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Single Case

Curcumin-QingDai Combination as Treatment for Moderate-Severe Ulcerative Colitis

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Keywords
Ulcerative colitis · Treatment · Inflammatory bowel disease

Abstract
Curcumin was shown in placebo-controlled trials to induce remission in mild-moderate ulcerative colitis (UC). QingDai (QD, Indigo), another herbal extract, showed efficacy in two UC trials from Japan, but evidence in the Western population is scant. We report on the use of curcumin-QingDai combination (CurQD) for the treatment of moderate-severe UC. Patient 1 was a 24-year-old male with severe UC refractory to cyclosporine and corticosteroids. He partially responded to infliximab but later lost response to an optimized dose of infliximab in combination with 6-mercaptopurine, presenting with worsening symptoms and severe Mayo 3 mucosal inflammation. Initiation of CurQD 2.5 g/day resulted in rapid cessation of blood per rectum. Complete clinical remission ensued within few weeks. Follow-up endoscopies performed 12 weeks later showed only minimal residual inflammation. Infliximab was later stopped due to reimbursement issues, and the patient was successfully maintained on lower doses of CurQD and 6-mercaptopurine for 31 months. Two flares have responded to a temporary increase in QD component dose. Patient 2 was a 59-year-old female with extensive UC not responding to maximal oral + topical 5-ASA and corticosteroids. Despite severe mucosal ulceration (Mayo 3) found on endoscopy, she refused the recommendation for biologics and opted for a short-term limited trial of CurQD. This was initiated at 2,000 mg/day and induced rapid clinical remission. Lower endoscopies performed after 2 and 5 months on CurQD showed complete mucosal healing, and the patient maintained her clinical remission on low-dose CurQD for 49 months. No adverse events were noted in the 2 patients.

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory condition of the colon, which is treated by a host of anti-inflammatory and immune-modulating agents. Nonetheless, these medications portend some health risks and fall short of inducing clinical remission in all patients. Thus, there is still a need for exploring additional novel agents for UC. In a previous placebo-controlled trial, we reported the efficacy of a 95% gut-directed formulation of curcumin as add-on therapy with 5-ASA in inducing clinical and endoscopic remission in mild-moderate UC patients [1]. Another traditional Chinese medicine herbal extract named QingDai (QD, Indigo) was found to be effective in more severely active UC in two placebo-controlled trials from Japan, where it is popularly used [2, 3]. Both curcumin and QD are approved herbal supplements in Israel and some other countries and are used by UC patients. However, published experience on QD use in the West is still very limited, comprising a recent small case series from the USA [4]. Moreover, the combination of these two herbs has not been hitherto reported. We herein report 2 patients treated in our center with a curcumin-QingDai combination (CurQD).

Case Report

Patient 1 was a 24-year-old male with extensive UC for 2 years. He had severe course, with a prior prolonged hospitalization for acute severe colitis, refractory to cyclosporine. He then improved with infliximab, which was later optimized due to partial response. 6-mercaptopurine was also added concurrently. Notwithstanding, he continued to suffer from 6 to 7 bowel movements daily, half of which with blood. At assessment, he had been on infliximab 7 mg/kg every 4 weeks with 100 mg/day of 6-mercaptopurine for over 4 months. Infliximab levels were 11.9 μg/mL without antidrug antibodies. CRP was nine times the upper normal limit. Stool calprotectin was 670 mg/g, and sigmoidoscopy showed Mayo 3 inflammation up until 30 cm from the anal verge (Fig. 1a). Infectious workup including immunohistochemistry for CMV was negative. Swapping biologic was considered, but the patient opted for a short-term trial of herbal treatment. Therefore, CurQD was initiated at 1,000 mg curcumin and 1,500 mg of QD daily, as add-on to infliximab and 6-MP. CurQD capsules were supplied by EviNature (Binyamina, Israel) after manufacturing at a GMP facility (Bara Herbs, Yokenaam, Israel) and have passed regulatory-required testing for heavy metals, pesticides, and microbial contaminants as well as HPLC and LC-MS to ascertain curcumin, indigo, and indirubin content. Bleeding ceased within 10 days of starting CurQD, and the patient gained complete remission within several weeks. Two follow-up lower endoscopies performed at 8 and 12 weeks after CurQD initiation showed marked endoscopic improvement to a Mayo 1 mucosal appearance on the later examination (Fig. 1a). The patient was maintained on the same infliximab dose with 6-MP and with a gradual tapering of CurQD combination to 500 mg of QD every other day and 2 g of curcumin daily. A clinical and endoscopic flare occurred 3 months later, which responded to dose increase of QD component back to 1,000 mg/daily, followed by its dose reduction to 500 mg/day. Eight months later, while in complete remission, the patient stopped infliximab due to logistic hurdles during prolonged travel abroad. He has since remained in complete remission on CurQD and 6-MP until his last follow-up, 31 months after starting the herbal extract. No adverse events were noted, and a cardiac echocardiogram performed after 16 months of CurQD treatment was normal.

Patient 2 was a 56-year-old female diagnosed with extensive UC a year earlier. The disease did not respond to maximal oral and topical mesalamine therapy. Her symptoms did not improve with budesonide-MMX at 9 mg/daily, and she presented with 4–5 bloody bowel movements a day, weakness, and abdominal pain. Hemoglobin level was 10.3 g/dL, CRP was 6 times of upper normal limit, and a sigmoidoscopy showed severely ulcerated Mayo 3 grade inflammation

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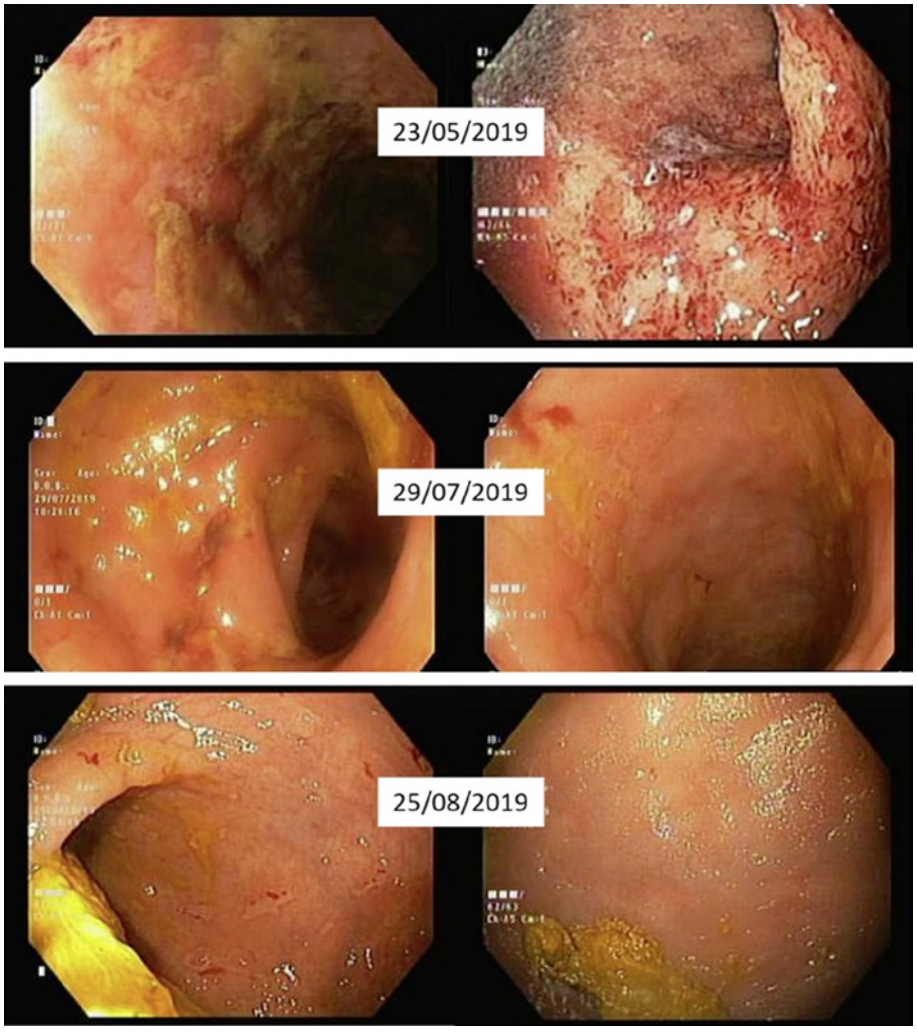
up to 45 cm (Fig. 1b). Vedolizumab was prescribed, but the patient was wary of receiving intravenous biologic medications. Thus, a short-term trial of 2 g/day CurQD combination was offered. Rectal bleeding and increased bowel movements resolved rapidly and a repeat sigmoidoscopy 7 weeks later revealed marked improvement in mucosal appearance and a repeat sigmoidoscopy after 5 months of CurQD showed mucosal scarring and complete healing (Fig. 1b). The patient has since been maintained on 3 g/day mesalamine with CurQD, at a tapered QD dose of 500 mg/every-other-day with 1,000 mg/daily curcumin for 49 months until the last follow-up visit. Two flares during this period were accompanied by endoscopic inflammation and calprotectin elevation, and both episodes responded to a temporary increase of QD dose to 1,000 mg/daily, which was then tapered back to alternating-day 500 mg dose. An echocardiogram performed 15 months after commencing CurQD was unremarkable.

Discussion

Although the therapeutic arsenal of both biologics and small molecules is increasing for active UC, some patients remain refractory or intolerant to current agents, and others may experience adverse events from immune-suppressive agents. Moreover, even in the era of



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(Figure continued on next page.)

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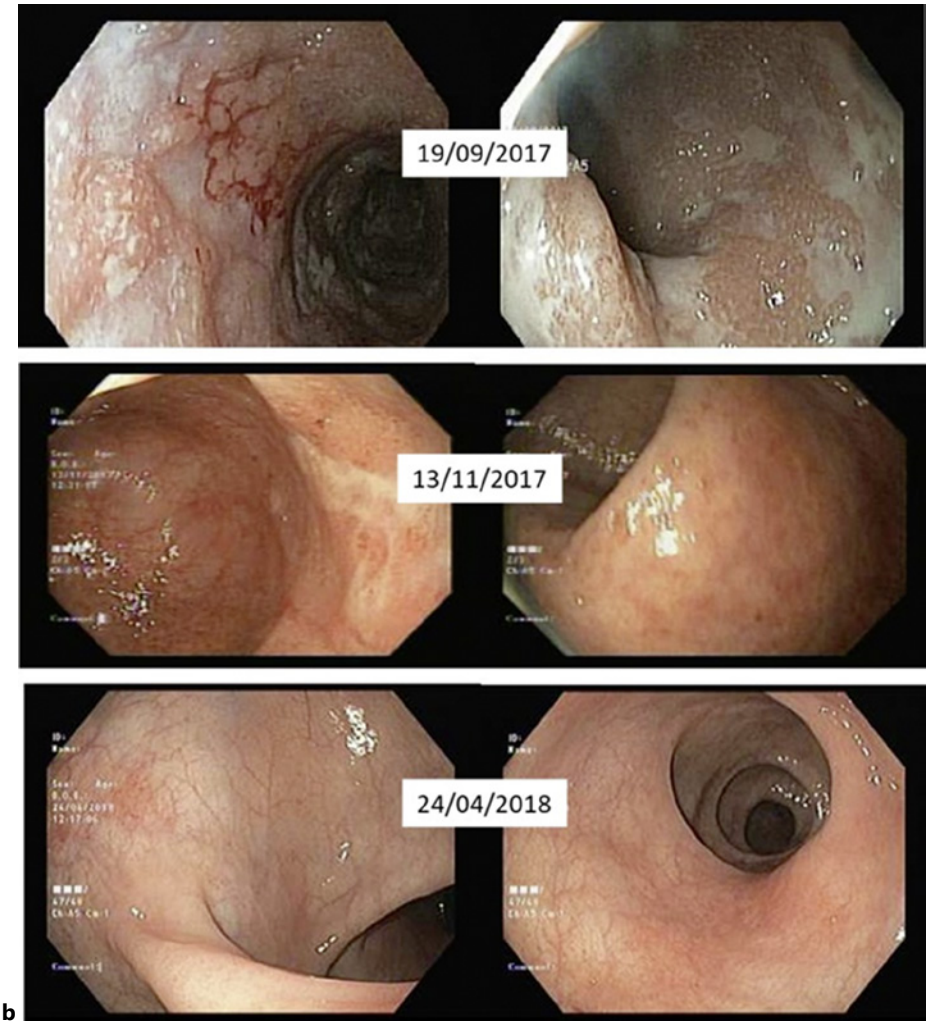

Fig. 1. a Consecutive lower endoscopy images obtained in patient 1. **b** Consecutive lower endoscopy images obtained in patient 2.

biosimilars, high medication costs still comprise a barrier to the wide use of these drugs in some territories. Traditional medicine herbal extracts, which have been popularly used for many centuries, may offer an affordable oral-route option for some patients. However, providing evidence-basis for their efficacy remains a challenge. QD and curcumin have been separately tested in placebo-controlled trials and were found effective in active UC [1–3, 5], and some high quality studies have provided preliminary clues as to possible mechanisms of these herbs in ameliorating gut inflammation [6, 7]. Over the last 6 years, we have used these two herbal supplements in combination in over 300 patients, and a randomized placebo-controlled trial using this combination is ongoing (NCT03720002). As exemplified by the 2 cases presented, our clinical experience has shown that a CurQD combination may be effective in moderate-severe UC patients, some of whom were resistant to biologics and/or corticosteroids. Pulmonary hypertension was reported as a rare but reversible adverse event of prolonged high-dose QD administration [8]. We have not encountered this disorder in any of the patients we treated in clinics over the last 6 years. This could be either due to the different manufacturing and sourcing of the Japanese compound, or due to different genetic predisposition in the Israeli Western population. However, our clinical practice, as exemplified in these 2 cases, is to try to taper and

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stop the QD after induction while continuing curcumin alone as maintenance for patients in remission. This clinical strategy may also contribute, at least partly, to the absence of observed pulmonary hypertension in any of the patients we treated over the last 6 years. In patients unable to completely stop QD due to emerging symptoms, we have opted for maintenance with the minimal QD dose that controls the symptoms. A cardiac echocardiogram after 6–12 months of therapy, as an additional cautionary measure, may yet be pertinent in such patients.

In summary, we herein present one of the few reports on QD use in the Western UC population. Moreover, a combination of curcumin and QD (CurQD) is shown for the first time to induce and maintain remission in patients with moderate-severe UC. More evidence is warranted to further explore this intriguing herbal combination in active UC patients.

Statement of Ethics

Ethical approval is not required for case reports in accordance with national guidelines. Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Conflict of Interest Statement

Shomron Ben-Horin has received advisory board and/or consulting fees from Abbvie, Takeda, Janssen, Celltrion, Pfizer, GSK, Ferring, Novartis, Roche, Gilead, NeoPharm, Predicta Med, Galmed, Medial Earlysign, and Eli Lilly and research support from Abbvie, Takeda, Janssen, Celltrion, Pfizer, and Galmed. The Chaim Sheba Medical Center has filed intellectual property requests on the combination of curcumin and QD. EviNature is a spin-off company of Sheba Medical Center; Shomron Ben-Horin and Nir Salomon are employed by and hold equity in EviNature. The UK has received speaker fees from Abbvie, Janssen, BMS, Rafa, Novartis, Pfizer, and Takeda; research support from Takeda and Janssen; and consulting fees from Takeda and CTS.

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Author Contributions

Prof. Shomron Ben-Horin and Nir Salomon treated the 2 patients, acquired the data, and drafted the manuscript. Prof. Uri Kopylov participated in data interpretation and revised the manuscript for important intellectual content. All the authors approved the final version of the manuscript for publication and agreed to be accountable for all study aspects.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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