Allogeneic stem cell transplantation in difficult-to-treat rheumatoid arthritis

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Despite impressive improvements in the treatment of rheumatoid arthritis (RA), a significant proportion of patients remain refractory to existing therapies (1). In these patients, haematopoietic stem cell transplantation (HSCT) could be considered as rescue therapy (2). We present the first case of haploidentical HSCT with RA as sole indication.

A 20-year-old female patient presented in July 2015 with arthritis of the right knee and thumb, evolving to a polyarthritis of large and small joints. Analysis of synovial fluid showed evident inflammation, without crystal deposition. Microbiology and autoimmune serology were negative. She was consecutively treated with multiple conventional, biological, and targeted synthetic disease-modifying anti-rheumatic drugs (Supplementary Fig. S1). However, all interventions failed to induce sustained remission or were discontinued due to side effects. Severe systemic inflammation and progressive joint deformation continued, necessitating continuous use of high-dose steroids (Fig. 1).

Ultimately, after extensive multidisciplinary and multicentric discussion and in full informed consent, the procedure for allogeneic HSCT was initiated. In the absence of HLA-matched donors, her haploidentical father acted as donor. HLA-DRB1 alleles of the donor were 07:01, 15:01 and those of the recipient were 01:01, 07:01. Conditioning and graft-versus-host disease (GVHD) prophylaxis followed the Baltimore protocol for sickle cell disease (3). Haematological recovery with normal peripheral blood counts occurred within four weeks after stem cell infusion. No life-threatening adverse events emerged immediately after transplantation. However, the patient developed acute GVHD grade III two months later, involving skin, gut, and liver. This complication was beneficially treated with low-dose systemic steroids and ruxolitinib. Other adverse events were Polyomavirus cystitis, resolving spontaneously, and Cytomegalovirus primo-infection, responding to valganciclovir. At the time of writing, three years post-transplant, there is partial T-cell immunity reconstitution (CD4 T-cells 250/μl) and full donor chimerism. RA disease activity decreased rapidly, obtaining sustained DAS28-CRP remission six months post-transplant. Unfortunately, due to severe pretransplant joint destruction, functionality remains poor (HAQ score 2.7).

Autologous HSCT appeared promising in the 1990s as most patients achieved at least partial remission. However, due to frequent relapses, it was abandoned in the early 2000s (4-6). Allogeneic HSCT has been used almost exclusively in the context of RA and concurrent haematological diseases, given the less favourable safety profile compared to autologous HSCT (Suppl. Table S1). Current evidence suggests that: (a) Allogeneic HSCT is able to induce sustained drug-free remission in RA. (b) Relapse may be higher in case of donors or recipients with HLA-DRB1 alleles predisposing to RA. (c) The likelihood of relapse does not appear to be related to the number of failed therapies, the disease duration, the intensity of conditioning chemo- and radiotherapy, the use of serotherapy for GVHD prophylaxis, the occurrence of GVHD, and, most intriguing, the degree of chimerism.

To our knowledge, this is the first report of haploidentical HSCT in a patient with RA without haematological comorbidities. Furthermore, in contrast to the previous reports of allogeneic HSCT listed in Supplementary Table S1, our case is unique in having exchanged an RA-predisposing DRB1-allele for a non-predisposing allele. This could explain the excellent outcome in our patient. This case shows that despite the high risk of transplant-related mortality and morbidity, allogeneic HSCT can be justified in cases of severe refractory RA after extensive counselling and in shared decision. A limitation of our case report is the continuing immunosuppressive treatment for GVHD with ruxolitinib. However, given the previous failure of two JAK inhibitors (baricitinib and upadacitinib) pretransplant, it is unlikely that this treatment accounts for sustained disease remission.

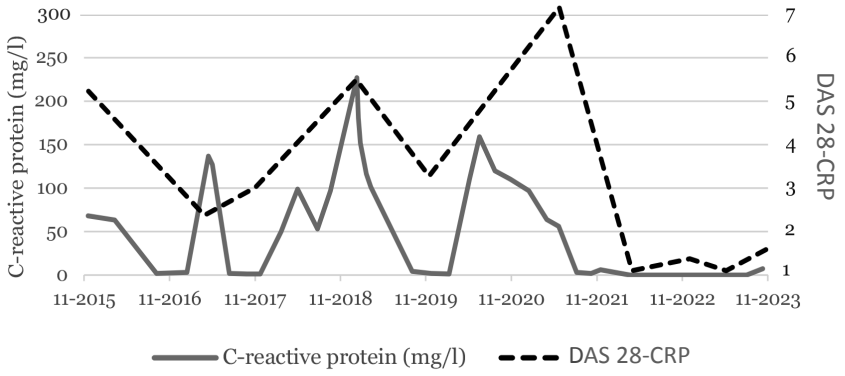

Fig. 1. Biochemical evolution of C-reactive protein (full line, scale on the left-hand side) and DAS28-CRP-scores (dotted line, scale on the right-hand side).
DAS28: Disease Activity Score 28 joints; CRP: C-reactive protein

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