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CASE REPORT

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The use of oral tacrolimus in a case of short bowel syndrome

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Abstract Achieving adequate oral immunosuppression in a renal transplant patient who develops short bowel syndrome provides a significant challenge. We report a case where oral tacrolimus has been used to provide immunosuppression in an established renal transplant patient who developed short bowel syndrome secondary to mesenteric infarction. After reviewing the literature, we conclude that tacrolimus can be used as first-line immunosuppression in patients with short bowel syndrome.

Keywords Short bowel syndrome · Oral immunosuppression · Tacrolimus

Case report

The patient was a 38-year-old haemodialysis-dependent Caucasian woman who developed end-stage renal failure in 1989 secondary to bilateral renal artery stenosis. Her reno-vascular disease was caused by an unclassified vasculitis with many features of mid-aortic syndrome [1].

In 1991, cadaveric renal transplantation was performed, which achieved good primary function under her regimen of cyclosporine, azathioprine and prednisolone. However, 6 months after transplantation, she developed biopsy-confirmed cyclosporine-induced nephrotoxicity, after which she was maintained on azathioprine and prednisolone alone.

Two months prior to her admission, an angiogram was performed to investigate mesenteric angina. Angiography demonstrated occluded coeliac, superior mesenteric, splenic and inferior mesenteric arteries and occlusion of both renal arteries with associated renal scarring, but a patent hepatic artery and aortic lumen. Flow to the liver and upper abdominal organs arose from her left internal iliac artery and was retrograde to the colonic marginal artery and retrograde in the gastroduodenal artery to the hepatic artery.

She was admitted in January 2001 with acute abdominal symptoms. A laparotomy was performed, which revealed an infarcted small bowel, and an ischaemic liver and gall bladder thought to be a result of a recent clot found in the common hepatic and gastroduodenal arteries. The small bowel was resected from the fourth part of the duodenum to the terminal ileum, a 5-cm segment of which remained. In addition, a prosthetic arterial graft was fashioned from the aorta, end-to-side to the distal hepatic artery. At a re-look laparotomy 48 h later, a duodeno-ileal anastomosis was completed.

Post-operatively the patient was dependent on total parenteral nutrition (TPN). Her immunosuppression was achieved with intravenous azathioprine (150 mg o.d.) and hydrocortisone (50 mg q.i.d.). During this time her renal function was stable, her creatinine eventually falling below 100.

Monitoring of blood levels of azathioprine is not available locally as a routine at present, thus, there are no means by which one can assess if any orally administered azathioprine is being absorbed into the small bowel, its usual site of absorption. Intravenous azathioprine is classified as a cytotoxic agent; therefore, it was not possible for us to discharge the patient home on TPN and intravenous immunosuppression.

In view of the previous cyclosporine toxicity she was switched onto oral prednisolone (5 mg o.d.) and oral tacrolimus, initially at 0.1 mg/kg b.i.d. (6 mg b.i.d.), with a target trough level between 5 and 10 ng/ml. Therapeutic levels of tacrolimus were achieved by day 5. After a period of elevated tacrolimus levels she was eventually maintained on only 0.0083 mg/kg b.i.d. (0.5 mg b.i.d.). It was noted that her trough levels became even more elevated after the administration of imidazole antifungal agents. Her renal function remained stable, following the change in immunosup-

pression, with no evidence of rejection. Despite her having only 5 cm of terminal ileum, her small bowel absorption was sufficient to maintain normal levels of vitamin B12 and folate.

Discussion

We report an uncommon situation where oral tacrolimus has been used to provide immunosuppression in a patient who developed short bowel syndrome many years after a well-established renal transplantation. Novelli et al. [2] described two cases where oral tacrolimus had been used following orthotopic liver transplantation in infants with congenital short bowel syndromes and TPN-induced liver failure. They used doses of 0.14–0.28 mg/kg per day of oral tacrolimus, with resultant trough levels between 7.2 and 13.7 ng/ml.

The pharmacokinetics of oral tacrolimus absorption in short bowel syndrome were investigated by Thielke et al. [3]. As part of a pre-operative assessment for liver transplantation, they compared the absorption of tacrolimus, Neoral and Sandimmun in a 39-year-old woman with Crohn's disease, who had only approximately 0.6 m of small bowel, following multiple surgical resections. They were able to achieve therapeutic levels, having discovered that absorption of tacrolimus and Neoral was reduced, in comparison with that in healthy individuals, but was similar in profile to that in liver transplant recipients.

These cases highlight the fact that oral tacrolimus can be used therapeutically when there is a paucity of small bowel. Regazzi et al. [4] studied the pharmacokinetics of oral tacrolimus in pigs that were either enterectomized (from the first jejunal loop to the ileocaecal valve) or underwent small bowel transplantation. Interestingly, they found that the enterectomized pigs had higher blood concentrations of tacrolimus than the pigs with transplants. In addition, they reported that enterectomized pigs had a lower rate of absorption, but a higher extent of absorption. They believed that enterectomy led to decreased cytochrome-P 450-induced metabolism within the small bowel mucosa, with subsequently higher blood levels.

They concluded that absorption occurred mainly in the duodenum, with some contribution from the colon. Novelli et al. [2] stated that reduced gut motility and gastric stasis may help in elevating tacrolimus levels in the presence of short bowel syndrome.

Our observation in our patient that imidazole antifungal agents led to even further elevation of the tacrolimus levels can be explained by competition for the CYP3A enzyme system. This drug interaction is well documented and may be of clinical benefit if difficulties arise when one is trying to achieve therapeutic levels of oral tacrolimus. However, it must be highlighted that amongst their many side effects, imidazole antifungal agents can cause fatal hepatotoxicity and must, therefore, be used with great caution.

We achieved adequate tacrolimus levels with only duodenum and 5 cm of terminal ileum present. This would support the information in the data sheet that the upper intestine, in particular the stomach and duodenum, is the main site of tacrolimus absorption. We conclude that tacrolimus should be considered as first-line immunosuppression in patients with short bowel syndrome.

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