Role of topical tacrolimus in the management of proctitis, perianal manifestations in Crohn's disease, and chronic pouchitis: a systematic review

George Salem ,[1] Kai Ding,[2] Atsushi Sakuraba,[3] Russell Cohen[3]

[1]Department of Internal Medicine, Section of Digestive Diseases and Nutrition, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA
[2]Department of Biostatistics and Epidemiology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA
[3]University of Chicago, Chicago, Illinois, USA

Correspondence to
Dr George Salem, Oklahoma City, Oklahoma, USA; george-salem@ouhsc.edu

Accepted 19 January 2021
Published Online First 23 February 2021

ABSTRACT

Several published studies have evaluated the safety and effectiveness of oral and intravenous tacrolimus for the management of patients with inflammatory bowel disease (IBD). However, little is known about the effectiveness of topical tacrolimus in this patient population. The aim of this systematic review was to evaluate the current state of literature to evaluate the safety and effectiveness of rectal administration of topical tacrolimus, in the form of suppository, ointment, and/or enema in patients with ulcerative proctitis, perianal Crohn's disease (CD), and chronic refractory pouchitis. Electronic database searches were conducted in international databases since their inception until February 2020. Study subjects were categorized into three groups: topical tacrolimus for patients with proctitis, perianal CD, and chronic refractory pouchitis. The primary end point of this study was the remission rate. Secondary end points were response rate and the incidence of AEs. Eleven studies were included in the final assessment in this systematic review. This provided information from 188 patients. Tacrolimus was administered topically as suppositories, ointment, or enema. Clinical remission was achieved in 57.1%, 57.14%, and 70.0% in patients with proctitis, fistulizing perianal CD, and chronic pouchitis. The most commonly reported side effect was perianal itching and burning. Reversible nephrotoxicity occurred in a single patient. No clear correlation was found between blood levels and clinical outcomes. Topical tacrolimus is effective for a subset of patients with IBD. The adverse effects were minimal and tolerable. Well-designed randomized clinical trials are warranted to establish the appropriate dose and administration method.

To cite: Salem G, Ding K, Sakuraba A, *et al*. *J Investig Med* 2021;**69**:796–803.

INTRODUCTION

Inflammatory bowel diseases (IBDs), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic, immune-mediated conditions caused by dysregulated immune response to normal or altered gut microbiome in a genetically susceptible host.[1 2] It is estimated that 1.3% (~3 millions) of adults in the USA were diagnosed with IBD in 2015.[3 4] Up to 40% of patients with UC have inflammation confined to the rectum, described as involvement within 18 cm of the anal verge and distal to the rectosigmoid junction, defined as ulcerative proctitis (UP).[5] Restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) has been the preferred surgical approach in patients with UC with a refractory disease course and in patients with dysplastic lesions in the colon not amenable to endoscopic therapy.[6–8] It is reported that up to 40% of patients with IPAA developed acute pouchitis within the first 5 years of pouch creation, with approximately 17% of patients eventually developing chronic, antibiotic-refractory pouchitis.[9–11] Perianal fistula occurs in up to 26% of patients with CD, with 10% of patients having perianal disease manifestations that predated other luminal gastrointestinal symptoms.[12–14]

Tacrolimus (FK506), a calcineurin inhibitor, is a potent macrolide immunosuppressant. It was first isolated from the fermentation broth of the fungus *Streptomyces tsukubaensis*, a species found in the soil sample from Tsukuba, Japan.[15 16] It suppresses T-cell proliferation and activation by inhibiting the nuclear translocation of a family of transcription factors (nuclear factor of activated T cells), leading to decreased production of interleukin (IL)-2.[17 18] It has been shown that rectal administration of tacrolimus suppresses the function of activated macrophages in the colonic mucosa and promotes their apoptosis in IL-10 knock-out and dextran sulfate sodium-induced colitis in mice models, leading to improvement in clinical and histological colonic inflammation scores.[19]

There are different modalities of topical drug administration when given rectally. The decision on the mode of delivery depends mainly on the disease extent (proctitis vs left side colitis), the ability of the patient to retain the drug (enema vs foam vs suppository), and the patient's preference. While suppositories' topical effect is limited to the rectum, enemas may be beneficial for a disease extent up to the splenic flexure.[20 21]

When given orally, tacrolimus is found to be an effective agent for induction of remission in patients with moderate-to-severe,

corticosteroid-refractory UC.[22–32] A recently published systematic review and meta-analysis has shown that systemic administration of tacrolimus induces remission in patients with luminal and perianal CD.[33] A few reports have shown positive outcomes for the management of pouchitis with oral tacrolimus.[25 26 34 35]

Topical tacrolimus, administered rectally in the form of ointment, suppository, or enema, has been used in cases of UP refractory to standard medical therapy with oral/topical 5-aminosalicylic acid (5-ASA), immunomodulators, and biologics. Fewer reports from cases of perianal CD and pouchitis show a promising signal.

This systematic review is conducted to evaluate the current state of literature to evaluate the safety and effectiveness of rectal administration of topical tacrolimus, in the form of suppository, ointment, and enema in patients with UP, perianal CD, and chronic refractory pouchitis.

METHODS

Literature search

Electronic database searches were conducted by one investigator (GS) in international databases, including PubMed, Embase, MEDLINE, and Web of Science, for full-text articles and meeting abstracts, published in English language, from their inception until February 2020. Abstracts from conference meetings from the American Gastroenterological Association, American College of Gastroenterology, American Society of Colon and Rectal Surgery, European Crohn's and Colitis Organization, and the United European Gastroenterology were manually searched from 1965 to 2019 in order to identify abstracts.

The search terms were "ulcerative colitis", "ulcerative proctitis", "proctitis", "perianal Crohn's disease", "perianal fistula", "pouchitis", "chronic pouchitis", "chronic antibiotics refractory pouchitis", "tacrolimus", "topical tacrolimus", "Prograf", and "FK506".

Articles were restricted to those involving human subjects and included comparative studies and controlled trials. Reference lists in all relevant studies were examined to identify additional articles for inclusion. The inclusion criteria for articles were (1) studies investigating the therapeutic effects of topical tacrolimus in patients with proctitis, (2) studies investigating the therapeutic effects of topical tacrolimus in patients with perianal CD, (3) and studies investigating the therapeutic effects of topical tacrolimus in patients with chronic pouchitis. Articles were excluded if they reported single case reports, review articles, use of topical tacrolimus for indications other than proctitis, perianal CD, or chronic pouchitis, and studies not published/data reported in English language.

Following the PICO formula: P (participant: patient of any age with established diagnosis of proctitis, CD with perianal manifestations, or chronic refractory pouchitis); I (intervention: tacrolimus administered rectally); C (comparison: patients using different topical agents, placebo, or no tacrolimus); O (outcome: clinical remission and response rate).

Categorization and end points

Studies were categorized into and analyzed according to three different groups: topical administration of tacrolimus in patients with proctitis (group 1), topical administration of tacrolimus in patients with perianal CD (group 2), and topical administration of tacrolimus in patients with chronic pouchitis (group 3).

The primary end point was clinical remission, as defined in the identified publications. The secondary end points were clinical response and incidence of adverse events (AEs) related to topical use of tacrolimus.

Risk of bias

Retrieved articles were screened based on time, and then contact by one author (GS), and categorized into 'include' and 'exclude'. Included articles were independently reviewed by two authors (GS and KD), who were not blinded to the authors, journal, institution, or year of publication. Data extraction was performed by two authors (GS and KD). Any disagreement was resolved by discussion. Assessment for methodology and risk of bias is addressed in the online supplemental material using the Cochrane risk of bias tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions*.[36]

Assessment of bias was judged as 'yes': low risk of bias, 'no/not used': high risk of bias, and 'unclear': unknown risk of bias. Selection bias was judged as 'low risk': if randomization sequence was concealed and not predictable, 'moderate risk': if randomization was predictable or sequence was not concealed, 'high risk': if there was a risk-based assignment to treatment groups, or there was a non-consecutive sampling of eligible patients in an observational study.

RESULTS

A total of 191 studies were identified. One hundred and seven studies were duplicates. Full-text eligibility was assessed in 84 studies. Six meeting abstracts had patients included in another full-manuscript form. One was in Russian language and was excluded. Eleven studies were included in the final assessment (online supplemental figure 1, Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram). They were categorized into and analyzed according to the three different groups delineated previously. The studies, in total, provided information from 188 patients with IBD who received treatment with topical tacrolimus in suppository, ointment, or enema form.

Proctitis

A total of seven studies were identified (online supplemental table 1 and figures 1 and 2).[37–43] One randomized, double-blind, placebo-controlled, clinical trial (randomized controlled trial (RCT)) studied the efficacy and safety of topical tacrolimus, in ointment form, for induction of remission in patients with UP.[39] A second, double-blind, RCT compared the efficacy and safety of topical tacrolimus and topical beclomethasone, in suppository form, in a similar patient population.[41] Two studies were done prospectively,[37 38] and three were done retrospectively.[40 42 43] Four studies used tacrolimus in suppository form (111/147, 75.51%),[38 40 41 43] two studies in ointment form (19/147, 12.92%),[37 39] and one study in enema form (17/147, 11.56%).[42] The mean dose of tacrolimus was 3.28 mg/day (range: 1–6 mg/day). The median treatment duration was 8 weeks (range: 3–204 weeks). End points were assessed and

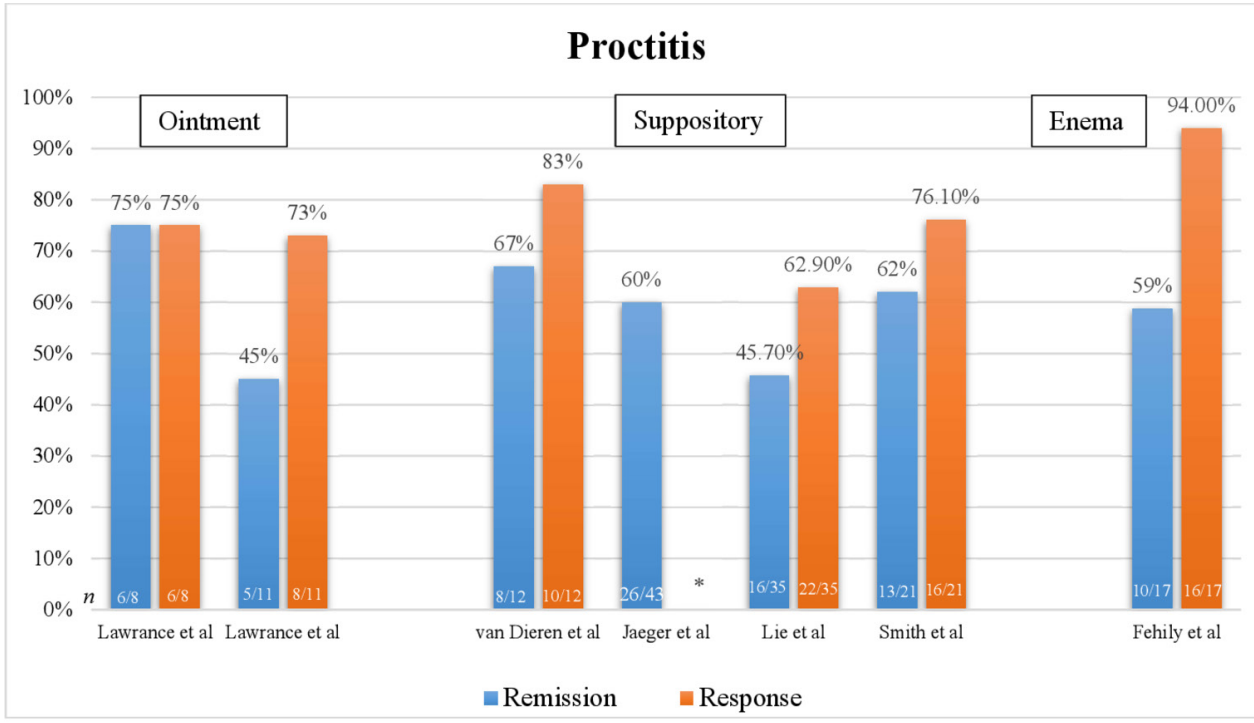

Figure 1 Results of the studies assessing the effectiveness of topical tacrolimus in patients with proctitis.

recorded at the end of the treatment duration of each study (median: 8 weeks, range: 3–204 weeks). Safety was assessed in five studies with serial clinic visits with history and physical exams and blood tests—mainly complete blood count (CBC), comprehensive metabolic panel (CMP), and tacrolimus blood levels. The visits and blood draws were done every other week during the treatment duration and at baseline before starting tacrolimus.[37–41] Two studies did not provide details about the methodology of assessing safety and side effects in their cohorts.[42 43]

Clinical response data were available in 104 patients treated with tacrolimus. Clinical response was defined as a reduction in the Mayo Clinic score of ≥3 points and a decrease of >30% from the baseline score, with a decrease

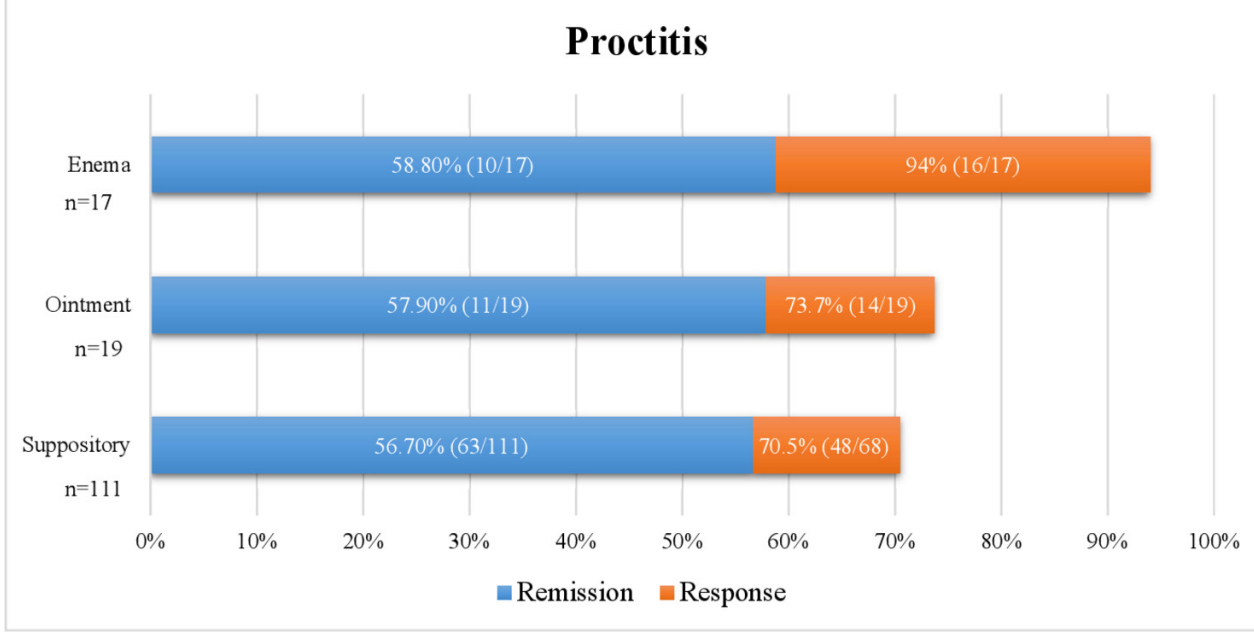

Figure 2 Results of the studies comparing the effectiveness of topical tacrolimus in patients with proctitis based on the form of administration.

of ≥1 point on the rectal bleeding subscale, or an absolute rectal bleeding score of 0 or 1 among all studies. Seventy-eight patients achieved clinical response (75%). Remission data were available in 147 patients. Clinical remission, as an end point, was defined and recorded according to the investigators' preference in each individual study—Modified Mayo score of 2 or less and no subscore of more than 1, Simple Clinical Colitis Activity Index of 4 or less, or patient-reported outcome of −2 of zero. Eighty-four patients achieved clinical remission (57.14%) after induction with topical tacrolimus (figures 1 and 2). Tacrolimus blood levels were recorded in five studies.[37–41] The levels ranged from undetectable to 32.2 ng/mL. Suppository form was most commonly used in patients with proctitis, followed by ointment, and one study with enema (figure 2).

The most commonly reported side effect was perianal burning/itching (10/155, 6.45%). Six patients reported headaches (6/155, 3.87%), and five had tremors (5/155, 3.22%). One patient had a mild increase in creatinine (up to 1.5 g/dL), and the level was normalized after stopping treatment with tacrolimus. The tacrolimus blood level for this particular patient was not recorded in that publication.[40]

Perianal CD

Three studies looked at the safety and effectiveness of topical tacrolimus in patients with perianal CD (online supplemental table 2).[44–46] Pediatric patients were the subjects of interest in two studies,[44 46] and one study evaluated adult patients with perianal CD. One study was a randomized, double-blind, placebo-controlled trial[45]; one was done prospectively[44]; and one was done retrospectively.[46] Tacrolimus was applied topically in an ointment form in all three studies. Results from 23 patients with perianal fissures/ulcers (9/23) and fistulas (14/23) were recorded. Thirteen of the 23 patients (56.52%) were pediatric subjects. The dose of tacrolimus ointment used in three studies ranged between 0.6 and 2.0 mg/g/day. The median treatment duration was 12 weeks (range: 4–24 weeks). End points were assessed and recorded at the end of the treatment duration of each study (median: 12 weeks, range: 4–24 weeks). Patients were followed up to 24 weeks to evaluate for AEs in one study.[45] At 2 weeks, patients were contacted by phone to evaluate for side effects. Blood pressure was checked at weeks 4 and 12. Creatinine was checked at baseline and weeks 4 and 12. Tacrolimus level was measured at week 4. Two studies did not provide details about the methodology of assessing safety and side effects in their cohorts.[44 46]

Data on response to topical tacrolimus in adults were reported in one study.[45] At 12 weeks, one patient had complete response (1/6, 16.67%), defined as cessation of drainage of all fistulas maintained until the end of the treatment period or for ≥2 consecutive visits, and one patient in the placebo arm experienced partial response (1/6, 16.67%), defined as a reduction of ≥50% from baseline in the number of actively draining fistulas on two or more consecutive visits. In patients with perianal ulceration, three patients experienced clinical improvement (3/4, 75%)—as assessed by the attending physician considering depth, surface area involved, and overall appearance of ulcers. None of the patients who received topical tacrolimus showed complete resolution of ulcers (0/4, 0%). None of the patients assigned to the placebo arm experienced any form of improvement (0/3, 0%). The overall response rate between tacrolimus and placebo was not statistically significant. Tacrolimus levels were available for 16 patients. Fourteen had an undetectable whole-blood tacrolimus level. Two patients treated for ulcerating disease had detectable levels of 4.2 and 3.6 ng/mL. The degree of improvement in these patients was similar to that experienced by the other patient in that group, with none experiencing complete healing.

The pediatric population showed more encouraging results in terms of response to topical tacrolimus in patients with perianal disease. The treatment duration for those two studies ranged from 4 to 24 weeks (median: 12 weeks). End points were evaluated and recorded at the end of the treatment duration. In two studies,[44 46] seven out of eight pediatric patients with perianal fistulas were reported to have response topical tacrolimus (87.5%). One had complete closure of external opening, with complete resolution of pain,[44] and six patients demonstrated no radiographical evidence of active inflammation on MRI and were asymptomatic after a 12-week course of topical therapy (figure 3).

Tacrolimus blood levels were recorded in two studies. The levels ranged from undetectable to 4.2 ng/mL.[44 45]

Side effects were reported in two studies. Two pediatric patients had relapse in perianal symptoms after stopping therapy; one adult patient experienced local skin irritation; two patients developed perianal abscess; and one patient had temporary reduction in kidney function after 8 weeks of ointment use. This was normalized at week 12 without intervention or interruption of therapy.

Chronic antibiotic-refractory pouchitis

A single study was found evaluating the applicability of using topical tacrolimus, in enema form, in patients with chronic, antibiotic-refractory pouchitis (online supplemental table 3).[47] Ten patients were prospectively enrolled and treated with 4–5 mg/day (~0.08 mg/kg) of daily tacrolimus enema for a total of 8 weeks. Enema was retained in the ileal pouch for at least 10 min after application, to allow adequate exposure. The efficacy of treatment was defined based on Pouchitis Disease Activity Index (PDAI) scores of the parameters assessed, which were clinical symptoms, endoscopic findings, and histopathological findings. These parameters were assessed within a week of treatment and after 8 weeks of treatment. Safety was assessed by performing serial physical exams and laboratory tests (CBC, CMP, γ-glutamyl transpeptidase, and whole-blood tacrolimus blood levels), performed before treatment and on the 2nd, 7th, 14th, 28th, and 56th days of treatment.

The mean PDAI score decreased significantly from 15.9±0.8 points to 7.8±0.8 points after 8 weeks ($p<0.01$). Nine patients (90%) showed clinical response, defined as a drop in clinical PDAI subscore of more than 3 points, while seven patients (70%) achieved complete remission, defined as a clinical PDAI subscore of 0 (figure 4). Complete endoscopic or histological remission was not achieved in any of the 10 recruited patients; however, all patients had a statistically significant drop in their endoscopic and histological PDAI subscores.

The median value of the serum tacrolimus level at week 8 was 3.8 ng/mL (range: 1.2–8.2). Three patients (30%)

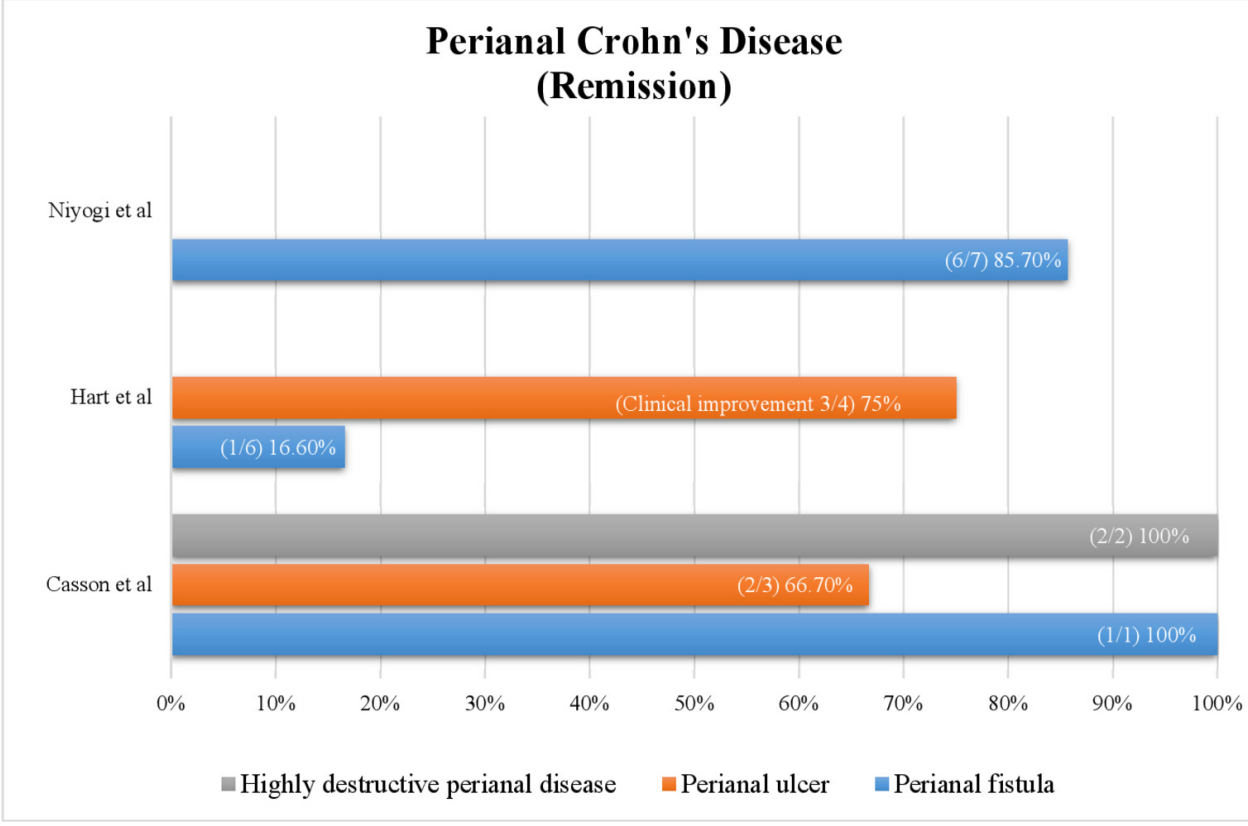

Figure 3 Results of the studies assessing the effectiveness of topical tacrolimus in patients with perianal manifestations of Crohn's disease.

reported mild burning in the pouch. This did not lead to discontinuation of therapy. During the 8-week follow-up period, no liver dysfunction, renal dysfunction, cytopenia, or glucose intolerance was detected in any of the recruited patients.

DISCUSSION

This is the first systematic review evaluating the safety and effectiveness of topical tacrolimus in patients with IBD, with different disease phenotypes for active luminal and penetrating disease behaviors.

The clinical remission rates widely varied between the three different categories of interest. Clinical remission was achieved in 57.1% of patients induced with topical tacrolimus for proctitis. However, pediatric patients with penetrating disease behavior had encouraging results, with 87.5% of patients treated with topical tacrolimus having an evidence of clinical and radiographical evidence of remission. The overall remission rate for penetrating disease phenotype was 57.14% (8/14). Seventy per cent of patients with chronic refractory pouchitis achieved complete clinical remission.

Clinical response rates were reasonably comparable between the three different groups, as this was noted in 75% of patients with proctitis, 75% of patients with perianal CD (fissuring), and up to 90% of patients with chronic refractory pouchitis (figure 5).

The methods of drug administration varied between the groups. Suppository form was most commonly used in patients with proctitis, followed by ointment, and one study

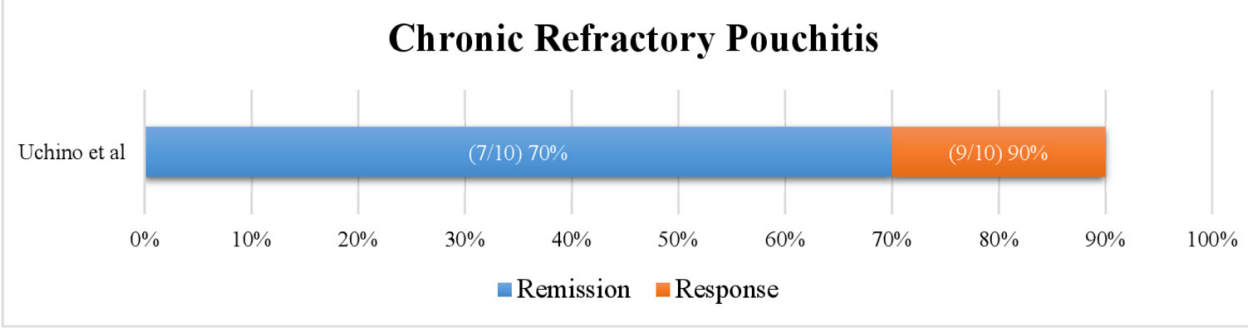

Figure 4 Results of the study evaluating the effectiveness of topical tacrolimus in patients with chronic pouchitis.

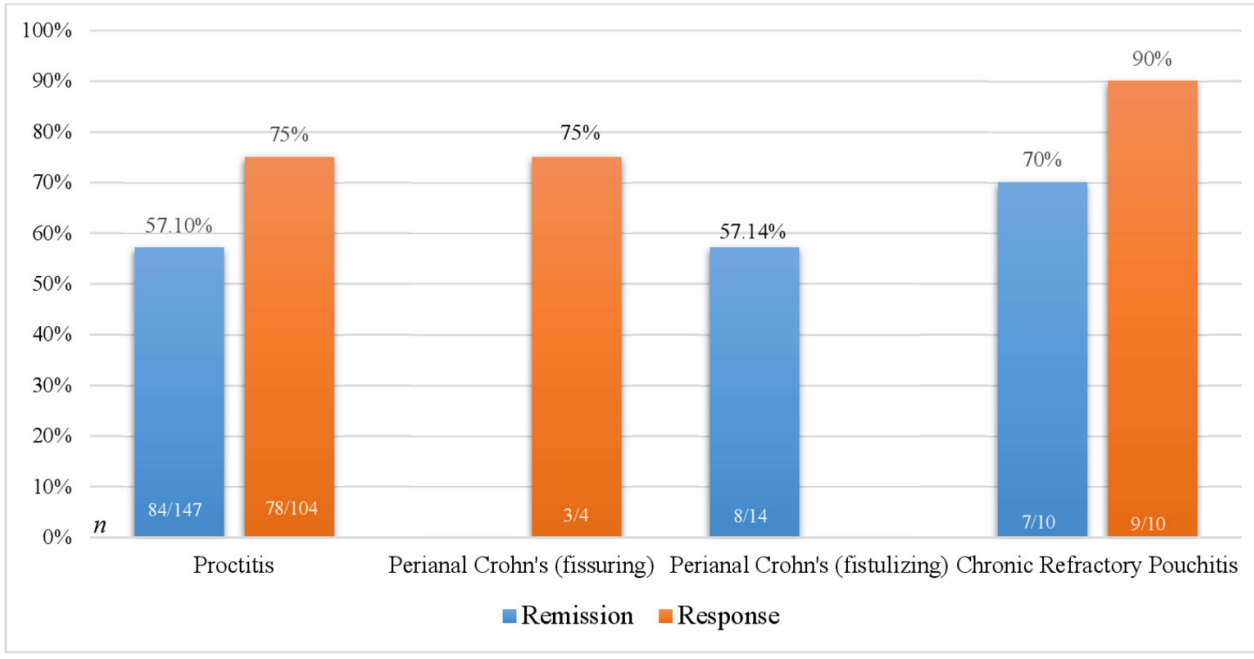

Figure 5 Overall results showing the effectiveness of topical tacrolimus in patients with proctitis, perianal manifestations of Crohn's disease, and chronic refractory pouchitis.

with enema (figure 3). The remission rates were comparable between the three different methods of administration in this patient population (56.7%, 57.9%, 58.8%, respectively). All studies evaluating the effectiveness in perianal CD used ointment form. Enema form was the administration method used in the study of patients with chronic refractory pouchitis.

The doses of topical tacrolimus in this systematic review ranged between 1 and 6 mg/day in cases of proctitis, 0.6–2 mg/g/day in cases of perianal CD, and 4–5 mg/day in patients with chronic refractory pouchitis. A wide variation of treatment duration was noted between the three different groups.

The mean tacrolimus blood levels were higher in cases of ointment or enema use, compared with cases when tacrolimus was administered in suppository form. There was no clear correlation between tacrolimus blood levels and clinical and endoscopic outcomes when reviewed in cases of proctitis.

Topical tacrolimus is considered safe when used topically. The most common side effect was perianal burning and itching, followed by headaches. Tremors and elevated creatinine were less commonly reported, when compared with oral or intravenous dosing.[48] A clear association between tacrolimus blood levels and AEs was not evident in this systematic review.

Topical tacrolimus has been an agent of interest for the management of proctitis. The RCT implemented by Lawrance *et al* had to be prematurely stopped because of the substantial therapeutic effect of topical tacrolimus, in ointment form, when compared with placebo.[39] When used in a suppository form, in this patient population, 2 mg/day was not inferior to topical beclomethasone,[41] which makes topical tacrolimus an attractive agent in patients with marginal response to topical and oral 5-ASA agents, before treatment escalation to topical, or oral, steroid. The form of administration (suppository vs ointment) is largely dependent on the patients' preferences, as the clinical remission rates were comparable between the two different forms. If the decision is made to proceed with the suppository form, it is reasonable to start with 2 mg two times per day (morning and bedtime) for 4–8 weeks and then to de-escalate to 2 mg once a day, at bedtime, for maintenance purposes, if remission is achieved. If ointment is the preferred method for administration, a 1.5 mg two times per day (morning and bedtime) for 4–8 weeks is the suggested induction dose, followed by one application per day for maintenance of remission, if remission is achieved. This is in agreement with the available evidence described in the different studies in this systematic review. It is recommended to have a blood pressure recorded in chart, with CBC and CMP at baseline. CBC and CMP tests should be repeated 2–4 weeks after starting tacrolimus to evaluate for cytopenia, elevation in creatinine, or increased liver enzymes, and need for dose adjustments, with a repeat blood pressure measure at week 4, then every 4–8 weeks while on tacrolimus, if no side effects are noted.

A positive signal was noted in pediatric patients with perianal manifestations of CD when compared with adult patients, in the available literature. For this patient population, an aggressive management with systemic agents, like antitumor necrosis factor alpha, anti-integrins, or anti-ILs, is highly recommended due to the progressive, destructive behavior of this disease phenotype in adults. This is in agreement with the widely accepted guidelines for the management of adults with perianal manifestations of CD.[49 50] Despite the encouraging results of using tacrolimus enema in patients with chronic pouchitis, more studies are needed to appropriately evaluate the benefit of this modality of treatment in this patient population.

The availability of topical tacrolimus for rectal administration in the USA is limited to the access to compounding pharmacies, as formulary prepackaged tacrolimus products for commercial use, including ointment forms, are intended for oral or cutaneous/external use. The technical aspect of compounding suppositories, ointments, and enemas can be different, depending on the compounding pharmacies' preferences. Suppository forms can be prepared by mixing the content of a 5 mg tacrolimus capsule (Prograf; Astellas Pharma, Tokyo, Japan; or a generic form of tacrolimus capsule), with melted Adeps solidus (Witepsol H15; Spruyt Hillen, IJsselstein, the Netherlands) 1:1000 (w/w). Subsequently, the admixture is divided over 2 mL suppository molds (2 mg tacrolimus/suppository) and then solidified. For ointment preparations, 5 mL of propylene glycol is mixed with the desired amount of tacrolimus powder. Subsequently, 70 mL of paraffin liquid BP is gradually added by serial dilution and trituration until evenly mixed. This process is repeated with 125 mL of paraffin white soft BP. An enema solution can be prepared by using the decapsulated content of a commercially available tacrolimus capsule (Prograf, Astellas Pharma; or a generic form of tacrolimus capsule) with the desired milligram dosage of tacrolimus. The enemas can then be prepared by compounding the desired dosage in 100 mL of enema water.

We used the best available evidence in the current body of literature to evaluate the safety and effectiveness of topical tacrolimus in the management of patients with IBD, with different disease phenotypes and behaviors. However, this systematic review has several limitations. The quality of studies included in this review was suboptimal to answer such complicated questions, as the majority of the data was abstracted from case series, and only three studies were implemented as RCTs; two were placebo-controlled, and one was a non-inferiority study comparing the efficacy to rectal beclomethasone. The sample size in each study was relatively small to draw an informed conclusion about the value of adding topical tacrolimus in patients with a complex disease course. The different methods of application, dosing, and treatment duration limited the ability to offer a clear set of recommendations regarding the most efficacious therapeutic regimen in similar conditions, especially in cases of proctitis. The lack of objectively measured end points in multiple studies, mainly endoscopic and radiographical end points, could have led to the suboptimal estimation of the true effect of the topical application of tacrolimus.

CONCLUSION

Topical tacrolimus can be used for the management of certain luminal manifestations of IBD, refractory to topical and/or systemic immune-suppression therapies. The advent of various formulations has resulted in more topical options for patients with proctitis, perianal manifestations of CD, and chronic refractory pouchitis. Topical tacrolimus can be a valuable option for patients with proctitis, with marginal response to topical or oral formulations of 5-ASA, before escalation to steroid options. There was no clear correlation between tacrolimus blood levels and clinical and endoscopic outcomes when reviewed in cases of proctitis. It has been found to be fairly safe and well tolerated in adults and pediatric populations. However, due to the small number of studies, with the inherent limitations of the non-randomized nature of the majority of included trials, well-designed randomized clinical trials are warranted to further assist in the management of this subset of patients, with disease phenotypes and behaviors that are known to be notoriously difficult to treat.

Contributors GS and KD collected and analyzed the data and designed the study. GS wrote the manuscript. KD, AS, and RC reviewed the final draft of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethics approval was not required for this systematic review because available data from previously published studies, in which informed consent waa obtained by primary investigators, was retrieved and analyzed.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

George Salem http://orcid.org/0000-0003-4985-2514

REFERENCES

1 Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med* 2009;361:2066–78.
2 Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature* 2011;474:307–17.
3 Dahlhamer JM, Zammitti EP, Ward BW, *et al*. Prevalence of inflammatory bowel disease among adults aged ≥18 years — United States, 2015. *MMWR Morb Mortal Wkly Rep* 2016;65:1166–9.
4 Ng SC, Shi HY, Hamidi N, *et al*. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018;390:2769–78.
5 Satsangi J, Silverberg MS, Vermeire S, *et al*. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;55:749–53.
6 Allison J, Herrinton LJ, Liu L, *et al*. Natural history of severe ulcerative colitis in a community-based health plan. *Clin Gastroenterol Hepatol* 2008;6:999–1003.
7 Ullman T, Odze R, Farraye FA. Diagnosis and management of dysplasia in patients with ulcerative colitis and Crohn's disease of the colon. *Inflamm Bowel Dis* 2009;15:630–8.
8 Laine L, Kaltenbach T, Barkun A, *et al*. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastroenterology* 2015;148:639–51.
9 Lohmuller JL, Pemberton JH, Dozois RR, *et al*. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis. *Ann Surg* 1990;211:622–7. discussion 627-629.
10 Mahadevan U, Sandborn WJ. Diagnosis and management of pouchitis. *Gastroenterology* 2003;124:1636–50.
11 Shen B. Pouchitis: what every gastroenterologist needs to know. *Clin Gastroenterol Hepatol* 2013;11:1538–49.
12 Schwartz DA, Loftus EV, Tremaine WJ, *et al*. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. *Gastroenterology* 2002;122:875–80.
13 Peyrin-Biroulet L, Loftus EV, Colombel J-F, *et al*. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010;105:289–97.
14 Kotze PG, Shen B, Lightner A, *et al*. Modern management of perianal fistulas in Crohn's disease: future directions. *Gut* 2018;67:1181–94.

15 Pritchard DI. Sourcing a chemical succession for cyclosporin from parasites and human pathogens. *Drug Discov Today* 2005;10:688–91.
16 Thomson AW. FK-506--how much potential? *Immunol Today* 1989;10:6–9.
17 Schreiber SL, Crabtree GR. The mechanism of action of cyclosporin A and FK506. *Immunol Today* 1992;13:136–42.
18 Wiederrecht G, Lam E, Hung S, *et al*. The mechanism of action of FK-506 and cyclosporin A. *Ann N Y Acad Sci* 1993;696:9–19.
19 Yoshino T, Nakase H, Honzawa Y, *et al*. Immunosuppressive effects of tacrolimus on macrophages ameliorate experimental colitis. *Inflamm Bowel Dis* 2010;16:2022–33.
20 Gionchetti P, Venturi A, Rizzello F, *et al*. Retrograde colonic spread of a new mesalazine rectal enema in patients with distal ulcerative colitis. *Aliment Pharmacol Ther* 1997;11:679–84.
21 Rubin DT, Ananthakrishnan AN, Siegel CA, *et al*. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol* 2019;114:384–413.
22 Ogata H, Matsui T, Nakamura M, *et al*. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006;55:1255–62.
23 Ogata H, Kato J, Hirai F, *et al*. Double-blind, placebo-controlled trial of oral tacrolimus (FK506) in the management of hospitalized patients with steroid-refractory ulcerative colitis. *Inflamm Bowel Dis* 2012;18:803–8.
24 Högenauer C, Wenzl HH, Hinterleitner TA, *et al*. Effect of oral tacrolimus (FK 506) on steroid-refractory moderate/severe ulcerative colitis. *Aliment Pharmacol Ther* 2003;18:415–23.
25 Baumgart DC, Wiedenmann B, Dignass AU. Rescue therapy with tacrolimus is effective in patients with severe and refractory inflammatory bowel disease. *Aliment Pharmacol Ther* 2003;17:1273–81.
26 Ng SC, Arebi N, Kamm MA. Medium-term results of oral tacrolimus treatment in refractory inflammatory bowel disease. *Inflamm Bowel Dis* 2007;13:129–34.
27 Yamamoto S, Nakase H, Mikami S, *et al*. Long-term effect of tacrolimus therapy in patients with refractory ulcerative colitis. *Aliment Pharmacol Ther* 2008;28:589–97.
28 Schmidt KJ, Herrlinger KR, Emmrich J, *et al*. Short-term efficacy of tacrolimus in steroid-refractory ulcerative colitis - experience in 130 patients. *Aliment Pharmacol Ther* 2013;37:129–36.
29 Landy J, Wahed M, Peake STC, *et al*. Oral tacrolimus as maintenance therapy for refractory ulcerative colitis--an analysis of outcomes in two London tertiary centres. *J Crohns Colitis* 2013;7:e516–21.
30 Kawakami K, Inoue T, Murano M, *et al*. Effects of oral tacrolimus as a rapid induction therapy in ulcerative colitis. *World J Gastroenterol* 2015;21:1880–6.
31 Ikeya K, Sugimoto K, Kawasaki S, *et al*. Tacrolimus for remission induction in ulcerative colitis: Mayo endoscopic subscore 0 and 1 predict long-term prognosis. *Dig Liver Dis* 2015;47:365–71.
32 Matsuoka K, Saito E, Fujii T, *et al*. Tacrolimus for the treatment of ulcerative colitis. *Intest Res* 2015;13:219–26.
33 Iida T, Nojima M, Nakase H. Therapeutic efficacy and adverse events of tacrolimus in patients with Crohn's disease: systematic review and meta-analysis. *Dig Dis Sci* 2019;64:2945–54.
34 de Oca J, Vilar L, Castellote J, *et al*. Immunodulation with tacrolimus (FK506): results of a prospective, open-label, non-controlled trial in patients with inflammatory bowel disease. *Rev Esp Enferm Dig* 2003;95:459–64.
35 Satake M, Sakuraba H, Hiraga H, *et al*. Successful treatment with tacrolimus of refractory pyoderma gangrenosum with pouchitis after restorative proctocolectomy for ulcerative colitis. *Immunol Med* 2018;41:142–6.
36 Higgins JPT, Thomas J, Chandler J, *et al*, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd edition, 2011.
37 Lawrance IC, Copeland T-S. Rectal tacrolimus in the treatment of resistant ulcerative proctitis. *Aliment Pharmacol Ther* 2008;28:1214–20.
38 van Dieren JM, van Bodegraven AA, Kuipers EJ, *et al*. Local application of tacrolimus in distal colitis: feasible and safe. *Inflamm Bowel Dis* 2009;15:193–8.
39 Lawrance IC, Baird A, Lightower D, *et al*. Efficacy of rectal tacrolimus for induction therapy in patients with resistant ulcerative proctitis. *Clin Gastroenterol Hepatol* 2017;15:1248–55.
40 Jaeger SU, Klag T, Hoeger K, *et al*. Tacrolimus suppositories in therapy-resistant ulcerative proctitis. *Inflamm Intest Dis* 2019;3:116–24.
41 Lie MRKL, Kreijne JE, Dijkstra G, *et al*. No superiority of tacrolimus suppositories vs beclomethasone suppositories in a randomized trial of patients with refractory ulcerative proctitis. *Clin Gastroenterol Hepatol* 2020;18:1777–84.
42 Fehily SR, Felicity MC, Kamm MA. *Simple water-based tacrolimus enemas for refractory proctitis*. In: Journal of Gastroenterology and Hepatology, 2019.
43 Smith R, Weekes H, Morgan L, *et al*. *Tacrolimus suppositories: a safe and effective treatment for treatment-refractory proctitis. in*. European Crohn's and Colitis Organization Meeting, 2019: P588.
44 Casson DH, Eltumi M, Tomlin S, *et al*. Topical tacrolimus may be effective in the treatment of oral and perineal Crohn's disease. *Gut* 2000;47:436–40.
45 Hart AL, Plamondon S, Kamm MA. Topical tacrolimus in the treatment of perianal Crohn's disease: exploratory randomized controlled trial. *Inflamm Bowel Dis* 2007;13:245–53.
46 Niyogi A, Agarwal T, Broadhurst J, *et al*. Management of perianal abscess and fistula-in-ano in children. *Eur J Pediatr Surg* 2010;20:35–9.
47 Uchino M, Ikeuchi H, Matsuoka H, *et al*. Topical tacrolimus therapy for antibiotic-refractory pouchitis. *Dis Colon Rectum* 2013;56:1166–73.
48 McSharry K, Dalzell AM, Leiper K, *et al*. Systematic review: the role of tacrolimus in the management of Crohn's disease. *Aliment Pharmacol Ther* 2011;34:1282–94.
49 Torres J, Bonovas S, Doherty G, *et al*. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis* 2020;14:4–22.
50 Lichtenstein GR, Loftus EV, Isaacs KL, *et al*. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol* 2018;113:481–517.