Beguin Research Director of the National Fund for Scientific Research (FNRS, Belgium). This work was supported by grants from "La Fondation Bonjean- Oleffe", "L'Association sportive contre le cancer", "Le Fonds de Recherche Scientifique du CHU Sart-Tilman" and the National Fund for Scientific Research (FNRS, Belgium).

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Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received April 22, 2003; accepted May 20, 2003.

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Response to mycophenolate mofetil therapy for refractory chronic graft-versus-host disease

Preliminary results of our study suggest that mycophenolate mofetil (MMF) might be a useful treatment in patients who have failed or could not tolerate conventional immunosuppressive therapy for chronic graft-versus-host disease (GVHD). In addition, the favorable toxicity profile and steroid-sparing effect of MMF may be particularly attractive features of this medication.

haematologica 2003; 88:837-839
(*http://www.www.haematologica.org/837.htm)*

Studies in animal models and preliminary clinical trials indicate that mycophenolate mofetil (MMF) might be an effective agent for the treatment of graft-versus-host disease (GVHD).[1-5] We analyzed 21 adult patients given a hematopoietic stem cell transplantation (HSCT) who received MMF for treatment of chronic GVHD.

Peripheral blood stem cell grafts (n=14) or marrow grafts (n=7) were infused from HLA-matched sibling (n=18) or unrelated (n=3) donors. Seventeen patients with hematologic malignancies received conventional myeloablation prior to their transplant, 4 patients with hematologic malignancies (n=3) or solid tumor (n=1) were transplanted after a nonmyeloablative preparative regimen. GVHD prophylaxis consisted of cyclosporine (CSA) and a short course of methotrexate (MTX) in 17 cases. Four patients received CSA and MMF as part of the non-myeloablative protocol; CSA was tapered off by day 100 if no GVHD developed, whereas MMF was discontinued on day +30. Extensive chronic GVHD developed in 15 patients, while limited chronic GVHD occurred in 6 (Table 1). Multiple organ involvement (> 2 organs) was observed in 67% (14 of 21) of the patients.

Eighteen of the 21 patients were evaluable for response to MMF treatment. In 12 cases, MMF was introduced because of ineffectiveness of previous immunosuppressive therapies (i.e. progression or no improvement of chronic GVHD after 6 weeks of previous treatment). Three patients were enrolled in the study because of dependence on steroids (i.e. the need for > 20 mg/day methylprednisolone for more than 6 weeks) and resistant disease; in 3 cases MMF was introduced because of intolerance to previous treatments.

MMF was administered at the dose of 1 g *bid.* in 16 patients; two patients received MMF at the dose of 500 mg *bid.* because of low body weight (< 50 Kg) and co-existing nausea and vomiting. Patients were treated with MMF in addition to CSA/tacrolimus and steroids (n=11), CSA alone (n=5) or tacrolimus alone (n=2).

The median time from onset of chronic GVHD to the initiation of MMF treatment ranged between 0 and 2503 days (median 235 days). The duration of therapy has ranged from 51 days to 23 months (median 184 days).

Five complete clinical responses (i.e. complete resolution of all GVHD manifestations) and 8 partial clinical responses (i.e. greater than 50% response in organ involvement, but less than a complete resoponse) were observed, for a clinical response rate of 72% (13 of 18). Nine of 13 evaluable patients with extensive chronic GVHD and 4 of 5 evaluable patients with limited chronic GVHD had a clinical response. The distribution of responses according to organ involved by chronic GVHD is shown in Table 2. Three patients had stable disease and were, therefore, counted as non-responders. Two patients experienced progression of disease while receiving MMF.

Steroid dose was decreased by ≥ 50% in 9 of 11 (82%) evaluable patients, and in 6 cases steroid therapy could be discontinued. The estimated probability of stopping all immunosuppression at 2 years after starting the study was 24% (95% CI, 2%-85%). The most common side effects of MMF

Table 1. Clinical features of chronic GVHD.

No. of Patients	21
Time to chronic GVHD after transplantation median days (range)	110 (93-178)
Type of onset	
Progressive	10 (48%)
Quiescent	8 (38%)
De novo	3 (14%)
Grade of chronic GVHD	
Limited	6 (29%)
Extensive	15 (71%)
Organ involvement	
Skin	19
Oral mucosa	16
Liver	17
Lungs	3
Eye	5
Gastrointestinal tract	5
Joint	2
Polyserositis	1
Platelets $<100 \times 10^9$/ L, *no. (%)*	9 (43%)
Immunosuppression at study entry	
Cyclosporine/FK506	7
Cyclosporine/FK506+Steroids	14

Table 2. Clinical response by organ system.

		Clinical Response	
Organ involvement	*No.*	*CR (%)*	*PR (%)*
Skin	15	3 (20)	5 (33)
Oral mucosa	15	3 (20)	7 (47)
Liver	13	3 (23)	4 (31)
Lung	3	0	0
Eyes	3	0	0
Gastrointestinal tract	2	0	1 (50)
Joints	1	0	0
Polyserositis	1	0	0
Thrombocytopenia	6	4 (67)	0

were gastro-intestinal symptoms (nausea, vomiting and cramps), which occurred in 6 (33%) patients. Leukopenia occurred in 2 (11%) patients. Ten serious infectious complications occurred in 8 patients. Two (11%) patients discontinued MMF because of toxicity (n=1 nausea and significant leukopenia [WBC 1350/mm^3, ANC 648/mm^3]; n=1 severe nausea and vomiting).

The Kaplan-Meier estimate of survival from initiation of MMF for this group of 18 patients was 71% (95% CI, 13%-97%) at 2 years. Overall, 3 of the 18 (17%) evaluable patients died. Two patients died of progressive disease. One patient relapsed after the transplant and died with extensive chronic GVHD characterized by polyserositis with a large pericardial effusion and constrictive pericarditis.

The median Karnofsky performance scores for patients with clinical response, and those with stable disease or progressive chronic GVHD were 100% (range 80%-100%) and 80% (range 70%-90%), respectively.

These preliminary results support the hypothesis that MMF can be used safely and has encouraging efficacy in the treatment of patients with chronic GVHD who fail to benefit from conventional therapy, although it should be emphasized that our results may have been influenced by the short observation period and the small number of patients studied, and therefore should be considered suggestive rather than definitive.

The relative lack of toxicity, including life-threatening infectious complications, is an attractive feature of the drug, given the already impaired immune function of patients with extensive chronic GVHD. Furthermore, MMF reduced corticosteroid requirements, thereby reducing the risk of complications due to iatrogenic immunosuppression. The early combination of MMF with other treatment strategies may further improve response rate and survival of these patients. Additional studies are needed to test this hypothesis.

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Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received March 7, 2003; accepted May 27, 2003.

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