search. When there were multiple meta-analyses on the same therapy, we retained all the overlapping meta-analyses for a more comprehensive review and compared the results among overlapping meta-analyses.

Two investigators (DYJ, SK) also recorded the first author, published year, design of the study, comparison, outcome, the number of individual studies, type of metrics, summary effect, meta-analysis models used, and overall effect *p*-value from each meta-analysis of the eligible articles. Heterogeneity defined as I^2 index and Egger *p*-value (publication bias) were extracted from the articles if they were presented. The proportion of the number of significant studies over total included studies was also documented.

2.3. Statistical analysis for meta-analysis

We comprehensively performed re-meta-analyses, using the raw data from each article to obtain summary effect and its 95% confidence interval (CI) under both fixed and random effect [17] using Comprehensive Meta-Analysis (CMA) software for Windows 8. Identical types of metrics were adopted for re-analysis. Heterogeneity was tested by I^2 index, which estimates the ratio of between-study variance to the sum of between-study and within-study variances [18]. It measures the percentage of variability within the effect sizes thought to be arisen from between-study heterogeneity [18]. It ranges from 0% to 100%; ratios over 50%, and 75% respectively demonstrate large and very large heterogeneity [18]. Publication bias was determined by the regression asymmetry test, as suggested by Egger [19]. We also examined whether an effect of each meta-analysis and that of the largest study of each meta-analysis had the same, “concordant” direction [20].

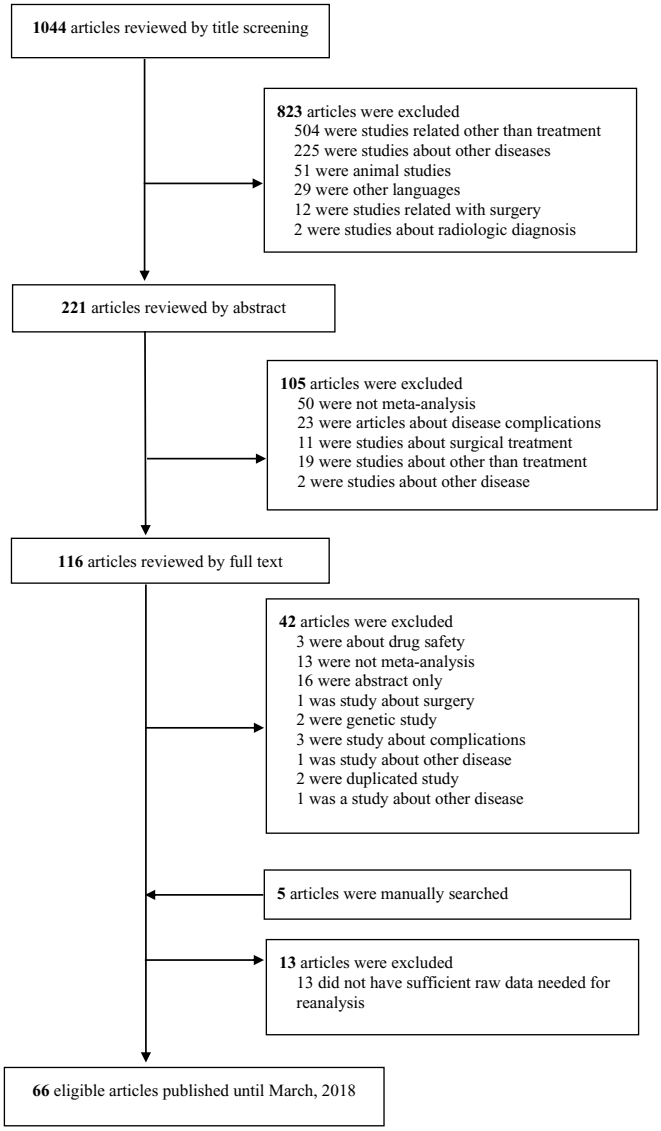

Fig. 1. Flow chart of literature search.

2.4. Interpretation of the results of meta-analysis

Although the current interpretation of the meta-analysis results is a statistical significance of *p*-value $< .05$, there have been several efforts to interpret the results of meta-analysis cautiously [20]. To help clinicians to understand the meta-analysis results easily and correctly, we considered and applied 5 principles to interpret them as below.

(1) Whether both random and fixed effects are significant.
(2) Whether the number of patients who participated in RCTs is large (> 1000 cases)
(3) Whether the results of meta-analysis are concordant or discordant with that of the largest study.
(4) Whether there is a high heterogeneity in the results of meta-analysis.
(5) Whether there is a publication bias in the results of meta-analysis.

3. Results

Out of 1044 articles identified, 928 were excluded after screening of the title and abstract. Among the remaining 116 articles, 13 studies irrelevant to the efficacy of pharmacotherapy for IBD (e.g.,

Table 1
Summary of the meta-analyses regarding induction and maintenance treatment of ulcerative colitis.

Author, year	Study design	Comparison	Outcome	No. of studies	No. of cases/ controls	Type of metrics	Reported summary effect (95% CI)[a]	M	Reported *p* value	Largest effect (95% CI)[b]	*p* value (largest)[b]
Outcome for induction treatment (clinical remission or response)											
Aminosalicylates and steroids											
Wang, et al. 2016	RCT	5-ASA vs placebo	Failure to maintain clinical or endoscopic remission	8	743/555	RR	0.69 (0.62–0.77)	F	< 0.00001	0.64 (0.48–0.85)	0.002
Ford, et al. 2011	RCT	5-ASA vs Placebo	Remission induction	11	1470/616	RR	0.79 (0.73–0.85)	R	< 0.00001	0.81 (0.68–0.96)	0.016
Ford, et al. 2011	RCT	High or standard dose 5-ASA vs low dose ASA	Remission induction	8	647/368	RR	0.91 (0.85–0.98)	R	0.01	0.81 (0.63–1.04)	0.102
Romkens, et al. 2012	RCT	Oral 5-ASA ≥ 3g vs < 3g	Mucosal healing	9	703/924	RR	1.19 (1.07–1.32)	R	0.002	1.29 (0.84–1.98)	0.249
Wang, et al. 2016	RCT	5-ASA vs sulfasalazine	Failure to maintain clinical or endoscopic remission	12	871/784	RR	1.14 (1.03–1.27)	F	0.014	1.29 (1.02–1.61)	0.030
Feagan, et al. 2013	RCT	5-ASA vs 5-ASA comparator	Failure to induce clinical remission	11	1022/946	RR	0.94 (0.86–1.02)	F	0.11	0.88 (0.67–1.17)	0.382
Zhu, et al. 2013	RCT	Once daily dosing regime with a divided dosing regime of oral delayed-release mesalamine	Induction of clinical remssion	3	364/363	RR	1.04 (0.93–1.16)	F	0.52	1.04 (0.94–1.17)	0.430
Feagan, et al. 2012	RCT	Once daily mesalamine versus conventional dosing	Failure to induce global/clinical remission	3	370/368	RR	0.95 (0.82–1.10)	F	0.49	0.86 (0.59–1.25)	0.430
Li, et al. 2016	RCT	Once daily vs multiple daily mesalamine therapy	Remission rates with the prescribed medication for induction trials	7	729/740	RR	1.03 (0.99–1.10)	R	0.269	0.95 (0.86–1.05)	0.355
Ford, et al. 2012	RCT	Topical vs oral 5-ASA	Remission induction	4	105/109	RR	0.82 (0.52–1.28)	R	0.38	1.17 (0.81–1.68)	0.412
Ford, et al. 2011	RCT	Glucocorticoid vs placebo	Failutre to induce remission	5	226/219	RR	0.65 (0.45–0.93)	R	0.02	0.70 (0.58–0.83)	0.000
Manguso, et al. 2016	RCT	Oral BDP vs oral PD or 5-ASA	Clinical remission	4	333/344	OR	1.30 (0.76–2.23)	R	0.34	0.82 (0.46–1.48)	0.510
Manguso, et al. 2016	RCT	Oral BDP vs oral PD or 5-ASA	Clinical response	5	352/363	OR	1.41 (1.03–1.93)	F	0.03	0.97 (0.60–1.57)	0.896
Zhao, et al. 2016	RCT	BDP vs 5-ASA (oral or enema)	Inducing remission and clinical improvement	7	580/368	OR	0.76 (0.56–1.03)	F	0.68	0.72 (0.40–1.29)	0.267
Immunomodulators and biologics											
Lasa, et al. 2017	RCT	Tacrolimus vs placebo	Failure in clinical response	2	76/51	RR	0.58 (0.45–0.73)	R	< 0.00001	0.58 (0.42–0.79)	0.001
Komaki, et al. 2016	RCT	Tacrolimus vs placebo	Clinical remssion at 2 weeks	2	51/50	RR	4.61 (2.09–10.17)	R	0.00015	3.75 (1.41–9.95)	0.008
Gisbert, et al. 2009	RCT	AZA vs placebo or 5-ASA	Induction of clinical remssion	4	89/83	OR	1.59 (0.59–4.29)	R	0.36	1.66 (0.61–4.48)	0.319
Jin, et al. 2015	RCT	Vedolizumab vs placebo	Clinical remission	3	901/221	OR	2.72 (1.76–4.19)	F	0.000	2.92 (1.55–5.50)	0.001
Brickston, et al. 2014	RCT	Vedolizumab vs placebo	Failure to induce clinical remission	4	382/224	RR	0.86 (0.80–0.91)	F	< 0.00001	0.88 (0.82–0.94)	0.000
Jin, et al. 2015	RCT	Vedolizumab vs placebo	Clinical response	3	901/221	OR	2.69 1.94–3.74)	F	0.000	2.60 (1.75–3.86)	0.000

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Table 1 (*continued*)

Author, year	Study design	Comparison	Outcome	No. of studies	No. of cases/ controls	Type of metrics	Reported summary effect (95% CI)[a]	M	Reported *p* value	Largest effect (95% CI)[b]	*p* value (largest)[b]
Lin et al., 2015	RCT	Anti-a4b7 antibody vs placebo	Clinical remission	3	381/222	OR	2.839 (1.656–4.867)	F	0.000	3.56 (1.615–7.861)	0.002
Lin et al., 2015	RCT	Anti-a4b7 antibody vs placebo	Clinical response	4	418/231	OR	2.609 (1.836–3.709)	F	0.000	2.601 (1.655–4.087)	0.000
Cholapranee, et al. 2017	RCT	Anti-TNF vs placebo	Induction	7	1188/1116	OR	1.99 (1.53–2.58)	–	–	1.82 (1.26–2.64)	0.001
Huang, et al. 2011	RCT	TNF-α blockers vs control (placebo or prednisolone or corticosteroid)	Short term response	6	758/514	OR	2.36 (1.34–4.15)	R	0.003	3.20 (2.03–5.03)	0.000
Huang, et al. 2011	RCT	TNF-α blockers vs control (placebo or prednisolone or corticosteroid)	Mucosal healing	7	788/537	OR	1.59 (0.91–2.78)	R	0.10	2.99 (1.89–4.71)	0.000
Zhang, et al. 2016	RCT	Adalimumab vs placebo	Short term results for clinical remission	3	685/472	RR	1.50 (1.08–2.09)	F	0.02	1.77 (1.10–2.86)	0.020
Chen et al. 2016	RCT	Adalimumab 160/ 80mg vs placebo	Inducing clinical remission at 8 weeks	3	468/472	RR	1.62 (1.15–2.29)	F	0.006	1.77 (1.10–2.86)	0.020
Chen et al. 2016	RCT	Adalimumab 160/ 80mg vs placebo	Inducing clinical response at 8 weeks	3	468/472	RR	1.37 (1.19–1.59)	F	< 0.0001	1.46 (1.18–1.80)	0.000
Zhang, et al. 2016	RCT	Adalimumab vs placebo	Short term results for clinical response	3	685/472	RR	1.33 (1.16–1.52)	F	< 0.0001	1.46 (1.18–1.60)	0.000
Ford, et al. 2011	RCT	Infliximab vs placebo	Remission induction	5	539/288	RR	0.72 (0.57–0.91)	R	0.006	0.60 (0.49,0.73)	0.000
Christophorou, et al. 2015	RCT, NRCT	Infliximab vs infliximab and immunosuppressant	Remission at 4–6 months	3	271/251	OR	0.50 (0.34–0.73)	F	0.001	0.64 (0.37–1.11)	0.109
Seow, et al. 2008	RCT	Type I IFN vs placebo	Remission	3	112/56	RR	1.24 (0.81–1.90)	F	0.33	1.15 (0.67–1.98)	0.619
Others											
Ganji-Arjenaki, et al. 2017	RCT	Probiotics vs control	Remission	18	772/850	RR	0.884 (0.808–0.967)	F	0.007	1.072 (0.728–1.58)	0.725
Shen, et al. 2014	RCT	Probiotics vs control	Remission./response rate	9	328/321	RR	1.51 (1.10–2.06)	R	0.01	2.73 (1.50–4.97)	0.001
Mardini, et al. 2014	RCT	Adding VSL#3 to a UC regimen vs placebo	Achieving clinical remission	3	162/157	OR	2.370 (1.456–3.859)	–	0.001	4.023 (1.833–8.830)	0.001
Jonkers, et al. 2012	RCT	VSL#3 vs control	Remission induction	3	178/173	RR	1.69 (1.17–2.43)	–	–	2.73 (1.50–4.97)	0.001
Sang, et al. 2010	RCT	Probiotics vs non-probiotics	Remission induction	7	219/180	RR	1.35 (0.98–1.85)	R	0.07	0.92 (0.73–1.16)	0.465
Fujiya, et al. 2014	RCT	Probiotics vs placebo	Response rate	5	184/178	RR	1.81 (1.40–2.35)	F	–	3.25 (1.50–7.03)	0.003
Khan, et al. 2011	RCT	Antibiotics vs placebo	Inducing remission in active UC	9	309/313	RR	0.64 (0.43–0.96)	R	0.03	0.96 (0.84–1.08)	0.465
Rahimi, et al. 2007	RCT	Antibiotics vs placebo	Clinical remssion	10	263/267	OR	2.14 (1.48–3.09)	F	< 0.0001	3.76 (1.37–10.52)	0.005
Gupta, et al. 2016	RCT	Antibiotics vs placebo	Clinical response to antibiotics among hospitalized patients receiving intravenous corticosteroids	3	–	OR	1.08 (0.50–2.32)	F	0.958	1.150 (0.320–4.136)	0.831
Wang, et al. 2012	RCT	Antibiotics vs placebo	Clinical improvement	9	310/316	OR	2.17 (1.54–3.05)	F	< 0.00001	2.73 (1.51–4.96)	0.001
Ji, et al. 2013	RCT	Acupuncture and/or moxibustion vs 5-ASA	Efficacy	10	473/278	OR	5.42 (3.38–8.68)	F	< 0.00001	5.00 (1.88–13.32)	0.001
Lee, et al. 2010	RCT	Moxibustion vs conventional drug	Response rate	6	254/153	RR	1.24 (1.11–1.38)	R	< 0.0001	1.38 (0.96–1.99)	0.080
Mcgrath, et al. 2004	RCT	Transdermal nicotinie vs placebo or standard therapy	Clinical and/or signoidoscopic remission	5	137/133	OR	1.39 (0.37–5.24)	R	0.63	2.30 (0.86–6.12)	0.095

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Table 1 (*continued*)

Author, year	Study design	Comparison	Outcome	No. of studies	No. of cases/ controls	Type of metrics	Reported summary effect (95% CI)[a]	M	Reported *p* value	Largest effect (95% CI)[b]	*p* value (largest)[b]
Outcome for maintenance treatment (maintenance of remission or relapse)											
Aminosalicylates											
Ford, et al. 2011	RCT	5-ASA vs Placebo	Preventing relapse	11	849/653	RR	0.65 (0.55–0.76)	R	< 0.00001	0.65 (0.48–0.86)	0.003
Ford, et al. 2011	RCT	High or standard dose 5-ASA vs low dose ASA	Preventing relapse	7	649/885	RR	0.79 (0.64–0.97)	R	0.02	0.91 (0.72–1.15)	0.415
Ford, et al. 2012	RCT	Topical 5-ASA vs placebo	Preventing relapse in quiescent UC	7	331/224	RR	0.60 (0.49–0.73)	R	< 0.00001	0.52 (0.35–0.79)	0.002
Nikfar, et al. 2009	RCT	Mesalamine vs sulfalazine	Relapse	6	262/259	RR	0.98 (0.78–1.23)	F	0.85	1.22 (0.79–1.89)	0.380
Li, et al. 2016	RCT	Once daily vs multiple daily mesalamine therapy	Remission rates with the prescribed medication for maintenance trials	10	1968/2002	RR	1.03 (0.99–1.07)	R	0.293	1.00 (0.93–1.07)	0.901
Zhu, et al. 2012	RCT	Once daily dosing regime with a twice-daily dosing regime of oral delayed-release mesalamine	Maintenance of clinical remssion	4	981/1014	RR	1.02 (0.92–1.13)	R	0.73	1.00 (0.95–1.06)	0.989
Tong, et al. 2012	RCT	Once daily vs multiple daily mesalamine	Preventing relapse in quiescent UC	8	1413/1447	RR	1.00 (0.89–1.12)	–	–	0.71 (0.53–0.94)	0.019
Ford, et al. 2011	RCT	Once daily mesalamine dosing vs a conventional dosing schedule	Preventing relapse in quiescent UC	7	1349/1396	RR	0.94 (0.82–1.08)	R	0.37	0.99 (0.81–1.22)	0.914
Feagan, et al. 2012	RCT	Once daily mesalamine versus conventional dosing	Failure to maintain global/clinical remission at 12 months	7	1394/1432	RR	0.92 (0.83–1.03)	F	0.17	1.01 (0.82–1.25)	0.901
Immunomodulators and biologics											
Timmer, et al. 2016	RCT	AZA vs placebo	Failure to maintain remission	4	115/117	RR	0.68 (0.54–0.86)	F	0.0016	0.77 (0.57–1.05)	0.098
Gisbert, et al. 2009	RCT	AZA vs placebo or 5-aminosalicylates	Maintenance of clinical remssion	6	124/112	OR	2.56 (1.51–4.34)	F	0.0005	4.16 (1.60–10.80)	0.004
Khan, et al. 2011	RCT	Immunosupperssive therapy (AZA or MTX) vs placebo	Preventing relapse	5	94/91	RR	0.67 (0.38–1.18)	R	0.16	0.75 (0.52–1.08)	0.120
Cholapranee, et al. 2017	RCT	Anti-TNF vs placebo	Maintenance	5	822/745	OR	2.59 (1.84–3.66)	–	–	1.82 (1.16–2.86)	0.009
Mao, et al. 2017	RCT	Biologics (infliximab or adaliumab) vs placebo	Hospitalization	2	964/727	OR	0.48 (0.29–0.80)	R	–	0.370 (0.267–0.513)	0.000
Others											
Shen, et al. 2014	RCT	Probitoics vs control	Maintaining remission	5	392/337	RR	0.89 (0.66–1.21)	R	0.47	1.07 (0.73–1.58)	0.725
Naidoo, et al. 2011	RCT	Probiotics vs mesalazine	Occurrence of relapse	3	277/278	OR	1.33 (0.94–1.90)	F	0.11	1.40 (0.90–2.18)	0.137
Turner, et al. 2011	RCT	Omega-3 fatty acids vs placebo	Maintaining remission	3	72/66	RR	1.01 (0.71–1.44)	R	0.96	1.06 (0.69–1.64)	0.777

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Table 1 (*continued*)

Author, year	I^2 (*p* value)[g]	No. of sigfinicant study/total study[c]	Egger *p* value[f]	Reanalyzed fixed summary effect (95% CI)	P[d] (fixed)	Reanalyzed random summary effect (95% CI)	P[e] (random)	Interpretation			
								Both random and fixed effect significant	> 1000 cases	Con-cordant	Not large I^2 (no heterogeneity)/ no bias
Outcome for induction treatment (clinical remission or response)											
Aminosalicylates and steroids											
Wang, et al. 2016	15 (0.32)	3/8	0.13	0.69 (0.62–0.77)	< 0.001	0.72 (0.64–0.81)	< 0.001	Yes	Yes	Yes	Yes/Yes
Ford, et al. 2011	58 (0.009)	8/11	0.02	0.78 (0.74–0.83)	< 0.001	0.79 (0.73–0.86)	< 0.001	Yes	Yes	Yes	No (Yes)/No
Ford, et al. 2011	0 (0.46)	1/8	0.02	0.89 (0.82–0.97)	0.009	0.91 (0.85–0.98)	0.012	Yes	Yes	No	Yes/No
Romkens, et al. 2012	0 (0.61)	2/9	0.56	1.17 (1.04–1.32)	0.007	1.19 (1.07–1.32)	0.002	Yes	Yes	No	Yes/Yes
Wang, et al. 2016	17 (0.28)	2/12	0.94	1.14 (1.03–1.27)	0.014	1.12 (0.99–1.27)	0.070	No	Yes	No	Yes/Yes
Feagan, et al. 2013	0 (0.94)	0/11	0.61	0.95 (0.88–1.04)	0.26	0.96 (0.89–0.104).	0.32	No	Yes	Yes	Yes/Yes
Zhu, et al. 2013	0 (0.53)	0/3	0.91	1.04 (0.92–1.16)	0.517	1.04 (0.942–1.15)	0.422	No	No	Yes	Yes/Yes
Feagan, et al. 2012	0 (0.39)	0/3	0.51	0.95 (0.82–1.10)	0.486	0.97 (0.84–1.12)	0.661	No	No	Yes	Yes/Yes
Li, et al. 2016	21 (0.292)	0/7	0.01	1.04 (0.97–1.11)	0.290	1.01 (0.95–1.08)	0.703	No	Yes	Yes	Yes/No
Ford, et al. 2012	64 (0.04)	1/4	0.16	0.73 (0.57–0.92)	0.009	0.72 (0.38–1.36)	0.313	No	No	Yes	No/Yes
Ford, et al. 2011	81 (0.0003)	4/5	0.23	0.68 (0.59–0.78)	< 0.001	0.65 (0.45–0.93)	0.019	Yes	No	Yes	No (Yes)/Yes
Manguso, et al. 2016	54 (0.09)	1/4	0.46	1.24 (0.87–1.75)	0.236	1.30 (0.76–2.23)	0.341	No	No	Yes	No/Yes
Manguso, et al. 2016	40 (0.16)	1/5	0.29	1.41 (1.03–1.93)	0.031	1.51 (0.98–2.33)	0.061	No	No	Yes	Yes/Yes
Zhao, et al. 2016	0 (0.68)	0/7	0.79	0.76 (0.56–1.03)	0.076	0.76 (0.56–1.03)	0.077	No	No	Yes	Yes/Yes
Immunomodulators and biologics											
Lasa, et al. 2017	0 (1.00)	2/2	> 0.5	0.58 (0.45–0.74)	< 0.001	0.58 (0.45–0.74)	< 0.001	Yes	No	Yes	Yes/Yes
Komaki, et al. 2016	0 (0.48)	2/2	N/A	4.74 (2.16–10.41)	< 0.001	4.61 (2.09–10.17)	< 0.001	Yes	No	Yes	Yes/ −
Gisbert, et al. 2009	47 (0.13)	1/4	0.86	1.57 (0.83–2.97)	0.171	1.59 (0.59–4.29)	0.361	No	No	Yes	Yes/Yes
Jin, et al. 2015	14.4 (0.311)	2/3	0.39	2.72 (1.76–4.19)	< 0.001	2.69 (1.67–4.31)	< 0.001	Yes	Yes	Yes	Yes/Yes
Brickston, et al. 2014	0 (0.57)	2/4	0.84	0.86 (0.80–0.92)	< 0.001	0.87 0.82–0.92)	< 0.001	Yes	No	Yes	Yes/Yes
Jin, et al. 2015	0 (0.945)	2/3	0.77	2.69 (1.94–3.74)	< 0.001	2.69 (1.94–3.74)	< 0.001	Yes	Yes	Yes	Yes/Yes
Lin et al., 2015	12.4 (0.319)	2/3	0.06	2.84 (1.66–4.87)	< 0.001	2.78 (1.54–5.03)	0.001	Yes	No	Yes	Yes/Yes
Lin et al., 2015	36.8 (0.191)	3/4	0.71	2.61 (1.84–3.71)	< 0.001	2.54 (1.49–4.32)	0.001	Yes	No	Yes	Yes/Yes
Cholapranee, et al. 2017	53.7 (0.044)	6/7	0.29	1.93 (1.63–2.30)	< 0.001	1.99 (1.53–2.58)	< 0.001	Yes	Yes	Yes	No (Yes)/Yes
Huang, et al. 2011	76 (0.001)	2/6	0.94	2.42 (1.92–3.05)	< 0.001	2.36 (1.34–4.15)	0.003	Yes	Yes	Yes	No/Yes
Huang, et al. 2011	77 (0.0003)	2/7	0.49	1.83 (1.46–2.30)	< 0.001	1.59 (0.91–2.78)	0.104	No	Yes	No	No/Yes
Zhang, et al. 2016	0 (0.45)	1/3	0.29	1.51 (1.08–2.09)	0.015	1.50 (1.08–2.09)	0.016	Yes	Yes	Yes	Yes/Yes
Chen et al. 2016	25 (0.27)	2/3	0.49	1.62 (1.15–2.29)	0.006	1.59 (1.05–2.40)	0.030	Yes	No	Yes	Yes/Yes
Chen et al. 2016	0 (0.56)	2/3	0.91	1.37 (1.19–1.59)	< 0.001	1.37 (1.18–1.59)	< 0.001	Yes	No	Yes	Yes/Yes
Zhang, et al. 2016	0 (0.43)	1/3	0.88	1.33 (1.16–1.52)	< 0.001	1.32 (1.15–1.52)	< 0.001	Yes	Yes	Yes	Yes/Yes
Ford, et al. 2011	70 (0.009)	2/5	0.12	0.63 (0.56–0.71)	< 0.001	0.72 (0.57–0.91)	0.006	Yes	No	Yes	No/Yes
Christophorou, et al. 2015	0 (0.49)	2/3	0.29	0.50 (0.34–0.72)	< 0.001	0.50 (0.34–0.73)	< 0.001	Yes	No	No	Yes/Yes
Seow, et al. 2008	0 (0.58)	0/3	0.15	1.24 (0.81–1.90)	0.33	1.17 (0.77–1.82)	0.43	No	No	Yes	Yes/Yes
Others											
Ganji-Arjenaki, et al. 2017	88.7 (0.000)	6/18	0.71	0.88 (0.81–0.96)	0.006	0.95 (0.74–1.22)	0.684	No	Yes	Yes	No/Yes
Shen, et al. 2014	65 (0.004)	2/9	0.06	1.41 (1.20–1.66)	< 0.001	1.51 (1.10–2.06)	0.01	Yes	No	Yes	No/Yes
Mardini, et al. 2014	29 (0.24)	1/3	0.99	2.37 (1.46–3.86)	0.001	2.39 (1.30–4.41)	0.005	Yes	No	Yes	Yes/Yes
Jonkers, et al. 2012	47 (0.15)	2/3	0.27	1.73 (1.32–2.27)	< 0.001	1.69 (1.17–2.43)	0.005	Yes	No	Yes	Yes/Yes
Sang, et al. 2010	62 (0.02)	1/7	0.06	1.25 (1.06–1.48)	0.008	1.35 (0.98–1.85)	0.068	No	No	Yes	No/Yes
Fujiya, et al. 2014	0 (0.4333)	3/5	0.32	1.81 (1.40–2.33)	< 0.001	1.71 (1.34–2.19)	< 0.001	Yes	No	Yes	Yes/Yes
Khan, et al. 2011	69 (0.001)	2/9	0.04	0.76 (0.66–0.88)	< 0.001	0.64 (0.43–0.96)	0.03	Yes	No	No	No/No
Rahimi, et al. 2007	26.5 (0.200)	3/10	0.66	2.16 (1.50–3.12)	< 0.001	2.08 (1.32–3.27)	0.002	Yes	No	Yes	Yes/Yes
Gupta, et al. 2016	0 (0.956)	0/3	0.75	1.08 (0.50–2.32)	0.845	1.08 (0.50–2.32)	0.845	No	–	Yes	Yes/Yes
Wang, et al. 2012	16.9 (0.29)	3/9	0.58	2.17 (1.54–3.05)	< 0.001	2.09 (1.40–3.12)	< 0.001	Yes	No	Yes	Yes/Yes
Ji, et al. 2013	17 (0.28)	4/10	0.54	5.42 (3.38–8.68)	< 0.001	4.96 (2.84–8.66)	< 0.001	Yes	No	Yes	Yes/Yes

(*continued on next page*)

Table 1 (*continued*)

Author, year	I^2 (*p* value)[g]	No. of sigfinicant study/total study[c]	Egger *p* value[f]	Reanalyzed fixed summary effect (95% CI)	P[d] (fixed)	Reanalyzed random summary effect (95% CI)	P[e] (random)	Interpretation			
								Both random and fixed effect significant	> 1000 cases	Con-cordant	Not large I^2 (no heterogeneity)/ no bias
Lee, et al. 2010	16 (0.31)	2/6	0.02	1.29 (1.16–1.44)	< 0.001	1.24 (1.11–1.38)	< 0.001	Yes	No	No	Yes/No
Mcgrath, et al. 2004	74 (0.004)	2/5	0.75	1.23 (0.71–2.14)	0.459	1.39 (0.37–5.24)	0.631	No	No	Yes	No/Yes
Outcome for maintenance treatment (maintenance of remission or relapse)											
Aminosalicylates											
Ford, et al. 2011	52 (0.02)	7/11	0.15	0.64 (0.58–0.71)	< 0.001	0.65 (0.55–0.76)	< 0.001	Yes	Yes	Yes	No (Yes)/Yes
Ford, et al. 2011	59 (0.02)	2/7	0.03	0.82 (0.72–0.93)	0.002	0.79 (0.64–0.97)	0.023	Yes	Yes	No	No/No
Ford, et al. 2012	21 (0.27)	5/7	0.02	0.59 (0.50–0.69)	< 0.001	0.60 (0.50–0.73)	< 0.001	Yes	No	Yes	Yes/No
Nikfar, et al. 2009	0 (0.63)	0/6	0.55	0.98 (0.78–1.23)	0.846	0.95 (0.75–1.19)	0.647	No	No	Yes	Yes/Yes
Li, et al. 2016	16.3 (0.293)	2/10	0.23	1.03 (0.99–1.07)	0.187	1.03 (0.98–1.08)	0.222	No	Yes	Yes	Yes/Yes
Zhu, et al. 2012	66 (0.03)	1/4	0.78	1.01 (0.96–1.06)	0.682	1.02 (0.92–1.13)	0.731	No	Yes	Yes	
Tong, et al. 2012	41 (0.105)	1/8	0.44	1.00 (0.89–1.13)	0.999	0.98 (0.83–1.16)	0.796	No	Yes	No	Yes/Yes
Ford, et al. 2011	33 (0.17)	1/7	0.47	0.95 (0.85–1.06)	0.349	0.94 (0.82–1.08)	0.369	No	Yes	Yes	Yes/Yes
Feagan, et al. 2012	40.9 (0.15)	1/7	0.29	0.92 (0.83–1.04)	0.171	0.91 (0.79–1.05)	0.192	No	Yes	Yes	Yes/Yes
Immunomodulators and biologics											
Timmer, et al. 2016	0 (0.6)	0/4	0.09	0.68 (0.54–0.86)	0.002	0.71 (0.56–0.89)	0.003	Yes	No	No	Yes/Yes
Gisbert, et al. 2009	29 (0.22)	1/6	0.94	2.56 (1.49–4.45)	0.001	2.55 (1.28–5.06)	0.008	Yes	No	Yes	Yes/Yes
Khan, et al. 2011	56 (0.06)	0/5	0.35	0.68 (0.51–0.92)	0.012	0.67 (0.38–1.18)	0.162	No	No	Yes	No/Yes
Cholapranee, et al. 2017	51.4 (0.084)	5/5	0.27	2.51 (1.98–3.18)	< 0.001	2.58 (1.83–3.65)	< 0.001	Yes	Yes	Yes	No (Yes)/Yes
Mao, et al. 2017	76.1 (0.346)	2/2	N/A	0.47 (0.37–0.60)	< 0.001	0.48 (0.29–0.81)	0.006	Yes	Yes	Yes	No (Yes)/ –
Others											
Shen, et al. 2014	35 (0.19)	1/5	0.50	0.92 (0.73–1.15)	0.448	0.90 (0.66–1.21)	0.465	No	No	Yes	Yes/Yes
Naidoo, et al. 2011	11 (0.32)	0/3	0.72	1.33 (0.94–1.90)	0.109	1.33 (0.90–1.96)	0.16	No	No	Yes	Yes/Yes
Turner, et al. 2011	0 (0.93)	0/3	0.44	1.01 (0.71–1.44)	0.963	1.02 (0.72–1.45)	0.925	No	No	Yes	Yes/Yes

Abbreviations: No., number; UC, ulcerative colits; RCT, randomized controlled trial; NRCT, non-randomized controlled tiral; IFN, interferon; BDP, beclomethasone dipropionate; PD, prednisone; 5-ASA, 5-aminosalicylic acid; TNF, tumor necrosis factor; AZA, Azathioprine; MTX, methotrexate; VSL3#, probiotics; TNF, tumor-necrosis factor; OR, odds ratio; RR, relative risk; M, models of meta-analysis; F, fixed effects; R, random effects.

[a] Summary random effects effect size (95% CI) of each meta-analysis.

[b] Effect size (95% CI) and *p*-value from the largest study in each meta-analysis.

[c] Proportion of the number of statistically significant studies to to the total number of studies.

[d] *p*-value from summary fixed effects effect size (95% CI) of each meta-analysis.

[e] *p*-value from summary random effects effect size (95% CI) of each meta-analysis.

[f] *p*-value from the Egger regression asymmetry test for evaluation of publication bias.

[g] I^2 metric of inconsistency (95% confidence intervals of I^2) and *p*-value of the Cochran Q test for evaluation of heterogeneity.

complications of medical treatment, efficacy of surgical treatment, and genetic studies), and 29 non-meta-analytical studies were excluded after scrutinizing the full text of each article. Additionally, five articles were manually searched and included in our review, while 13 articles were eliminated because raw data necessary for further analysis were not available from the text. Overall, 66 articles were found to be eligible for this systematic review [21–86] (Fig. 1).

We conducted quantitative synthesis of the meta-analyses from the 66 articles (Tables 1 and 2). Re-analyzed articles corresponded to 657 primary studies, with a majority of them being randomized controlled trials (RCTs) but also some observational studies (OSs) such as cohort studies. The total number of cases and controls combined together in the re-analyses was 112,217.

3.1. Ulcerative colitis

3.1.1. Characteristics of meta-analysis analyzing efficacy of pharmacotherapy in cases with ulcerative colitis

There were 46 articles with 62 meta-analyses describing the efficacy of pharmacotherapy for UC, comprising 365 individual studies with 62,371 cases and controls. The median value of the number of individual studies included in each meta-analysis was five with interquartile range (IQR) 3–7. In addition, the median value of the number of cases and controls per meta-analysis was 744 with IQR 521–1477. For 24 (39%) meta-analyses about UC, the sum of the number of cases and controls exceeded 1000, of which 14 (23%) demonstrated statistically significant results under random effect model. 36 (58%) had significant p-value < .05 under random effect model, and 18 (29%) showed greater significance with p-value < .001. All the reported outcomes were identically regenerated in our re-analysis.

However, 12 (19%) showed discordant results between random and fixed effects model, four of which had large heterogeneity ($I^2 \geq 50\%$). There were 11 (18%) meta-analyses which had evidence of a publication bias assessed by Egger's test, and three (5%) were indeterminate due to insufficient number of studies. 10 (16%) presented a discordant direction between an effect of a meta-analysis and that of the largest study of the meta-analysis.

3.1.2. Induction treatment of ulcerative colitis

Regarding induction treatment of UC using aminosalicylates, 5-ASA was more effective than placebo (> 1000 cases, concordant direction). Controversial results have been obtained when high doses or a fixed dose of 5-ASA of 3g or above were analyzed. High or standard dose of 5-ASA was shown to be more effective than low dose of ASA (> 1000 cases), but this result was discordant with that of the largest study. One of the included studies out of 8 RCTs showed a positive effect, limited by a publication bias. Oral 5-ASA ≥ 3g was shown to be more effective than < 3g of 5-ASA (> 1000 cases), but this result was discordant with that of the largest study and only two of the 9 RCTs showed a positive effect. There were no differences in the comparisons of 5-ASA vs. sulfasalazine, 5-ASA (including balsalazide, Pentasa, olsalazine, MMX mesalazine, Ipocol, and 5-ASA micro-pellets) vs. 5-ASA comparator (including Asacol,Claversal, and Salofalk), once daily vs. multiple doses over a day of mesalamine therapy and topical vs. oral 5-ASA.

Regarding induction treatment of UC using steroids, glucocorticoid was more effective than placebo (concordant direction, effective in 4 of the 5 RCTs), but the number of patients was < 1000, requiring confirmation by further large RCTs in the future. However, there were no differences in the comparisons of oral beclomethasone dipropionate (BDP) vs. oral prednisone (PD) or 5-ASA and BDP vs 5-ASA (oral or enema).

Regarding induction treatment of UC using immunomodulators, tacrolimus was shown to be more effective than placebo, but the number of patients was very small (100–200 cases), requiring confirmation by further large RCTs in the future. In addition, there was no difference in the comparison of azathioprine (AZA) vs. placebo or 5-ASA.

Regarding induction treatment of UC using biologics, vedolizumab (anti-integrin a4b7 antibody) was more effective than placebo (> 1000 cases, concordant direction) without any heterogeneity or publication bias. Anti-TNF-α was also more effective than placebo (> 1000 cases, concordant direction) without any heterogeneity or publication bias. However, mucosal healing did not differ when anti-TNF-α blockers where compared to the respective controls (placebo or prednisolone or corticosteroid). According to the analyses by different kinds of anti-TNF-α blockers, adalimumab was more effective than placebo (> 1000 cases, concordant direction) without any heterogeneity or publication bias. Infliximab was also more effective than placebo (concordant direction), but the overall number of patients was smaller (< 1000 cases). Infliximab and a concomitant immunosuppressive agent was shown to be more effective than infliximab alone, but this result was discordant with that of the largest study and the number of patients was small (< 1000 cases), requiring confirmation in the future. In addition, there was no difference in the comparison of type I interferons (IFN) vs. placebo.

Regarding induction treatment of UC using probiotics, previous meta-analyses showed that probiotics were more effective than placebo. While the number of included RCTs in these analyses ranged from 3 to 9, a more recent meta-analysis included 18 RCTs demonstrated no difference [41]. Regarding the effect of antibiotics on clinical improvement of UC, our analysis revealed that antibiotics might be more effective than placebo (> 1000 cases, concordant direction) without any heterogeneity or publication bias.

Acupuncture and/or moxibustion was shown to be more effective than 5-ASA, but the number of patients was small (< 1000 cases), requiring further validation. Response rates were shown to be better with moxibustion than with conventional drug therapy, but the number of patients was small (< 1000 cases) and this result was discordant with the largest study. Clinical and/or sigmoidoscopic remission was not different between transdermal nicotine application and placebo or standard therapy.

3.1.3. Treatment in the maintenance phase of ulcerative colitis

In the maintenance of remission, the use of 5-ASA was more effective than placebo (> 1000 cases, concordant direction) in preventing relapses. High or standard dose of 5-ASA was shown to be more effective than low dose of ASA (> 1000 cases) in preventing relapse, but this result was discordant with that of the largest study and there was a high heterogeneity and a publication bias. Topical 5-ASA was shown to be more effective than placebo in preventing relapse in quiescent UC, but the number of patients was small (< 1000 cases) and with a publication bias. There were no differences in the comparisons of mesalamine vs. sulfalazine, once daily vs. multiple doses of mesalamine therapy, and once daily mesalamine dosing vs. a conventional dosing schedule in the prevention of relapse.

Among immunomodulatory agents, AZA was shown to be more effective than placebo or 5-ASA to maintain remission, but the number of patients was small (200–300 cases), and individual results were discordant. Moreover, AZA was shown to be more effective than placebo or 5-ASA in maintaining remission, but the number of patients was small (200–300 cases), and only one of the 6 individual studies showed better efficacy of AZA, which requires confirmation. In addition, there was no difference in the comparison of immunosupperssive therapy (AZA or MTX) vs. placebo in preventing relapse.

In the maintenance of remission, anti-TNF-α was more effective than placebo (> 1000 cases, concordant direction) without any heterogeneity or publication bias in maintaining remission or hospitalization. Other agents showed similar efficacy compared to placebo or controls regarding occurrence of relapses.

Table 2
Summary of the meta-analyses regarding induction and maintenance treatment of Crohn's disease.

Author, year	Study design	Comparison	Outcome	No. of studies	No. of cases/ controls	Type of metrices	Reported summary effect (95% CI)[a]	M	Overall effect *p* value	Largest effect (95% CI)[b]	P (largest)[b]
Outcome for induction treatment (clinical remission or response)											
Aminosalicylates and steroids											
Ford, et al. 2011	RCT	5-ASA vs Placebo	Remission induction	6	565/345	RR	0.89 (0.80–0.99)	R	0.03	1.10 (0.92–1.31)	0.319
Lim, et al. 2016	RCT, OS	Sulfasalazine vs placebo	Induction of remission (CDAI < 150), therapeutic response (VHI decrease ≥25%) or clinical improvement	3	141/148	RR	1.52 (0.95–2.43)	R	0.078	1.46 (0.90–2.35)	0.122
Hanauer, et al. 2004	RCT	Pentasa 4g vs placebo	Intent-to-treat endpoint analysis of the CDAI score	3	304/311	MD	−18 (−35, −1)	F	0.04	−8 (−33,16)	0.521
Ford, et al. 2011	RCT	Glucocorticoid vs budesonide	Failutre to induce remission	6	304/365	RR	0.82 (0.68–0.98)	R	0.03	0.91 (0.68–1.22)	0.528
Immunomodulators and biologics											
Chande, et al. 2013	RCT	AZA or 6-MP vs placebo	Clinical reemission or improvement	5	197/183	RR	1.23 (0.97–1.55)	R	0.084	1.37 (0.82–2.28)	0.226
Prefontaine, et al. 2010	RCT	AZA or 6-MP vs placebo	Remission	8	209/216	OR	2.43 (1.62–3.64)	F	0.00063	1.57 (0.75,3.29)	0.227
Khan, et al. 2011	RCT	Immunosupperssive therapy (Aza, 6-MP, MTX, cyclosporine) vs placebo	Remission induction	8	350/287	RR	0.84 (0.76–0.94)	R	0.002	0.75 (0.61–0.93)	0.008
Cholapranee, et al. 2017	RCT	Anti-TNF vs placebo	Induction	2	94/77	OR	3.93 (0.77–20.09)	–	–	2.50 (0.99–6.34)	0.053
Ford, et al. 2011	RCT	Anti-TNF vs placebo	Remission induction	10	1598/1158	RR	0.87 (0.80–0.94)	R	0.0004	0.95 (0.88–1.02)	0.181
Peyrin-Biroulet, et al. 2008	RCT	Anti-TNF therapy vs placebo	Induction of remission at week 4	9	1449/899	RD	11% (6–16%)	R	< 0.001	8% (3–13%)	0.004
Peyrin-Biroulet, et al. 2008	RCT	Anti-TNF therapy vs placebo	Short and long term induction	3	705/516	RD	8% (3–12%)	R	< 0.001	11% (5–17%)	0.004
Huang, et al. 2011	RCT	Adalimumab vs placebo	Clinical remission at week 4	2	384/240	OR	2.98 (1.78–4.99)	F	< 0.0001	3.49 (1.73–7.02)	0.000
Song, et al. 2014	RCT	Adalimumab vs placebo	70-point response	4	515/328	OR	2.30 (1.70–3.12)	F	< 0.00001	2.09 (1.34–3.27)	0.001
Huang, et al. 2011	RCT	Adalimumab vs placebo	Clinical response at week 4	2	384/240	OR	1.93 (1.33–2.79)	F	0.0005	1.90 (1.18–3.05)	0.008
Da, et al. 2013	RCT	Certolizumab vs placebo	Remissioon induction	3	500/307	OR	1.361 (0.974–1.901)	F	0.071	1.412 (0.923–2.158)	0.111
Chalhoub, et al. 2017	RCT, OS	Adalimumab monotherapy vs combination therapy	Induction of remission	12	1696/1400	OR	0.86 (0.70–1.06)	R	0.17	0.75 (0.58–0.97)	0.030
Kopylov, et al. 2014	RCT, OS	Adalimumab monotherapy vs combination therapy with immunomodulators	Induction of clinical remission	7	976/1008	OR	0.78 (0.64–0.95)	F	0.01	0.75 (0.58–0.97)	0.030
Lin, et al. 2011	RCT	Combination therapy of infliximab and immunosuppressives vs monotherapy	Induction remssion at 48–54 weeks	8	568/708	OR	1.83 (1.44–2.32)	F	< 0.00001	2.71 (1.70–4.30)	0.000

(*continued on next page*)

Table 2 (*continued*)

Author, year	Study design	Comparison	Outcome	No. of studies	No. of cases/ controls	Type of metrices	Reported summary effect (95% CI)[a]	M	Overall effect *p* value	Largest effect (95% CI)[b]	P (largest)[b]
Apoorva, et al. 2015	RCT	Anti-integrin agents (natalizumab or vedolizumab) vs placebo	Inducing remssion in active luminal CD	8	1726/946	RR	0.87 (0.84–0.91)	R	< 0.00001	0.91 (0.81–1.01)	0.084
Lin et al., 2015	RCT	Anti-a4b7 antibody vs placebo	Clinical remission	6	1513/712	OR	2.108 (1.460–3.043)	R	0.000	1.370 (0.964–1.948)	0.079
Lin et al., 2015	RCT	Anti-a4b7 antibody vs placebo	Clinical response	5	1495/700	OR	1.607 (1.327–1.947)	F	0.000	1.325 (0.956–1.836)	0.091
Apoorva, et al. 2015	RCT	Natalizumab vs placebo	Inducing remission in active luminal CD on prior anti-TNF exposure	5	911/283	RR	0.87 (0.80–0.95)	R	0.003	0.94 (0.80–1.09)	0.398
Ford, et al. 2011	RCT	Natalizumab vs placebo	Remission induction	5	1238/533	RR	0.88 (0.83–0.94)	R	0.0001	0.91 (0.81–1.01)	0.084
Others											
Ganji-Arjenaki, et al. 2017	RCT	Probiotics vs control	Remission	9	320/321	RR	0.870 (0.747–1.013)	F	0.072	1.056 (0.793–1.406)	0.708
Shen, et al. 2014	RCT	Probiotics vs control	Remission./response rate	3	40/34	RR	0.89 (0.70–1.13)	R	0.35	1.00 (0.63–1.56)	0.983
Fujiya, et al. 2014	RCT	Probiotics vs placebo	Response rate	4	139/141	RR	1.17 (0.81–1.70)	F	–	1.46 (0.35–6.14)	0.608
Khan, et al. 2011	RCT	Antibiotics vs placebo	Inducing remission in active CD	10	702/458	RR	0.85 (0.73–0.99)	R	0.03	0.79 (0.64–0.98)	0.029
Wang, et al. 2012	RCT	Antibiotics vs placebo	Clinical improvement	14	429/403	RR	1.35 (1.16–1.58)	F	0.0001	1.33 (1.05–1.68)	0.018
Huang, et al. 2009	RCT	Antibacterial therapy vs placebo	Clinical remssion	7	225/188	OR	1.02 (0.67–1.55)	F	–	0.87 (0.42–1.80)	0.711
Huang, et al. 2009	RCT	Antibacterial therapy vs placebo	Clinical response	7	134/134	OR	1.52 (0.91–2.55)	F	–	2.91 (0.96–8.82)	0.059
Rahimi, et al. 2006	RCT	Broad-spectrum antibiotic therapy vs placebo	Clinical improvement	19	431/373	OR	2.257 (1.678–3.036)	F	< 0.001	1.024 (0.462–2.270)	0.950
Feller, et al. 2009	RCT	Nitroimidazole vs placebo	Remission in patients with active disease and relapse in patients with inactive disease	3	–	OR	3.54 (1.94–6.47)	R	–	4.79 (1.91–11.99)	0.001
Feller, et al. 2009	RCT	Clofazimine only or in combination vs placebo	Remission in patients with active disease and relapse in patients with inactive disease	4	–	OR	2.86 (1.67–4.88)	R	–	2.59 (1.32–5.10)	0.006
Outcome for maintenance treatment (maintenance of remission or relapse)											
Aminosalicylates											
Ford, et al. 2011	RCT	5-ASA vs Placebo	Preventing relapse	16	1222/1274	RR	0.97 (0.90–1.05)	R	0.45	1.23 (1.03–1.48)	0.023
Camma, et al. 1997	RCT	Mesalamine (5-ASA) vs control	Relapse	15	1047/1050	RD	−6.3% (−10.4, −2.1%)	F	0.0028	−11.1% (−21.9, −2.0%)	0.045
Immunomodulators and biologics											
Cholapranee, et al. 2017	RCT	Anti-TNF vs placebo	Maintenance	2	88/75	OR	19.71 (3.51–110.84)	–	–	40.14 (2.34–688.00)	0.011
Peyrin-Biroulet, et al. 2008	RCT	Anti-TNF therapy vs placebo	Maintenance after open-label induction	4	806/526	RD	23% (18–28%)	R	< 0.001	26% (19–34%)	0.000
Ford, et al. 2011	RCT	Anti-TNF vs placebo	Preventing relapse	5	844/546	RR	0.71 (0.65–0.76)	R	< 0.00001	0.70 (0.63–0.77)	0.000
Jean, et al. 2017	RCT, OS	Adalimumab vs Adalimumab + immunomodulators	Maintenance of remission	9	1026/859	OR	0.97 (0.79–1.19)	R	0.75	0.87 (0.62–1.22)	0.416

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Table 2 (*continued*)

Author, year	Study design	Comparison	Outcome	No. of studies	No. of cases/ controls	Type of metrices	Reported summary effect (95% CI)[a]	M	Overall effect *p* value	Largest effect (95% CI)[b]	P (largest)[b]
Kopylov, et al. 2014	RCT, OS	Adalimumab monotherapy versus combination therapy with immunomodulators	Maintenance of clinical remission	4	337/496	OR	1.08 (0.79–1.48)	R	0.61	1.18 (0.69–2.01)	0.546
Da, et al. 2013	RCT	Certolizumab vs placebo	Remission maintenance	2	546/538	OR	1.888 (1.390–2.565)	F	0.000	2.260 (1.514–3.373)	0.000
Mao, et al. 2017	RCT	Biologics (infliximab or adalizumab) vs placebo	Surgery	3	1041/592	OR	0.23 (0.13–0.42)	R	–	0.37 (0.16–0.82)	0.017
Others											
Shen, et al. 2014	RCT	Probitoics vs control	Maintaining remission	7	165/166	RR	1.09 (0.69–1.74)	R	0.71	1.39 (0.33–5.88)	0.656
Rahimi, et al. 2008	RCT	Probiotics vs placebo	Clinical relapse	7	130/123	OR	0.920 (0.523–1.619)	F	0.8853	2.222 (0.653–8.189)	0.158
Jonkers, et al. 2012	RCT	L. jhonsonil vs control	Preventing relapse	2	71/74	RR	0.93 (0.63–1.38)	–	–	0.77 (0.53–1.11)	0.161
Shen, et al. 2009	RCT	Lactobacillus vs placebo	Clinical relaspe	6	179/180	RR	1.15 (0.90–1.48)	F	0.26	0.73 (0.49–1.08)	0.115
Patton, et al. 2016	RCT	Anti-tuberculous therapy vs placebo	Relapse	4	112/94	RR	0.58 (0.45–0.75)	F	0.00003	0.71 (0.55–0.91)	0.008
Turner, et al. 2011	RCT	Omega-3 fatty acids vs placebo	Maintaining remission	6	523/516	RR	0.77 (0.61–0.98)	R	0.03	0.90 (0.73–1.11)	0.326

Author, year	I^2 (95% CI) (P)[g]	No. of sigfinicant/ total study[c]	Egger *p* value[f]	Reanalyzed fixed summary effect (95% CI)	P[d] (fixed)	Reanalyzed random summary effect (95% CI)	P[e] (random)	Interpretation			
								Both random and fixed effect significant	> 1000 cases	Con-cordant	Not large I^2 (no heterogeneity)/ no bias
Outcome for induction treatment (clinical remission or response)											
Aminosalicylates and steroids											
Ford, et al. 2011	30 (0.21)	1/6	0.52	0.89 (0.82–0.98)	0.012	0.89 (0.80–0.99)	0.031	Yes	No	No	Yes/Yes
Lim, et al. 2016	41 (0.18)	1/3	0.04	1.54 (1.13–2.11)	0.007	1.52 (0.95–2.43)	0.078	No	No	Yes	Yes/No
Hanauer, et al. 2004	56.8 (0.099)	1/3	0.55	−17.70 (−34.93, −0.47)	0.044	−20.16 (−47.23, 6.91)	0.144	No	No	Yes	No/Yes
Ford, et al. 2011	0 (0.51)	0/6	0.50	0.81 (0.68–0.97)	0.022	0.82 (0.69–0.99)	0.033	Yes	No	No	Yes/Yes
Immunomodulators and biologics											
Chande, et al. 2013	9 (0.35)	1/5	0.49	1.25 (1.00–1.56)	0.056	1.23 (0.97–1.55)	0.084	No	No	Yes	Yes/Yes
Prefontaine, et al. 2010	92 (0.0029)	3/8	0.58	2.43 (1.62–3.64)	< 0.001	2.66 (1.17–6.08)	0.020	Yes	No	No	No/Yes
Khan, et al. 2011	0 (0.44)	2/8	0.60	0.83 (0.74–0.93)	0.002	0.84 (0.76–0.94)	0.002	Yes	No	Yes	Yes/Yes
Cholapranee, et al. 2017	36.2 (0.211)	0/2	N/A	3.42 (1.46–8.06)	0.005	3.74 (0.81–17.37)	0.092	No	No	Yes	Yes/−
Ford, et al. 2011	68 (0.001)	5/10	0.23	0.87 (0.84–0.91)	< 0.001	0.87 (0.80–0.94)	< 0.001	Yes	Yes	No	No/Yes
Peyrin-Biroulet, et al. 2008	60.1 (0.010)	5/9	0.72	11% (8–14%)	< 0.001	11% (6–16%)	< 0.001	Yes	Yes	Yes	No (Yes)/Yes
Peyrin-Biroulet, et al. 2008	0 (0.712)	1/3	0.23	7% (3–11%)	0.002	7% (3–11%)	0.002	Yes	Yes	Yes	Yes/Yes
Huang, et al. 2011	0 (0.53)	2/2	N/A	2.98 (1.78–4.99)	< 0.001	3.00 (1.79–5.01)	< 0.001	Yes	No	Yes	Yes/−
Song, et al. 2014	0 (0.69)	3/4	0.30	2.30 (1.70–3.12)	< 0.001	2.30 (1.70–3.11)	< 0.001	Yes	No	Yes	Yes/Yes
Huang, et al. 2011	0 (0.93)	2/2	N/A	1.93 (1.33–2.79)	0.001	1.93 (1.33–2.78)	0.001	Yes	No	Yes	Yes/−
Da, et al. 2013	0 (0.454)	0/3	0.19	1.36 (0.97–1.90)	0.071	1.36 (0.97–1.90)	0.071	No	No	Yes	Yes/Yes
Chalhoub, et al. 2017	26 (0.19)	2/12	0.73	0.85 (0.73–1.00)	0.046	0.86 (0.70–1.06)	0.168	No	Yes	No	Yes/Yes
Kopylov, et al. 2014	0 (0.59)	1/7	0.95	0.78 (0.64–0.95)	0.013	0.78 (0.64–0.95)	0.015	Yes	Yes	Yes	Yes/Yes

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Table 2 (*continued*)

Author, year	I^2 (95% CI) (P)[g]	No. of sigfinicant/ total study[c]	Egger *p* value[f]	Reanalyzed fixed summary effect (95% CI)	P[d] (fixed)	Reanalyzed random summary effect (95% CI)	P[e] (random)	Interpretation			
								Both random and fixed effect significant	> 1000 cases	Con-cordant	Not large I^2 (no heterogeneity)/ no bias
Lin, et al. 2011	20.3 (0.27)	3/8	0.86	1.83 (1.44–2.32)	< 0.001	1.80 (1.35–2.41)	< 0.001	Yes	Yes	Yes	Yes/Yes
Apoorva, et al. 2015	0 (0.46)	4/8	0.13	0.86 (0.82–0.91)	< 0.001	0.87 (0.84–0.91)	< 0.001	Yes	Yes	No	Yes/Yes
Lin et al., 2015	54.5 (0.052)	4/6	0.07	1.88 (1.51–2.33	< 0.001	2.11 (1.46–3.04)	< 0.001	Yes	Yes	No	No (Yes)/Yes
Lin et al., 2015	34.99 (0.188)	2/5	0.58	1.61 (1.33–1.95)	< 0.001	1.63 (1.27–2.09)	< 0.001	Yes	Yes	No	Yes/Yes
Apoorva, et al. 2015	0 (0.61)	1/5	0.27	0.88 (0.80–0.96)	0.005	0.87 (0.80–0.95)	0.003	Yes	Yes	No	Yes/Yes
Ford, et al. 2011	0 (0.72)	1/5	0.29	0.88 (0.83–0.94)	< 0.001	0.88 (0.83–0.94)	< 0.001	Yes	Yes	No	Yes/Yes
Others											
Ganji-Arjenaki, et al. 2017	40.1 (0.100)	1/9	0.93	0.87 (0.75–1.01)	0.072	0.85 (0.69–1.06)	0.153	No	No	Yes	Yes/Yes
Shen, et al. 2014	0 (0.74)	0/3	0.36	0.91 (0.71–1.18)	0.481	0.89 (0.70–1.13)	0.347	No	No	Yes	Yes/Yes
Fujiya, et al. 2014	27.9 (0.2446)	0/4	0.19	1.17 (0.81–1.70)	0.399	1.13 (0.69–1.86)	0.623	No	No	Yes	Yes/Yes
Khan, et al. 2011	44 (0.072)	3/10	0.72	0.83 (0.75–0.92)	< 0.001	0.85 (0.73–0.99)	0.031	Yes	Yes	Yes	Yes/Yes
Wang, et al. 2012	0 (0.68)	2/14	0.93	1.35 (1.16–1.58)	< 0.001	1.33 (1.14–1.54)	< 0.001	Yes	No	Yes	Yes/Yes
Huang, et al. 2009	6.6 (0.378)	0/7	0.41	1.02 (0.67–1.55)	0.942	1.01 (0.64–1.59)	0.983	No	No	Yes	Yes/Yes
Huang, et al. 2009	0 (0.580)	0/7	0.61	1.52 (0.91–2.55)	0.108	1.52 (0.90–2.57)	0.119	No	No	Yes	Yes/Yes
Rahimi, et al. 2006	19.2 (0.220)	4/19	0.09	2.26 (1.68–3.04)	< 0.001	2.33 (1.64–3.31)	< 0.001	Yes	No	No	Yes/Yes
Feller, et al. 2009	0 (0.431)	2/3	0.57	3.54 (1.94–6.46)	< 0.001	3.54 (1.94–6.46)	< 0.001	Yes	No	Yes	Yes/Yes
Feller, et al. 2009	0 (0.857)	1/4	0.06	2.85 (1.67–4.88)	< 0.001	2.85 (1.67–4.88)	< 0.001	Yes	No	Yes	Yes/Yes
Outcome for maintenance treatment (maintenance of remission or relapse)											
Aminosalicylates											
Ford, et al. 2011	28 (0.14)	1/16	0.29	0.98 (0.91–1.05)	0.490	0.97 (0.90–1.05)	0.446	No	Yes	No	Yes/Yes
Camma, et al. 1997	12.9 (0.53)	4/15	0.26	−8.0% (−12.0, −4.0%)	< 0.001	−8.0% (−14.0, −4.0%)	< 0.001	Yes	Yes	Yes	Yes/Yes
Immunomodulators and biologics											
Cholapranee, et al. 2017	0 (0.521)	2/2	N/A	23.01 (4.14–129.98)	< 0.001	19.71 (3.51–110.84)	0.001	Yes	No	Yes	Yes/−
Peyrin-Biroulet, et al. 2008	64.1 (0.039)	3/4	0.96	20% (15–25%)	< 0.001	20 (11–29%)	< 0.001	Yes	Yes	Yes	No (Yes)/Yes
Ford, et al. 2011	5 (0.38)	5/5	0.15	0.70 (0.65–0.76)	< 0.001	0.71 (0.65–0.76)	< 0.001	Yes	Yes	Yes	Yes/Yes
Jean, et al. 2017	0 (0.63)	0/9	0.69	0.97 (0.79–1.19)	0.748	0.97 (0.79–1.19)	0.750	No	Yes	Yes	Yes/Yes
Kopylov, et al. 2014	0 (0.66)	0/4	0.42	1.08 (0.79–1.48)	0.613	1.08 (0.79–1.48)	0.613	No	No	Yes	Yes/Yes
Da, et al. 2013	46.4 (0.127)	1/2	0.42	1.89 (1.39–2.57)	< 0.001	1.86 (1.22–2.83)	0.004	Yes	Yes	Yes	Yes/Yes
Mao, et al. 2017	5.8 (0.346)	3/3	0.01	0.25 (0.14–0.46)	< 0.001	0.25 (0.13–0.46)	< 0.001	Yes	Yes	Yes	Yes/No
Others											
Shen, et al. 2014	0 (0.28)	0/7	0.82	1.19 (0.75–1.89)	0.452	1.09 (0.69–1.74)	0.705	No	No	Yes	Yes/Yes
Rahimi, et al. 2008	38.3 (0.137)	0/7	0.03	0.92 (0.52–1.63)	0.777	0.82 (0.36–1.88)	0.641	No	No	Yes	Yes/No
Jonkers, et al. 2012	54 (0.14)	0/2	N/A	0.90 (0.69–1.18)	0.458	0.93 (0.63–1.38)	0.724	No	No	Yes	No/−
Shen, et al. 2009	43.6 (0.11)	0/6	0.22	1.15 (0.90–1.48)	0.261	1.20 (0.84–1.73)	0.324	No	No	Yes	Yes/Yes
Patton, et al. 2016	47 (0.13)	2/4	0.09	0.58 (0.45–0.75)	< 0.001	0.48 (0.25–0.92)	0.027	Yes	No	Yes	Yes/Yes
Turner, et al. 2011	58.4 (0.03)	2/6	0.11	0.82 (0.72–0.95)	0.006	0.77 (0.61–0.98)	0.031	Yes	Yes	No	No/Yes

Abbreviations: No., number; OR, odds ratio; RR, relative risk; MD, mean difference; RD, risk difference; M, models of meta-analysis; F, fixed effects; R, random effects; CD, Crohn's disease; RCT, randomized controlled trial; OS, observational study; BDP, beclomethasone dipropionate; PD, prednisone; 5-ASA, 5-aminosalicylic acid; TNF, tumor necrosis factor; AZA, Azathioprine; 6-MP, 6-mercaptopurine; CDAI, crohn disease activity index; VHI, van hees index; L. jhonsonil, lactobacillus probiotics; pentasa, mesalamine; VHI, Van Hees index.

[a] Summary random effects effect size (95% CI) of each meta-analysis.

[b] Effect size (95% CI) and *p*-value from the largest study in each meta-analysis.

[c] Proportion of the number of statistically significant studies to to the total number of studies.

[d] *p*-value from summary fixed effects effect size (95% CI) of each meta-analysis.

[e] *p*-value from summary random effects effect size (95% CI) of each meta-analysis.

[f] *p*-value from the Egger regression asymmetry test for evaluation of publication bias.

[g] I2 metric of inconsistency (95% confidence intervals of I2) and *p*-value of the Cochran Q test for evaluation of heterogeneity.

3.2. Crohn's disease

3.2.1. Characteristics of meta-analysis analyzing efficacy of pharmacotherapy in cases with Crohn's disease

For CD, overall 33 articles with 48 meta-anaylses were re-analyzed, and 13 articles of them discussed the efficacy of treatments for both UC and CD. The total number of individual studies involed in the meta-anaylses was 292, and the number of cases and controls combined was 49,846. The median of the number of individual studies included in each meta-analysis for CD was six with IQR 3–8. The median number of cases and controls per meta-analysis was 812 with IQR 352–1451. Furthermore, 20 (42%) meta-analyses included > 1000 cases and controls, and 17 (35%) of them showed statistical significance. There were 30 (63%) significant results with a p-value < .05 under random effects model and 17 (35%) had a p-value below 0.001. All the re-analyzed outcomes had consistant significance compared with reported results, as was in UC. There were four (8%) outcomes which had different significance depending on the type of model (i.e., random or fixed effect model) and five out of six had small heteogenetiy in contrast with UC. 40 (83%) meta-analyses showed small heterogeneity (I^2 < 50%), seven had large heterogeneity (50% ≤ I^2 < 75%), and one had very large heterogeneity (I^2 ≥ 75%). Seven (15%) meta-anaylses were found to have a publication bias and Egger's test were inapplicable in five (10%) meta-anayses. Thirteen (27%) presented discordant direction between an effect of a meta-analysis and that of the largest study of the meta-analysis.

3.2.2. Induction treatment of Crohn's disease

5-ASA was more effective than placebo, but the number of patients was small (<1000) and this result was discordant with that of the largest study and only one of the 6 RCTs showed a positive effect. There were no differences in the comparisons of sulfasalazine vs. placebo and mesalazine vs. placebo. Glucocorticoid was more effective than budesonide, but the number of patients was small (< 1000) and this result discordant with that of the largest study and none of the 6 individual RCTs showed a significant result.

Immunomodulation in the management of CD showed conflicting results among meta-analysis when AZA or 6-mercaptopurine (MP) were compared to placebo. Our analysis revealed that immunosupperssive therapy with AZA, 6-MP, MTX or cyclosporine was shown to be more effective than placebo. However, the number of patients was below 1000 cases, requiring confirmation by further large RCTs in the future.

Biologics have been tested in a significant number of patients with CD. Overall, anti-TNF-α was more effective than placebo (> 1000 cases, concordant direction) without any heterogeneity or publication bias. Analyses of different anti-TNF-α blockers indicated that adalimumab was more effective than placebo (concordant direction) without any heterogeneity or publication bias, but the number of patients was small (< 1000 cases). Earlier meta-analyses showed that adalimumab combined with immunomodulators was better than adalimumab monotherapy (> 1000 cases, concordant direction) without any heterogeneity or publication bias. However, a recent larger meta-analysis showed that there was no difference in remission induction between adalimumab combined with immunomodulators and adalimumab monotherapy and only 2 of the 12 individual RCTs showed a significant result. In addition, there was no difference in the comparison of certolizumab vs placebo.

Anti-integrin agents (natalizumab or vedolizumab) were more effective than placebo (> 1000 cases) without any heterogeneity or publication bias, but this result was discordant with the largest study.

The use of probiotics in the induction of remission was not associated with a better efficacy in comparison to placebo. Antibiotics were shown to be ineffective in previous meta-analysis including 7 RCTs, but more recent large meta-analyses including 10–19 RCTs demonstrated that antibiotics were more effective than placebo in remission induction or response defined as improvement of CD. Among specific antibiotic measurese, the use of nitroimidazole or clofazimine was shown to be more efficacious than placebo, but the number of patients was small (< 1000 cases), requiring further validation.

3.2.3. Treatment in the maintenance phase of Crohn's disease

Conflicting results regarding the efficacy of aminosalicylates on the relapse risk of CD have been reported in the two meta-analysis. One meta-analysis showed that there were no differences in the comparison of 5-ASA to placebo, while the other showed superiority of 5-ASA (> 1000 cases, concordant direction) without any heterogeneity or publication bias.

Among immunomodulatory treatment forms, AZA was shown to be more effective than placebo, but the number of patients was < 1000 cases and this result was discordant with that of the largest study. Biologic agents have been used in the most recent decades. Anti-TNF-α was more effective than placebo (> 1000 cases, concordant direction) without any heterogeneity or publication bias in maintaining remission or preventing relpase. However, there was no difference in the maintenance of remission between adalimumab combined with immunomodulators and adalimumab monotherapy. In addition, although there was no difference in remission induction between certolizumab vs placebo, but certolizumab was shown to be more effective than controls in remission maintenance (> 1000 cases, concordant direction) without any heterogeneity or publication bias. Anti-TNF-α biologics (infliximab or adalizumab) were also efficacious in reducing the odds of surgery than placebo (> 1000 cases, concordant direction) without a heterogeneity.

Among other therapeutic strategies, the use of probiotics was not more effective than placebo. Anti-tuberculous therapy was shown to be more efficacious than placebo in preventing relapse, but the number of patients was small (< 1000 cases). Omega-3 fatty acids were shown to be more efficacious than placebo in maintaining remission, but this result was discordant with that of the largest study.

4. Discussion

In this review, we systematically collected and reanalyzed 110 meta-analyses, 62 for UC and 48 for CD which evaluated the comparative efficacy of drugs for IBD. To the best of our knowledge, this is the most comprehensive analysis of meta-analyses on treatment effects of IBD. Also, we suggested the 5 principles to interpret the results of meta-analysis to help clinicians to understand the results easily and draw firm conclusions from our results.

In summary, 5-ASA was more effective than placebo (> 1000 cases, concordant direction) in both the induction and maintenance treatment of UC. In CD, 5-ASA was shown to be more effective than placebo in the induction of remission, but the number of patients was small (< 1000) and this result was discordant with that of the largest study. There were conflicting results on the efficacy of 5-ASA on the relapse risk of CD. Two meta-analysis reported contradictory results and therefore these findings should be interpreted with caution. This discrepant result might be due to different individualized studies included in the meta-analysis and the different metrics used in these meta-analyses.

Sulfasalazine was comparable effective as 5-ASA in the treatment of UC, either induction or maintenance, but had no additional benefit over placebo in the induction treatment of UC.

In our analysis, it appeared that immunomodulators are more effective than placebo, but problems which arose by small number of patients, discordant results with the largest study and risk of biases clearly impacted generalizability of the results.

Biologics have revolutionized the management of IBD. As expected, the use of either anti-TNF-α or anti-integrin antibodies was effective in both entities either in the induction or in maintaining remission in a significant proportion of patients (> 1000 cases) without any heterogeneity or publication bias.

It is well known that TNF-α plays an important role in mediating gut

inflammation in IBD. Therefore, the use of anti-TNF-α agents has been a well established option of treatments in severe IBD, if initial treatment with steroids or immunomodulators does not work. Since the first generation anti-TNF-α, infliximab, was introduced, the next-generation anti-TNF-α agents (adalimumab, golimumab, and certolizumab) have been developed and applied in the treatment of IBD [2–4,8,10]. However, about 10%–30% of patients with IBD do not respond to these drugs, possibly because other biologic pathways are involved in the gut inflammation, requiring the need for a new drug development [8].

In addition, the migration and trafficking of circulating leukocytes and the recruitment of various kinds of immune cells to the intestinal mucosa are known to be important pathogenesis of gut inflammation in IBD. This is mediated by interactions between cell adhesion molecules (CAMs) on the leukocyte surface, called integrins which are heterodimeric receptors composed of various α and β (α4β1, α4β7, and αEβ7) and vascular cell adhesion molecule-1 (VCAM-1) on vascular endothelial cells, mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on intestinal endothelial cells, and E-cadherin on mucosal epithelial cells [8]. Therefore, targeting leukocyte inhibition by anti-integrin therapies would be an important therapeutic strategy as a treatment option of IBD by decreasing the trafficking of immune cells to the endothelium and suppressing the recruitment of inflammatory cells to intestinal lesions [8].

Inconclusive results exist with respect to the use of probiotics, antibiotics or omega-3 fatty acids, which all need corroboration of their results in larger RCTs.

Currently, the interpretation of the meta-analysis results is based on the statistical significance of p-value $< .05$. However, there have been several efforts to interpret the results of meta-analysis cautiously [20] and we suggested 5 important principles to interpret them.

The first was whether both random and fixed effects results of meta-analysis are significant. Although many meta-analyses of IBD treatment have reported significant results based on either random or fixed models, fixed effect model does not presume diverse underlying uncertainties and perhaps produces narrower CI than nominal width [87,88] and therefore, there is a relatively higher possibility to manifest exaggerated degree of precision in meta-analysis [87]. In addition, although we did not mention the degree of p-value for each outcome, the lower the degree of p-value, the higher the reliability for each outcome.

The second was whether the number of patients participating in a RCT is large (> 1000 cases). The results of small RCTs can be changed if a large trial is performed. Although there is no definite number of patients for ‘large’, some recent suggestions are the sum of cases and controls which should be larger than 1000. The larger number of patients participating in a RCT, the higher the reliability for each outcome. Conversely, if the number of patients is smaller than 1000 cases, a confirmation by further large RCTs may be required.

The third essential point was whether the results of meta-analysis are concordant or discordant with the findings of the largest study, that means the study including the largest number of patients in a RCT. Even though none of the individual RCTs is significant, the results of meta-analysis can show significant results and we are not considering the outcome as having convincing evidence.

The fourth is whether there is a high heterogeneity in the results of a meta-analysis. Although there is no definite criterion for ‘large’ heterogeneity, recent suggestions suggested that the respective cut-off should be more than 50%. The larger the heterogeneity, the higher the probabilty that biases for the reliability of each outcome are present. In this case, the result should be interpreted with caution. If the heterogeneity is large but studies show the same direction for the outcome, it may be due to differences in the size of the association. In this case, we should not consider a high heterogeneity as a bias and rather judge it as a not significant heterogeneity.

The fifth was whether there is a publication bias in the results of meta-analysis. A p-value of < 0.05 for Egger's regression asymmetry test is regarded as evidence for publication bias. Where publication bias is present, published studies may not be a representative sample of the available evidence and this bias can distort the results of meta-analyses.

Even though more than half of the reported associations were evaluted as significant in our review, application of these 5 principles implies that all of these claimed associations may not be the truth. Although there is no single credible method to definitely examine validity of reported associations, it can be said that meta-analyses which have satisfied higher standards are probably more convincing. We hope our efforts to be helpful for clinicians to interpret the reported treatment effects for IBD.

5. Conclusion

In conclusion, we performed a comprehensive review of meta-analysis on comparative effectiveness of pharmacotherapy of IBD and our review will be able to augment our understanding of the treatment of UC and CD. Moreover, assessing the evidence should provide a guideline for interpreting the statistically significant findings and further intensify the discussion regarding the optimal treatment choice for IBD.

Conflicts of interest

All authors state that they have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations.

Authorship

All authors made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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