CASE REPORT

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Conversion from Mycophenolate Mofetil to Enteric-coated Mycophenolate Sodium (*myfortic*®) Resolves Gastrointestinal Disorders in a Patient with Severe Idiopathic Aplastic Anaemia

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1. Case Study

A female patient was diagnosed with severe aplastic anaemia (SAA) in September 1997 at the age of 12 years. Her leukocyte count was 2000 cells/mm^3 (neutrophils 220 cells/mm^3), and her haemoglobin level was 42 g/l (reticulocytes 27 500 cells/mm^3, platelets 7000 cells/mm^3). Bone marrow biopsy confirmed the diagnosis, showing poor marrow function with very few haematopoietic cells. Transaminase levels were normal and there was no history of viral infections or the use of drugs that could have induced an adverse reaction. There was no evidence of immune markers demonstrating paroxysmal nocturnal haemoglobinuria, and no cytogenetic features to suggest Fanconi disease. The patient's condition was thus considered to be idiopathic. Renal function was normal (serum creatinine 48 μmol/l).

Initially, in the absence of a suitable related or unrelated bone marrow donor, immunosuppressive treatment comprising cyclosporine microemulsion (CsA-ME), equine antilymphocyte antibodies and corticosteroids was initiated, and led to a partial improvement. However, each attempt to taper the CsA-ME dose resulted in haematological relapse (figure 1), and the patient remained dependent on CsA-ME monotherapy. Beginning in early 2002, while the patient was receiving CsA-ME 8 mg/kg per day, progressive renal impairment was observed and serum creatinine rose to 160 μmol/l. In January 2003, mycophenolate mofetil (MMF) 1000 mg/day was introduced and the CsA-ME dose was reduced to 4 mg/kg per day. The patient rapidly developed gastrointestinal disorders (several daily episodes of nausea and diarrhoea) and after a few days she refused to continue taking MMF. She thus continued on CsA-ME monotherapy at a dose of 3–4 mg/kg per day for 4 months. Intravenous and oral MMF at a daily dose of 1000 mg was reintroduced in July 2003, but severe gastrointestinal disorders occurred again. In August 2003, the patient was converted from MMF to enteric-coated mycophenolate sodium (EC-MPS, *myfortic*®) at a dose of 720 mg/day in an attempt to improve gastrointestinal tolerability. EC-MPS was well tolerated; in particular, no gastrointestinal adverse events were reported and compliance was good. She received low-dose CsA-ME (2 mg/kg per day) for a further 4 months, after which it was discontinued.

After 6 months' of monotherapy with EC-MPS, laboratory tests showed that haematological parameters had stabilized: the leukocyte count was 2600 cells/mm^3 (neutrophils 33%, lymphocytes 62%) and the haemoglobin level was 90 g/l without transfusions (figure 1). There was a small decrease in the platelet count (44 000 cells/mm^3) that might have reflected haematological toxicity of

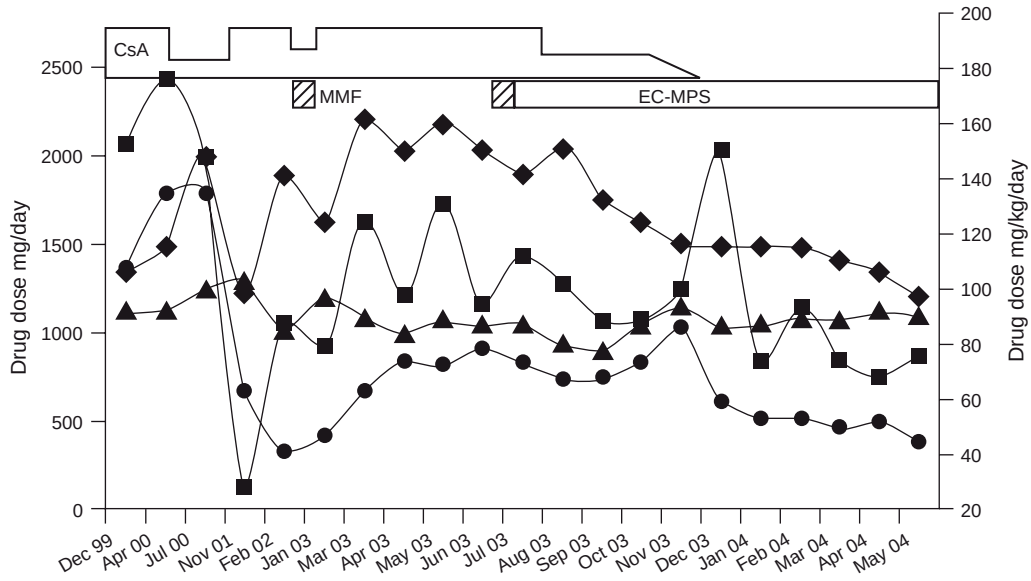

Fig. 1. Key laboratory parameters and immunosuppressant medication use over time. CsA, Cyclosporine A; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil. ■ = ANC, absolute neutrophil count (mm^3); ● = platelets (g/l); ▲ = haemoglobin (g/l); ◆ = serum creatinine (μmol/l).

EC-MPS. Serum creatinine and blood urea nitrogen levels returned to normal (97.4 μmol/l and 6.14 mmol/l, respectively). Laboratory tests remained stable until the end of 2004, after which her haematological condition unfortunately worsened, and the patient died in August 2005 as a result of fungal infection.

2. Discussion

SAA is an uncommon abnormality of the haematopoietic progenitor cell compartment, which is considered idiopathic in approximately half of cases. SAA is believed to be an autoimmune process involving T lymphocytes[1] and *in vitro* studies have demonstrated that two cytokines produced by T cells (IFN-γ and tumour necrosis factor; TNF) play a key role in inhibiting the proliferation of early and late haematopoietic progenitor cells and stem cells.[2] The overproduction of IFN-γ and TNF induces haematopoietic cell apoptosis and affects the mitotic cycle.[2]

Therapy is generally based on two strategies: bone marrow transplantation from a human leukocyte antigen-matched donor or immunosuppressive therapy for patients in whom an allograft is not possible. Patient survival has improved in recent years, with a current survival rate of approximately 80%.[3,4] The standard immunosuppressive regimen comprises antilymphocyte antibodies and cyclosporine, which has good long-term efficacy;[5] other agents (cyclophosphamide, anti-IL-2 receptor antibodies and mycophenolic acid; MPA) have been less well studied.[6] MPA inhibits T and B-lymphocyte proliferation via the inhibition of inosine monophosphate dehydrogenase. It selectively blocks the polyclonal proliferation of activated cytotoxic T lymphocytes, thus suppressing the overproduction of IFN-γ and TNF that may lead to myelosuppression in SAA. MPA has also been shown to promote the apoptosis of polyclonal activated T cells.[7] These data suggest that a sustained haematological response could be expected with MPA in SAA, but few published data are available.[6]

MMF therapy is often hindered by gastrointestinal disorders. EC-MPS, an enteric-coated formulation of MPA, may improve the gastrointestinal safety

profile and therefore positively impact on patient compliance. In our young patient, who developed renal insufficiency while receiving CsA-ME, conversion from MMF to EC-MPS as a result of severe gastrointestinal complications led to the resolution of the gastrointestinal disorders. She continued to take EC-MPS, enabling the subsequent discontinuation of CsA-ME, with progressive normalization of renal function, and showed a sustained partial haematological response.

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