High Dose Therapy and Autologous Hemopoietic Stem Cell Transplantation in Rheumatoid Arthritis — The Feasibility of Phase III Trials

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ABSTRACT. If a niche is to be established for autografting in the treatment of severe rheumatoid arthritis (RA), investigators should have the common goal of providing higher levels of evidence. Autografting in RA can be envisaged only for severe RA that has resisted all safer available treatments, and given the relatively large numbers necessary for statistical power in randomized studies, investigators will need to work together. This article summarizes the current literature and discusses practical issues relating to future trials. (J Rheumatol 2001;28 Suppl 64:55–9)

Key Indexing Terms:
RHEUMATOID ARTHRITIS STEM CELL TRANSPLANTATION CLINICAL TRIALS

INTRODUCTION

Support for hematopoietic stem cell transplantation (HSCT) as a potential treatment for autoimmune disease was originally provided by animal studies[1-3]. In humans, evidence has been provided by patients with autoimmune diseases who have undergone HSCT for conventional indications, such as aplastic anemia and malignancy. Such reports suggest allogeneic HSCT to be potentially curative of autoimmune disease, but to date its substantial morbidity and mortality have limited its application. Although autologous HSCT was unlikely to be curative, the potential of substantial responses in "coincidental" cases led to the publication of guidelines[4] and a number of pilot studies of "autografting" in a variety of autoimmune diseases[5,6].

Severe resistant rheumatoid arthritis (RA) is potentially a good candidate disease for experimental treatment with high dose therapy and autografting. Severe RA causes significant morbidity and shortens the lives of affected individuals. Its costs are considerable both to the individual and society. Compared with some other systemic autoimmune diseases, efficacy is easily and noninvasively assessed and it is possible to select patients with good vital organ function who would be expected to tolerate high dose therapy well. Notwithstanding, the use of high dose therapy and autografting in RA has met with mixed feelings among rheumatologists and hematologists. Although RA has an associated mortality, it is spread over many years, and the main problems are reduced quality of life and disability that have to be pitched against the potential of early procedure related mortality. In addition, recent years have seen the introduction of more effective antirheumatic drug regimens, notably tumor necrosis factor blockers, which have a good safety profile and are effective in many patients with resistant RA. Clearly, if we are to envisage a niche for autografting in resistant RA, it should be reserved for only those patients failing less toxic therapies and in whom the benefits are likely to justify the risks. Safety considerations should be paramount and therapy should be offered only to those fit enough to withstand the toxicity. Inevitably, given these provisions, recruitment to well powered trials may be limited and collaboration between investigators will be essential.

Evidence based decision making is considered a cornerstone in modern medical practice (Table 1). At present, with the exception of some mobilization studies, the existing data in autografting for RA consist largely of level III and IV evidence. If a role is to be established for autografting in the treatment of RA, investigators should have the common goal of providing higher levels of evidence, i.e., level II and ultimately level I. The aim of this review is to summarize and appraise the existing data and discuss the possibilities for multicenter trials.

THE EVIDENCE SO FAR

The published data for autografting in RA is reviewed elsewhere in these proceedings. They comprise:

Table 1. Levels of evidence.

Ia	Metaanalysis of randomized controlled trials
Ib	At least one randomized controlled trial
IIa	At least one well designed controlled study without randomization
IIb	At least one other type of well designed quasiexperimental study
III	Well designed non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV	Expert committee reports or opinion and/or clinical experience of respected authorities

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1. Mobilization studies, both as dedicated studies and integrated within other reports[7-15] (Table 2).
2. Series and case reports providing phase I/II data[7,12-19] (Table 3).
3. Registry data. At the beginning of 2000, 39 cases of RA had been registered in the International Autoimmune Disease Database based in Basel (personal communication, Prof. A. Tyndall). Cases have also been collected in the IBMTR Autoimmune Disease Registry in Milwaukee (personal communication, Dr. C. Bredeson). An analysis of cases is planned in early 2001 on 50 to 60 cases, with the aim of investigating relationships between response and patient related factors, such as HLA typing, presence of rheumatoid factor, duration of disease, number of disease modifying antirheumatic drugs (DMARD) that patients have failed, and treatment related aspects such as the type of high dose therapy regimen and degree of CD34+ purification of the graft. The analysis will be important in clarifying criteria for patient selection and treatment regimen in future trials.

APPRAISAL OF EXISTING DATA

The existing data can be summarized as follows:
1. CD34+ cells can be successfully mobilized from patients with severe RA with granulocyte-colony stimulating factor (at various doses). Cyclophosphamide (at various doses, with and without etoposide) increases CD34+ yields to enable CD34+ enrichment and may be associated with an improvement in disease variables, and possibly prevent flare. In an analogy to oncological practice, it may be desirable to use intermediate doses of chemotherapy to achieve at least partial remission and show chemoresponsiveness pretransplant.
2. High dose therapy and autograft seems to be feasible using a number of types of chemotherapy and degrees of T cell depletion. A reasonable level of phase I data exist for high dose cyclophosphamide. This regimen is not myeloablative, and the role of CD34+ purified grafts following this type of chemotherapy is unclear, as marrow and immune reconstitution are possible in the absence of an autograft, albeit at a slower rate. The multicenter Australian trial may provide further information for the role of CD34+ selection following high dose cyclophosphamide. The use of the myeloablative regimen, busulfan and cyclophosphamide (BuCy), in conjunction with a highly purified graft has been associated with significant complications in 2 patients. Although clinical responses have been impressive, further phase I data are necessary for the use of BuCy in patients with RA.
3. High dose therapy and autografting produces responses in a majority of patients considered to have resistant RA. There are no detailed reports in patients failing tumor necrosis factor blockade. There is a heterogeneity of response ranging from profound improvements lasting more than 2 years to little or no response at all. Possible explanations include the variation in intensity of different regimens, but the heterogeneity of eligibility criteria and patients fulfilling such criteria may be important.
4. The role of additional therapies such as methylprednisolone, antithymocyte globulin, and low dose total body irradiation and varying degrees of T cell depletion is unclear, although no striking relationship is observed in the small number of cases available.
5. Disease flare/relapse occurs eventually in most patients. The control of disease using DMARD to which the patient had been previously resistant is interesting, but yet to be formally substantiated. The use of the high dose therapy as a procedure that "debulks" or "resets" the aberrant immune system raises the question of maintenance treatment to control subclinical "minimal residual disease," analogous to the use of maintenance treatment post autograft in patients with multiple myeloma and low grade lymphoproliferative disorders.

RANDOMIZED TRIALS AND THE ALTERNATIVES

Patient selection. For any trial of autografting in RA, carefully chosen patient selection criteria are essential to maximize the benefit:risk ratio. From a rheumatological point of view, maximal benefit will be achieved through selecting patients early in the course of the disease. Prognostic markers may be useful here, but, ultimately, the attendant risks of the procedure mean that patients must prove resistant to safer, conven-

Table 2. Summary of mobilization studies.

Center	Patients	Chemotherapy	G-CSF Dose, µg/kg/day	Flare?	Improvement
Leeds[8]	5	None	5	None	None
Sydney[9]	5	None	5	1/5	None
Sydney[9]	5	None	10	2/5	None
Paris[10]	4	Cytoxan 4 g/m^2	5	None	4/4
Pavia[11]	3	None	10	None	None
Pavia[11]	3	Cytoxan 4 g/m^2	10	None	Yes
Chicago[12]	4	Cytoxan 2 g/m^2	5	None	Not stated
Leeds[7]	6	Cytoxan 2 g/m^2	263 µg/day	None	None
Brussels[13]	2	Cytoxan 1.5 g/m^2 etoposide 300 mg/m^2	5	None	2/2
Perth[14]	1	Cytoxan 4 g/m^2	10	Yes	None

Table 3. Summary of studies of high dose therapy and autografting.

Center	Patients	Chemotherapy	PBSC Selection
Perth[15]	1	Cytoxan 200 mg/kg	None
Brussels[13]	2	Busulfan 16 mg/kg, cytoxan 200 mg/kg, ATG 90 mg/kg	Double
Chicago[12]	4	Cytoxan 200 mg/kg, ATG 90 mg/kg, methylprednisolone 3 g (+ TBI 4 Gy in 1 pt)	Single
Sydney[16]	4	Cytoxan 100 mg/kg	None
Sydney[16]	4	Cytoxan 200 mg/kg	None
Australia[17]	14	Cytoxan 200 mg/kg	Single/none
Leeds[7]	6	Cytoxan 200 mg/kg	Double
Leiden[18]	8	Cytoxan 200 mg/kg	Single
Omaha[19]	2	Cytoxan 200 mg/kg, ATG 120 mg/kg	None

PBSC: peripheral blood stem cell, ATG: antithymocyte globulin, TBI; total body irradiation.

Table 4. Sample size calculation in randomized controlled trials.

Detectable Difference in HAQ Score	Sample Size	With 20% Dropouts
0.2	99	124
0.25	63	79
0.3	44	55

tional treatments. From a hematological point of view, risks of mortality and morbidity should be minimized, with the selection of patients with good vital organ function. It is possible that some subgroups of patients may prove more responsive to autografting than others. Analysis of registry data should be invaluable in this respect.

Statistical considerations (personal communication, J.M. van Laar, Leiden). Any randomized study should be sufficiently well powered to answer a specific question. An estimate of numbers necessary to achieve sufficient power can be calculated for the endpoints in a specific study. The following is an example of such a calculation using a standard statistical software program (STATA 5.0) and the Health Assessment Questionnaire (HAQ) score as the endpoint.

In randomized controlled trials, sample sizes can be calculated using the formula:

$$n/\text{group} = 2[(Z_\alpha + Z_\beta) \times SD/\Delta]^2$$

In this formula Z_α corresponds to the Type I (α) error rate, Z_β corresponds to the Type II (ß) error rate, SD is the standard deviation, and Δ is the magnitude of the difference being sought. The Z_α in many trials corresponds to a p value of 0.05 and the ß is often set at 0.1 to 0.2 (= false negative error = 1 – power). The SD used in most sample size calculations is based on the standard deviation of the population at baseline, assuming the SD of the treated groups are equal. In a 2 arm study with $\alpha = 0.05$ (2 sided) and ß = 0.20 and SD HAQ = 0.5, the sample sizes are calculated as shown in Table 4.

A change in HAQ score of 0.2 has been considered clinically meaningful[20]. In case of a potent therapy such as HSCT versus conventional antirheumatic drug treatment, the aim of the study should be to detect a difference in HAQ of 0.3; using this calculation, a study would have to recruit about 100 patients.

Proof of principle — early, late, or impossible? To establish a role for autografting in severe refractory RA, a phase III trial should ideally consist of a well powered randomized trial against a conventional alternative (Figure 1). Such a "proof of principle" study could be performed "early," i.e., soon, based on present data. Provided proof of priniciple was confirmed, subsequent studies would then be aimed at refining the procedure. Alternatively, a proof of principle study could await results of further studies aiming to optimize various aspects of the procedure, although this would take several years.

Given the relative toxicity and mortality of autografting and the fact that RA is rarely immediately life threatening, the only reasonable control arm in a randomized trial is likely to

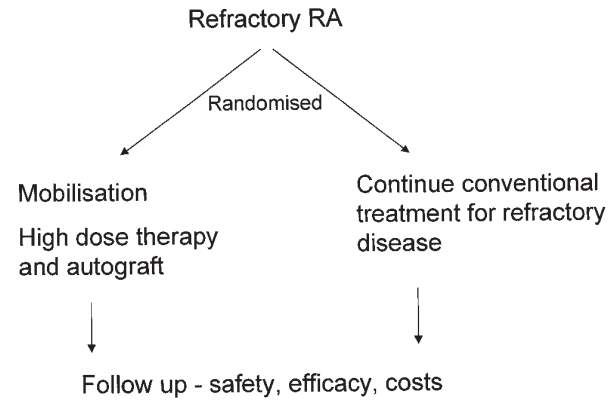

Figure 1. Proof of principle trial.

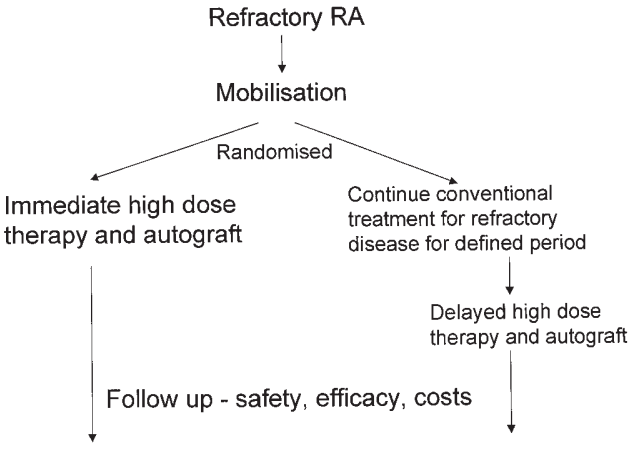

Figure 2. "Staggered" proof of principle trial.

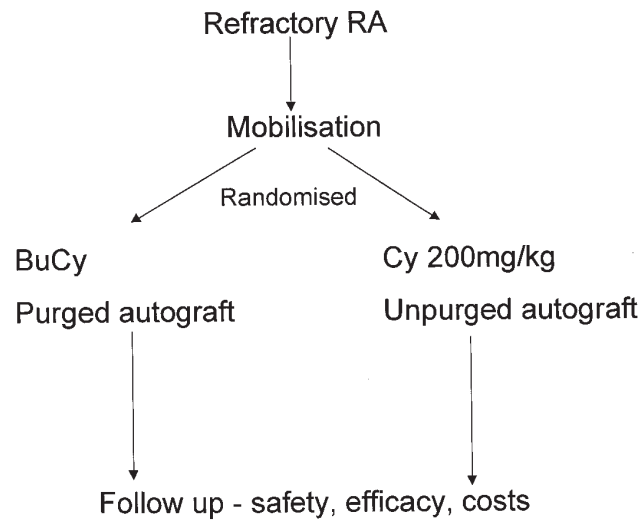

Figure 3. Myeloablative/purged versus nonmyeloablative/unpurged trial.

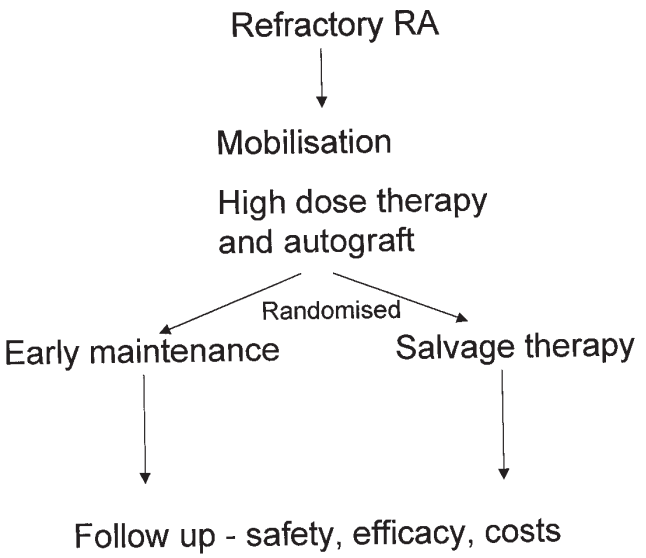

Figure 4. Maintenance/salvage trial.

be continued ineffective conventional treatment, and clearly such a trial is unlikely to recruit patients. A proof of principle study might be more attractive if the design were staggered and offered late transplant in the control arm (Figure 2).

Optimization studies. Randomized trials could also focus on optimizing aspects of the procedure, i.e., randomized comparisons of high dose therapy and purging (Figure 3) and salvage/maintenance therapy (Figure 4).

Other approaches. If a randomized study were to prove difficult or impossible, an alternative approach would be prospective registry based analysis such as patient-adjusted clinical epidemiology (PACE)[21], although this would require registration of all cases of RA fulfilling defined criteria within a given population.

CONCLUSIONS

If a niche is to be established for autografting in the treatment of severe RA, investigators should have the common goal of providing higher levels of evidence. As of March 2000, the numbers of patients with RA treated with autografting have been small, i.e., fewer than 60 patients over 4 years worldwide.

A phase III trial may be possible but will depend on:

1. The recruitment of patients to a particular study for sufficient statistical power.
2. The ability of the investigators to work together.
3. Analysis of registry data producing important data with respect to patient selection and exact nature of therapy. Future studies should incorporate narrow selection criteria in view of the heterogeneous nature of RA.
4. The question to be addressed, in particular whether investigators feel that "proof of principle" is essential or impossible.
5. Effective data collation. Disease-specific data collection forms have been prepared.

Autografting in RA can be envisaged only for severe RA that has resisted all safer available treatments; and given the relatively large numbers necessary for statistical power in randomized studies, investigators will need to work together. Investigators should be prepared to err on the side of undertreatment with risk of relapse as opposed to exposing patients to significant risk of mortality.

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