

Polysaccharide antibody responses are impaired post bone marrow transplantation for severe combined immunodeficiency, but not other primary immunodeficiencies

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Summary:

Established treatment of severe combined immunodeficiencies (SCID) and other primary immunodeficiencies (PID) is bone marrow transplantation (BMT). Normal lymphocyte numbers and protein antigen responses are present within 2 years of BMT, polysaccharide antibody responses appear last. *Streptococcus pneumoniae* infection causes significant morbidity and mortality post-BMT. Previous studies have shown good protein antigen responses post-BMT for SCID and PID, but had not examined the polysaccharide responses. We retrospectively analysed pneumococcal polysaccharide (PPS) responses in our patient series.

In total, 22 SCID and 12 non-SCID PID were evaluated, all >2 years post BMT: 17 SCID, 12 PID received chemotherapy conditioning; 17 SCID, three PID had T-cell depleted (TCD) BMT, others had nonconditioned whole marrow BMT. All had normal Haemophilus influenza B and tetanus antibody responses. Of 22 SCID, 13 vs 11/12 PID responded to PPS vaccine ($P=0.05$). There was no association with donor age, GvHD, B-cell chimerism, or IgG2 level. Fewer TCD marrow recipients responded to PPS ($P=0.04$). Analysis of the SCID group showed no association of PPS response with type of marrow received. This is the first study to specifically examine PPS antibody responses following SCID and PID BMT. Pneumococcal conjugate vaccine antibody responses should be examined in these children.

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immunity with an incidence of about 1/30 000–1/70 000.¹ Without treatment, opportunistic or otherwise self-limiting infections lead to death within infancy. The only established treatment is bone marrow transplantation (BMT), which is curative in over 70% of SCID patients without a sibling donor, who undergo haploidentical T-cell depleted (TCD) transplantation.^{2,3} BMT is now accepted as definitive treatment for other types of primary immunodeficiency (PID) with current success rates of over 60%.⁴ Survivors generally appear to have normal immunity, growth, and development, but detailed studies of these outcomes are incomplete.⁵

Depending on the type of marrow infused, immune reconstitution is apparent 6 weeks to 4 months post BMT, with TCD marrow taking longest to reconstitute. Patients are usually immune competent within 2 years of BMT with normal numbers and function of lymphocytes including normal responses to protein antigens.³ Post BMT, most patients can discontinue antibiotic prophylaxis and replacement intravenous immunoglobulin (IVIG). Polysaccharide antibody responses, such as those against *Streptococcus pneumoniae*, appear last,^{6,7} recapitulating the ontogeny of polysaccharide responses in infants, but are generally present by 2 years post BMT. However, *S. pneumoniae* infection is a significant cause of morbidity and mortality in the late period post BMT in both adult and paediatric transplant series.⁸ Previous studies, looking at immune reconstitution post BMT for SCID, have documented good protein antigen responses,⁹ but not examined specific polysaccharide responses. One of our SCID patients acquired *S. pneumoniae* right upper lobe pneumonia 5 years post BMT while no patients transplanted for PID had problems with pneumococcal infection post BMT. We analysed our BMT series with particular respect to pneumococcal polysaccharide (PPS) responses, comparing those transplanted for SCID with those transplanted for other primary immunodeficiencies.

Patient population

As one of two UK centres performing BMTs for children with PID, our unit has transplanted 57 children with SCID (46 survivors) and 66 children with other forms of PID (34

Severe combined immunodeficiencies (SCID) are a group of inherited disorders, where different molecular defects result in profound impairment of both cellular and humoral

survivors) between 1987 and December 2002. Patients remained on IVIG until they had normal age-related serum IgM, IgA, and isohaemagglutinin levels, usually around 6 months for whole marrow transplants and 12 months for TCD transplants. At 3 months after stopping replacement IVIG, specific antibody titres were measured and primary immunisations including tetanus, diphtheria, *haemophilus influenza B* (Hib), pertussis, and killed Polio were commenced at monthly intervals. Patients with normal age-related T-cell numbers and normal T-cell proliferation to mitogens, and who responded to tetanus and Hib-conjugated protein vaccines with postvaccination specific antibody titres within the normal range received measles, mumps, and rubella triple vaccination (MMR). Pneumococcal polysaccharide vaccine (Pneumovax II[®]) was given at least 2 years post BMT, only to those patients who had demonstrated an adequate antibody response to tetanus, Hib, and MMR vaccines. Patients still on IVIG ($n=8$), those not vaccinated with PPS vaccine ($n=7$) and those less than 2 years post BMT ($n=31$) were excluded.

A total of 22 SCID patients were eligible for evaluation (Table 1). Of these, 16 had T-B+SCID (five common gamma chain mutation), two had T-B-SCID (one RAG mutation, one artemis mutation), four had ADA deficiency. Of 22 patients, 17 received cytoreductive conditioning with busulphan and cyclophosphamide and had TCD transplants according to standard European working party protocols. In all, 15 manipulated marrows were TCD *in vitro* with CAMPATH 1M, and two (patients 16, 21) received CD34+ enriched stem cells. Five patients received whole marrow infusions with no preparative chemotherapy (patients 8,9,10,19,20).

Of 12 non-SCID PID patients evaluated, three had Wiskott Aldrich syndrome, two had chronic granulomatous disease, two CD40 ligand deficiency, one ZAP 70 kinase deficiency, one hyperIgE syndrome, and three combined immune deficiency of unknown molecular basis (Table 2). All 12 patients received busulphan and cyclophosphamide conditioning according to standard European working party guidelines. Nine received whole marrow, two marrow TCD *in vitro* with CAMPATH 1M (patients 28, 30) and one CD34+ enriched stem cells (patient 29).

No patient received radiation as part of the conditioning protocol. No patient in the study received peripheral blood stem cells. All patients had normal splenic function with absence of Howell-Jolly bodies on post-BMT blood films, apart from patient 6, who underwent splenectomy during transplantation.

Method

A retrospective analysis of PPS antibody responses in patients transplanted for SCID compared to responses in those transplanted for other forms of PID was performed. Patients' case records were examined to determine diagnosis, age at BMT, type of marrow infused – whole or TCD, method of TCD, age of BM donor, conditioning regimen, length of follow-up, occurrence of GvHD, chimerism, lymphocyte numbers, IgG2 and IgA levels,

isohaemagglutinins, response to tetanus and Hib vaccination, and response to PPS vaccination.

Serum immunoglobulins and IgG subclasses were measured by rate nephelometry calibrated against International Standards and reported against age-specific normal ranges. Specific antibodies against tetanus, Hib, and pneumococcus were measured by enzyme linked immunosorbent assay (ELISA). The pneumococcal assay measured unabsorbed total IgG response against the 23 valent polysaccharide vaccine. A vaccination response was defined as a two-fold increase in post vaccination titre providing final titres were $>1 \mu\text{g/ml}$ (Hib IgG),¹⁰ $>0.1 \text{ IU/l}$ (tetanus IgG), and $>20 \text{ mg/l}$ (PPS IgG).¹¹ An absent response was defined as a final level below the lower limit of normal laboratory range and a poor response as a less than two-fold rise in antibody level with a final level above the lower limit of normal laboratory range, post vaccination.

Lymphocyte subsets were measured by flow cytometry using a Becton Dickinson FACScan (Becton Dickinson UK Ltd, Oxford) and analysed using the SimulSET 3.0F programme (Becton Dickinson).

B- and T-lymphocyte chimerism was assessed by electrophoretic separation of radioactive PCR products following amplification of dinucleotide repeat polymorphisms in DNA from separated T and B cells using standard protocols. Quantitative analysis of chimerism was not performed. Investigations were organised as part of routine clinical evaluation and care. Results were analysed with the two-tailed Fishers exact test for a difference in proportions.

Results

All patients were followed for more than 2 years post BMT. SCID patients were followed for a median of 7 years (range 2.33–14 years), non-SCID patients were followed for a median of 5 years (range 2.5–9 years). Of 22 SCID patients, 19 had mixed donor/recipient or donor B-cell chimerism (Table 1). All patients had a normal response to tetanus and Hib. Of 12 non-SCID patients 11, had mixed donor/recipient or donor B-cell chimerism (Table 2), and all had a normal response to tetanus and Hib. However, only 13 of 22 SCIDS *vs* 11 of 12 non-SCIDS responded to PPS vaccine ($P=0.05$ – Fisher's Exact test).

Other factors were examined for their potential influence on whether or not a patient responded to PPS vaccine. There was no significant difference between the groups when the number of child *vs* adult donors was compared. There were no serious episodes of GvHD among the patients and no difference between the groups. There was no association with B-cell chimerism or level of IgG2 and PPS response. Significantly fewer patients who had received TCD marrow responded to PPS ($P=0.04$). However, the majority of SCID patients received TCD marrow, whereas non-SCID patients received whole marrow. When the SCID group alone was analysed, antibody response to PPS antigen was not significantly associated with type of marrow received, although the numbers of SCID patients receiving whole marrow were small. SCID patients took significantly longer post transplant to mount an adequate PPS response than non-SCID patients ($P=0.05$).

Table 1 SCID patient and BMT characteristics and responses to PPS vaccination

Patient	A	Conditioning	TCD	FU (years)	Tet pre	Tet post	Hib pre	Hib post	PPS pre	PPS post	Time to PPS	IgG2	IgA	B cells (μ l)	Donor age (years)	Chimerism T/B cells	GvHD	Isohaem		Age at BMT (months)
																		A	B	
1	B+	bu16/cy	Yes	14	0.36	6.54	0.15	8.5	18	52	6	N	N	210	P 27	D/D	No	1/128	1/32	12
2	B+	bu16/cy	Yes	14	—	0.27	—	1.08	8	19 ^a	10	Low	N	273	P 23	D/D	No	1/2	—	3
3	B+	bu8/cy	Yes	10	—	0.35	1.14	2.93	7	59	6.5	Low	N	318	P 26	D/D	A2s/Ce	1/512	1/128	6
4	B+	bu8/cy	Yes	9	0.17	3.46	0.3	9	4	45	9	N	N	705	P 28	D/D	A1	1/64	1/16	2
5	B+	bu8/cy	Yes	8	0.2	1.87	1	10	5	39	2.16	N	N	201	P 34	D/D	A1s	1/256	1/64	1
6	B+	bu8/cy	Yes	8	0.11	6.59	0.74	9.0	4	13 ^a	2.75	N	Low	795	P	D/R	No	—	1/256	29
7	B+	bu8/cy	Yes	7	0.17	7	0.75	5.25	3	57	2	N	N	480	P 26	D/m	No	—	1/256	2
8	B+	Nil	No	7	0.27	2.83	0.69	10	11	67	6	N	N	203	U 38	D/m	No	1/64	—	1
9	B+	Nil	No	5.5	0.09	3.1	0.1	1.7	3	3 ^a	5	Low	Low	700	U32	D/m	Cs/g	—	1/2	6
10	B+	Nil	No	3	0.44	7	2.63	9.0	15	25 ^a	2.33	N	N	242	S cord	D/m	No	1/2	1/1	1
11	B+	bu8/cy	Yes	5	0.27	0.72	1.11	9.0	4	31	3	N	N	417	P	D/R	No	1/64	1/32	1
12	CgC	bu8/cy	Yes	13	0.42	2.57	0.4	2.24	10	17 ^a	9	N	N	328	P 26	D/m	No	—	1/8	2
13	CgC	bu8/cy	Yes	9	0.07	2.5	1.5	9	26	132	4.33	Low	N	262	P 30	D/D	A2s	1/64	1/32	18
14	CgC	bu8/cy	Yes	8	0.4	1.87	1.78	10	3	3 ^a	5	Low	Low	445	P 36	D/m	A1	—	1/2	12
15	CgC	bu8/cy	Yes	5	0.16	2.59	1.6	9.5	6	17 ^a	3.66	Low	N	454	P 28	D/D	A1/Cl	—	1/1	12
16	CgC	bu8/cy	Yes ^b	4	0.11	4.91	0.53	6.09	1	3 ^a	3.5	N	Low	693	P 32	D/m	No	1/64	1/4	8
17	ADA	bu16/cy	Yes	13	0.12	0.65	0.54	5.68	4	14 ^a	9.5	Low	N	300	P 35	m/m	No	—	—	4
18	ADA	bu16/cy	Yes	6	0.05	7	0.92	9.5	3	53	3.5	N	N	49	U 43	D/m	A2s/Cl	1/1	1/2	15
19	ADA	Nil	No	4	0.05	7.0	1.71	5.83	6	137	2.58	N	Low	144	S 2	D/m	No	—	1/32	1
20	ADA	Nil	No	3	0.16	7.0	3.0	9.0	6	104	2	Low	N	116	U cord	D/m	No	1/4	1/4	4
21	RAG	bu8/cy	Yes ^b	2.33	0.66	5.81	0.4	9.0	3	71	2	N	N	302	P27	D/D	No	—	1/4	24
22	artemis	bu8/cy	Yes	6	0.2	1.9	0.74	4.6	3	135	4	Low	Low	88	P 22	D/R	No	1/64	—	7

CgC = common gamma chain deficiency; ADA = adenosine deaminase deficiency; B+ = B-cell positive SCID – molecular diagnosis unknown; RAG = recombination activating gene; bu8(16) = busulphan 8 (16) mg/kg; cy = cyclophosphamide 200 mg/kg; TCD = T-cell depletion; FU = length of follow-up; PPS = pneumococcal polysaccharide antibody; N = normal; donor: P = parent, S = sib, U = unrelated, cord = umbilical cord blood; chimerism: D = donor, R = recipient, m = mixed donor and recipient; GvHD = graft-versus-host disease, A = acute, C = chronic, 1,2 = grade 1,2, s = skin, l = liver, e = extensive; iso-haem = iso-haemagglutinin titre; low IgG2, IgA = <2 s.d. below the age-related normal mean value.

^aAbsent/poor response.

^bCD34+ stem cell selection.

Table 2 Non-SCID primary immunodeficient patient and BMT characteristics and responses to PPS vaccination

Patient	A	Conditioning	TCD	FU (years)	tet pre	tet post	Hib pre	Hib post	PPS pre	PPS post	time to pps	IgG2	IgA	B cells (µl)	Donor age (years)	Chimerism T/B cells	GvHD	Isohaem	Age at BMT (years)
23	WAS	bul6/cy	No	8	0.19	1.88	1.52	6.4	10	90	2.58	N	N	450	U 38	m/m	no	NR	3
24	WAS	bul6/cy	No	5	0.08	0.4	0.09	0.5	—	113	3.5	N	N	315	U 20	D/m	A/Cs	1/1	5.5
25	WAS	bul6/cy	No	3	0.06	0.2	0.9	1.7	10	69	1.5	N	N	1025	S 13	D/D	no	1/16	11
26	XLGG	bul6/cy	No	5	1	4	1.04	6.03	9	36	1.67	N	N	1200	S 5	m/m	A2s	—	4.5
27	XLGG	bul6/cy	No	4	—	4.9	2.5	10	5	191	1.17	N	N	217	S 16	m/D	no	—	14
28	CD40L	bul6/cy	Yes	6	0.05	7	0.3	9	5	18 ^a	4.58	N	N	1014	U 32	m/R	A1s	1/128	3
29	CD40L	bul6/cy	Yes ^b	2.5	—	2.09	—	4.3	3	25	1.67	Low	Low	1538	U	m/m	no	—	1.1
30	ZAP-70	bul6/cy	Yes	9	0.08	4	1.8	9.3	15	80	7	N	N	680	U 26	D/D	A1	—	1
31	HlgE	bul6/cy	No	6	0.07	4.03	0.5	9	6	32	4	N	N	591	U 41	D/D	A/C	1/64	7
32	NK cell	bul6/cy	No	3	0.36	6.54	—	9	9	39	1.58	N	N	385	S 10	D/D	no	1/16	8
33	CID	bul6/cy	No	7	0.14	7	2.72	5.85	46	> 125	2.58	N	Low	1156	S 2	D/m	no	1/32	1.5
34	CID/IL2	bul6/cy	No	5	0.2	2.56	2.04	9.5	10	156	2.33	N	N	225	U 42	D/D	A14	—	0.6

WAS = Wiskott-Aldrich Syndrome; XLGGD = X-linked chronic granulomatous disease; CD40L = CD40 ligand deficiency; ZAP-70 = ZAP-70 kinase deficiency; HlgE = hyper IgE syndrome; NK cell def = natural killer cell deficiency; CID/IL2 = combined immunodeficiency/interleukin 2 defect; bul6 = busulphan 16 mg/kg; cy = cyclophosphamide 200 mg/kg; TCD = T-cell depletion; FU = length of follow-up; PPS = pneumococcal polysaccharide antibody; N = normal; donor: S = sib, U = unrelated; chimerism: D = donor, R = recipient, m = mixed donor and recipient; GvHD = graft-versus-host disease, A = acute, C = chronic, 1,2 = grade 1,2, s = skin, l = liver, e = extensive; isohaem = isohaemaglutinin titre; low IgG2, IgA = <2 s.d. below the age-related normal mean value.
^aAbsent/poor response.
^bCD34+ stem cell selection.

Discussion

While the survival following BMT for PID is improving and survivors can look forward to normal growth, development and immunity, pneumococcal infection following BMT remains a problem in both adult and paediatric series with significant morbidity and mortality.^{12,13} A number of factors have been associated with this increased risk of pneumococcal infection including low IgG2 subclass¹³ and low pneumococcal antibody titres.¹⁴ Chronic GVHD in particular seems to lead to a depressed response to pneumococcal polysaccharide antigen post BMT.^{15,16} In this series, differences were not because of the age of the bone marrow donor. No differences in cell lineage specific chimerism were found, although B-cell microchimerism was not measured. Other recognised factors such as chronic GVHD and low IgG2 were not significantly different between the groups.

It is recognised that patients vaccinated less than 2 years post BMT may not respond to PPS antigen, as the donor immune system recapitulates normal infant immune maturation with delay of polysaccharide antibody response.¹⁷ All patients were vaccinated at least 2 years post BMT. The difference in response to PPS antigen between the two groups is not because of the length of follow-up. In fact the length of follow-up for the SCID group is longer than for the non-SCID group. We have demonstrated that non-SCID patients are more likely to make a response to PPS antigen than SCID patients post BMT. Previous studies looking at immune reconstitution following BMT for PID have documented good protein antigen responses, but have not specifically examined the response to polysaccharide antigen.⁹

There are a number of possible explanations for our findings. Firstly, differences in response to polysaccharide antigens between the two groups may be because of the type of immunodeficiency. Patients with SCID are born with an absence of T cells and sometimes B cells, whereas although other forms of PID may have dysfunctional T cells or dysfunctional myeloid-derived cells, there is generally some preserved lymphoid function. Our series was too small to tease out differences between the SCID subtypes that might identify important cellular phenotypes in determining PPS antibody responses. There is evidence to suggest that in SCID patients, even with normal donor T-cell function, recipient B cells remain dysfunctional or nonfunctioning.¹⁸ B-cell microchimerism was not analysed and it may be that in the SCID group, a subset of polysaccharide-specific B cells remain of recipient rather than donor origin, and so are unable to respond to polysaccharide antigen.

Secondly, chemotherapeutic cytoreductive conditioning may damage thymic epithelium and so adversely affect subsequent donor-derived T-cell development.¹⁹ Although antipolysaccharide antibody responses are classically described as T-cell independent responses, there is increasing evidence to show that in humans at least, T cells are important in mounting a polysaccharide antibody response.²⁰ However, all patients had adequate classical protein T-cell dependent antibody responses and furthermore, all the non-SCID patients who have normal antipolysaccharide responses received chemotherapy.

Thirdly, marrow TCD may play an important role in the subsequent immune development. In the non-SCID group, two of three patients receiving TCD marrow responded to PPS antigen compared to nine of 17 patients receiving TCD marrow in the SCID group. Although there was not a significant difference between the groups, the numbers of patients analysed in this group, particularly of SCID patients receiving whole marrow, are small, and so the results need to be interpreted with caution. The process of TCD may remove key stromal cells which are important in the initial innate part of the immune response. However all, but two, of our TCD BMTs were with Campath 1 M, which should leave stromal cells intact.²¹ Although chemotherapy conditioning may affect stromal cells, all the non-SCID group with normal antipolysaccharide responses received chemotherapy.

This is the first study to specifically examine the PPS antibody response in children transplanted for PID and only looked at PPS IgG responses. Both patient groups make IgM responses to red blood cell isoagglutinin antigens, implying ability to mount an IgM response to polysaccharide antigen. Further studies are required in these patients to examine the antibody response against other polysaccharide antigens such as meningococcus. If a defective IgG response to these antigens is confirmed, a defect in polysaccharide-specific IgM to IgG isotype switch would be suggested. Further areas for investigation include examining the avidity of PPS antibody made in the SCID group. Finally, the response to pneumococcal conjugate vaccine in this group of children should be examined.

References

- Ryser O, Morell A, Hitzig WH. Primary immunodeficiencies in Switzerland: first report of the national registry in adults and children. *J Clin Immunol* 1988; **8**: 479–488.
- Antoine C, Miller S, Cant AJ *et al*. Long term survival and hematopoietic stem-cell transplantation for immunodeficiencies: a survey of the European experience (1968–1999). *Lancet* 2003; **361**: 553–560.
- Haddad E, Landais P, Friedrich W *et al*. Long-term immune reconstitution and outcome after HLA-nonidentical T-cell-depleted bone marrow transplantation for severe combined immunodeficiency: a European retrospective study of 116 patients. *Blood* 1998; **91**: 3646–3653.
- Fischer A, Landais P, Friedrich W *et al*. Bone marrow transplantation (BMT) in Europe for primary immunodeficiencies other than severe combined immunodeficiency: a report from the European group for BMT and the European group for immunodeficiency. *Blood* 1994; **83**: 1149–1154.
- Gennery AR, Dickinson AM, Brigham K *et al*. CAMPATH-1 M T cell depleted bone marrow transplantation for severe combined immunodeficiency: long term follow up of 19 children treated in the period 1987–1998 in a single centre. *Cytotherapy* 2001; **3**: 221–232.
- Velardi A, Cucciaioni S, Terenzi A *et al*. Acquisition of Ig isotype diversity after bone marrow transplantation in adults. *J Immunol* 1988; **141**: 815–820.
- Avanzini MA, Carra AM, Maccario R *et al*. Antibody response to pneumococcal vaccine in children receiving bone marrow transplantation. *J Clin Immunol* 1995; **15**: 137–144.
- Engelhard D, Cordonnier C, Shaw PJ *et al*. On behalf of the Infectious Disease Working Party of the European Bone Marrow Transplantation (IDWP-EBMT). Early and late invasive pneumococcal infection following stem cell transplantation: a European Bone Marrow Transplantation survey. *Br J Haematol* 2002; **117**: 444–450.
- Haddad E, Le Deist F, Aucouturier P *et al*. Longterm chimerism and B cell function after bone marrow transplantation in patients with severe combined immunodeficiency with B cells: a single centre study of 22 patients. *Blood* 1999; **94**: 2923–2930.
- Peltola H, Kayhty H, Virtanen M, Makela PH. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type B. *J Infect Dis* 1983; **147**: 1100.
- Griffiths H, Lea J, Bunch C *et al*. Predictors of infection in chronic lymphocytic leukaemia (CLL). *Clin Exp Immunol* 1992; **89**: 374–377.
- Winston JD, Schiffman G, Wang DC *et al*. Pneumococcal infections after human bone marrow transplantation. *Ann Intern Med* 1979; **91**: 835–841.
- Sheridan JF, Tutschka PJ, Sedmak DD, Copelan EA. Immunoglobulin G subclass deficiency and Pneumococcal infection after allogeneic bone marrow transplantation. *Blood* 1990; **75**: 1583–1586.
- Giebink GS, Warkentin PI, Ramsay NKC, Kersey JH. Titers of antibody to pneumococci in allogeneic bone marrow transplant recipients before and after vaccination with pneumococcal vaccine. *J Infect Dis* 1986; **154**: 590–596.
- Hammarstrom V, Pauksen K, Azinge J *et al*. Pneumococcal immunity and response to immunization with pneumococcal vaccine in bone marrow transplant patients: the influence of graft versus host reaction. *Support Care Cancer* 1993; **1**: 195–199.
- Witherspoon RP, Storb R, Ochs HD *et al*. Recovery of antibody production in human allogeneic marrow graft recipients: Influence of time posttransplantation, the presence or absence of chronic graft-versus-host disease, and anti-thymocyte globulin treatment. *Blood* 1991; **58**: 360–368.
- Rijkers GT, Sanders LAM, Zegers BJM. Anti-capsular polysaccharide antibody deficiency states. *Immunodeficiency* 1993; **5**: 1–21.
- White H, Thrasher A, Veys P *et al*. Intrinsic defects of B cell function in X-linked severe combined immunodeficiency. *Eur J Immunol* 2000; **30**: 732–737.
- Min D, Taylor PA, Panoskaltis-Mortari A *et al*. Protection from thymic epithelial cell injury by keratinocyte growth factor: a new approach to improve thymic and peripheral T-cell reconstitution after bone marrow transplantation. *Blood* 2002; **99**: 4592–4600.
- Griffioen AW, Toebes EAH, Rijkers GT *et al*. The amplifier role of T cells in the human *in vitro* B cell response to type 4 pneumococcal polysaccharide. *Immunol Lett* 1992; **32**: 265–272.
- Hale G, Waldmann H. CAMPATH-1 monoclonal antibodies in bone marrow transplantation. *J Hematother* 1994; **3**: 15–31.