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Successful Treatment of Refractory Ulcerative Proctitis in a Pediatric Patient Using Topical Tacrolimus

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INTRODUCTION

Pediatric ulcerative colitis is a chronic inflammatory condition with an incidence that varies from 0.3 to 15 per 100,000 person-years worldwide (1). In 6%–25% of cases, the disease is limited to the rectum (defined as up to 15 cm proximal from the dentate line) (2,3). In some of these cases, it is difficult to achieve remission of the disease despite several treatments, including immunomodulatory regimens. Here we present a case of refractory ulcerative proctitis, treated successfully using tacrolimus suppositories.

CASE DESCRIPTION

We present a case of a 15-year-old male patient who was diagnosed with ulcerative proctitis at 12 years of age. His complaints included abdominal pain, frequent unformed stools, and rectal bleeding. Laboratory investigations excluded abnormalities such as anemia, deficiencies or signs of inflammation and imaging studies (abdominal sonography and MR enterography) were normal. Fecal calprotectin was 9370 μg/g and endoscopic evaluation showed diffuse inflammation of the most distal 15 cm from the dentate line and a small "cecal patch" of inflammation. Histologic examination described distorted crypt architecture with diffuse chronic active inflammation without granulomas.

The patient was initially treated with 5-aminosalicylic acid and budesonide enemas. Due to lack of effect, oral corticosteroids were given, with beneficial effect. Thiopurine therapy was initiated (up to 4 mg/kg/d), which led to the longest symptom-free interval of 6 months, followed by a loss of control. Endoscopic reevaluation showed a slight progression in the inflammation to 20 cm from the anal verge resulting in anti-TNF therapy (ie, infliximab) to be started. This therapy had some positive effect in the first 2 months but subsided despite adequate through levels. Endoscopic reevaluation showed marked inflammation that extended up to 25 cm from the anal verge (Fig. 1). At this point, his PUCAI was 70 and fecal calprotectin >30,000 μg/g. The preparation of the tacrolimus suppositories was performed by a compounding pharmacy (Pharmaline pharmacy, Oldenzaal, The Netherlands) according to the Good Manufacturing Practices guidelines. The preparation was carried out in a laminar flow cabinet, wearing gloves and safety glasses. The content of 5 mg Prograft capsules was mixed with a suppository fat base (Witepsol). To create suppositories containing 2 mg of tacrolimus, the mixture was subsequently poured using a squeeze bottle into 2.3 mL molds and solidified.

Tacrolimus was started as monotherapy 2 mg once daily. Within 3 weeks, the patient had complete resolution of symptoms (PUCAI 0) and normal laboratory tests, including blood counts, renal function (urea, creatinine, sodium, potassium), liver function (AST, ALT, γ-GT, bilirubin) and blood glucose. However, laboratory investigation at 8 weeks showed mildly elevated bilirubin of total 21 mmol/L (1.23 mg/dL) and lipase of 124 U/L with no abnormalities in other blood tests. The tacrolimus through level was 4 μg/L (therapeutic range 5–20 μg/L), taken at 24 hours after the last dose. Because the elevated bilirubin and lipase levels were considered to be a side effect of tacrolimus use, the dose was initially tapered to 1 mg once daily. Although this resulted in complete normalization of both bilirubin and lipase, tacrolimus through levels remained detectable (3.9 ng/mL). In order to prevent possible side effects of long-term tacrolimus use, we aimed for undetectable through levels by further decreasing the dose to 1 mg every other day. At this dose, through levels were undetectable while the patient remained in clinical remission with PUCAI score of 0 and fecal calprotectin of 62 μg/g.

After a follow-up period of 2 years, the patient had experienced 2 exacerbations of the disease. The first was after noncompliant use (1–2 times a week) during 1 month and the second was 11 months after ceasing therapy completely on his own initiative. In both exacerbations, symptoms resolved quickly (within a week) after restarting therapy at 1 mg every other day.

DISCUSSION

Ulcerative proctitis, even though it is characterized by a limited area of inflammation, may cause severe, persistent symptoms which are difficult to treat. A study of 38 pediatric patients showed persistent symptoms at 6 months after diagnosis in 8% of the cases. During later follow-up, despite several treatments, 55% of the patients were asymptomatic and 5% had persistent symptoms (4). Furthermore, expansion of inflammation proximal to the rectosigmoid occurs in approximately 30%–40%, without any known risk factors or predictors besides having persistent or recurrent disease activity (2–4). The risk for requiring colectomy is similar to more extensive colitis (3). This emphasizes the need for adequate therapy, in order to control symptoms and to reduce the risk of disease progression. To avoid systemic side effects of immunosuppression as much as possible, the aim of treatment would be to achieve remission using local treatment.

Tacrolimus is a classical calcineurin inhibitor that is currently most often used for immunosuppression after organ transplantation. In adult studies, oral tacrolimus has been shown to be effective in treating refractory ulcerative colitis, but may lead to serious side effects such as myelosuppression, hypertension and hyperkalemia (5). Topical tacrolimus is absorbed and active in human rectal mucosa (6). The use of topical tacrolimus for proct(osigmoid)itis in adult patients led to significant higher rates of clinical response (73% vs. 10% placebo), clinical remission (45% vs. 10% placebo)

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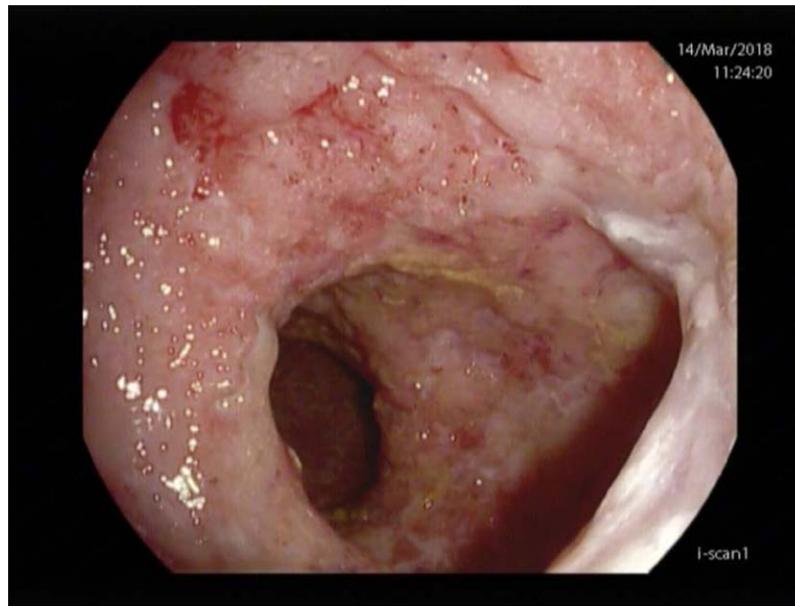

FIGURE 1. Endoscopic image of proctosigmoiditis before treatment with tacrolimus.

and mucosal healing (73% vs. 10% placebo) without serious adverse events (6,7). Reported side effects were a reversible increase to 1.5 mg creatinine/dL and symptoms including headaches, hypertension and arthralgia. No correlation was found between tacrolimus through levels and the outcome or aforementioned side effects (7).

The regimens for topical tacrolimus administration that have been studied are ointment (2 times daily 3mL containing 1.5 mg), enema (150 mL containing 2–4 mg once daily) and suppository (2 mg once daily). Detectable through levels in study participants varied from non-detectable to 23.2 μg/L with averages of 0.7 μg/L (range undetectable −1.7) to 4.2 μg/L (± 1.6) at 4 weeks (6,7). Normal therapeutic range for systemic treatment of ulcerative proctitis and extensive colitis is aimed at 5–20 μg/L (5,7).

In our patient, remission occurred with subtherapeutic through levels and persisted even when levels were undetectable. This effect has previously been shown and could be attributed to the local absorption and activity in the intestinal mucosa, often without significant systemic uptake (6,8). In children, the efficacy and possible side effects of topical tacrolimus have not been studied. One case report describes a patient with a J-pouch after colectomy for ulcerative proctitis who developed acute renal injury during tacrolimus treatment. This patient had relatively high through levels (7.1–9.3 ng/mL) and a suspected viral illness with vomiting and diarrhea. At that point, at 4 hours after the last dose, a peak level was measured of 36.8 ng/mL. The renal injury was fully recovered after cessation of tacrolimus therapy and intravenous fluid rehydration (9).

CONCLUSION

This case report is the first to our knowledge to present the successful treatment of refractory ulcerative proctitis in a pediatric patient using tacrolimus suppositories and may aid physicians in treating similar patients. We suggest considering tacrolimus suppositories in patients with refractory symptoms, despite first-line treatments using mesalamine and topical steroids. Regular monitoring for side effects such as hepatotoxicity and nephrotoxicity would be warranted and aiming for undetectable through levels may permit long term use.

In order to gain more information about both short- and long-term efficacy and side effects in children, research should be performed using this therapy in the pediatric population.

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