Mesenchymal stem cells expanded *in vitro* with human serum for the treatment of acute and chronic graft-*versus*-host disease: results of a phase I/II clinical trial

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ABSTRACT

This trial evaluated the feasibility and efficacy of the infusion of mesenchymal stem cells expanded using human serum for the treatment of refractory acute or chronic graft-*versus*-host disease. Twenty-eight expansions were started. In 22, a minimum of more than $1x10^6$ mesenchymal stem cells/kg were obtained after a median of 26 days; this threshold was not obtained in the remaining cases. Ten patients received cells for the treatment of refractory or relapsed acute graft-*versus*-host disease and 8 for chronic disease. One patient treated for acute graft-*versus*-host disease obtained a complete response, 6 had a partial response and 3 did not respond. One of the chronic patients achieved complete remision, 3 a partial response, and 4 did not respond. The current study supports the use of this approach in less heavily treated patients for both acute and chronic graft-*versus*-host disease. The trial has been registered at *ClinicalTrials.gov: identifier NCT00447460.*

Key words: mesenchymal stem cells, graft-*versus*-host disease, allogeneic stem cell transplant.

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Introduction

Mesenchymal stem cells (MSCs) are multipotent stem cells that can differentiate into osteoblasts, adipocytes and chondrocytes.[1] MSCs appear to be immunosuppressive *in vitro* and inhibit T-cell responses[2,3] as well as modulate B-lymphocyte proliferation and differentiation.[4]

Several clinical trials have been designed in an attempt to explore their therapeutic potential in acute graft-*versus*-host disease (GVHD),[5,6] while the information available on the efficacy of MSCs in the chronic GVHD setting is far more limited[7] (*www.clinicaltrials.gov*). We have previously shown that the expansion of MSC using human serum is feasible,[8] and their immunomodulatory properties were preserved and comparable with MSC expanded using FCS. In order to prevent viral or prion contamination, we designed a phase I/II clinical trial in order to evaluate the potential benefit of the infusion of MSC expanded using human serum (HS) among patients diagnosed with either refractory acute or chronic graft-*versus*-host disease. (*Code: CSM/EICH2005; N EudraCT: 2005-003674-14, PEI: 06-076, ClinicalTrials.gov identifier NCT00447460*).

Design and Methods

Mesenchymal stem cell collection and expansion

MSCs were obtained from 30-50 mL of bone marrow from healthy donors of patients who had previously failed treatment once informed consent for donation had been obtained. The method and results of the procedure are shown in the *Online Supplementary Appendix*. Among patients receiving related donor transplants, MSCs were obtained from the same family donor, while for patients receiving an unrelated donor transplant, a related haploidentical donor or a mismatched unrelated donor was used. One day before the harvest, a plasmapheresis was planned in order to obtain 1,500-2,000 mL of HS as previously reported, which was used for the *in vitro* MSC expansion. Overall, 28 expansions were started although MSCs were not infused in 11 cases. Reasons for not infusing the cells are summarized in Table 1.

The online version of this article has a Supplementary Appendix.

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MSC expansion procedure, cell characterization and obtaining platelet lysate were performed according to standard procedures and are shown in the *Online Supplementary Appendix*.

Patients' characteristics and MSC infusion

Overall, 18 patients diagnosed with either acute (n=10) or chronic (n=8) GVHD refractory to prior treatment were included in the study once written informed consent had been obtained. Refractory GVHD was defined as progression or absence of response to last treatment. Patients' characteristics are summarized in Table 2. Eleven patients had received reduced intensity conditioning and 6 received myeloablative conditioning. Fourteen patients had received hematopoietic stem cells from an unrelated donor and 7 received them from an HLA-mismatched donor. Eight patients had received GVHD prophylaxis based on a calcineurin inhibitor plus methotrexate.

Inclusion criteria were: patients who had undergone an allogeneic stem cell transplant and developed GVHD refractory to conventional treatment; adequate cardiac and pulmonary functions; aged between 18 and 65 years; signed informed consent from patient and donor. Exclusion criteria were: patients who did not fulfill all of the inclusion criteria; progression of the hematologic disease; active infection; women who were either pregnant or at risk of pregnancy. The study was conducted between February 2007 and December 2009.

Patients received 1-2x10^6 MSCs/kg intravenously in a single dose. Eventually, when a partial response was obtained or in the case of relapse after achieving complete remission, patients could receive a second dose of MSCs at least two weeks after the first infusion. Patients who were receiving 6-methylprednisolone were kept on the same doses for at least seven days after MSC infusion and a taper of 10% every five days was planned later when there was a response. Other immunosuppressive drugs were managed according to the criteria of the attending physician. Response to therapy was measured according to previously reported criteria.[9-11]

Patients were taken off the study if fewer than 1x10^6 MSCs/kg were obtained after eight weeks of expansion. All patients receiving at least one dose of MSCs were included in the safety and efficacy analysis.

The treatment protocol was reviewed and approved by the local authorities and ethical committee of all participanting centers.

Table 1. MSC expansion.

ID	Culture medium	Total α number	Days of Culture	Type of donor	Donor sex/age	Infused yes/no	Reason for not infusing
12	AS + PL	0.00	60	haploidentical	F/48	No	Not expanded
5	AS	6	15	MRD	F/61	No	Death prior to expansion (*)
11	AS	15	34	haploidentical	M/41	Yes	
9	AS	38	25	haploidentical	M/50	Yes	
8	AS	40	13	haploidentical	M/39	No	Death prior to expansion (*)
6	AS	44	33	MRD	F/65	No	Death prior to expansion (*)
7	AS	53	33	MRD	M/38	Yes	
3	AS	56	43	haploidentical	F/50	No	Death prior to expansion (*)∞
23	AS + PL	69	24	MRD	M/67	No	Response to prior therapy
13	AS + PL	79	47	haploidentical	M/56	Yes	
1	AS	100	25	haploidentical	F/44	Yes	
14	AS + PL	100	33	haploidentical	M/47	Yes	
18	AS	119	35	haploidentical	F/42	Yes	
15	AS	132	23	haploidentical	F/33	No	Relapse
16	AS	150	27	haploidentical	F/37	Yes	
17	AS	178	27	haploidentical	M/42	No	Response to prior therapy
4	AS	180	30	haploidentical	M/48	Yes	
2	AS	186	36	haploidentical	M/42	Yes	
21	AS	245	30	MRD	M/57	Yes	
19	AS	268	23	haploidentical	F/33	No	Response to prior therapy
20	AS	335	24	haploidentical	M/44	Yes	
22	AS	350	26	haploidentical	F/29	Yes	
27	AS	350	20	haploidentical	M/55	Yes	
25	AS + PL	410	19	MRD	M/40	Yes	
28	AS + PL	450	29	MMURD	M/33	No	Response to prior therapy
24	AS + PL	520	26	MRD	M/40	Yes	
29	AS	792	17	MRD	M/51	No	Death prior to expansion (¥) ∞
26	AS + PL	884	26	MMURD	F/53	Yes	

AS: autologous serum; PL: platelet lysate; MRD: matched related donor; MMRUD: mismatched unrelated donor; F: female; M: male; (∞) MSCs were finally infused into a different patient after informed consent had been obtained; (*) cause of death: GVHD progression; (¥) death due to infection; (α): total number ×10^6.

Statistical analysis

Variables of the expansion procedure were analyzed from the day of inclusion in the trial, i.e. the day when informed consent was signed. Mean and median values and their corresponding 95% confidence intervals (CIs) and ranges were calculated for each continuous variable. Student's two-sample t test and Pearson's X^2 test were used to compare continuous and qualitative variables. In those comparisons where the number of cases precluded the use of parametric tests, the Mann-Whitney test and Fisher's exact test were used. To analyze patient outcome after infusion, events were calculated from the time of MSC infusion. GVHD related mortality was defined as *death due to causes directly related to GVHD* and those deaths attributed to immunosuppression in patients requiring treatment for GVHD were also considered as GVHD related mortalities.

SPSS (version15.0; SPSS Inc, Chicago, IL, USA) was used for most of the statistical analyses. Computations and testing of cumulative incidences were performed with the cmprsk routine in R (version 1.9.1).

Differences were considered to be statistically significant when two-tailed values of $P < 0.05$ were obtained.

Results

In vitro *expansion of MSC*

Overall, 28 expansions were started. In 2 of them, a minimum of more than $1x10^6$ MSCs/kg recipient body weight were obtained after a median period of 26 days (range 15-47 days), while the threshold was not obtained after eight weeks of culture in the other 6 cases (Table 1). In 5 out of 20 cases expanded using AS, the final threshold was not reached, compared with one out of 8 cases expanded using AS plus PL (P=0.4), although it should be noted that PL was used only for those cases that had poor expansion kinetics. No significant differences were observed in the number of cells expanded with respect to the sex or type of the donor.

Table 2. Patients' characteristics (N=18).

Patient ID	a/c GVHD	Sex/Age	Conditioning regime	Stem cell source	Type of donor	HLA	GVHD prophylaxis
1	Acute	F/50	RIC	PB	Unrelated	Matched	CSA+MMF
2	Chronic	M/45	RIC	BM	Unrelated	Mismatched	CSA+MMF
4	Acute	F/21	RIC	BM	Unrelated	Mismatched	Tacro+MMF
7	Chronic	F/63	RIC	PB	Unrelated	Mismatched	Tacro + MMF
9	Acute	M/43	RIC	BM	Unrelated	Mismatched	Tacro + MTX + ATG
11	Chronic	M/37	Myelo	PB	Unrelated	Matched	CSA + MTX
13	Chronic	M/31	Myelo	PB	Unrelated	Matched	Tacro + MTX
14	Chronic	M/21	Myelo	BM	Unrelated	Mismatched	CSA + MTX
16	Acute	F/43	RIC	PB	Unrelated	Matched	Tacro + MTX +ATG
18	Chronic	F/66	RIC	PB	Related	Matched	CSA + MTX
20	Chronic	F/32	RIC	PB	Related	Matched	CSA + MTX
21	Chronic	F/52	Myelo	PB	Related	Matched	Tacro + MMF
22	Acute	M/29	Myelo	BM	Unrelated	Mismatched	Tacro + MTX
24	Acute	F/31	Myelo	PB	Related	Matched	CSA + MTX
25	Acute	M/21	Myelo	PB	Unrelated	Matched	CSA + MTX
26	Acute	M/62	RIC	PB	Unrelated	Matched	Tacro + Rapa
27	Acute	F/24	RIC	PB	Unrelated	Matched	None
29	Acute	M/49	RIC	PB	Unrelated	Mismatched	Tacro + Rapa

Response and outcome

Table 3 shows the type of GVHD and line of treatment. In the aGVHD setting, 5 patients received a single infusion, while one patient each received two and three infusions, and 3 patients received four infusions after having obtained partial response to the first infusion. None of those patients receiving more than one dose showed a better quality response. One patient obtained complete remission, 6 obtained partial response, and 3 patients did not respond to MSC infusion. At final follow up, 2 patients were alive and 8 had died, 2 due to GVHD and the others from causes different from other than GVHD.

Table 3 shows data concerning refractory cGVHD. Four patients received MSC as second-line and 4 patients as at least third-line treatment. Four patients received a single dose, 3 received two doses and one patient received three doses of MSCs. The median dose of cells infused was $2x10^6$/kg (range 0.3-$3.7x10^6$/kg). One patient achieved complete remission, 3 showed a partial response and 3 did not respond. Notably, the patient who achieved complete remission had severe thrombocytopenia that resolved after MSC infusion and remained in complete remission at the time of writing; however, 2 patients obtaining a partial response subsequently relapsed.

Discussion

Several clinical trials have already shown the feasibility and efficacy of MSC infusion in patients diagnosed with graft-*versus*-host disease.[5-7] However, these trials used MSCs expanded using fetal calf serum, which could potentially favor the transmission of zoonoses. As we have previously reported, human autologous serum represents a good alternative that allows for the expansion of MSCs[8] with biological characteristics similar to those expanded in the presence of FCS. Thus, the current trial provides confirmation in the clinical setting that expansion of MSCs is feasible and may yield enough MSCs without FCS, although the addition of platelet lysate to the autologous serum may increase the number of expanded cells in those few cases with slow growth kinetics. This finding is consistent with those of previous *in vitro* studies[12-16] and a clinical trial using this approach has already been reported.[17]

No severe adverse event was observed either among donors or among patients during or after the infusion of MSCs. While several patients developed infectious episodes after MSC administration, its occurrence in 4 of the 10 patients with refractory acute GVHD is not an unusually high incidence of infection in this setting. No infectious episodes were reported among the 8 patients treated for chronic GVHD so the MSCs did not appear to increase the risk in this subset of patients. As regards efficacy of the procedure, among patients diagnosed with acute GVHD, one patient achieved and maintained complete remission while only 3 patients did not respond. Given the very high risk encountered by the patients in our trial and the many prior lines of therapy, this response rate is encouraging. However, this did not translate into

better survival, largely due to the severe performance status of the patients.

The poor prognosis of aGVHD refractory to steroids has led to the search for new treatments but, even though some groups have reported promising results in terms of response, long-term overall survival remains in the range of 5-15% in this subset of patients.[18,19] Regarding cGVHD, again a number of immunosuppressive agents have demonstrated some activity, but most of these treatment options have not been systematically investigated, patients' characteristics vary greatly between studies and evidence is limited to phase II trials. Accordingly, a com-

Table 3. Outcome of patients receiving MSCs for acute/chronic GVHD.

ID patient	Organ involvement and global grade	Line of treatment	Number of cells infused x10^6/kg (1st)	Number of cells infused x10^6/kg (2nd)	Number of cells infused x10^6/kg (3rd)	Number of cells infused x10^6/kg (4th)	Response to MSC	Duration of the response	Status at last follow up	Cause of death
1 aGVHD	Gut IV	4	1.6				No response	-	Dead	GVHD
4 aGVHD	Skin, liver, gut III	3	1.6	1.6			PR	1 month	Dead	Relapse
9 aGVHD	Gut IV	3	0.6				PR	3 days*	Dead	VOD
16 aGVHD	Gut II	3	1.3	1.3	1.0	0.7	PR	1 month	Dead	Infection[a]
22 aGVHD	Skin, gut III	4	1.1	1.1	1.1	1.0	PR	1 month	Dead	Infection[b]
24 aGVHD	Skin, gut IV	5	1.8	2.9			No response	-	Dead	GVHD, relapse, multiorgan failure
25 aGVHD	Gut II	3	2.9	1.6			No response	-	Dead	Infection, multiorgan failure
26 aGVHD	Skin, gut, liver II	3	1.0	1.0	1.09		PR	2 weeks*	Dead	Sepsis[d]
27 aGVHD	Gut IV	3	0.9	0.9	0.9	0.9	PR	1 week	Dead	Sepsis[d]
29 aGVHD	Gut III/IV	3	1.1	1.20			CR	11 months **	Alive	
2 cGVHD	Gut severe	3	1.20	1.04			PR	3 months	Dead	Liver biopsy
7 cGVHD	Skin, mouth, gut, liver moderate/ severe	6	0.6				NR	-	Dead	GVHD
11 cGVHD	Ocular, skin mouth, gut Severe	2	0.20				PR	1 year	Alive	
13 cGVHD	Mouth, Thrombocytopenia slight	3	0.80				CR	1 year **	Alive	
14 cGVHD	Skin, gut Severe	4	0.80		1.20		NR	-	Dead	Toxicodermia
18 cGVHD	Muscleskeletal, gut Severe	3	1.05	1.05			PR	5 months	Alive	
20 cGVHD	Muscleskeletal, skin Severe	5	0.80	0.80	1.05	1.05	NR	-	Alive	
21 cGVHD	Skin, gut Severe	3	1.01				NR	-	Alive	

**Until exitus; **Until last follow up; - No response; pneumonia two months after the last infusion of MSCs; pulmonary aspergillosis one month after the last dose of MSCs; (a) aspergillus and adenoviral reactivation more than two months after the last infusion of MSCs; (b) sepsis due to* E. coli.

parison of the results from the current study and other approaches is not feasible.[20]

There is little published information about the use of MSCs in the treatment of cGVHD and no clinical trials have been performed in this setting. The current study includes the largest number of patients treated with MSC for cGVHD. Remarkably, 3 patients showed a partial response and one achieved complete remission. The latter had mucosal involvement plus life-threatening thrombocytopenia that resolved after a single dose of MSCs. We have previously reported that patients with immune thrombocytopenic purpura had functional abnormalities in MSCs, which may influence the physiopathology of the disease and could support the use of MSCs for the treatment of these patients.[21]

In conclusion, the current study is the first clinical trial to evaluate the feasibility and safety of MSCs expanded *in vitro* using autologous serum for the treatment of acute and chronic GVHD. In terms of MSC expansion, this procedure yields enough cells in most cases, although the addition of platelet lysate may improve the growth kinetics. No adverse events could be directly attributed to the MSCs. The current study supports the development of new trials focused on the use of this approach in less heavily treated patients in order to confirm the efficacy of the procedure and its impact on outcome.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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