MEETING REPORT

Haemopoietic stem cell transplantation in the treatment of severe autoimmune diseases 2000

A Tyndall, J Passweg, A Gratwohl

A meeting report on behalf of the European League Against Rheumatism (EULAR), the European Group for Blood and Marrow Transplantation (EBMT), the International Bone Marrow Transplantation Registry (IBMTR), and the International Autoimmune Disease Stem Cell Project

Abstract

An international meeting took place in Basel, Switzerland from 5 to 7 October 2000 involving 180 participants from 30 countries, with the aim of assessing the existing data on autologous haemopoietic stem cell transplantation (HSCT) in the treatment of severe autoimmune disease, and to decide on future trial planning.

Data on 390 patients were presented: 260 from the EBMT/EULAR Basel European/Asian database, 87 from North America (55 from the IBMTR), 39 from Australia, and 4 others. The major disease categories and number of patients receiving transplant were: multiple sclerosis (MS) 127, systemic sclerosis (SSc) 72, rheumatoid arthritis (RA) 70, juvenile idiopathic arthritis (JIA) 36, systemic lupus erythematosus (SLE) 34, dermatomyositis/polymyositis (DM/PM) 5, idiopathic thrombocytopenic purpura (ITP) 7. Single or several cases of other autoimmune diseases were reported.

Clinically significant responses were seen in two thirds of all the cases and in all disease categories, with a more accentuated trend towards relapse in JIA and RA. Treatment was associated with a significant morbidity and mortality. In the EULAR/EBMT database (71 centres in 22 countries), a mobilisation associated mortality of 1.5% and an overall procedure related mortality (actuarially adjusted at 12 months) of 9% (confidence interval 6 to 12%) were found, with significant variation between diseases. The North American data showed similar results. Higher mortalities were seen in SSc and systemic JIA, with only one death reported in RA.

After presentation of the data and workshop discussion a consensus was reached on several aspects: prospective randomised phase III trials are now appropriate in SSc, MS, and RA. A protocol is ready for SSc (ASTIS Trial), concepts are clear for MS and RA. Further phase I and II data are required in SLE, JIA, and vasculitis. The need for continuing collection of all cases after mobilisation by the standardised EBMT and IBMTR data forms was emphasised.

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Department of Rheumatology, University Hospital, Basel, Switzerland
A Tyndall

Division of Haematology, Department of Internal Medicine, University Hospital, Basel, Switzerland
J Passweg
A Gratwohl

Correspondence to:
Professor A Tyndall, Department of Rheumatology, Felix Platter Spital Burgfelderstrasses 101, 4012, Basel, Switzerland
alan.tyndall@fps-basel.ch

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Five years ago a joint committee of the EBMT and EULAR set about the task of evaluating the potential role of intensive immunosuppression and autologous haemopoietic stem cell transplantation (HSCT) in the treatment of severe autoimmune disease.[1] The topic has been much discussed since then and been the subject of several reviews, small series, and case reports.[2–6] Several meetings have occurred over this time bringing together colleagues from different fields, including transplantation medicine, rheumatology, immunology, neurology, and paediatrics.

This continuing discussion, shared standardised data collection (table 1), and the experience in the meanwhile acquired from breast cancer trials with HSCT have all suggested that

Table 1 Combined international data

Disease	*No*	*Disease*	*No*
Multiple sclerosis	127	Dermatomyositis	5
Myasthenia	1	MCTD*	3
Polyneuropathy	1	Cryoglobulinaemia	3
		Behçet's disease	3
SSc*	72	Wegener's disease	3
SLE*	34	ITP*	7
Rheumatoid arthritis	70	AIHA*	2
Psoriatic arthritis	2	PRCA*	4
Juvenile chronic arthritis	36	Evans's syndrome	1
Ankylosing spondylitis	1	TTP*	2
Sjögren's syndrome	1	Other	?

*SSc = systemic sclerosis; SLE = systemic lupus erythematosus; MCTD = mixed connective tissue disease; ITP = idiopathic thrombocytopenic purpura; AIHA = autoimmune haemolytic anaemia; PRCA = pure red cell aplasia; TTP = thrombotic thrombocytopenic purpura.

Table 2 Outcome — EBTM database (major autoimmune diseases)

	*MS**	*SSc**	*RA**	*JCA**	*SLE**	*ITP**
Missing	2	1	—	—	—	—
No transplant	1	8	1	—	—	—
TRM*	7	6	1	5	3	1
Too early	4	6	2	1	—	—
Worse	20	3	7	1	1	2
Better then worse	4	11	18	7	5	—
Stable disease	26	1	1	1	—	2
Better	31	30	13	20	14	2
Total	95	66	43	35	23	7

MS = multiple sclerosis; SSc = systemic sclerosis; RA = rheumatoid arthritis; JIA = juvenile idiopathic arthritis; SLE = systemic lupus erythematosus; ITP = idiopathic thrombocytopenic purpura; TRM = treatment related mortality.
Clinical state from global doctor's assessment only.

early phase I and II pilot study data should be followed by randomised controlled trials (RCTs).This has led researchers and institutions such as the Food and Drug Administration (W Schwieterman, personal communication) to ask whether prospective RCTs should and could be designed based on the accumulated data rather than theoretical aspects alone. RCTs should start soon for those autoimmune diseases in which adequate phase I and II data have been generated—that is systemic sclerosis (SSc), multiple sclerosis (MS), and rheumatoid arthritis (RA).

Some discussions early in this project focused on the concept of "cure" through eradication of aberrant immune cells. Five years and 400 patients later the concept has shifted to a "resetting" of the immune system. Strategies based on HSCT treatment concentrate on limiting severe or fatal organ damage and reducing cumulative doses of immunosuppressive drugs, rather than curing in all cases.

In addition, the higher than expected procedure related mortality[7]has focused attention on patient selection. This has become even more important because during the course of the past five years, new factors have emerged altering the concept. The introduction of anti-tumour necrosis factor α (anti-TNFα) treatment in RA[8]and the definition of prognostic factors in SSc outcome[9]have to be integrated into a trial design.

Such trials offer also a unique opportunity to study the post-transplant evolution and immunopathology of an autoimmune disease when and if it relapses.

Table 3 ASTIS trial selection criteria

Inclusion:	Age 16–60
	Diffuse skin SSc* plus at least one vital organ affected (defined)
	Duration of skin disease (excluding sclerodactyly) <4 years
	Initial skin score (modified Rodnan max 51) >14
Exclusion:	Left ventricular ejection fraction <45% normal
	Uncontrolled cardiac arrhythmias
	Uncontrolled hypertension
	Pulmonary diffusion capacity <40% predicted
	Respiratory failure—Pa_{O_2} <8 kPa (60 mm Hg)
	Mean pulmonary artery pressure >50 mm Hg
	Renal failure—creatinine clearance <40 ml/min
	>5 g cumulative dose Cy* or >3 months Cy 2 mg/kg/day

Further details available at: www.astistrial.com
*SSc = systemic sclerosis; Cy = cyclophosphamide.

This meeting aimed at summarising the accumulated evidence based data with reference to each of the above points and for each disease, with a view to designing RCTs.

Outcome of HSCT in the treatment of ADs

Table 2 shows a combined toxicity and benefit analysis from the Basel database, October 2000 for all the major ADs represented (269 cases). Improvement is imprecisely defined, according to the entering centre's statement of "complete remission", "partial remission", "no response", "worse", or "dead". This was adopted from the EBMT convention but will be more precisely defined in the future. As outcome varies significantly between diseases, it will be discussed in the context of each disease for which a more precisely defined retrospective analysis has been undertaken.

Systemic sclerosis

Analysis of data on the first 41 patients showed that 69% achieved an improved skin score of 25% or more from baseline, with a trend towards stabilisation of the lung function. A treatment related mortality (TRM) of 17% was seen early on, which came down to 12.5% when the next 24 sequentially reported patients were included[10](J van Laar, D Furst). TRM in those patients fulfilling the current entry criteria is in the order of 7.7%. Half of the patients with SSc fulfilling the entry criteria have a five year survival rate.

Several protocols were used, mostly either cyclophosphamide (Cy) + granulocyte colony stimulating factor (G-CSF) mobilisation followed by Cy 200 mg/kg body weight conditioning with a T cell depleted graft, or Cy 120 mg/kg body weight together with 8 Gy total body irradiation (TBI; USA). Different patterns of toxicity were seen: cardiac events with high dose Cy (M Binks) and pneumonitis with TBI (R Nash). In addition, patients with a mean pulmonary artery pressure of >50 mm Hg either did not respond or did not survive the stress of neutropenic fever and shock during the treatment. Future protocols have been modified according to this experience—for example, stricter cardiac screening and lung shielding with TBI based regimens.

A European based RCT is finalised, called the ASTIS (Autologous Stemcell Transplantion International Scleroderma) Trial.

This protocol is available from either the EBMT web site (www.EBMT.org) or www.astistrial.com, and in summary consists of HSCT versus 12 × monthly Cy 750 mg/m^2 pulse treatment. The HSCT consists of mobilisation with Cy 4 g/m^2 (in two doses) and G-CSF (Neupogen), followed by conditioning with Cy 200 mg/kg in 4 doses and ATG (antithymocyte globulin) total 7.5 mg/kg in three doses. The graft product will be CD34 selected.

Table 3 summarises the entry criteria. The principles are to select patients with a poor prognosis, but not so severely damaged as to attract a high TRM or hopeless outcome.

The primary end point is event-free survival, with events being end organ failure (arbitrarily but precisely defined). It is calculated that 100 patients in each arm will be required in this multicentre and international trial.

All interested centres are invited to contact <astistrial-fps@unibas.ch>

In the USA a radiation based RCT protocol is being developed, consistent with the phase I and II experience. However, consensus has been reached on major end points, control arm, and selection criteria internationally.

Multiple sclerosis

MS is still a difficult disease to assess, being heterogeneous and probably having different causes—for example, primary progressive MS may be purely degenerative. Still, some conclusions can be reached based on this early experience.

Of the 85 patients with more than two months' follow up, 47 (55%) had secondary progressive disease and 19 (22%) primary progressive disease. The median time interval between diagnosis and HSCT was 7.5 years (1–33), and 76/85 (89%) had had a deterioration of at least one EDSS (Expanded Disability Status Scale—ranging from 0 = no disability to 10 = dead from disease) point in the year before the HSCT. Median entry EDSS was 6.5 (4.5–8.5) points (A Fassas, G Mancardi, H Oppenshaw).

In the whole group 72% (61/85) survived for three years without progression and in the non-primary progressive group (the majority—67/85 (79%) patients) this was 78% (52/67). This compares with 60% in β interferon trials.

Improvement of more than one EDSS point was seen in 18 (21%), with later progression in six.

TRM occurred in five (6%) patients and death from progressive disease in two (2%)

Active magnetic resonance imaging (MRI) lesions in the central nervous system, a surrogate marker for treatment success, were markedly reduced, even from the first mobilising doses of Cy. All MRIs which were inactive at baseline remained so. In secondary progressive MS, 38% were active before and 13% after transplant. For primary progressive MS, these figures were 27% before and 1% after transplant.

G-CSF mobilisation associated flares, in one case fatal, were reported and need to be taken into account when planning prospective trials. Also, flares after transplant (possibly related to infection activation) and fatal infection suggest that a functional disability of more than 6.5 on the EDSS should be an exclusion criterion. Such patients are, in general, at higher risk from concomitant illness.

RCTs are both desired and in the USA becoming mandatory from the health authorities.

Patient selection: Secondary progressive MS with an EDSS score of 3.5–6.5.

At least three years' follow up in most patients is required to confirm the current data on shorter follow up times.

The HSCT arm will be BEAM (BCNU, VP 16, ara-C, melphalan) and ATG in Europe, probably without graft manipulation. The American protocol has yet to be defined. The control arm will be discussed; either mitoxantrone or β interferon.

A focused working party of neurologists and haematologists was formed to bring the open questions to a firm conclusion within 12 months.

Rheumatoid arthritis

A retrospective analysis was performed on 70 cases (P Emery, J Snowden).The procedure was well tolerated, with one only death overall and none in the Cy only conditioning regimens.

Most patients responded, sometimes dramatically, with ACR responses similar to those seen after anti-TNFα treatment. However, around 50% relapsed having synovitis flares. All groups reported that many relapses responded well to standard treatment with a single disease modifying antirheumatic drug (DMARD)—methotrexate, leflunomide, or cyclosporin, drugs which had failed before transplant. A small number of observations indicate that cyclosporin A may have a negative impact on T cell immune reconstitution after transplant for naive T cell repopulation and thymic function, and it is not recommended as the first DMARD for maintenance after transplant (abstract P30).

There was no suggestion that T cell depletion of the graft product gave a more favourable outcome, as reported by the five centre, Australian study of 33 patients (S Millikan), and no one regimen was clearly better than another. Some patients with RA were found to have improved significantly after 4 g Cy as mobilisation, and did not proceed to HSCT.

Consensus was reached on the need and feasibility for an HSCT RCT in RA. This is called the ASTIRA (Autologous Stemcell Transplantation International Rheumatoid Arthritis) Trial (S Bingham, P Emery).

Patient selection: Those (*a*) for whom treatment for at least three months with three DMARDs or more (including methotrexate and one combination) as well as anti-TNFα treatment has failed; (*b*) who have had RA for more than two years and less than 10 years; and (*c*) who have progressive, destructive, seropositive disease.

At entry all patients are mobilised with 4 g Cy/m^2 and harvested, then randomly allocated to a group receiving Cy 200 mg/kg HSCT or a group continuing with "best available" maintenance treatment.

The primary end point is the number of patients who, at six months after transplantation, respond to drugs to which they were previously resistant—that is, the number of patients achieving a moderate/good EULAR or ACR 20 response. Patients in the mobilisation only arm who fail to respond adequately will switch to HSCT at six months.

Juvenile idiopathic arthritis

Most of the cases of juvenile idiopathic arthritis (JIA) were the systemic, polyarticular type, and 15 of these were from the two centre Netherlands groups in Utrecht and Leiden (reported by N Wulffraat). These children received a bone marrow obtained HSCT and were conditioned with Cy 200 mg/kg, TBI (4 Gy), and ATG. In this cohort eight full remissions and two partial remissions were recorded, as well as two deaths through macrophage activation syndrome. Internationally, a further 10 complete remissions were noted, and one other death through macrophage activation syndrome (table 4).

Protocols were modified accordingly to avoid transplantation during a phase of significant systemic activity, which should be controlled with corticosteroid treatment.

The impact of the modified protocol using bolus prednisolone to control systemic disease before HSCT has not been assessed, but may reduce it to below the current 15%, making a comparative trial feasible. The final protocol, hopefully international, will be worked on over the next 12 months and reported (chairperson N Wulffraat)

Systemic lupus erythematosus

In the combined international experience of 34 patients with systemic lupus erythematosus (SLE), the largest series is from Chicago[11]with one mobilisation death, one death from disease progression three months after mobilisation, and seven patients in remission, median follow up eight months (range 1–25). The protocol was mobilisation with Cy 2 g/kg body weight and G-CSF, followed by conditioning with Cy 200 mg/kg and ATG (reported by R Burt).

In the 23 patients registered in Basle, 14 are described as improved, five initially improved then relapsed, and one progressed despite HSCT. There were three TRMs. Median follow up 14 months (D Jayne, A Marmont).

The heterogeneity of patient selection criteria and treatment protocols was especially noted in the SLE subgroup.

Insufficient data are available to allow immediate RCT planning. A summary of the overall experience will be written using the EBMT/EULAR, IBMTR, and other data sources. This was presented at the 6th International SLE Congress, Barcelona, 27 March 2000.

A focus group under the chairmanship of D Jayne will meet to define further the required phase I and II data lacking.

Future multicentre RCTs will exclude critically ill patients with vital organ failure.

Vasculitis

Experience is essentially anecdotal at present (P Bacon).

Four cases of Wegener's granulomatosis were reported, all having an initially complete response, and two then relapsing at 2.3 and 3 years, respectively. As with other autoimmune diseases, relapse was often easier to control after transplant.

Table 4 Results after auto-SCT for JIA* in European and North American centres. Reproduced with the kind permission of N Wulffraat and the EBMT/EULAR database*

No	Centre	Age at disease start (years)	Age at ASCT* (years)	TCD* (Y/N)	Conditioning	Follow up (months)	Outcome	Present antirheumatic drugs
1–11	Utrecht, NL	1–7	7–14	CD2/3 (6)	Cy*, ATG*, TBI* (4 Gy)	4–36	7 remission, 1partial remission, 1 fatal MAS*	Low steroids (2) NSAIDs (1)
12–14	Leiden, NL	2–10	4, 6, 14	CD2/3 (1) CD34 (2)	Cy, ATG, TBI (4 Gy)	12–15	1 remission, 1 partial remission, 1 fatal MAS	Salazopyrin (1)
15	Paris, Fr	8	9	CD34	Cy, ATG	—	Day 18 fatal MAS	
16–17	Goteborg, Swe		4–9	CD2/3	Cy, ATG, TBI (4 Gy)	3–10	Both remission	Low steroids (1)
18–22	Triest, It	3–15	8–20	VCR	Cy, ALG (3) Flu*, ALG* (2)	12–36	Remission (3) Relapse (2)	Etanercept (1), NSAIDs (1)
23	Portland US	2	10	CD34	Cy, ATG, TBI (4Gy)	7	Complete remission	None
24–25	Brussels, Be	1–7	8, 17	CD34	Cy, ATG	7–19	Complete remission	None
26	Brussels, Be		15	CD34	Cy, ATG	—	Fatal cardiac toxicity	—
27–28	Osaka, JP	1–5	3–8	CD34	CY, ATG (1) VP16, TT* (1)	4–11	No response (1) Remission (1)	Low steroids None
29	Newcastle, UK	3	10	CD34	Cy, ATG	2	Remission	Low steroids
30	Slowakije	18	35	None	Bu*, Cy, ATG	6	Partial remission	Low steroids
31	Newcastle, UK	21	23	Campath	Cy, Campath	2	Amyloidosis, septic shock, no MAS	
32	Ferrara, It	33	35	CD34 (PSCM)	Cy, ATG	18	ATG related toxicity, Complete remission	Low steroids

*SCT = stem cell transplantation; JIA = juvenile idiopathic arthritis; ASCT = autologous stem cell transplant; TCD = T cell depletion; Cy = cyclophosphamide; ATG = anti-thymocyte globulin; TBI = total body irradiation; ALG = anti-lymphocyte globulin; Flu= fludarabine; TT = thiotepa; Bu = busulfan; MAS = macrophage activation syndrome; NSAIDs = non-steroidal anti-inflammatory drugs.

Table 5 Cause of death—EBMT/EULAR database

Haemorrhage (CNS, pulmonary)	4
Cardiac	4
Interstitial pneumonitis	3
Septicaemia/infection NOS	10
Fungal	1
Viral	2
Protozoal	1
Vaso-occlusive disease	1
Other	2

Cryoglobulinaemia, with variable degrees of vasculitis features, was reported, with a complete response in two cases. One case of classical polyarteritis nodosa with complete remission and three cases of Behçet's disease with an unknown degree of vasculitis and short follow up were also presented.

Insufficient data are present to allow RCT planning; more phase I and II pilot data are required.

Toxicity and deaths

Appropriately, safety was the main aim of the initial phase I studies reported to the different databases. In the Basel database (A Gratwohl, J Passweg) the overall TRM of 9%, actuarially adjusted to 12 months, is comparable with that in North America of 11% (K Sullivan).

Causes of death were as previously seen in transplantation medicine (table 5), with some unexpected trends. As previously mentioned, patients with SSc seem to have an increased susceptibility towards cardiotoxicity or failure to adapt to even minor infection complications, possibly reflecting occult SSc myocardial involvement. This has led to stricter cardiac patient exclusion criteria. Also, the use of rabbit ATG in the conditioning of some patients has been associated with an Epstein-Barr virus lymphoproliferative syndrome in two cases (R Nash, Seattle, personal communication). Future trials with rabbit ATG will use a maximum total dose of 7.5 mg/kg recipient's body weight. This might have been a dose effect or related to the radiation conditioning (8 Gy). Two episodes of suspected radiation induced fatal lung disease have resulted in the incorporation of lung shielding into future protocols. Since this modification, no further such events have been reported.

A G-CSF induced flare, leading to a fatal outcome in one case of MS,[12] might be prevented by simultaneous pulse prednisolone treatment.

In systemically ill patients with JIA, a macrophage activation syndrome was associated with a fatal outcome in three patients. Clearly, active systemic disease should be controlled (for example, with methylprednisolone pulse treatment) before HSCT.

A positive note was that although not significant, a trend towards a reduced TRM was seen in 1999 and 2000, reflecting perhaps tighter patient selection or a learning curve.

Only prospective studies and follow up will prove if the early TRM will be counterbalanced by better survival than for conventionally treated patients.

Mobilising and conditioning regimen effects *(A Gratwohl, A Kashyap)*

An overall 1.5% procedure related mortality was seen in the Basle database from mobilisation. Some of these were considered due to Cy cardiac toxicity and others to a G-CSF associated autoimmune disease flare. In others, especially pulmonary hypertension associated with SSc, neutropenic fever and shock were overwhelming events due to a compromised cardiopulmonary system. Such patients are excluded from future trials.

Although most of the phase I and II studies employed one of the four basic conditioning protocols originally proposed in a consensus statement,[13] there was a significant variation in the intensity relating to the use of ATG or antilymphocytic globulin and purging.

The more intense regimens were associated with more complications, and to see if a clinical benefit was also obtained, an analysis of the whole Basle database was undertaken. The TBI and/or busulfan based regimens were considered to be intense (n=58), BEAM as moderate (n=80), and Cy and fludarabine (n=123) as less intense. The TRM probabilities at one year were respectively 9% to 29% (95% CI), 3% to 13%, and 0% to 8%.[14] These data should be interpreted with caution because diseases more likely to be associated with vital organ dysfunction (for example, SSc) tended to receive more intense regimens, as compared with RA, which has fewer risk factors and less intense conditioning. Although there was no clear improvement in remission induction or durability from the more intense regimens, a trend towards fewer relapses was seen with the more intense protocols. More data are required.

For conventional allografting and the recently developed non-myeloablative (mini) allograft, the risk of graft versus host disease and the early positive results from autologous HSCT exclude this from currently planned RCTs, though it may soon be time to consider such HSCTs for patients who have relapsed after autografting for whom a matched related donor is available.

Stem cell biology and immune reconstitution

The plasticity of haemopoietic stem cells was demonstrated by the observation that differentiation and commitment of B cells are separately controlled (C Schaniel). If the PAX 5 gene was knocked out, then an early B cell could, under appropriate "biological pressure" (that is, a T cell deficient animal) return to a stem cell status and then differentiate into T cells.[15] The same pre-B cell could replenish all haemopoietic cell lines except erythrocytes.

Despite general statements that the immune system "repeats ontogeny" after autologous HSCT, this is only partly so for B cell reconstitution, with B cell subsets seen which normally only appear in neonates (E Roosneck). T cells which have recently left the thymus retain a circular piece of DNA, the result of T cell receptor gene splicing, called a T cell receptor excision circle (TREC). They are only present

Table 6 Recommended core set of parameters

Immune reconstitution		
• Full blood count and differential		
• B cells	Antibody	Serum Igs
		Serum IgG subclasses
	CD19	
• T cells	CD3, CD4, CD8	
	CD4/CD45 RA, CD4/CD34RO	
• NK cells	CD16/CD56+/CD3−	
• Measured and stored: 0, 3, 6, 9, 12, 24, 48 months		

Contact Dr J Isaacs (rrrjdi@leeds.ac.uk) or Dr F Ponchel (mmefp@leeds.ac.uk) for studies of thymic function after stem cell transplantation.

for a short time and disappear when the cell proliferates (J Isaacs, F Ponchel). The measurement of TRECs gives an indication of thymic function, shown to be reduced in patients with RA even before HSCT (abstract P30). In patients with RA T cell reconstitution, particularly of the CD4+ subset, is severely impaired. Measurement of TRECs suggests that this is largely a consequence of the reduced thymic function (see below). Thus there is an early expansion of CD4+ CD45RO+ "memory" cells, which are probably expanding in the periphery to fill the void left by the conditioning. Much later, TREC positive naive T cells reappear (CD4+ CD45 RA+). The T cell receptor repertoire is restricted after autologous stem cell transplantation, which is no different from previously published experience.[16]

Some groups have shown prolonged (four years) reduction of helper T cell numbers after HSCT, especially if T cell purging was employed. This has been associated with infection risk, but not so far with degree of response or durability of remission.

Prospective coordination of immune reconstitution in a variety of autoimmune diseases will be offered by Drs Isaacs and Ponchel (rrrjdi@leeds.ac.uk, mmefp@leeds.ac.uk) (table 6). Standardised measurements at each centre are recommended at set times before and after transplantation (table 5), as well as standardised serum and DNA storage. More complex studies will be organised between interested groups.

Data were presented on some predictors of autoimmune disease response (abstract P4) and relapse, such as return of rheumatoid factor and synovial B cells in RA (Leeds and Australia) and B memory cells in SLE (Berlin, abstract P26).

Data collection

The past 3 years of EBMT/IBMTR collaboration have produced a standardised core set of data for the major autoimmune disease subgroups internationally (M Horowitz, J Passweg). This will allow useful clinical analysis of outcomes across databases and avoid double registrations. Such forms are available for MS, SSc, RA, JIA, and SLE from the following web sites:

For the Americas: www.IBMTR.org

For all other centres (Europe, Australia, Asia): www.EBMT.org

Patients in clinical trials should also be so registered.

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For managing and coordinating the central data collection: C Bocelli-Tyndall.

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