Sirolimus-Induced Ulceration of the Small Bowel in Islet Transplant Recipients: Report of Two Cases

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Sirolimus (SRL) has been used for most islet recipients over the past 5 years. It provides balanced immunosuppression in combination with low-dose calcineurin inhibitors, while avoiding corticosteroids. This regimen decreases the risk of nephrotoxicity, neurotoxicity and diabetogenicity. SRL has also been used selectively in clinical liver and kidney transplantation. A number of common side effects including anemia, leucopenia, thrombocytopenia, hypercholesterolemia, mouth ulceration, joint pain, extremity edema and impaired wound healing have been associated with the use of SRL. As SRL is used more frequently, evidence has been gathered on its rare but severe side effects. We report 2 patients who underwent islet transplantation and developed symptomatic small bowel ulceration that resolved after complete withdrawal of SRL. Although small bowel ulceration is rare, it can potentially progress to more serious complications if not treated adequately. Our experience highlights an uncommon but potentially serious adverse effect of high-dose SRL in islet recipients.

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Background

Sirolimus (SRL) is a macrocyclic triene with immunosuppressive activity increasingly used in organ transplant recipients for induction and long-term maintenance therapy (1). The drug was isolated from Streptomyces hygroscopicus and identified as an anti-fungal and chemotherapeutic agent before its immunosuppressive effects were recognized (2). SRL is currently used as an effective alternative to calcineurin inhibitors (cyclosporine and tacrolimus) because it inhibits the interleukin-2 and growth factor-mediated signal transduction in both B and T lymphocytes without affecting the calcineurin receptor sites through inhibition of the mammalian target of rapamycin (mTOR) (3). This property is extremely attractive since it reduces nephrotoxicity, diabetes and neurotoxicity (4). On the other hand, the use of SRL to prevent rejection in transplant patients has been associated with a number of side effects including: leucopenia, thrombocytopenia, hypertriglyceridemia, hypercholesterolemia, mouth ulceration, peripheral edema, joint pain, pulmonary fibrosis, wound infections and wound dehiscence (5–8).

Since the introduction of the Edmonton Protocol and more recent variants, the clinical outcomes for islet transplantation have been transformed and more patients with Type I diabetes are referred to selected centers (9). Mainstay immunosuppression for most recent islet transplants has been glucocorticoid-free, with SRL, low-dose tacrolimus and anti-CD25 induction (9). In our center, an inductive course of an anti-IL2-R mAb (daclizumab) is given routinely with each transplant, and continued at 2-week intervals for five doses. Low-dose aspirin (81 mg) is given for the first 14 days post-transplant then discontinued, and no non-steroidal anti-inflammatory medications are prescribed. This combination has improved early rates of insulin independence, but does not prevent ongoing slow deterioration of islet function over time (9,10). Target SRL levels are generally 12–15 ng/mL for the first 3 months and lowered to 7–10 ng/mL thereafter. Tacrolimus target trough levels are maintained between 4–6 ng/mL.

We have observed unique side effects of small bowel ulceration presumed to be secondary to SRL therapy in two islet recipients after undergoing uncomplicated percutaneous intraportal islet transplantation.

Report of Two Cases

Patient A
A 49-year-old Caucasian woman, insulin dependent diabetic since the age of 12, underwent her first islet transplant on April 21, 2001. Her past medical history was significant for hypothyroidism, Type I diabetes and severe recurrent migraine attacks, for which she was previously taking verapamil, which was discontinued prior to transplantation. The procedure was unremarkable (islet mass 343,656 IE, 6,363 IE/kg) and she was discharged home on the following day on the combination of SRL (8 mg qd) and
tacrolimus (2 mg bid) taken as oral tablets. After her first transplant, she required 30% of her pre-transplant insulin therapy. At 3 weeks post-transplant, the SRL levels were noted to be extremely high (level 142 ng/mL) on a dose of 8 mg SRL per day. SRL therapy was withheld immediately, and the levels followed closely (Figure 1). It emerged subsequently that this patient had in fact restarted verapamil therapy for migraine prophylaxis against medical advice to the contrary. The patient was instructed to discontinue further verapamil intake and use simple analgesics instead. She initially complied but then resumed verapamil treatment without our knowledge. SRL dosing was reduced to 0.5 mg once every other day to maintain levels within range. On August 12, 2001, a second islet infusion was completed (523 000 IE, 9685 IE/kg, for a total cumulative islet mass of 16 049 IE/kg). The patient was rendered insulin independent with good glycemic control following the second islet infusion and she was discharged home on the same immunosuppression regimen used after the first transplant. On the 10th week after the second islet infusion, the patient presented with diffuse, persistent abdominal pain associated with nausea, vomiting and diarrhea. On physical examination, she had multiple aphthous oral ulcers and mild tenderness in all the abdominal quadrants with a palpable 4 cm mass in her right lower quadrant. The remaining exam was unremarkable. Her hospital admission hematological and biochemistry profiles are reported in Table 1. A triple phase abdominal CT scan revealed wall thickening of the terminal ileum and cecum with enlarged lymph nodes at the root of small bowel mesentery and some moderately prominent para-aortic nodes with appearances concerning for the possibility of post-transplant lymphoproliferative disease (PTLD) (Figure 2A). Blood, urine and stool cultures were negative for bacterial, viral, yeast and parasitic infections. Immunoglobulin panel for cytomegalovirus, Epstein Barr virus and PCR viral loading monitoring were all negative. The patient underwent a colonoscopy that revealed normal colonic mucosa. After the scope was advanced proximally to the ileocecal valve, multiple biopsies of a well-demarcated terminal ileum ulcer of 5 cm in maximum diameter were obtained (Figure 3A,B). Tissue staining and microbiologic analysis revealed an ulcer with acute nonspecific inflammatory changes characterized by mixed cellular population with no evidence of bacterial, viral or yeast infection (Figure 4A,4B). Special stains for EBV revealed no features suggestive of PTLD. At this point we discontinued SRL therapy permanently.

The patient’s nausea, vomiting and abdominal pain subsided but she refused to suspend verapamil therapy. We therefore converted immunosuppression over to tacrolimus (target 10–15 ng/mL) and mycophenolate mofetil (MMF, 1.5 g/day). Glycemic control did not deteriorate after conversion to higher dose tacrolimus and MMF. In fact the patient remained insulin free with excellent glycemic control (HbA1c 4.9%) and had an entirely normal glucose potentiated arginine-induced insulin secretion (GPAIS) response 1 year post-transplant (Figure 5). A follow-up abdominal CT scan performed 3 months later showed complete resolution of the intestinal wall thickening and lymph node enlargement (Figure 2B).
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Figure 2: Computerized triphasic scan of the abdomen and pelvis of patient A. Image A was obtained at 4 months post-transplant and demonstrates a 4 cm mass in the right lower quadrant just proximal to the ileocecal valve (arrow). There is lymphadenopathy along the mesenteric fold of the terminal ileum. Image B shows the complete resolution of the ileocecal mass at 8 months post-transplant (2 months post withdrawal of sirolimus).

Figure 3: (A and B) Endoscopic images of the terminal ileum in patient A. The mucosa appears edematous, erythematous and with several submucosal hemorrhagic changes. In Figure 3A, the arrow indicates the area of the ulcer. Figure 3B shows a closer view of the mucosa. Multiple biopsies were obtained from the ulcer and from the inflamed mucosa proximally and distally to the ulceration.

Patient B
A 40-year-old Caucasian female developed type I diabetes at 4 years of age, and underwent a pancreatic islet cell transplant on December 25, 2003. She received a total of 285 271 IE (5282 IE / kg body weight). She was discharged home on the following day on SRL 9 mg qd and tacrolimus 1.5 mg bid. Her past history included blindness secondary to diabetic retinopathy, autonomic neuropathy, hypothyroidism, microalbuminuria and hypertension. Concurrent medications included fosinopril, levothyroxine, multivitamins and insulin. During the following months, the patient’s general condition remained well except for occasional episodes of hyperglycemia that were treated with 50% of her pre-transplant dose of short-acting insulin.

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On February 3, 2004, the patient received a second islet transplant (268 289 IE, 5261 IE/kg body weight, for a cumulative total of 10 543 IE/kg). Serologic levels of SRL during the post-transplant period remained in the therapeutic range (12–15 ng/mL) with a maximum level of 18.6 ng/mL observed 10 days after her discharge. At 3 weeks after the second transplant, as the patient became insulin independent, she developed several small oral ulcerations, generalized weakness, poor appetite, anemia, leucopenia and thrombocytopenia. Her vitals signs were normal. She was re-admitted to hospital for investigation. Her serologic flow tests showed a retrospective positive cross match against the second islet transplant. She received 2 gm per kg/body weight i.v. immunoglobulin treatment for 48 h. During this admission, the patient complained of vague abdominal discomfort with mild diarrhea. Her physical examination was unremarkable and her abdomen was soft and non-tender with normal bowel sounds. A rectal examination revealed positive fecal occult blood. Serological assessment for CMV and EBV infection were negative. Her hematology and biochemistry blood tests on presentation are shown in Table 1. To correct her neutropenia, 300 mcg of granulocyte colony stimulating factor (GCSF) was given in several occasions. Blood, urine and stool cultures were all negative for bacterial, viral and fungal infection. During her hospitalization, her abdominal symptoms progressed and she developed diaphragmatic spasms. Upper and lower gastrointestinal endoscopies were obtained. The colonic and terminal ileum mucosa appeared normal as well as the stomach and duodenum. When the scope was further advanced beyond the terminal ileum, a discrete area of mucosal ulceration similar to the one reported for the previous patient was identified (Figure 3). The ulcer was biopsied and the patient’s immunosuppression regimen was modified to tacrolimus (target 8–10 ng/mL) and MMF (1 gm bid), and the SRL was discontinued for a period of 3 weeks until her symptoms completely resolved. Microscopy demonstrated acute inflammatory changes with a mixed cellular infiltrate. Immunohistochemistry for CMV early antigen and in-situ hybridization for EBV were negative. The patient’s symptoms improved promptly. The patient was subsequently restarted on low-dose SRL (5–10 ng/mL) and tacrolimus, and the MMF was discontinued. A follow-up colonoscopy performed 1 month after discharge revealed complete resolution of the ulcerated mucosa in the terminal ileum and the patient remains well since and insulin free.

**Discussion**

Increased incidence of oral aphthous ulcers, bone marrow suppression (anemia, leucopenia and thrombocytopenia) and hyperlipidemia are well-described side effects of the use of SRL in transplantation as we observed in both patient A and B. Ulcerations of the small intestine, however, are rare and not easy to diagnose in the general population (11), and even more challenging in immunosuppressed...
patients. In canine models, high serum concentration of SRL have been associated with gastrointestinal vasculitis (12) and ulcerations (13), possibly as a result of differential expression of P70S6kinase within the intestinal mucosa of different species. This effect has not been observed in humans to our knowledge. The pathophysiology of oral aphthous ulcerations, more frequently observed with the use of SRL in islet transplant recipients, remains poorly understood (14). It has been hypothesized to result from simultaneous inhibition of epithelial cell replication and the overgrowth of microbacterial flora (15). A similar mechanism could explain the formation of ulcers in other parts of the gastro-intestinal tract although rarely observed in clinical practice.

On the contrary, PTLD is well-described in immunosuppressed patients, but not as yet in islet-alone recipients (16,17). The incidence of PTLD after transplant varies according to the age of the recipient, EBV status of donor and recipient, immunosuppression regimen and type of transplant (18). Isolated PTLD can mimic other forms of malignant tumors and surgical excision is recommended when the diagnosis is dubious (19). Primary gastrointestinal PTLDs usually present with anorexia, weight loss, nausea, abdominal pain and thickening of the wall of the segment of the intestine involved (20). These symptoms are identical to the presentation of our 2 patients who suffered from ileal ulceration. When we were initially concerned about the possibility of PTLD, we lowered immunosuppression and withdrew SRL therapy. Serology and mucosal biopsies ruled out PTLD as an underlying cause in both recipients. The gastrointestinal symptoms improved and the ulceration resolved rapidly after withdrawal of SRL. Although graft loss from the discontinuation of
immunosuppressive medications is a potential risk (20), we did not observe any decline of islet graft function in these individuals. In fact, patient A maintained an entirely normal glucose stimulation profile despite being on high-dose tacrolimus and MMF. Although this regimen is associated with risk of diabetes, the patient remained insulin free after 47 months with normoglycemia, normal HbA1c and her oral glucose stress test revealed well-preserved islet function.

Summary

We describe two cases of symptomatic ulcerations of the small intestine in patients treated with SRL after successful islet-alone transplantation. This is a potentially serious side effect of SRL that, to our knowledge has not been described previously in transplantation. Although the 2 patients had similar clinical presentation that included abdominal pain, oral aphthous ulcerations, bone marrow suppression and hyperlypemia, in the first case, the cause of severe terminal ileum ulceration was undoubtedly due to supra-therapeutic SRL levels resulting from the interaction between SRL and the occult intake of verapamil by the patient. On the other hand, the second patient had SRL levels within the therapeutic ranges for the entire post-transplant period. Both patients received temporary low-dose aspirin for 14 days after each transplant, and neither patient was taking aspirin or other NSAID medications at the time of presentation with ileal ulceration.

The presentation of a right lower quadrant mass in an SRL-treated patient needs to be fully investigated with a primary goal to rule out malignancy and abscess. SRL-related intestinal ulceration should be included in the differential diagnosis, with upper and lower endoscopies likely being the investigations of choice. In the absence of definitive diagnosis, consideration should be given to alteration of SRL-based immunosuppression to an alternative. Our 2 patients affected by small bowel ulcerations had a benign course that responded to the discontinuation of the immunosuppression medications without graft function loss. With the increasing use of SRL in transplantation, it may be helpful to recognize this rare and previously unreported side effect.

References
