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EDITORIAL

Allogeneic haematopoietic stem cell transplantation for severe autoimmune diseases: great expectations but controversial evidence

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Autoimmune diseases (ADs) have been defined as a 'fascinating but still poorly understood group of diseases', which pose 'some of the most baffling scientific questions and daunting clinical challenges in internal medicine'.[1] This statement still holds true, and it is generally recognized that ADs result from three interacting components: genetic, environmental and regulatory.[2,3] In spite of this complexity and of considerable overlap, there is a tendency to distinguish ADs with an impaired immune system, also known as primary ADs, from those that are predominantly antigen driven.[4] There is no better demonstration of the latter than the clinical studies that have shown the disappearance of autoantibodies (antithyroid, anti-tissue transglutaminase) following removal of the antigens (by thyroidectomy or by gluten-free diet, respectively).[5,6] The proposal that transplantation with genetically engineered stem cells with the culprit antigen expressed by donor-antigen-presenting cells in the thymus might result in immunological tolerance[7] is in accordance with this current line of thought, which includes the Matzinger 'danger' model of autoimmunity.[8,9] A different outlook is apparent for the primary ADs, in which profound abnormalities of the patients' immune system are in the foreground. Systemic lupus erythematosus (SLE) is the most prominent example of this type of pathogenetic mechanism, where the intrinsic tendency of B cells to respond excessively to immune stimulation is thought to be an essential feature of the disease,[10] and causes a veritable 'autoantibody explosion'.[11]

Following pioneering experimental studies,[12,13] autologous haematopoietic stem cell transplantation (autoSCT) has now become an accepted therapeutic procedure for severe ADs, despite the paradox of trying to restore tolerance by transplanting the patients' own stem cells. Extensive reviews have been published, some very recently.[14–17] Even if there is still some uncertainty as to whether genuine tolerance may be really achieved,[18,19] disease progression has been clearly shown to be delayed, especially following high-dose conditioning, albeit with the drawback of some transplant-related mortality (TRM).[20] In order to reduce TRM to a minimum, more specifically lymphoablative conditioning regimens have been proposed.[21] However, in spite of its accepted therapeutic significance, of the long-term remissions that can be sometimes achieved[22,23] and of the capacity to respond to treatment again in previously refractory patients, no authentic cure can be expected.[24–26] This is well exemplified by two patients with coexisting AD and malignant disease in whom autoSCT was followed by cure of the malignancy but not of the AD.[27,28]

The suggestion that allogeneic SCT (alloSCT) might have a more far-reaching effect was based originally on the favourable results in patients with AD coexisting with other diseases.[29] A position paper was published recently that stated that alloSCT was expected to be highly effective for inducing sustained remissions or 'cure' of autoimmune diseases.[30] A series of mechanisms were considered, including immunomodulation, tolerization by regulatory T cells and, most importantly, immune-mediated destruction of autoreactive cells.[31] By analogy with the multiple clinical diversifications of immune cellular immunotherapy,[32] this last effect was defined as graft-versus-autoimmunity (GVA).[33,34] As with the more common and better known graft-versus-leukaemia effect, also GVA was found to be more robust when associated with graft-versus-host disease.[35,36]

On the other hand, it has been claimed that mixed chimaerism might be sufficient to keep under control the autoreactive mechanisms. This is certainly true in experimental autoimmunity, where it has been investigated and confirmed in numerous laboratories.[37–39] However, the situation is far from being so straightforward in clinical medicine. Here, along with cases in which post-alloSCT mixed chimaerism proved effective in controlling the AD,[40,41] there are others in which it was accompanied by relapse of AD.[42,43] The concept that complete remission of AD depends upon full donor chimaerism has been validated by the favourable effects of donor lymphocyte transfusions (DLI) post transplant, designed to obtain full donor chimaerism.[44–46] Unfortunately, there are also cases in which the AD relapsed in spite of full donor chimaerism. The first is the now famous patient with rheumatoid arthritis (RA) in Toronto, who underwent alloSCT from her HLA-identical brother because of gold-induced aplasia, and then relapsed with RA 2 years later despite continuing full donor chimaerism.[47] Chimaerism was assessed by cytogenetics and by tandem repeat-based DNA typing. In the other case of two concomitant diseases, a patient with seropositive RA received a nonmyeloablative allogeneic peripheral blood SCT because of multiple myeloma, achieved complete remission of both diseases with disappearance of paraprotein and rheumatoid factor (RF), but relapsed with RA 10 months after transplantation.[48] It may be noted that the HLA-identical brother donor had weak RF positivity. In addition, peripheral blood transplants are devoid of mesenchymal cells, which may have a beneficial effect on AD.[49] Perhaps the most informative case of AD

relapsing in spite of full donor chimaerism has been recently observed in Genoa. This was a patient with refractory Evans syndrome who had been transplanted with bone marrow from his HLA-identical sister in 2000, and had received five DLIs in order to achieve full donor chimaerism and complete clinical and haematologic remission.[50] However, he had a catastrophic relapse 5 years later. Full donor chimaerism persisted, and the supernatants of *ex vivo*-cultured and expanded B lymphocytes contained immunoglobulin (Ig)G and IgM that did not react with the panel of erythrocytes against which the antibodies eluted from the patient's Coombs-positive red cells[51] were directed.

The immunologic interpretation of these almost paradoxical relapses in patients with full post transplant donor chimaerism is still obscure. T cells appear to be involved in the RA relapses, and it has been hypothesized that residual recipient cells could sensitize HLA-identical donor T cells to perpetuate the immunologic imbalance underlying RA.[48] However, in a typical B-mediated disease such as Evans syndrome, a more appropriate interpretation could originate from the notion of long-lived recipient plasma cells, the contribution of which to long-standing, refractory humoral autoimmunity has been shown recently.[52,53] Short-lived plasma blasts have been shown to become long-lived plasma cells, occupying postulated survival niches. In NZB/W mice, a typical model for SLE, long-lived autoreactive plasma cells have been demonstrated in the bone marrow and in the spleen.[54] However, it is a classical notion that they can be eradicated following alloSCT, a finding that was pivotal for the development of stem cell therapy for autoimmunity in humans.[55] An array of cytokines are necessary for plasma cell survival, such as the well-known interleukin-6 and also BAFF and APRIL,[56] but the most relevant for plasma cell maintenance has been shown to be Blimp-1.[57] Allotransplantation in lupus mice has been shown to overcome the disease,[12–14] but, in the light of these observations, one could suspect that a greater degree of refractoriness may be found in human patients with systemic autoimmune diseases than suspected previously.

Single case reports, no matter how carefully studied, cannot provide the final answer but still they should not be ignored. If it were confirmed that minimal residual autoimmune disease is capable of surviving the GVA effects of alloSCT, then the possible advantage of alloSCT over the safer, although perhaps immunologically less appealing, autoSCT procedure would inevitably be reduced.

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