

Review

Immune ablation and stem-cell therapy in autoimmune disease Introduction

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Received: 5 April 2000
Accepted: 5 May 2000
Published: 24 May 2000

Arthritis Res 2000, 2:268–269

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Estimates of the prevalence of autoimmune diseases range from 3 to 7%, and the treatment of a minority of these patients with severe progressive disease is not satisfactory. It has been recognized that the autoimmune basis of human disease results from the failure of multiple components of the immune system, but the most frequently used criteria to establish the autoimmune nature of a disease is the presence of defined reactions against self-antigens as a major component in the pathophysiology. This concept gave rise to the hypothesis that a stable cure of autoimmune disease can only be expected if the patient's autoreactive immunocompetent cells are replaced by cells that are not autoreactive. In this issue of *Arthritis Research*, three therapeutic strategies are discussed that pursue this goal: allogeneic hematopoietic stem-cell transplantation, autologous hematopoietic stem-cell therapy following intensive suppression, and intense immune suppression alone [1–3].

Work in experimental animals with induced autoimmune disease convincingly showed that ongoing disease could be cured by bone marrow transplants from healthy animals. Pertinent to the translation into clinical practice of such treatment are the findings of Van Bekkum and coworkers (reviewed in [3]) that autologous stem-cell therapy is as effective as allogeneic transplantation. These observations were made in mice with adjuvant arthritis and experimental allergic encephalomyelitis.

During the past decade multiple case histories have described long-term remissions and possible cures of autoimmune disease after allogeneic bone marrow transplantation. However, the current morbidity and mortality related to this treatment are unacceptable for most autoimmune diseases. Therefore, autologous stem-cell therapy after intense immune suppression received considerable attention because of the lower toxicity and greater

feasibility. A variety of diseases were selected, including rheumatoid arthritis, juvenile chronic arthritis, systemic sclerosis, systemic lupus erythematosus, Crohn's disease and multiple sclerosis. The results so far, both with respect to efficacy and toxicity observations, are encouraging, but remissions rather than cures have been obtained.

Another unresolved issue is whether stem-cell therapy is indeed crucial to obtain efficacy in a patient treated with intense immune suppression. The problem of late oncogenicity after severe immune suppression in young patients should also be taken into account. The central question is of course whether intense immune suppression followed by stem-cell rescue is capable of achieving tolerance. This goal has been achieved in experimental work but has not yet been demonstrated in the clinic. To further develop this therapeutic strategy more information on the correlation between clinical responses and immunological sequelae after intervention is urgently needed. It cannot be excluded that intense immune ablation followed by autologous stem-cell rescue cannot eradicate autoreactive memory lymphocytes, and that allogeneic bone marrow transplantation is necessary to achieve this goal. The recent introduction of myelosuppressive regimens that exploit the presence of chimaeric myelopoiesis, as well as the usefulness of donor lymphocyte immune effects, is an additional promising development in treatment of malignant and nonmalignant diseases. The possibility of a graft anti-autoimmunity effect may be advantageous in the maintenance of remission.

Further work should involve comparative studies that may reveal whether the results of these new strategies are superior to those of conventional therapy. Such work should be performed in close collaboration between multiple medical disciplines to address the fundamental questions associated with this therapeutic strategy.

References

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