

Meta-analysis of ciprofloxacin in treatment of Crohn's disease

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Abstract. The aim of the present study was to evaluate the efficacy of ciprofloxacin (cipro) for the treatment of Crohn's disease (CD) through a meta-analysis of randomized controlled trials. The PubMed, Embase and Cochrane Library databases were searched up to May 2014, with no language restrictions, for randomized placebo-controlled trials. Additional references were obtained from the reviewed studies. Five studies were in accordance with the criteria and were included in the meta-analysis. The pooled risk ratio (RR) of all the studies was 1.35 [95% confidence interval (CI), 1.03-1.76; $P=0.03$]. In three studies, cipro was used for the treatment of CD with perianal fistula and the pooled RR was 1.66 (95% CI, 1.16-2.39; $P=0.006$). In two studies, cipro was used to treat active CD and the pooled RR was 1.13 (95% CI, 0.77-1.66; $P=0.54$). Thus in conclusion, cipro exhibits a significant efficacy for the treatment of CD, in particular with perianal fistula.

Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract and the pathogenesis is not entirely clear. Several factors are considered to contribute to the chronic intestinal inflammatory process in patients with CD. These factors include environmental exposures, a genetic disposition and an unbalanced immune reaction to the commensal micro-organism of the gut (1,2). The theoretical foundation for using antibiotics as the main CD treatment is based on increasing evidence implicating intestinal bacteria in the pathogenesis of the disease (3,4). Certain clinical trials have demonstrated the efficacy of antibiotics in inducing and maintaining CD remission and preventing CD recurrence (5). However, the use of antibacterial therapy for CD is also controversial, even this approach is frequently and successfully adopted in clinical practice (6).

The purpose of the present study was to evaluate the usefulness of ciprofloxacin (cipro), which is a staple antibiotic for treatment of CD. A meta-analysis was performed involving randomized controlled trials only.

Materials and methods

Inclusion/exclusion criteria. Studies that were in line with the following criteria were included: i) Randomized controlled trials that assess the efficacy of cipro for the treatment of CD; ii) studies that are published as a full article; and iii) other inflammatory bowel disease therapy allowed is the same in the two groups of the trial.

Studies were excluded if: i) Patients were <18 years, pregnant, had systemic disease, or had significant renal or hepatic disease; ii) specifically evaluate post-operative CD patients; and iii) the control group was not treated with placebo.

Search strategy. A search of the PubMed, Embase and Cochrane Library was performed up to May 2014. A search strategy was constructed using a combination of the following words: (Ciprofloxacin or quinolone or antibiotic) and (Crohn's disease or inflammatory bowel disease). Studies published in any language were included. A manual search of the references listed in the studies retrieved from the online databases and from previously published systematic reviews was also performed to identify further relevant studies.

Data extraction. Two investigators (Wu and Ji) extracted data. Any difference regarding the study inclusion, data extraction and interpretation were resolved by consensus prior to the final analysis. Study variables were gathered in the following categories: Study design, demographics, interventions, duration, extent of disease and co-therapy permitted. To avoid the inclusion of duplicated data in final analysis, retrieved studies were carefully evaluated and checked by comparison of author names, geographical locations and period of study.

Assessment of risk of bias in included studies. The investigators independently, but without being blinded to the authors or journal, assessed the risk of bias in the studies that met the inclusion criteria. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials (7) was used, which includes the following criteria: Adequacy random-sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; and incomplete outcome

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data. In all the cases, an answer of 'yes' indicates a low risk and an answer of 'no' indicates a high risk of bias.

Statistical methods. Meta-analysis was carried out by combining the risk ratio (RR) between the cipro and control groups of the individual studies in a global RR. The intention-to-treat analysis was performed that included all patients who started the medication. Statistical heterogeneity tested was performed using the χ^2 statistic and I^2 , and an I^2 value $>50\%$ was considered to have substantial heterogeneity (8). A fixed-effects model was selected when the heterogeneity test showed I^2 value $<50\%$, otherwise, a random-effects model was used. Funnel plot was used as an indicator of publication bias (9). Analyses were conducted using Review Manager (RevMan software, version 5.3, 2014; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Search results. The search identified 987 potentially relevant studies, of which 951 were excluded following title and abstract screening. In total, 36 studies were retained for full-text review. Initially, 18 review studies were discarded. By analyzing detail data, six retrospective studies and four uncontrolled studies were excluded. Two controlled studies were excluded as the control group was treated with non-placebo and another controlled study was excluded as it specifically evaluated post-operative patients. Finally, five studies (10-14) were identified involving 293 patients that fulfilled the inclusion criteria (Fig. 1).

Characteristics of included studies. The characteristics of included studies and patients are presented in Table I. Three studies came from North America, whereas the others were from Europe. There were 146 (49.8%) males from the available data regarding the gender in all the studies. The mean age of patients ranged 30-45.2 years. In two studies, the intervention was monotherapy and there were 38 patients treated with cipro. In the other three studies, cipro groups were accepted with combination therapy. There were 45 patients treated with cipro plus anti-tumor necrosis factor and 66 patients treated with cipro plus metronidazole (metro) and budesonide. All the included trials had a number of methodological limitations (Table II).

Efficacy results. When including all the studies, there was a statistically significant effect of cipro used for induction of remission in CD patients at 10-12 weeks [RR=1.35; 95% confidence interval (CI), 1.03-1.76; $P=0.03$] (Fig. 2). Subgroup analysis was performed to assess the specific effects of cipro used for CD with perianal fistula or active CD, respectively. Three studies (11,13,14) involving 112 patients indicated that cipro had a specific affect in achieving remission of CD with perianal fistula (RR=1.66; 95% CI, 1.16-2.39; $P=0.006$). Two studies (10,12) involving 181 patients did not appear to be specifically effective with regards to cipro inducing remission in active CD (RR=1.13; 95% CI, 0.77-1.66; $P=0.54$).

Heterogeneity and publication bias. The present study did not cause significant heterogeneity in the meta-analysis ($\chi^2=6.37$;

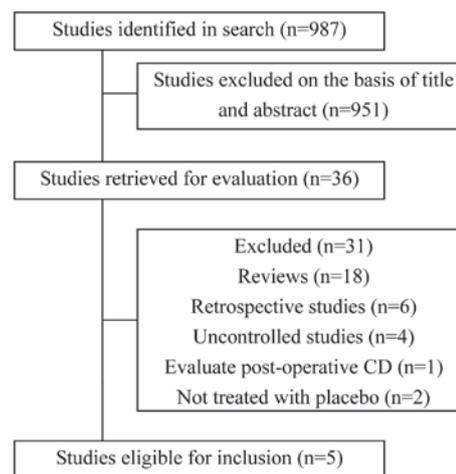


Figure 1. Flow diagram of the study selection process. CD, Crohn's disease.

$I^2=37\%$; $P=0.17$) (Fig. 2). Therefore, a fixed-effect model was used for the meta-analysis. A funnel plot is a helpful tool to estimate publication bias in a meta-analysis. Inspection of the funnel plot revealed a reasonably symmetrical distribution of studies. Accordingly, it was considered that there was no significant publication bias.

Discussion

With regards to the association between intestinal bacteria and CD, numerous antibiotic regimens have been performed as primary therapy to try to modify the intestinal flora and reduce invasion and colonization of harmful bacteria (15). However, the role of intestinal bacteria in the pathogenesis of CD is not completely clear. Due to the complexity of intestinal microbial communities, all the harmful intestinal bacteria cannot be identified (16). Therefore, broad-spectrum antibiotics are considered more effective than narrow-spectrum antibiotics for the treatment of CD (17). Cipro is a quinolone with good activity against the majority of enteric bacteria (18) and the emergence of cipro resistance is relatively infrequent (19). Certain clinical trails have evaluated the efficacy of cipro for CD treatment.

In a small and uncontrolled study (20) of early stage, four active CD patients were treated with cipro. Each patient had a significant improvement in abdominal pain and diarrhea coinciding with the institution of cipro. A retrospective study (21) involving 233 inpatients with active CD showed similar achievement rates of a complete or partial remission obtained between cipro plus metro or cipro alone. An uncontrolled trial (22) indicated that cipro in combination with metro was well-tolerated and beneficial for achieving clinical remission for patients with active CD, particularly when there was involvement of the colon. A study (23) in Japan found that combination therapy of cipro and metro for four weeks significantly decreased the C-reactive protein in all the patients involved. In a randomized non-placebo controlled trial (24) involving 40 CD patients, complete remission was observed in 56% patients treated with cipro and 55% patients treated with mesalazine. The result indicated that cipro was as effective as mesalazine in treating mild to moderate flare-up

Table I. Characteristics of the studies included in the meta-analysis.

Study (year)	Country	Study population	Mean age, years	Male, %	Outcome	Interventions		Duration, weeks	(Refs.)
						Cipro	Control		
Arnold <i>et al</i> (2002)	USA	Single-center	43	59.6	CDAI <150	Cipro 500 mg bid	Placebo	12	(10)
Dewint <i>et al</i> (2014)	The Netherlands	Multicenter	36	52.9	≥50% reduction of fistulas	Cipro 500 mg bid + adalimumab	Placebo + adalimumab	12	(11)
SteinWhart <i>et al</i> (2002)	Canada	Multicenter	32	42.5	CDAI<150 + budesonide	Cipro 500 mg bid budesonide	Placebo + budesonide	12	(12)
Thia <i>et al</i> (2009)	USA/ Canada	Multicenter	35	67.7	≥50% reduction of fistulas	Cipro 500 mg bid	Placebo	10	(13)
West <i>et al</i> (2004)	The Netherlands	Single-center	34	50.0	≥50% reduction of fistulas	Cipro 500 mg bid + infliximab	Placebo + infliximab	12	(14)

Cipro, ciprofloxacin; CDAI, Crohn's disease activity index; bid, *bis in die* (twice daily).

Table II. Methodological quality summary for each included study.

Study (year)	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data	(Refs.)
Arnold <i>et al</i> (2002)	Yes	Unclear	No	Yes	(10)
Dewint <i>et al</i> (2014)	Yes	Unclear	Yes	Yes	(11)
Steinhart <i>et al</i> (2002)	Yes	Unclear	Yes	Yes	(12)
Thia <i>et al</i> (2009)	Yes	Unclear	Yes	Yes	(13)
West <i>et al</i> (2004)	No	Unclear	Yes	Yes	(14)

Yes, low risk of bias; no, high risk of bias.

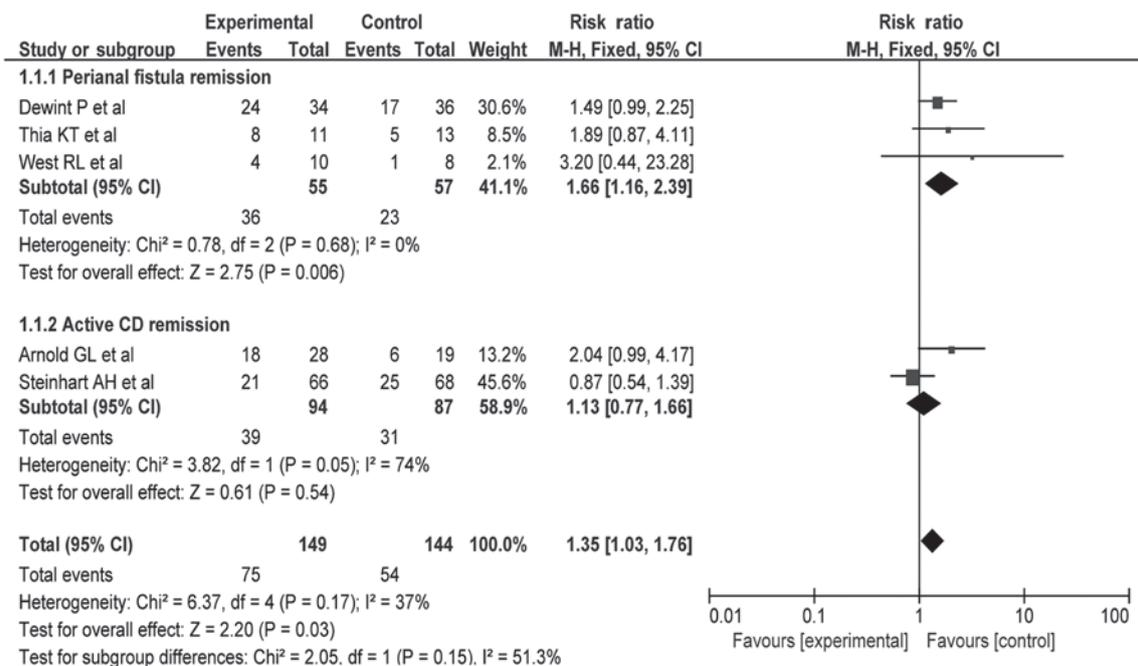


Figure 2. Meta-analysis of ciprofloxacin for treating CD. CI, confidence interval; CD, Crohn's disease.

of CD. Another non-placebo controlled trial (25) involving 41 patients concluded that cipro plus metro could be an alternative to steroids in treating the acute phase of CD.

Perianal fistula occurs in $\leq 40\%$ of CD patients and its natural history is characterized by chronicity with rarely spontaneous healing of the fistula tracts (26). Despite enhance medical and surgical treatment, the majority of patients continue to suffer from perianal symptoms and have to accept extensive surgery, such as proctocolectomy (27). Wolf (28) reported that five CD patients of perianal disease were treated with cipro for 1-2 months, which caused relief of symptoms and healing of fissures in four patients. Following discontinuation of cipro, three of the four responders underwent recurrence. Uza *et al* (29) carried out a combination therapy of cipro, metro and azathioprine to 10 patients with fistulizing CD. Complete responses were observed in all six patients with external fistulas, and in only one of four patients with internal fistulas. Turunen *et al* (30) treated 10 patients with severe perianal or fistulous CD with cipro for ≥ 3 months and seven of the 10 patients responded. Two exhibited healed lesions >2 years and five others relapsed after discontinuing the antibiotic, but responded again to 1-3 month courses of cipro.

The present meta-analysis of five randomized placebo-controlled trials indicates that cipro is effective to relieve the activity of CD. In a study (12) involving 134 patients, cipro plus metro was ineffective to patients with active CD of the ileum, however this combination therapy may improve outcome when there is involvement of the colon. In another study (10), there was a significantly beneficial effect of cipro for treatment of active CD. After 3 months of therapy, remission was observed in 72% of patients treated with cipro and 50% of patients treated with placebo, respectively, and after 6 months of therapy the mean Crohn's disease activity index was 111.7 for the cipro group in contrast to 205.4 for the placebo group. However, the data of different remission rate according to the classification of disease location was absent. The other three studies included 112 patients with fistulizing CD. In two studies (11,14) involving 45 patients treated with cipro plus anti-tumor necrosis factor, remission of fistulas was observed in 71% of patients treated with cipro and 45% of patients treated with placebo, respectively, and the results demonstrated that cipro was significantly effective to CD patients with perianal fistula. Another small sample size study (13) also showed fistula remission occurred more frequently in patients treated with cipro compared to treatment with placebo, but the differences were not significant.

However, the results of the present meta-analysis are limited. Firstly, the total number of samples in all the studies was not quite enough for a meta-analysis. Secondly, as the intervention in certain studies was combination therapy, it was difficult to accurately evaluate the effects of cipro. Furthermore, as the adverse events of cipro were not recorded clearly in each study, the side-effects of cipro used to treat CD could not be assessed. Therefore, the meta-analysis has specific bias and a globally multicenter prospective study is required to confirm the results.

In conclusion, the present meta-analysis showed that cipro is beneficial for CD patients, particularly with perianal fistula. However, the study is associated with certain limitations and it is necessary to conduct further prospective studies of cipro in CD patients.

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