The Status of Stem Cell Transplantation for Rheumatoid Arthritis: A Rheumatologist's View

DANIEL E. FURST

ABSTRACT. Stem cell transplantation (SCT) for rheumatoid arthritis will only be appropriate for a very small proportion of patients — those with aggressive disease who have had inadequate responses to several disease modifying antirheumatic drug regimens, including tumor necrosis factor blockers. The presence of biopsy proven T cell infiltrates in the synovium may be a way to improve appropriate patient selection. While there is general agreement regarding patient selection, the specifics of these criteria are not yet delineated. As for patient selection, the most appropriate SCT regimen has not yet been agreed upon and further pilot studies in this area will be required. In contrast to the above areas in which there is a distinct lack of consensus, outcome measures are better defined in RA and should include remission rate, Disease Activity Scale or American College of Rheumatology 50 (ACR 50) and ACR 70 responses, as well as longterm benefit/risk ratios (or utilities). It would be appropriate to convene a 2–3 day conference in 1–2 years to decide on the above, after more pilot data have been developed. (J Rheumatol 2001;28 Suppl 64:60–1)

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A small proportion of patients with rheumatoid arthritis (RA) have very severe, destructive, resistant, and progressive disease. Despite new therapies such as the tumor necrosis factor (TNF) blockers, not all patients respond well. As pointed out by Arthur Kavanaugh, MD, anti-TNF does not work all the time, citing evidence of an inadequate response in 40% of patients. The percentage of nonresponders to TNF blockers is at least 20% and, in certain circumstances, may even be as high as Dr. Kavanaugh suggests. Thus, there continues to be a need for therapy for the most resistant patients.

PATIENT SELECTION

When undertaking treatment that has a 2 to 4% treatment related mortality rate (as documented by the European Bone Marrow Transplant Registry headed by Alan Tyndall, MD), appropriate patient selection is paramount. Among considerations, the degree of "resistance" to previous therapy is one of the more important. A number of patient inclusion criteria regarding treatment resistance were discussed at this symposium:

- Failure of 2 disease modifying antirheumatic drugs (DMARD) (proposed by John Moore, MD)
- Failure of 2 DMARD, a combination regimen, and a TNF blocking agent (Alan Tyndall, MD)
- Failure of more than 4 DMARD (John Snowden, MD; Richard Burt, MD)
- Failure of more than 4 DMARD, with possible inclusion of TNF blockers in one DMARD regimen (Jaap van Laars, MD)

Two speakers (Christopher Bredeson, MD, and Sarah Bingham, MD) indicated that tissue biopsies to detect the presence of T cells may be useful to predict response to stem cell transplantation (SCT) and that, by implication, tissue biopsies with T cells found in the synovial tissue should be an inclusion criterion.

Although there are clear similarities among these regimens, it is also clear that there is no uniform agreement on the most appropriate patient selection criteria with respect to treatment resistance.

Clear criteria for destructive disease and treatment failure are required, i.e., the failure of 3 or 4 DMARD regimens including a combination regimen, plus failure of a TNF blocker. Since each of the regimens results in response in some patients, this requirement would decrease the likelihood that a patient would be exposed to what remains a very dangerous therapy. It is also highly appropriate to include as a selection criterion the presence of a predefined amount of T cell infiltration in the synovial tissue. This would ensure that the patient's disease would respond to an appropriate SCT regimen and would increase the likelihood of success, particularly if the patient had already failed the above regimens. While it would be useful to have more tissue biopsy evidence, the literature supports the view that synovial tissue T cell infiltration is a measure of responsiveness. While patients with "end-stage" RA, in whom even remission would not improve quality of life or function, are inappropriate for this therapeutic technique (because so much bony damage has occurred), the

From the Virginia Mason Research Center, Seattle, Washington, USA.

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D.E. Furst, MD, Director, Arthritis Clinical Research Unit, Virginia Mason Research Center, Clinical Professor of Rheumatology and Immunology, University of Washington.

Address reprint requests to Dr. D.E. Furst, Virginia Mason Research Center, 1201 9th Ave, Seattle, WA 98101. E-mail: crgdef@vmmc.org

use of biopsy material could obviate the need for a specific disease duration criterion by emphasizing disease activity.

REGIMEN SELECTION

As in other autoimmune diseases, there is no consensus on the appropriate SCT regimen in RA. Controversy continues as to the pathogenesis of RA, although a majority of rheumatologists still believe the T cell is intimately involved (however, it may not be the only or even the primary cell associated with pathogenesis)[1]. James Talmadge suggests macrophages may be important targets for the treatment of RA, while Gary Firestein suggests the fibroblast may be an important cell type (the latter was not presented at this symposium)[1-3].

Several regimens have been used in patients with RA undergoing SCT, including varying doses of cyclophosphamide from as low as 120 mg/kg to 200 mg/kg. As reported at this symposium, 2 out of 9 patients did not respond even to 200 mg/kg cyclophosphamide and significant toxicity (without mortality) occurred, as outlined by Jaap van Laars.

While nonmyeloablative regimens were most frequently discussed, John Snowden and Richard Burt recommended a myeloablative regimen because they feel that the present regimens are not effective enough. They point out, however, that there are no data to support a specific myeloablative regimen at present. Even allografting using a nonmyeloablative regimen was speculatively considered (Peter McSweeney, MD), although it was considered in the context of the inefficacy of present regimens for the long term.

I leave the choice of the best SCT regimen to the transplant physicians, who are experts in this area. It is worth pointing out, however, that the most appropriate SCT regimen has not yet been found or tested.

As noted by Sarah Bingham, patients seem to respond to DMARD therapy nicely after relapse. Thus time to relapse may be a good measure of response and a 3 to 5 year followup allowing "usual" DMARD therapy might be a very appropriate extension of future trials of SCT for rheumatoid arthritis.

ENDPOINTS OF RESPONSE

Progress has been made in defining endpoints of response, which can be used to advantage in clinical trials of SCT in RA. The Disease Activity Scale (DAS) has been validated, as have the ACR 20 response criteria[4,5]. These measures can easily be modified to define patients with near remissions[6]. Remissions, too, have been defined and described in the literature. Thus, endpoints of response are available and should be used when testing SCT in RA.

Similarly it is appropriate to simultaneously examine a number of secondary endpoints such as the duration of ACR 50 or ACR 70 response, various measures of quality of life, and cost-benefit analysis.

CONCLUSIONS

There may be a place for stem cell transplantation in the treatment of RA. The patients who would benefit from this therapy likely represent only a small portion of the total population with RA (speculatively less than 10% of patients), but this represents a large number of patients over time.

I recommend further Phase I and II studies (pilot studies) under the aegis of the European Bone Marrow Transplantation Group or a North American equivalent organization (American Blood Marrow Transplant Society or the International Bone Marrow Transplant Registry) to further define appropriate patient selection criteria and the appropriate SCT regimens to test. The effort must remain multicentered and should, ideally, remain multinational. The cooperation shown between American, European, and Australian centers with respect to other autoimmune diseases should continue and even expand to include other continents.

Within the 2 years, after the patient selection criteria and the SCT regimen(s) have been further defined, it would be appropriate for involved parties to convene a 2 or 3 day conference to decide upon common selection criteria, one or 2 treatment regimens, and appropriate endpoints to start a controlled trial for stem cell transplantation in RA.

REFERENCES

1. Weyand CM, Goronzy JJ. Pathogenesis of rheumatoid arthritis. Med Clin North Am 1997;81:29-55.
2. Kingsley G, Panayi GS. Joint destruction in rheumatoid arthritis: biologic bases. Clin Exp Rheumatol 1997;17 Suppl:s3-114.
3. Firestein GS. Invasive fibroblast-like synoviocytes in rheumatoid arthritis. Passive responders or transformed aggressors? Arthritis Rheum 1996;39:1781-0.
4. van Riel PL, van Gestel AM, van de Putte LB. Development and validation of response criteria in rheumatoid arthritis: steps towards an international consensus on prognosis markers. Br J Rheumatol 1996;35 Suppl 2:4-7.
5. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1996;39:535-7.
6. Pinals RS, Baum J, Bland J, et al. Preliminary criteria for clinical remission in rheumatoid arthritis. Bull Rheum Dis 1982;32:7-10.