Differential effect of sirolimus vs prednisolone in the treatment of sclerosing encapsulating peritonitis

Sir,

A 56-year-old man presented in Autumn 2001 with increasing constipation, nausea, vomiting, abdominal swelling and pain, weight loss and malaise. His original renal disease was chronic glomerulonephritis, presenting at end-stage renal failure in 1979. He was haemodialysed briefly then received a cadaveric renal allograft which then failed in 1984, and so he started peritoneal dialysis. He switched from continuous ambulatory peritoneal dialysis (CAPD) to APD in 1994, and was treated with PD for a total of 16 years and 9 months. He had experienced nine episodes of peritonitis (three Staphylococcus aureus, five coagulase-negative Staphylococcus and one sterile peritonitis) and had needed three Tenckhoff cannulae between 1984 and 2001. In 1996, he underwent total parathyroidectomy. In 2000, he developed exertional chest pain and shortness of breath and was shown to have diffuse severe triple vessel coronary disease and aortic stenosis. In June 2001, he underwent coronary bypass grafting and aortic valve replacement, and as he recovered from this he experienced a sterile peritonitis episode, which necessitated removal of his Tenckhoff cannula and the start of haemodialysis.

Until this time his dialysis clearance and ultrafiltration had been adequate. He had maintained a stable body weight, and had experienced no bowel symptoms. However, in the first 3-month period after ceasing PD and starting haemodialysis he suffered from paroxysmal atrial fibrillation and a chest infection. His inflammatory markers did not settle after his bypass and valve replacement, and he lost weight and gradually developed the abdominal symptoms and signs listed above.

Rapidly, in Autumn 2001, he developed sub-acute then total small bowel obstruction and required total parenteral nutrition (TPN) and his gastrointestinal tract was rested completely with a nasogastric tube. A plain abdominal radiograph showed peritoneal calcification. A CT scan of his abdominal cavity revealed thickened and calcified peritoneum. An ascitic tap disclosed bloody ascites, with a high white and red cell and protein content (i.e. an
exudate). Malignant cells were not present, but many reactive mesothelial cells were seen on cytology.

After detailed discussion, and with informed consent, the patient started sirolimus (6 mg loading dose, 2 mg daily by mouth or nasogastric tube). Whole blood sirolimus levels were 26.6 ng/ml after 2 weeks, and 26.3 ng/ml after 9 weeks therapy. His condition was monitored by physical examination and assessment of abdominal distention, ileus, bowel sounds, nasogastric aspirate volumes, fever and elevation of CRP. The absence of significant or sustained bacterial infection to account for elevation of CRP was established by 17 negative blood cultures, eight sterile paracenteses (including negative staining and growth for AAFB and fungi), and a normal aortic homograft on echocardiography.

After 8 weeks of continued symptoms and signs of bowel obstruction the patient experienced mildly but progressively deranged liver function tests due to TPN.

Sirolimus was discontinued after 6 weeks continuous administration, just before a laparotomy. At this operation a gross pannus was found enveloping mainly small bowel in an inflammatory cocoon. Multiple peritoneal biopsies were taken which showed fibrosis and mild chronic inflammation, focal oedema and fibrin deposition. There was no malignancy and no evidence of tuberculous involvement. A careful enteroclysis was performed, and 2 weeks later, sirolimus was restarted by mouth/ing tube. There was some increased small bowel motility after the enteroclysis but the inflammatory markers remained significantly elevated (Figure 1) and his condition remained poor. After a further 4 weeks sirolimus therapy, with continued evidence of active sclerosing encapsulating peritonitis (SCP), the sirolimus was replaced by prednisolone 20 mg orally. Within 7 days there was a marked and sustained fall in CRP (Figure 1), and a marked improvement in small bowel motility, appetite and general condition. After a few days the patient was able to take oral nutrition with nutritional supplements and had a normal bowel habit, no vomiting, much decreased abdominal distention and markedly reduced ascites. A barium follow-through study showed normal small, bowel loop distribution and transit. Three months later there was some recrudescence of his symptoms, and a minor rise in CRP, so azathioprine was added to the prednisolone.

SCP is a very serious complication associated with PD, particularly after recurrent peritonitis and increasing time exposed to PD solutions. An inflammatory pannus surrounds small and large bowel loops in a cocoon, leading to atony and obstruction. Malnutrition, malaise and premature death are common with SCP. There is considerable anecdotal evidence that immunosuppression can ameliorate some of the pathological consequences of SCP. Most experience is with prednisolone and azathioprine [1].

Fibrosis is a cardinal feature of SCP [2]. Sirolimus (Rapamune, Wyeth-Ayerst, Madison, NJ)—a new, potent, immunosuppressant that acts during both co-stimulatory activation and cytokine-driven pathways via a unique mechanism: inhibition of a multifunctional serine-threonine kinase, mammalian target of rapamycin (mTOR)—is establishing itself as an immunomodulatory drug with unique properties [3]. As the inhibitory effect of sirolimus disables virtually all responses to cytokine mediators due to the widespread involvement of mTOR in multiple signalling pathways, it is likely also to retard proliferation of endothelial and vascular smooth muscle cells, an important component of the immuno-obliterative/fibrotic processes associated with chronic rejection. Endovascular coronary artery stents impregnated with sirolimus have been reported completely to abrogate the myo-intimal proliferation usually seen with coronary artery intervention [4]. We felt that with these properties sirolimus might also have been beneficial in the context of SCP.

The contrast between sirolimus and prednisolone in terms of the patient’s general condition, and SCP, could not have
been greater. The whole blood sirolimus levels were generous over a sustained period. Although it is customary to combine prednisolone therapy with another immunosuppressive agent in this clinical context, there is one other report of a rapid and sustained improvement in SCP with prednisolone monotherapy [5].

In conclusion we have found that sirolimus monotherapy, in contrast to prednisolone monotherapy, was ineffective as a treatment for acute SCP.

Guy’s Hospital  Ronak Rajani
London  John Smyth
UK  C. Geoff Koffman
Email: david.goldsmith@  Ian Abbs
gst.sthames.nhs.uk  David J. A. Goldsmith