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Stem cell transplantation: limits and hopes

The clinical course and severity of inflammatory rheumatic diseases vary considerably. A large proportion of patients have mild to moderate activity of the inflammatory process which can be successfully controlled by conventional therapeutic measures: traditional disease modifying antirheumatic drugs (DMARDs) for rheumatoid arthritis (RA) and some other forms of chronic arthritides, intermediate steroid doses or mild immunomodulatory agents for systemic lupus erythematosus (SLE) and other connective tissue diseases. Also, control of more severe disease is often manageable by more aggressive, established means, such as high dose methotrexate and combination treatment for RA, or pulse cyclophosphamide treatment and steroids in SLE. For most of these therapeutic approaches significant evidence has accumulated in randomised controlled trials.[1–3]

Without the possibility of making individual predictions, there are many patients whose diseases are not sufficiently responsive to the traditional measures. At least for RA, the armamentarium has recently been significantly enriched by new means of intervention,[4–6] among them biological agents which specifically target a key mediator of inflammation, tumour necrosis factor α (TNFα); more targets are currently being studied. The TNF blockers also appear to be quite efficient therapeutic agents for diseases which were often less easy to control, such as psoriatic arthritis,[7] or ankylosing spondylitis, which was regarded as intractable when treated with traditional DMARDs.[8]

However, despite some success of modern antirheumatic treatment, groups of patients exist, familiar to every rheumatologist, whose disease is resistant to therapeutic measures. This is still the case for a significant proportion of patients with RA whose continuing disease activity, refractory to traditional and new DMARDs, combination treatment, and biological agents, leads to a relentless progression of joint destruction; approximately 30–40% of patients with RA do not have clinical responses even when receiving the new agents. This is also the case for a significant number of patients with SLE or vasculitis, whose renal, pulmonary, or other organ disease does not respond to, or even recurs during, treatment with high dose immunosuppression. This is particularly true for patients with systemic sclerosis (SSc), for whom there is currently no remedy at all, except for some symptomatic measures. These patients, once vital organs or even the skin are severely affected, run a relentlessly bad and often rapidly fatal course. Although open trials have sometimes elicited hope,[9 10] controlled clinical investigations are rare in SSc and usually lead to negative results.[11] All these unfavourable situations constitute a major challenge not only for the caring rheumatologist but also for the whole rheumatological community and its clinical and basic scientists.

In the 1980s, remissions or dramatic improvement of pre-existing autoimmune rheumatic diseases were occasionally seen in patients treated with high dose chemotherapy and subsequent bone marrow transplantation for their leukaemia or bone marrow aplasia.[12–15] These observations fostered the idea that such therapeutic approach might be generally useful to treat or even cure autoimmune disorders. The idea was generated that high dose chemotherapy would eradicate the immunocompetent cells, including those B and T cells responsible for the destructive autoimmune process, while (autologous) bone marrow would allow reconstitution of a functioning but naive immune system, naive also towards the putative (eliciting) autoantigens. Because autoimmune diseases do not appear to pre-exist and the concurrence of disease in monozygotic twins of usually <30% suggested important environmental involvement in the aetiopathogenesis of these disorders, such an idea appeared compelling.

The fear of the relatively high procedure related risk of autologous bone marrow transplantation, initially hampering a more widespread acceptance of the above idea, was significantly reduced after peripheral blood derived autologous stem cell transplantation (ASCT) became established.[16 17]

In this issue of the *Annals*, Binks *et al* report on more than 40 patients with SSc in whom ASCT was performed (see p 577). This phase I/II trial report constitutes a first presentation of a multinational effort to assess the value of ASCT in systemic sclerosis and has been led for several years by Dr Alan Tyndall from Basel on behalf of the EULAR Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT) in collaboration with the European Group for Blood and Marrow Transplantation (EBMT). SSc was selected as model disease for such evaluation because, as detailed above, no treatment has been established for this disease to date. It is only fair to allow patients with an intractable condition, as severe as SSc, a last chance, given the lack of other therapeutic options.[18] Interpreting this open study, one finds good news and bad news.

Let us start with the bad news. In general, there was no improvement in major organ involvement. In particular, alveolar diffusion capacity deteriorated in many more patients (approximately 40%) than it improved in (approximately 10%); moreover, two patients died from rapidly progressive interstitial pneumonitis early after conditioning. Renal and cardiac disease did not appear to improve after the procedure. Skin disease deteriorated in some patients who had an initial improvement. Finally, procedure related mortality was of the order of 17% and overall mortality was 27% at one year, which may not be lower than expected from the natural course of the disease.[19]

However, there is also good news. Skin disease improved considerably in a large proportion of the patients, though the procedure did not cure the disease. In some, though few patients, there was an improvement in lung function. Moreover, all patients were apparently high risk patients, mostly with rapidly progressive diffuse scleroderma, and their life expectancy at one year might have been lower than 73%. And, finally, such treatment also constitutes a last resort for the caring physicians, helpless in their desire to

assist patients whose disease is not responsive to therapeutic measures, a disease without established standard treatment, and is a last resort for the desperate patient.

On the other hand, important questions arise from the results presented, and these questions will have to be addressed in co-operative studies between clinicians and basic scientists: How can patient selection be improved to (*a*) reduce treatment related mortality and (*b*) offer the procedure to the patients with the best chance of responding? How different is the immunological repertoire after ASCT from that before? When there is recurrence of disease, as is indicated by renewed progression in several patients, has the repertoire been "deranged" anew? Also, is microchimerism[20] still present after the procedure? New technologies, such as DNA and peptide microarrays,[21 22] may be helpful in resolving such questions.

The difficulty in curing scleroderma by an aggressive therapeutic regimen that is commonly successful in malignant haematological disorders also elicits the question, whether the cell populations eliminated by the procedure are really the most important players in the pathogenetic events or whether, rather, these events are driven by resident cells resistant to chemotherapy and radiation treatment, or by environmental factors, which even after ASCT affect the genetically still susceptible immune system of the host.

Although its spontaneous course is so diverse, SSc is probably rheumatology's most ominous disorder. Any promising attempt to alter the fate of this disease or to improve our understanding of its pathophysiology deserves full support by the rheumatological community.

Given the heterogeneity of the clinical presentation and course of scleroderma as well as the lack of established treatment options, the data presented now call for a randomised double blind sham controlled trial in patients who primarily have rapidly progressive skin disease. Careful patient selection and detailed description of the therapeutic protocol are mandatory. In the course of such a study, the above scientific questions ought to be considered. Additionally, in the course of such a study quality of life issues should also be investigated: How do patients perceive the burden of the procedure and its risks? How do they judge the actual change in their condition?

But what about disorders other than SSc? In some patients with RA who received allogeneic bone marrow transplantation, recurrence of disease, albeit milder, developed despite absence of residual haemopoiesis.[23 24] Conversely, donor stem cells from autoimmune patients did not necessarily transfer disease to the recipient.[25] Thus it has been speculated that host or environmental factors, retransplanted immunocompetent cells or, as discussed above, resident cells, may be important.[25] However, such factors probably differ in different disorders. SLE is yet another disease for which ASCT holds promise. In fact, given its commonly successful control by treatment with cytotoxic agents, high dose myeloablative treatment with autologous stem cell rescue may become a future choice in patients who resist more traditional treatments or whose disease still recurs severely after several conventional treatment cycles, provided that this can be proved in clinical trials.[26]

Thus ASCT may become an interesting option for patients with inflammatory rheumatic disease refractory to conventional treatment. The data of Binks *et al* provide important insights into the approach and degree of efficacy of ASCT in SSc in the recent past. These data also call for and reveal the need for well designed trials to prove its efficacy (and its long term success). However, already now we know that ASCT may be helpful only in a proportion of patients and may be curative in even fewer. Therefore an important aim must be to attempt to define those patients with the best chances for improvement. Additionally, the search for other remedies must go on.

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