MAJOR ARTICLE

Long-Term Antibiotic Treatment for Crohn's Disease: Systematic Review and Meta-Analysis of Placebo-Controlled Trials

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Background. We investigated the effectiveness of long-term antibiotic treatment in patients with Crohn's disease.

Methods. We performed a systematic review and meta-analysis of randomized clinical trials. Data sources were Medline (from 1966 through June 2009), EMBASE (from 1980 through June 2009), Cochrane Central Register of Controlled Trials (issue 3, 2009), and references from relevant publications. Trials that compared antibiotic therapy during at least 3 months with placebo were included. Outcomes were remission in patients with active disease and relapse in patients with inactive disease. Results from intention-to-treat analyses were combined in a random-effects meta-analysis, stratified by class of drug. Odds ratios (ORs) >1 indicate superiority of antibacterial treatment over placebo. Numbers needed to treat for 1 year to keep 1 additional patient in remission were calculated.

Results. Sixteen trials that examined 13 treatment regimens in 865 patients were included in the meta-analysis. The median duration of treatment was 6 months (range, 3–24 months). Three trials of nitroimidazoles showed benefit, with a combined OR of 3.54 (95% confidence interval [CI], 1.94–6.47). Similarly, the combined OR from 4 trials of clofazimine was 2.86 (95% CI, 1.67–4.88). For patients with active disease, the number needed to treat was 3.4 (95% CI, 2.3–7.0) for nitroimidazoles and 4.2 (95% CI, 2.7–9.3) for clofazimine. The corresponding numbers needed to treat for inactive disease were 6.1 (95% CI, 5.0–9.7) and 6.9 (95% CI, 5.4–12.0). No benefit was evident for classic drugs against tuberculosis (3 trials; OR, 0.58; 95% CI, 0.29–1.18). Results for clarithromycin were heterogeneous ($I^2 = 77\%$; $P = .005$) and not combined in the meta-analysis.

Conclusions. Long-term treatment with nitroimidazoles or clofazimine appears to be effective in patients with Crohn's disease.

The defect underlying the pathogenesis of Crohn's disease may be impaired innate immunity [1]. This hypothesis is supported by the association of Crohn's disease with variants of the *CARD15/NOD2* gene [2–4]. Defective *CARD15/NOD2* variants lead to decreased macrophage activation in response to intracellular lipopolysaccharides, which in turn could result in the activation of other inflammatory pathways [2]. Independent of the *CARD15/NOD2* genotype, impaired innate immunity could lead to intestinal content breaching the mucosal barrier of the bowel wall [5]. In the absence of adequate numbers of functional neutrophils to clear bacteria, these may be ingested by macrophages to form the granulomata and chronic inflammation typical of Crohn's disease. Consequently, there is renewed interest in the microbes associated with Crohn's disease. Several bacteria have been implicated, including, for example, *Listeria monocytogenes*, *Yersinia enterocolitica*, *Mycobacterium avium* subspecies *paratuberculosis*, or *Escherichia coli* [6–12].

If microbes are involved in the development and persistence of inflammation in Crohn's disease, then treatment with antibacterial drugs should be beneficial. However, at present, guidelines and opinion leaders consider antibiotics appropriate only in the management of some complications, such as sepsis, symptoms

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attributable to bacterial overgrowth, or perianal disease [13–15]. Despite this, there have been a number of trials of long-term antibacterial therapy that examined their effect on the course of Crohn's disease independent of such complications. With the exception of a meta-analysis of trials of antimycobacterial therapy [16], these trials have never been comprehensively reviewed. We therefore performed a systematic review and meta-analysis of randomized, placebo-controlled clinical trials to assess the effectiveness of long-term antibiotic treatment in patients with Crohn's disease.

METHODS

Literature search. We searched the Medline database from 1966 through June 2009 using keywords that denote Crohn's disease or inflammatory bowel diseases and antibacterial and antimycobacterial drugs. The results from this search were combined with the search strategy for controlled clinical trials of the Cochrane Collaboration [17]. Similar searches were performed in EMBASE for the period from 1980 through June 2009 and the Cochrane Central Register of Controlled Trials (issue 3, 2009). No language restrictions were applied. Finally, we checked references from relevant publications and review articles.

Eligibility criteria. Clinical trials were included if they used random allocation of patients to treatment groups and compared antibacterial agents, including combination regimens, with placebo in patients with Crohn's disease. The duration of treatment had to be at least 3 months to exclude studies of short-term antibiotic therapy in the management of bacterial complications during flare-ups of the disease. Studies administering concomitant steroids or other drugs were included if regimens were identical in the 2 groups. We excluded trials of patients with exclusive perianal Crohn's disease or trials that reported insufficient data to calculate odds ratios (ORs). Two reviewers (M.F. and K.H.) independently assessed the eligibility of publications. Discrepancies were resolved by consensus in consultation with a third reviewer (M.E.).

Data extraction, outcomes, and definitions. Two observers (M.F. and K.H.) independently extracted data using a standardized data extraction sheet, with differences resolved by consensus. We extracted bibliographic, sociodemographic, and clinical data, aspects of study quality, and results. Remission in patients with active disease and relapse in patients with inactive disease were the outcomes of interest. There was no single, standardized definition of outcomes, which may be explained by the fact that most trials were performed before the publication of the consensus statement on definitions of remission or relapse [18]. We used the definitions reported in the publications, including, for example, the Crohn's Disease Activity Index [19]. If a study presented outcome data at >1 point, we analyzed the data from the latest assessment during treatment.

Ethambutol, isoniazid, and rifamycins (eg, rifampicin and rifabutin) were considered to be classic drugs against infection with *Mycobacterium tuberculosis*, and trials of 1 or several antituberculosis drugs were combined in the meta-analysis. Similarly, trials of drugs from other drug classes, including nitroimidazoles (metronidazole and ornidazole), macrolides (clarithromycin), and riminophenazines (clofazimine), were also analyzed together.

Statistical analysis. Data were analyzed according to the intention-to-treat principle. Patients lost to follow-up or excluded from the study for other reasons were considered treatment failures (ie, not in remission or with relapse). Study results are presented as ORs with 95% confidence intervals (CIs). For studies with continuous outcome measures, results were converted to ORs using the method described by Hasselblad and Hedges [20]. The method is based on the fact that, when assuming logistic distributions and equal variances in the 2 treatment groups, the log OR corresponds to a constant multiplied by the standardized difference between means. We coded outcomes so that ORs >1 indicated superiority of antibacterial treatments over placebo. Results were combined in a random-effects meta-analysis, stratified by drug class, if the degree of between-trial heterogeneity was moderate or low. We assessed between-trial heterogeneity by calculating the I^2 statistic [21]. Low, moderate, and high levels of heterogeneity correspond to I^2 values of 25%, 50%, and 75%, respectively. Numbers needed to treat to keep 1 additional patient in remission were based on the combined ORs and typical proportions of patients in remission after 1 year in the placebo groups, with 95% CIs calculated as suggested by Altman [22]. Publication bias was examined by inspection of funnel plots. All analyses were performed with Stata statistical software, version 10.0 (StataCorp).

RESULTS

The process of identifying eligible studies is summarized in Figure 1. Forty-three potentially eligible publications were assessed in detail, and 16 trials [23–38] met the eligibility criteria (Table 1). A list of the 27 excluded trials with reasons for exclusion is available from the authors on request. Outcome measures were continuous in 4 trials [25, 27, 37, 38] and categorical in the others. Two trials [32, 37] compared 2 dosages of the antibacterial agent to placebo: we included the comparison with the higher dosage.

Study characteristics, definitions, and outcomes. Table 1 gives the characteristics of the 16 included trials. The median number of patients included in the trials was 48 (range, 14–213), and the median year of publication was 1995 (range, 1982–2008). Fifteen trials were parallel-group trials, and 1 trial [36] was a crossover study. The quality of reporting of study methods tended to be low. Only 4 studies [25, 30, 31, 38] described adequate methods of allocation concealment; in the

remaining studies, this was unclear. Two studies reported blinded outcome assessment [33, 38].

Eleven studies included only patients with active disease, 3 studies examined patients with inactive disease, and 1 study included both types of patients; in 1 study, it was unclear whether patients had active or inactive disease. In most studies the diagnostic criteria for Crohn's disease were described as standard clinical findings, with typical radiologic, endoscopic, or histologic lesions. Four studies did not report diagnostic criteria [28, 29, 33, 35]. Remission or recurrence of symptoms was the main outcome in all studies. In 15 studies, a disease activity index was used to assess outcomes (the Crohn's Disease Activity Index [19] in 11 studies), and in 1 study recurrence of lesions was the main outcome [33].

Treatment regimens. Thirteen different treatment regimens were examined. These regimens ranged from single drugs to combination regimens of up to 4 different drugs. The median duration of the active study period was 6 months (range, 3–24 months). Classic drugs against tuberculosis were used in 3 studies [25, 36, 38], nitroimidazoles were used in another 3 studies [33, 34, 37], clarithromycin was used in 4 studies [27, 28, 30, 35], and clofazimine was also used in 4 studies [23, 29, 31, 35] (Table 1). Three studies included a course of steroids, with the same decreasing doses over time in the 2 arms [23, 31, 35]. Seven studies allowed steroids as clinically indicated, and 4 studies explicitly excluded the use of steroids during the study period (Table 1).

Meta-analyses. The forest plot of the meta-analysis stratified by drug class is shown in Figure 2. The combined OR from the 3 trials [25, 36, 38], involving 107 patients, of classic antituberculosis drugs was 0.58 (95% CI, 0.29–1.18), indicating no benefit, with little between-trial heterogeneity ($I^2 = 0\%$). In contrast, the 3 trials [33, 34, 37] of nitroimidazoles, involving 206 patients, showed benefit: the combined OR was 3.54 (95% CI, 1.94–6.47), again with little heterogeneity ($I^2 = 0\%$). The results from the 4 studies [27, 28, 30, 35] of clarithromycin only or clarithromycin in combination, involving 287 patients, were highly heterogeneous ($I^2 = 77\%$; $P = .005$) and therefore not combined in the meta-analysis. The trials of clofazimine [23, 29, 31, 35], involving 322 patients, were homogenous ($I^2 = 0\%$), with a combined OR of 2.86 (95% CI, 1.67–4.88). A trial of 6 months of ciprofloxacin [24] also showed benefit, with an OR of 11.3, but wide CIs (95% CI, 2.60–48.8). There was little evidence of an effect in a trial of sulfadoxine combined with pyrimethamine [26] or a trial of rifaximin [32]. The funnel plot of the 16 studies included in the meta-analysis was symmetrical (Figure 3).

On the basis of the placebo groups of included studies [23, 31, 33–35] and 1 additional large study [39], we assumed that, after 1 year, 25% of control patients with active disease and 75% of control patients with inactive disease will be in remission after 1 year. For patients with active disease, the estimated number needed to treat to keep 1 additional patient in remission was 3.4 (95% CI, 2.3–7.0) for nitroimidazoles and 4.2 (95% CI, 2.7–9.3) for clofazimine. The corresponding figures for inactive disease were 6.1 (95% CI, 5.0–9.7) and 6.9 (95% CI, 5.4–12.0).

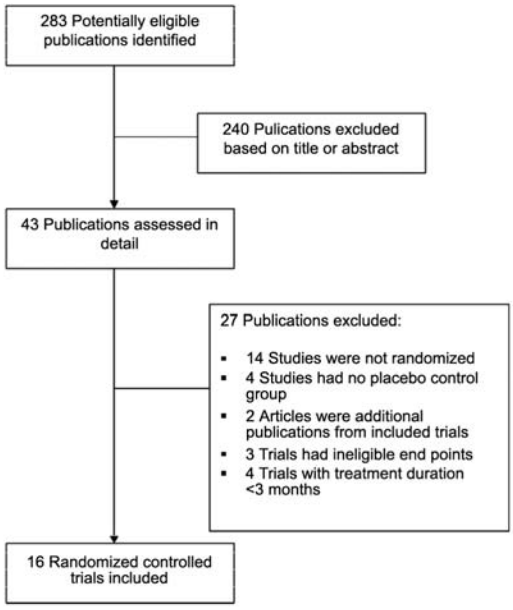

Figure 1. Identification of 16 eligible randomized, placebo-controlled clinical trials comparing antibacterial therapy of at least 3 months duration with placebo in patients with Crohn's disease.

DISCUSSION

This systematic review and meta-analysis examined whether antibacterial treatment for ⩾3 months was efficacious in patients with Crohn's disease. A substantial benefit was evident for nitroimidazoles and clofazimine based on several trials and for ciprofloxacin based on a single trial. Conversely, we found little evidence of a benefit for clarithromycin or the classic tuberculosis drugs.

Our review has several limitations. The number of trials meta-analyzed in each class of drug was small (3 or 4), and the trials also tended to be small, typically including ~50 patients with Crohn's disease. The methodologic quality of many trials was uncertain because of incomplete reporting of study procedures. Smaller trials tend to be of lower methodologic quality and to show larger treatment effects [40], which would be expected to be reflected in an asymmetrical funnel plot [41]. The funnel plot was, however, symmetrical, and results of trials of nitroimidazoles and clofazimine were homogenous. The latter trials included the large Australian trial involving >200 patients [23, 29, 31, 35]. Publication bias could also have distorted our results, but again this should have been reflected in

Table 1. Characteristics of 16 Randomized Controlled Trials of Antibiotic Treatment for ⩾3 Months Duration involving Patients with Crohn's Disease

Trial	Year	No. of patients	Intervention, duration of treatment	Steroid administration	Source of patients	Mean age of intervention group, years	Mean age of control group, years	Disease status	Outcome definition	Odds ratio (95% confidence interval)
Afdhal et al [23]	1991	49	Clofazimine, 100 mg/day, 12 months	Mean dose at entry, 45 mg of prednisone, gradually withdrawn during first 3 months	Not reported	25	32	Active	Relapse of disease: Crohn's Disease Activity Index score >10	2.77 (0.82–9.31)
Arnold et al [24]	2002	47	Ciprofloxacin, 1000 mg/day, 6 months	If clinically indicated	Outpatients	45	42	Active	No. of patients with Crohn's Disease Activity Index score <150	11.26 (2.60–48.8)
Basilisco et al [25]	1989	15	Rifabutin, 300 mg/day, 6 months	If clinically indicated	Outpatients	37[a]	36[a]	Active	Reduction in Bristol Simple Index score	0.57 (0.08–4.02)
Elliott et al [26]	1982	51	Sulfadoxine, 1500 mg/week, and pyrimethamine, 75 mg/week, 12 months	If clinically indicated	Not reported	Not reported	Not reported	Active	Decrease of Crohn's Disease Activity Index score >50	0.70 (0.22–2.19)
Goodgame et al [27]	2001	18	Ethambutol, 15 mg/kg/day and clarithromycin, 1000 mg/day, 3 months	If clinically indicated	Unclear	39	45	Active and inactive	Changes in Harvey-Bradshaw index	0.13 (0.02–0.79)
Graham et al [28]	1995	15	Clarithromycin, 1000 mg/day, 3 months	Not reported	Not reported	Not reported	Not reported	Active	Crohn's Disease Activity Index score <150	17.50 (1.22–250.4)
Kelleher et al [29]	1982	20	Clofazimine (dosage not reported), 6 months	Not reported	Not reported	Not reported	Not reported	Inactive	Relapse measured with Crohn's Disease Activity Index score	9.80 (0.44–219.3)
Leiper et al [30]	2008	41	Clarithromycin, 1000 mg/day, 3 months	Allowed up to 10 mg of prednisolone or 3 mg of budesonide	Outpatients	34	38	Active	Remission or response (Crohn's Disease Activity Index score <150 or decrease >70)	0.95 (0.24–3.81)

Prantera et al [31]	1994	40	Clofazimine, 50 mg/day, and ethambutol, 15 mg/kg/day, and dapsone, 600 mg/week, 9 months; rifampicin, 600 mg once	Methylprednisolone for 8 weeks, initially intravenously, in tapering doses, starting at 0.7–1.0 mg/kg/day	Not reported	34	34	Active	Maintenance of clinical remission measured with the Crohn's Disease Activity Index	3.50 (0.87–14.1)
Prantera et al [32]	2006	58	Rifaximin, 1600 mg/day, 3 months	Not allowed (patients excluded)	Not reported	38	42	Active	Crohn's Disease Activity Index score <150	2.07 (0.71–6.06)
Rutgeerts et al [33]	1995	60	Metronidazole, 20 mg/kg/day, 3 months	Not allowed (tapered after inclusion and stopped within 1 month)	Inpatients	33	37	Inactive, after resection	Assessment of the severity of the lesions in the neoterminal ileum	1.90 (0.62–5.86)
Rutgeerts et al [34]	2005	80	Ornidazole, 1000 mg/day, 12 months	Not allowed (tapered after inclusion and stopped within 1 month)	Inpatients	35[a]	31[a]	Inactive, after resection	Relapse defined as Crohn's Disease Activity Index score >250	4.20 (1.35–13.1)
Selby et al [35]	2007	213	Clarithromycin, 750 mg/day, and rifabutin, 450 mg/day, and clofazimine, 50 mg/day, 24 months	40 mg/day of prednisolone, tapered to 0 mg during the first 16 weeks	Outpatients	37	35	Active	Proportion of patients with at least 1 relapse	2.59 (1.32–5.10)
Shaffer et al [36]	1984	14	Ethambutol, 15 mg/kg/day, and rifampicin, 10 mg/kg/day, 12 months	If clinically indicated	Outpatients	34[b]	34[b]	Unclear	Relapse, defined as rise of Crohn's Disease Activity Index score >50	0.50 (0.06–4.47)
Sutherland et al [37]	1991	66	Metronidazole, 20 mg/kg/day, 4 months	Not allowed (stopped before entry into study)	Not reported	Not reported	Not reported	Active	Decrease in Crohn's Disease Activity Index score	4.79 (1.91–12.0)
Swift et al [38]	1994	78	Rifampicin, 450 or 600 mg/day, and isoniazid, 300 mg/day, and ethambutol, 15 mg/kg/day, 24 months	If clinically indicated	Unclear	37	36	Active	Decrease in Crohn's Disease Activity Index score	0.59 (0.26–1.34)

[a] Median value.
[b] Crossover study.

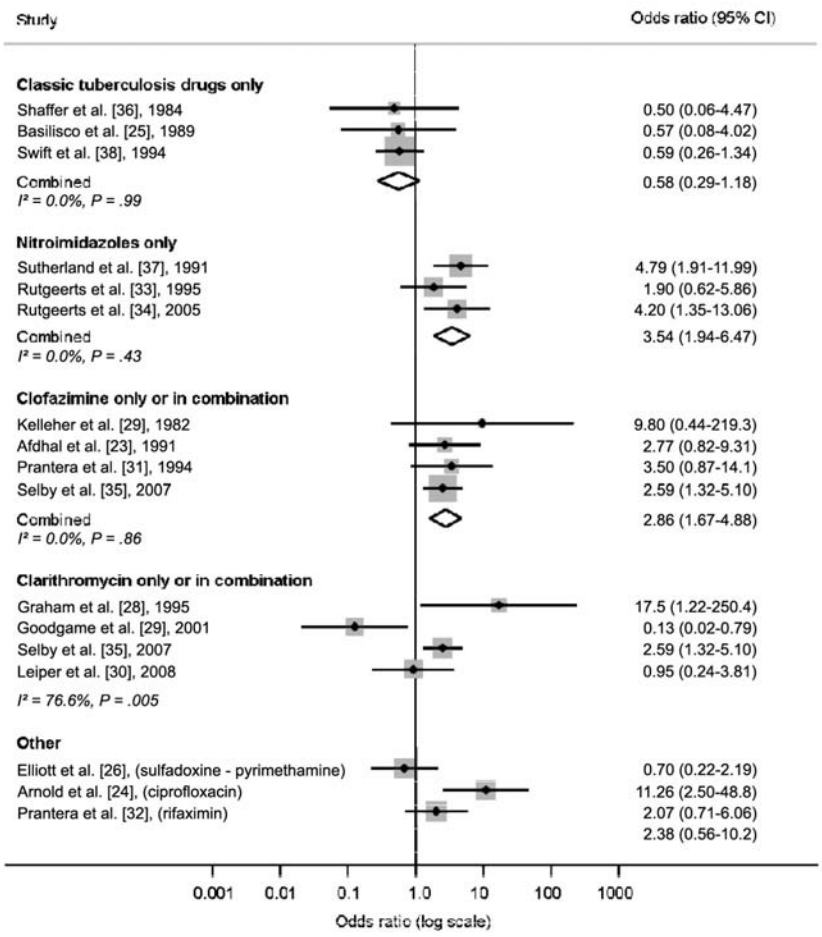

Figure 2. Meta-analysis of 16 randomized, placebo-controlled trials of antibacterial therapy for at least 3 months duration involving patients with Crohn's disease, stratified by drug classes. An odds ratio >1 indicates superiority of antibacterial treatment over placebo. The study from Selby et al [35] appears twice, once in the clarithromycin group and once in the clofazimine group. CI, confidence interval.

an asymmetrical funnel plot. Finally, studies will have included the 10%–15% of patients for whom the distinction between Crohn's disease and ulcerative colitis cannot be made with certainty (inflammatory bowel disease, type unclassified), and this might have attenuated treatment effects [42].

Since the first description of the similarities between Crohn's disease and Johne disease in cattle in 1913 [43], it has been suspected that *M. avium* subspecies *paratuberculosis*, which causes Johne disease, might also be a cause of Crohn's disease [9, 44]. We found that both classic drugs against *M. tuberculosis* and clarithromycin did not appear to be efficacious. Some have argued that effective regimens should consist of at least 2 different drugs, include a macrolide and rifamycin, and be administered for at least 6 months in a dosage similar to that used in the treatment of *M. avium* complex infections [45–48]. No randomized trials of such regimens are available at present. Interestingly, clofazimine was synthesized in the 1950s as a drug against tuberculosis. Granted orphan drug status in 1986, it is an important component of the treatment of leprosy and is also used for multidrug-resistant tuberculosis and *M. avium* complex infections in patients infected with human immunodeficiency virus [49]. Our meta-analysis showed a beneficial effect of clofazimine in Crohn's disease and found that results of the Australian trial [35] were compatible with those of the previous studies [23, 29, 31]. Of note, the published results of the Australian trial were not based on an intention-to-treat analysis and may have underestimated the beneficial effects of the drug [50].

The earlier trials of clofazimine [23, 29, 31] showed benefits in the absence of coadministered macrolides or rifamycins. The antibiotic activity of clofazimine includes some gram-positive bacteria, whereas gram-negative bacteria are uniformly resistant to clofazimine [51, 52]. Clofazimine also has immunomodulatory effects that have been attributed to the stimulation of the production of prostaglandin E_2 [49]. It is unclear to what extent the beneficial effect of clofazimine might be explained

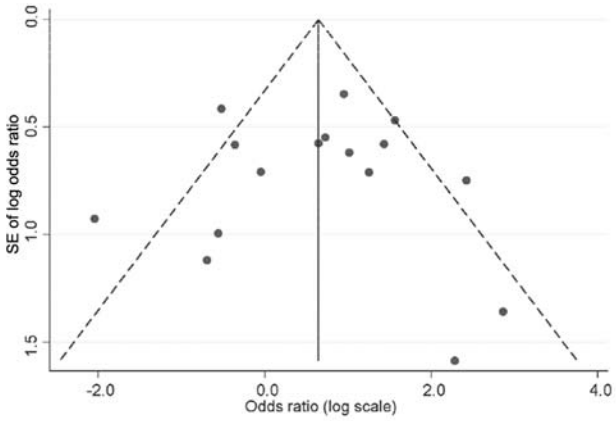

Figure 3. Funnel plot of 16 randomized, placebo-controlled trials using treatment regimens with antibacterial agents for at least 3 months in patients with Crohn's disease. Asymmetry of the plot is an indication of publication bias. SE, standard error.

by the immunomodulatory effects of the drug. Similarly, nitroimidazoles are widely used to treat infections by anaerobic bacteria, whereas facultative anaerobic and aerobic bacteria are uniformly resistant against nitroimidazoles [53, 54]. Anaerobic bacteria have, however, not been implicated in the pathogenesis of Crohn's disease [7]. Immunomodulatory activities, rather than the anti-infectious effects of nitroimidazoles, might thus also explain the beneficial effects observed in Crohn's disease [55, 56].

The current focus in the therapy of Crohn's disease is on tumor necrosis factor α blocking agents: a recent review of the medical management of Crohn's disease discussed this in detail but spent only 2 sentences on antibiotic therapy [15]. Nevertheless, long-term therapy with nitroimidazoles (metronidazole and ornidazole, in particular) is routinely used in some centers, outside the fairly narrow indications suggested by current guidelines [14, 15], but its efficacy has never been systematically assessed. Our review indicates that the benefit of some antibiotic regimens given for $\geqslant$3 months may be comparable to what is achieved with the anti–tumor necrosis factor α agents [57], with a potentially more favorable adverse effect profile and lower costs.

We believe that further research is justified to better define the role of antibacterial agents and combination regimens in Crohn's disease. Future studies should focus on clofazimine, alone or in combination with a macrolide and a rifamycin, as well as in combination with a nitroimidazole, and perhaps ciprofloxacin. Both pragmatic trials comparing different treatment strategies and smaller studies aiming to elucidate mechanisms of action are required. The potential role of different bacteria should be examined in such trials and interactions between drugs and potential adverse effects of long-term antibiotic treatment assessed [58]. Better characterization of patients, for example, by using the recently developed Montreal classification of inflammatory bowel disease [42], should also be considered when planning future studies. Finally, the accumulating evidence should be systematically reviewed in regular intervals to inform up-to-date guidelines of the treatment of Crohn's disease.

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Potential conflicts of interest. All authors: no conflicts.

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