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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Sirolimus Use in Refractory Crohn's Disease

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ABSTRACT

Treatment options for patients with inflammatory bowel disease are constantly evolving; however, medication-refractory disease remains an issue. Pediatric case series show the potential benefit of sirolimus therapy in refractory Crohn's disease (CD); however, limited data exist in adult patients. As such, we retrospectively identified and report clinical outcomes for 4 patients prescribed sirolimus for treatment of refractory CD. Despite a median sirolimus therapy duration of 524 days and some therapeutic benefits, all patients discontinued therapy due to adverse effects. Our findings suggest that while sirolimus may have clinical utility, its role may be limited by treatment-derived adverse effects.

KEYWORDS: inflammatory bowel disease; Crohn's disease; sirolimus; adverse effects; immunomodulator; poor wound healing; extremity edema

INTRODUCTION

The mainstay for maintenance treatment for inflammatory bowel disease (IBD) continues to include immunomodulator and biologic therapy.[1,2] Despite advances in therapy, a subset of patients with medication-refractory disease persists. Sirolimus is an immunosuppressive medication (ISM) whose mode of action includes inhibition of T-cell activation and proliferation.[3] Although typically used as an antirejection medication in patients with transplant, sirolimus has been successfully utilized for treatment of refractory Crohn's disease (CD) and ulcerative colitis in pediatric patients.[4] However, limited data and experience exist for the use of sirolimus in adults with medication-refractory IBD, and as such, we present this case series of sirolimus in adults with medication-refractory IBD.

CASE REPORT

Figure 1 details identifying patients with IBD treated with systemic sirolimus therapy. Tables 1–3 provide details regarding demographic, serologic, imaging, and medication data.

Patient 1: A 36-year-old woman with a history of hidradenitis suppurativa, obesity, and medication-refractory CD (Montreal A2, L3, B3) requiring strictureplasty and small bowel resection had previously failed 6 ISMs and was being treated with vedolizumab at the time of sirolimus initiation (Table 3). Pre-sirolimus colonoscopy revealed a perianal fistula but otherwise grossly normal colon and ileum and no granulomatous disease on pathology. Colonoscopy was not performed following sirolimus therapy initiation. Sirolimus treatment occurred for a total duration of 972 days. Provider documentation indicated that low-dose sirolimus (0.5 mg/d) was initiated due to its synergistic effect with vedolizumab which may be related to reducing immunogenicity, but there was no evidence that prior therapies were discontinued due to immunogenicity. Sirolimus was tolerated well, with dosing increased to 1 mg/d after 90 days. Laboratory evaluation showed reduction of C-reactive protein (CRP), but magnetic resonance enterography (MRE) at day 469 noted worsening small bowel wall thickening (Table 2). No clinical documentation was found detailing symptoms following repeat MRE or reduction in CRP. Owing to severe lower extremity edema, sirolimus was ultimately discontinued with edema resolution. The patient is currently maintained on vedolizumab monotherapy.

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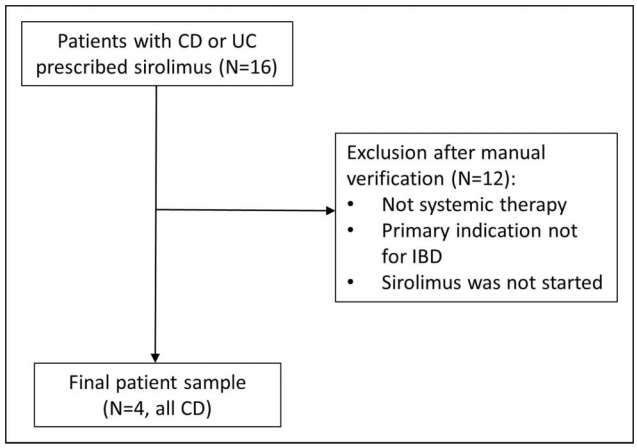

Figure 1. Patient selection. We retrospectively identified adult patients with IBD utilizing *International Classification Diseases-10* codes (K51.* and K52.*) who were prescribed systemic sirolimus for primary indication of IBD treatment. Patients with a history of bone marrow or organ transplantation and sole use of topical sirolimus were excluded. Sixteen patients with a diagnosis of IBD who had been prescribed sirolimus were identified. Subsequent manual verification and exclusion for bone marrow or organ transplant reduced the cohort to a sample of 4 patients, all of which have Crohn's disease. CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Patient 2: A 38-year-old woman with autoimmune enteropathy (AIE) and medication-refractory CD (Montreal A2, L3, B1) had previously failed 5 ISMs before sirolimus initiation. AIE was complicated by protein-wasting enteropathy requiring total parenteral nutrition (TPN). Her AIE was managed with budesonide and abatacept. Sirolimus was initiated at 5 mg daily with trough goal of 10–15 ng/mL. It was titrated up to 7 mg/d after 2 weeks, but her trough levels remained subtherapeutic, and the decision was made to titrate up at a rate of 1 mg/d until therapeutic levels were attained 3 months after initiation. Her sirolimus dosing eventually stabilized at 18 mg/d to assist with refractory CD and AIE treatment, for a total treatment duration of 1,055 days. Colonoscopy before sirolimus initiation was not performed, but postsirolimus showed blunted ileal villi, and pathology showed patchy crypt abscesses and apoptotic activity. Marked improvement in symptomology was noted once therapeutic levels were reached, and patient reported reduction of diarrhea along with reduction of CRP from 64 to 4.8 mg/L before discontinuation (Table 2). Clinical course was complicated by pathologic hip fracture requiring arthroplasty. Subsequently, poor wound healing and bacteremia necessitated sirolimus dose reduction and eventual discontinuation to optimize wound healing. Dose reduction was associated with increased diarrhea; MRE demonstrated worsening inflammation of sigmoid and rectum. The patient is currently exploring alternative treatments.

Patient 3: A 52-year-old woman with a history of asthma and chronic diarrhea presented with a new diagnosis of CTLA4 haploinsufficiency and CD (Montreal A3, L3, B1). She had previously failed 7 ISMs, with sirolimus initiated (5 mg/d) due to new cytogenetic findings. The patient tolerated 77 days of therapy before discontinuation. Colonoscopy was performed before sirolimus initiation, showing grossly normal colon and terminal ileum, and pathology showed intraepithelial lymphocytes suggestive of microscopic colitis. Repeat colonoscopy at 38 days after sirolimus discontinuation noted grossly normal colon and terminal ileum without notable changes from presirolimus evaluation. A small reduction of CRP was noted (Table 2). Cross-sectional imaging was not obtained. Clinical documentation revealed patient-reported improvement in diarrhea; however, several sirolimus-related adverse events (AE) occurred including acneiform skin eruptions, recurrent urinary tract infections, lower extremity edema, and severe arthralgia. In addition, new-onset anemia was noted following sirolimus initiation (hemoglobin decrease from 13 to 9.6 g/dL). Sirolimus was discontinued due to AEs, with subsequent resolution of skin eruptions, lower extremity edema, arthralgia, and anemia.

Patient 4: A 38-year-old man presented with a history of medication-refractory CD (Montreal A1, L3 B2p) requiring multiple abdominal surgeries resulting in short bowel syndrome and TPN dependence. The patient had trialed 7 ISMs before sirolimus initiation (2 mg/d), with concurrent prednisone and ustekinumab therapy, but there was no mention as to why triple therapy was preferred in this instance. Total sirolimus treatment duration was 60 days. The patient initially

Table 1. Baseline characteristics

Patient	Age	Gender	Ethnicity	BMI	Charlson comorbidity index	Age at CD diagnosis	CD Montreal	History of abdominal surgery related to CD and type
1	36	Female	White	35.3	0	19	A2, L3, B3	Yes, strictureplasty and small bowel resections
2	38	Female	White	31.25	1	32	A2, L3, B1	No
3	52	Female	White	27.2	1	37	A3, L3, B1	No
4	38	Male	White	16.7	0	8	A1, L3, B2p	Yes, strictureplasty and ileocecal and colic resections

Montreal classification was determined through review of records at the time of sirolimus initiation, including age of Crohn's disease onset (A1: younger than 16 years, A2: 17-39 years, A3: older than 40 years), disease location (L1: ileal, L2: colonic, L3: ileocolonic, L4: isolated upper), disease phenotype (B1: nonstricturing nonpenetrating, B2: stricturing, B3: penetrating/fistulating, p: perianal disease).
BMI, body mass index; CD, Crohn's disease.

Table 2. Sirolimus therapy

Patient	Dose (mg/d)	Goal trough range (ng/mL)	Age at sirolimus initiation	Duration of sirolimus therapy (d)	Presirolimus enterography (days prior to therapy initiation)	Postsirolimus enterography (days following therapy initiation)	Presirolimus CRP (mg/L)	Postsirolimus CRP (mg/L)	Reason for discontinuation
1	1	—	31	972	8 cm wall thickening of proximal ileum (49)	15 cm wall thickening and small bowel inflammation (469)	14.4	8.6	Lower extremity edema
2	18	10–15	35	1,055	No signs of active inflammation (279)	Severe proctocolitis (190)	64	4.4	Abdominal wound healing, lower extremity edema
3	5	10–15	49	77	—	—	5.3	4.8	Rash and recurrent urinary infections
4	2	7–12	37	60	Active inflammation of mid-ileum (116)	6 cm active inflammation of ileum with narrowing (60)	—	—	Poor wound healing and bleeding

CRP, C-reactive protein.

reported improvement in diarrhea; however, symptomatic improvement was short lived, and he continued to have significant abdominal cramping and vomiting in addition to bleeding around his TPN line. Magnetic resonance imaging before sirolimus therapy showed active ileal inflammation, with persistent inflammation on repeat MRI on day 60 of therapy. No inflammatory biomarkers or endoscopic evaluation was obtained before or after sirolimus therapy. Sirolimus therapy was ultimately discontinued along with ustekinumab at the patient's request due to minimal therapeutic benefit with concurrent superficial bleeding and poor wound healing. His CD is currently managed with daily prednisone monotherapy.

DISCUSSION

IBD treatment continues to evolve with the arrival of novel therapies; however, medication-refractory disease remains a challenge.[5] Although data regarding sirolimus therapy in the pediatric IBD population suggest clinical benefit, little is known regarding its use in adults with IBD.[4] This study represents the largest case series of sirolimus therapy in adults for a primary indication of medication-refractory IBD, providing insights into its clinical utility and limitations.

Sirolimus use in pediatric populations with IBD has included a 14 patient retrospective study reporting its use in patients with ulcerative colitis and CD as well as a recent case report with both noting improved mucosal healing and achieving clinical remission in the observed patients.[4,6] Current literature in adults is limited to a single case report describing sirolimus therapy in a middle-aged female with refractory ileocolonic CD, noting mucosal healing and biomarker improvement.[7] Similarly, our case series noted sirolimus therapy to coincide with symptomatic improvement in all patients, with CRP reduction noted in 3 of 3 patients tested. Nevertheless, of the patients with

Table 3. Immunosuppressive therapy

Patient	Therapy attempted prior to sirolimus	Therapy at the time of sirolimus initiation	Agents added during sirolimus therapy	Agents removed during sirolimus therapy
1	Adalimumab, azathioprine, budesonide, infliximab, tacrolimus, ustekinumab, vedolizumab	Vedolizumab	None	None
2	Adalimumab, azathioprine, infliximab, prednisone 20 mg, vedolizumab	Prednisone 20 mg	None	None
3	Abatacept, adalimumab, azathioprine, budesonide, infliximab, mesalamine, prednisone 20 mg	Prednisone 20 mg	None	Prednisone 20 mg
4	Adalimumab, certolizumab, infliximab, prednisone 20 mg, tacrolimus, ustekinumab, vedolizumab	Prednisone 20 mg, ustekinumab	None	Ustekinumab

available MRI before and following sirolimus therapy, continued inflammation was noted.

Two of patients were noted to have reduction of their ISMs after sirolimus therapy with patient 3 tapering off their prednisone and patient 4 discontinuing their ustekinumab (Table 3). Therapy discontinuation was not attributed to failure in treatment or development of immunogenicity. Two of patients received a multimodal regimen with sirolimus plus a biologic agent (vedolizumab in patient 1 and ustekinumab in patient 4). Although evidence for the clinical utility of combining sirolimus therapy with IBD-directed biologic agents is lacking, one potential consideration would be amplification of immunosuppression and thus reduced possibility of developing immunogenicity to the biologic agent.[3,8]

Our patients exhibited varying therapy duration, with all patients experiencing sirolimus-related AEs leading to discontinuation. Commonly reported AEs of sirolimus include dyslipidemia, proteinuria, anemia, impaired wound healing, and edema.[9] The most commonly observed AE in this study was poor wound healing (50%) and lower extremity edema (50%). It should be noted that elevated body mass index (>30) has been identified as an independent risk factor of poor wound healing when using sirolimus.[10] Of the 2 patients who experienced poor wound healing, one had a body mass index of >30. Furthermore, prior studies have noted edema to be correlated with sirolimus trough levels of ≥12 ng/mL, with improvement of edema when trough levels are reduced.[9] A trough level of 10 ng/mL was observed in one of 2 patients who discontinued therapy due to edema. Although dose reduction was not attempted before sirolimus discontinuation, it may have ameliorated edema and prevented complete discontinuation. In regard to other common AEs such as anemia and dyslipidemia, patient 3 exhibited significant anemia following sirolimus initiation that subsequently recovered following discontinuation. No patients experienced significant dyslipidemia.

In conclusion, with minimal data available for the use of sirolimus therapy in adults with treatment-refractory IBD, our findings suggest that its role may be limited by treatment-associated AEs. Further data are needed to investigate the efficiency and utility of sirolimus therapy in refractory IBD, with particular attention to treatment-limiting AE and attempted remedies before discontinuation.

DISCLOSURES

Author contributions: RK Siu: data acquisition, analysis, interpretation, and manuscript preparation. C. Karime: data analysis, preparation, critical review of manuscript. MF Picco, J. Kinnucan, FA Farraye, JG Hashash: study conception, design, and critical review of the manuscript. All authors approved the final manuscript before submission.

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Informed consent was obtained from 2 patients, and 2 other patients were no longer in the care of the original institution and attempts for consent were unsuccessful.

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