

Case Reports in Gastroenterology

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| Manuscript: | CRG-2022-5-6 |
| Title: | Curcumin-QingDai (CurQD) combination for moderate-severe ulcerative colitis: A report of two cases |
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| Keywords: | Colitis, Inflammatory bowel disease, Infliximab, Treatment, Ulcerative colitis |
| Type: | Case Report |

Curcumin-QingDai (CurQD) combination for moderate-severe ulcerative
colitis: A report of two cases

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Running title: Curcumin-QingDai (CurQD) for ulcerative colitis

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Keywords: ulcerative colitis, treatment, inflammatory bowel disease

Abbreviations: UC - ulcerative colitis, CRP - C reactive protein, QD – QingDai,
CurQD – Curcumin-QingDai combination

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 Western population is scant. We report on the use of curcumin-QingDai combination (CurQD) for treatment of moderate-severe UC. Patient 1 was a 24 years-old male with severe UC refractory to cyclosporine and corticosteroids. He partially responded to infliximab but later lost response to optimized dose of infliximab in combination with 6-mercaptopurine, presenting with worsening symptoms and severe Mayo 3 mucosal inflammation. Initiation of CurQD 2.5gr/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 dose CurQD and 6-mercaptopurine for 31 months. Two flares have responded to temporary increase of CurQD dose. Patient 2 was a 59 years-old female with extensive UC not responding to maximal oral+topical 5ASA 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 2000mg/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 two patients.

Case report

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 ulcerative colitis (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 have not been hitherto reported. We herein report two patients treated in our center with a curcumin-QingDai combination (CurQD).

Patient 1 was a 24 years-old male with extensive ulcerative colitis for two 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. He presented with 6-7 bowel-movements daily, half of which with blood. At presentation he has been on infliximab 7mg/kg every 4 weeks with 100mg/day of 6-mercaptopurine. Infliximab levels were 11.9 mcg/ml without anti-drug antibodies. CRP was nine-times the upper normal limit. Stool calprotectin was 670mg/gr and sigmoidoscopy showed Mayo 3 inflammation up until 30cm from the anal verge (Figure 1a). Infectious work-up including immunohistochemistry for CMV was negative. Swapping biologic was considered but the patient opted for short-term trial of herbal treatment. Therefore, CurQD (EviNature, Binyamina, Israel) was initiated at 1000mg curcumin and 1500mgQD daily, as add-on to infliximab and 6-MP. Bleeding ceased within 10 days 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 6MP and with

a gradual tapering of QD dose to 500mg every-other-day. A clinical and endoscopic flare occurred 3 months later, which responded to dose increase of QD back to 1000mg/daily, followed by dose reduction to 500mg/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 6MP 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 years-old female diagnosed with extensive colitis a year earlier, which did not respond to maximal oral and topical mesalazine therapy. She did not improve with budesonide-MMX at 9mg/daily and presented with 4-5 bloody bowel movements a day, weakness and abdominal pain. Hemoglobin level was 10.3g/dl, CRP was 6 times of upper normal limit and a sigmoidoscopy showed severely ulcerated Mayo 3 grade inflammation up to 45cm (Figure 1b). Vedolizumab was prescribed but the patient was wary of receiving intravenous biologic medications. Thus, a short-term trial of CurQD 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 five months of CurQD showed mucosal scarring and complete healing (Figure 1b). The patient has since been maintained on 3gr/day mesalamine with CUR-QD, at a tapered QD dose of 500mg/every-other-day with 1000mg/daily curcumin for 49 months until 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 1000mg/daily which was then tapered back to alternating-day

500mg 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 biosimilars, high medication costs still comprise a barrier to 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 six 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 two 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 six years. This could be either due to the different manufacturing and sourcing of the Japanese compound, or due to different genetic predisposition in Israeli Western population, or possibly secondary to our strategy whereby QD is tapered and stopped

after induction while continuing curcumin dosing unchanged. 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 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: SBH 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, & 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, SBH and NS are employed by and hold equity in EviNature. UK has received speaker fees from Abbvie, Janssen, BMS, Rafa, Novartis, Pfizer, Takeda, research support from Takeda and Janssen and consulting fees from Takeda and CTS

Funding Sources: This work was supported in part by the 7th Dr. Pinchas Borenstein Talpiot Medical Leadership Program of Sheba Medical Center (to SBH)

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

Data availability Statement: All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author

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Figure Legends

Figure 1a. Consecutive lower endoscopy images obtained in patient 1

Figure 1b. Consecutive lower endoscopy images obtained in patient 2



