

## Correspondence

### T-cell depletion improves outcome after autologous stem cell transplant in patients with systemic lupus erythematosus (SLE)

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New treatments must be developed for the 5–10% of systemic lupus erythematosus (SLE) treatment-refractory patients who do not respond to standard immunosuppressive therapies and/or patients with poor prognostic factors in order to improve their current 45% 10-year mortality.<sup>1–4</sup> The goal of hematopoietic stem cell transplant (HSCT) in treatment-refractory SLE is to ablate autoreactive immune cells through high-dose immunosuppressive therapy followed by HSCT. Currently, there are insufficient clinical data to compare unmanipulated vs T-cell-depleted grafts. We describe the outcome of two SLE patients transplanted with autologous stem cells with different degrees of T-cell depletion.

Patient 1 (MM), a 36-year-old Caucasian female, was diagnosed with SLE at 19 years of age. She initially presented with episodes of sterile meningitis that responded to antimalarials and low-dose prednisone. At age 24 she presented with episodes of nephritis, related to class IV membranous nephropathy, which responded to treatment with standard dose cyclophosphamide. At age 31 she had episodes of generalized seizures, lupus-related pancreatitis, bowel vasculitis, cyclophosphamide-refractory renal disease, and pancytopenia. At age 33 she was referred for autologous HSCT. Prior to transplant she had a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of 32, elevated serum creatinine, proteinuria, and non-detectable C4 level. She was taking prednisone 30–50 mg and cyclosporine 150 mg daily (Table 1).

Her mobilization regimen consisted of subcutaneous G-CSF 5 µg/kg per day for 8 days. Peripheral blood stem cell collection was performed daily until a CD34<sup>+</sup> cell dose of  $1.4 \times 10^6$  cells/kg was obtained using Isolex selection. This system allows for prestorage leukoreduction without compromising the storage time of the blood components. At 1 month after mobilization she underwent conditioning with cyclophosphamide 3 g/m<sup>2</sup>. Totally,  $1.27 \times 10^6$  CD34<sup>+</sup> cells/kg and  $8.18 \times 10^5$  CD3<sup>+</sup> cells/kg were infused on day 0 (Table 2).

Overall, she had poor CD34<sup>+</sup> selection and ultimately did not have a very good disease response. While at 2 months post-transplant she had an SLEDAI score of 0, this increased to an average of 9 over the next 22 months and was 4 two years post-transplant. She also continued to have significant proteinuria and decreased C4 levels. She currently remains active and free of symptoms on prednisone 10 mg and 1.5 g mycophenolate mofetil daily.

Patient 2 (EH), a 33-year-old African-American male, was diagnosed with SLE at the age of 25. He initially presented with fever, nausea, vomiting, elevated blood

pressure, and WHO class IIb lupus glomerulonephritis. He responded to treatment with high-dose steroids and remained in remission until he was 30 years old. He then presented with an exacerbation of glomerulonephritis that was reclassified as WHO class IV, which was managed with standard dose cyclophosphamide. The same year he was hospitalized for myocarditis and acute renal insufficiency, which were complicated by sepsis, pancytopenia, and acute respiratory distress syndrome. He responded to intravenous immunoglobulin therapy and was started on mycophenolate mofetil. He discontinued this 5 months later and was restarted on standard dose cyclophosphamide. He subsequently had another episode of myocardial dysfunction, which was treated with plasmapheresis and intravenous Solu-Medrol.

At 32 years of age, he was referred for autologous bone marrow transplant. Prior to transplant he had a SLEDAI score of 10, an elevated serum creatinine, and proteinuria. He was taking prednisone 20 mg and dapsone 100 mg daily (Table 1).

His mobilization regimen consisted of cyclophosphamide 2 g/m<sup>2</sup> with G-CSF 10 µg/kg. Peripheral blood stem cells were collected daily until a CD34<sup>+</sup> cell dose of  $1.4 \times 10^6$  cells/kg was obtained using Isolex selection. At 1 month after mobilization he underwent conditioning with intravenous cyclophosphamide 200 mg/kg and anti-thymocyte globulin (ATG) 50 mg/kg. On day 0 he received a total dose of  $4.92 \times 10^6$  CD34<sup>+</sup> cells/kg and  $3.99 \times 10^3$  CD3<sup>+</sup> cells/kg (Table 2).

Overall he was infused with a relatively T-cell-depleted autologous transplant and had a positive disease response. His SLEDAI score dropped from 10 pretransplant to 0 starting 4 months post-transplant and remained at this score for 12 months of follow-up. He had improvements in his creatinine clearance and proteinuria (Table 1). Currently, he is doing well on prednisone 5 mg daily.

In treating patients with autoimmune disease, it remains unclear whether autologous HSCT grafts should be purged of T cells.<sup>5</sup> For instance, one study of treatment refractory SLE patients receiving immunoablation followed by CD34<sup>+</sup> selected autologous HSCT suggests that T cells may significantly affect the response rate and durability of autoimmune remission.<sup>6</sup> However, other reports on patients with rheumatoid arthritis and multiple sclerosis have demonstrated no significant difference in outcomes.<sup>7,8</sup> The differing nature of disease pathogenesis among autoimmune diseases makes it likely that optimal lymphocyte selection will vary among diseases.<sup>9</sup>

Our report of two patients suggests that increased numbers of CD3 cells infused during autologous transplant can negatively affect disease response in SLE. The better clinical outcome in our patient who had ATG for the *in vivo* T-cell depletion also raises the possibility that cyclophosphamide and ATG may be a better conditioning regimen for SLE than cyclophosphamide alone. These findings warrant an analysis of clinical outcomes based on infused T-cell dose on a larger cohort of SLE patients.

**Table 1** Identifying and descriptive data for patients undergoing treatment

Age/gender	Organ involvement at initiation of stem-cell protocol	Immunosuppressive therapy		SLEDAI score	
		Pretransplant	Current	Pretransplant	Current
33/Female	Musculoskeletal CNS Renal Skin Gastrointestinal Vasculitis Hematological	Prednisone 30–50 mg daily Cyclosporine 75 mg b.i.d.	Prednisone 10 mg daily Mycophenylate 1.5 g daily	32	0 <sup>a</sup>
32/Male	Musculoskeletal Cardiovascular Hematological Renal	Prednisone 20 mg daily Dapsone 100 mg daily	Prednisone 5 mg daily	10	0 <sup>b</sup>

<sup>a</sup>48-month follow-up.<sup>b</sup>24-month follow-up.**Table 2** Mobilization and conditioning regimens for patients undergoing treatment

Patient	Mobilization regimen	Conditioning regimen	Total no. of cells infused	No. of CD34 cells infused (cells/kg)	No. of CD3 cells infused (cells/kg)
MM	G-CSF	Cyclophosphamide	$78.5 \times 10^6$	$1.27 \times 10^6$	$8.18 \times 10^5$
EH	G-CSF/ Cyclophosphamide	Cyclophosphamide/ ATG	$476.3 \times 10^6$	$4.92 \times 10^6$	$3.99 \times 10^3$

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