Autologous Hemopoietic Stem Cell Transplantation in Severe Rheumatoid Arthritis: A Report from the EBMT and ABMTR

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ABSTRACT. ***Objective.*** Since 1996, autologous hemopoietic stem cell transplantation (HSCT) has been used to treat severe rheumatoid arthritis (RA). To date, published reports have been individual cases or series containing small numbers. This study combined the worldwide experience in a single analysis.

Methods. The Autoimmune Disease Databases of the European Group for Blood and Marrow Transplantation (EBMT) and the Autologous Blood and Marrow Transplant Registry (ABMTR) were used to identify patients with RA treated with autologous HSCT. Further information relating to patient and treatment-specific variables was obtained by questionnaire.

Results. Seventy-six patients were registered from 15 centers. Seventy-three patients had received autologous HSCT, and in 3 patients hematopoietic stem cells (HSC) were mobilized but not transplanted. Transplanted patients (median age 42 yrs, 74% female, 86% rheumatoid factor positive) had been previously treated with a mean of 5 (range 2–9) disease modifying antirheumatic drugs (DMARD). Significant functional impairment was present, with a median Health Assessment Questionnaire (HAQ) score of 1.4 (range 1.1–2.0) and Steinbrocker score mean 2.39 (SD 0.58). The high dose treatment regimen was cyclophosphamide (CYC) alone in the majority of patients, mostly 200 mg/kg (n = 62). Seven patients received anti-thymocyte globulin (ATG) in addition to CYC, 2 patients busulfan and CYC (BuCYC), and one patient CYC with total body irradiation and ATG. One patient received fludarabine with ATG. Following treatment, one patient received bone marrow but the rest received chemotherapy and/or granulocyte colony-stimulating factor mobilized peripheral blood stem cells. The harvest was unmanipulated in 28 patients, the rest receiving some form of lymphocyte depletion, mostly through CD34+ selection. Median followup was 16 months (range 3–55). Responses were measured using the American College of Rheumatology (ACR) criteria. Forty-nine patients (67%) achieved at least ACR 50% response at some point following transplant. There was a significant reduction in the level of disability measured by the HAQ ($p < 0.005$). Most patients restarted DMARD within 6 months for persistent or recurrent disease activity, which provided disease control in about half the cases. Response was significantly related to seronegative RA ($p = 0.02$) but not to duration of disease, number of previous DMARD, presence of HLA-DR4, or removal of lymphocytes from the graft. There was no direct transplant related mortality, although one patient, treated with the BuCYC regimen, died 5 months post-transplant from infection and incidental non-small cell lung cancer.

Conclusion. Autologous HSCT is a relatively safe form of salvage treatment in severe, resistant RA. In these open label studies significant responses were achieved in most patients, with over 50% achieving an ACR 50 or more response at 12 months. Although the procedure is not curative, recurrent or persistent disease activity may be subsequently controlled in some patients with DMARD. Clinical trials are necessary to develop this approach in patients with aggressive disease who have failed conventional treatment including anti-tumor necrosis factor agents. (J Rheumatol 2004; 31:482–8)

Key Indexing Terms:
AUTOLOGOUS TRANSPLANTATION STEM CELLS RHEUMATOID ARTHRITIS

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Rheumatoid arthritis (RA) is the most common systemic autoimmune disease, affecting about 1% of the population. A minority of patients have severe disease that is not controlled by conventional treatments. In the short term, uncontrolled RA results in pain and stiffness, while longterm consequences are irreversible joint destruction, disability, reduced quality of life, and a shortened life expectancy. The economic costs are considerable, not only to the individual but also to the community[1,2].

Over the last 3 decades, animal experiments and serendipitous human data have supported a role for various types of stem cell transplantation in autoimmune diseases, including RA[3-5]. While the risks of allogeneic hemopoietic stem cell transplantation (HSCT) have remained too high for treatment of RA, pilot studies of autologous HSCT have continued in patients with severe RA since 1996[6-18]. To date, most reports are of single cases or small series. However, most patients have been additionally registered in databases of the European Group for Blood and Marrow Transplantation (EBMT) or the Autologous Blood and Marrow Transplant Registry (ABMTR) with a view to retrospective analyses of larger groups of patients. The aim of this study was to analyze the combined world experience of treating severe RA with intensive therapy and autologous HSCT.

MATERIALS AND METHODS

Study design. Patients who had received autologous HSCT for RA were registered by transplant centers in either the EBMT International Autoimmune Disease Stem Cell Database in Basel, Switzerland, or in the ABMTR Autoimmune Disease Database in Milwaukee, USA.

In 2000, data collection forms were sent out to all centers. The following patient related data were collected: age, sex, date of stem cell mobilization, rheumatoid factor (RF) status, HLA typing where available, Steinbrocker score, number of previous disease modifying antirheumatic agents (DMARD), and the duration of the disease prior to HSCT. The following treatment related data were collected: date and nature of mobilization regimen, date and nature of transplant preparative regimen, and the nature of any graft manipulation (i.e., CD34 selection, T cell depletion). The following outcome measures were requested: mortality and serious morbidity, American College of Rheumatology (ACR) response criteria[20,21], the score on the disability of the Health Assessment Questionnaire (HAQ)[22], and tender joint counts and RF titers at 3, 6, 12, 18 and 24 months post-transplant. Correspondents were also asked to broadly indicate whether there had been an increase in disease activity post-HSCT, whether this was the same as/better/worse than the pretransplant activity, and whether the response to the reintroduction of DMARD was the same as/better/worse than prior to transplant.

Statistical analysis. Descriptive methods with graphical display were used to summarize the dataset. Where comparison of groups was necessary, chi-squared tests and Wilcoxon rank sum tests were used to test significance.

RESULTS

Registrations. Over the period 1996 to 2000, there were 76 registrations. Patients had been treated on a number of different single and multicenter protocols. The eligibility criteria and treatment schedule varied between individual protocols. Seventy-three patients underwent high dose cytotoxic therapy and autologous HSCT. The additional 3 patients were mobilized but not transplanted; one failed to mobilize sufficient stem cells and 2 refused to proceed with treatment. One patient underwent 2 transplant procedures. All patients were treated within the context of phase I/II pilot studies with local ethical committee approval and informed consent. The demographics of the group are summarized in Table 1.

Transplanted patients had been treated with a mean of 5 DMARD in total, including combinations. Four of 73

Table 1. Summary of patient data.

Patient demographics	
Sex, female	54 (74%)
Age, yrs	42 (22–63)
Duration of disease, yrs	8 (2–20)
No. previous DMARD	5 (2–9)
Rheumatoid factor positive	59 (86%)
HLA-DR4	27/39 (69%)
Stem cell source	
Peripheral blood	72
Bone marrow	1
Mobilization regimen	
CYC + G-CSF ± other	31
G-CSF alone	41
Transplant preparative regimen	
CYC 100 mg/kg	3
CYC 200 mg/kg	59
CYC 200 mg/kg + ATG	7
CYC 200 mg/kg + ATG + TBI 4 Gy	1
Bu 16 mg/kg, CYC 120 mg/kg	2
Fludarabine + ATG	1
Graft manipulation	
None	28
CD34 selection	40
CD34 selection + T cell purging	4
Chemotherapy	1

CYC: cyclophosphamide; Bu: busulfan. G-CSF: granulocyte-colony stimulating factor.

patients had failed anti-tumor necrosis factor (TNF) agents. Significant functional impairment was present based on HAQ and Steinbrocker scores. Sixty-seven out of 68 evaluable patients were reported as having destructive arthritis. A minority had other organ involvement including ocular complications in 3, pulmonary complications in 2, and other extraarticular manifestations of rheumatoid disease in 5.

Transplant Techniques

Autologous graft. Peripheral blood stem cells were the source of hematopoietic stem cells (HSC) in all but one patient who received bone marrow. HSC were mobilized with either granulocyte colony-stimulating factor (G-CSF) alone or in combination with priming doses of chemotherapy, i.e., cyclophosphamide (CYC) 2 to 4 g/m^2 ± etoposide 300 mg/m^2. Harvested cells were either left unmanipulated or underwent CD34 selection ± additional T cell purging. The harvest of one patient was treated with chemotherapy to remove lymphocytes. Flare of RA was reported to occur in 8/56 patients (15%) in association with the mobilization procedure (with 4/23 evaluable in the CYC and G-CSF group and 4/30 evaluable in the G-CSF-only group). The mobilization procedure was reported to have reduced disease activity in 8/54 patients (15%).

Cytotoxic regimen. Patients received a variety of cytotoxic regimens. The majority received CYC 200 mg/kg, although this was combined with anti-thymocyte globulin (ATG) ± total body irradiation (TBI) in some cases (Table 1). Three patients received a lower dose of CYC at 100 mg/kg. Two patients received the more intensive BuCYC regimen (busulfan 16 mg/kg and CYC 120 mg/kg). One patient received an intensely immunosuppressive but less myelosuppressive regimen consisting of fludarabine and ATG.

Disease Outcomes

Mortality. There was a single post-transplant death from sepsis and an incidental non-small cell lung cancer occurring at 5 months post-transplant in a patient who had been treated with the BuCYC regimen and a highly purified autograft. The carcinoma was not considered by the investigators to be a late tumor effect due to the conditioning regimen. There was no mortality in patients treated with high dose CYC ± ATG or TBI.

Responses

ACR response, tender joint count, and HAQ score. ACR responses are summarized in Figure 1A. This indicates that at each time point substantial numbers of patients achieved the clinically significant ACR responses of 50, 70, 100 (complete remission) and the responses are sustained, at least for 18 months of followup. It should be stressed that these ACR responses were assessed in an open label setting and therefore are susceptible to reporting bias. In terms of the best ACR response, 3 patients achieved complete remission, 33 patients achieved an ACR 70, 13 patients ACR 50, 12 patients ACR 20, and 12 patients had no response.

At 6 months post-transplant (Figure 1B), slightly more than half of the evaluable patients with an ACR response of 50 or more had not restarted DMARD. The proportion of patients still not taking DMARD at 12 months post-transplant (Figure 1C) had slightly increased, but one-half of evaluable patients with ACR 70 or more remained free of DMARD treatment.

In view of the use of different joint count scales, the tender joint counts were transformed into percentage change from baseline. There was a significant reduction at all time points out to 18 months ($p = 0.0001$ at all time points to 18 months; Figure 2).

There was a significant reduction in the HAQ score at all time points to 18 months compared with baseline ($p < 0.005$ at all time points to 18 months; Figure 3).

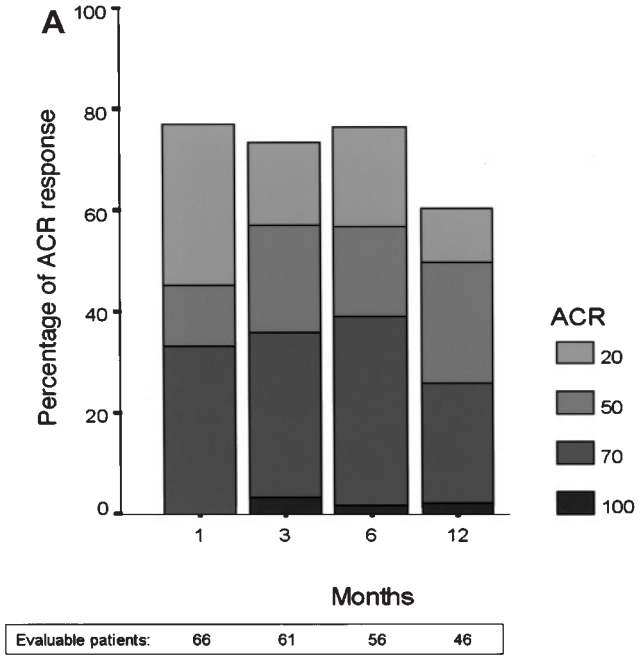
Other responses. Disease activity occurred at some stage in the post-transplant followup period in most evaluable patients (n = 58/63, 92%). Disease activity at the time of such relapse was described as being less than baseline in 20, the same as baseline in 25, and worse than baseline in 6. Data relating to reintroduction of DMARD were available only in a limited number of patients. By 6 and 12 months, 20/32 (63%) and 17/23 (74%) patients, respectively, were confirmed to have restarted some form of DMARD. In the evaluable patients who restarted DMARD post-transplant, the response was described as being better than prior to transplant in 21/43 (49%) and as being the same or worse in 22/43 (51%).

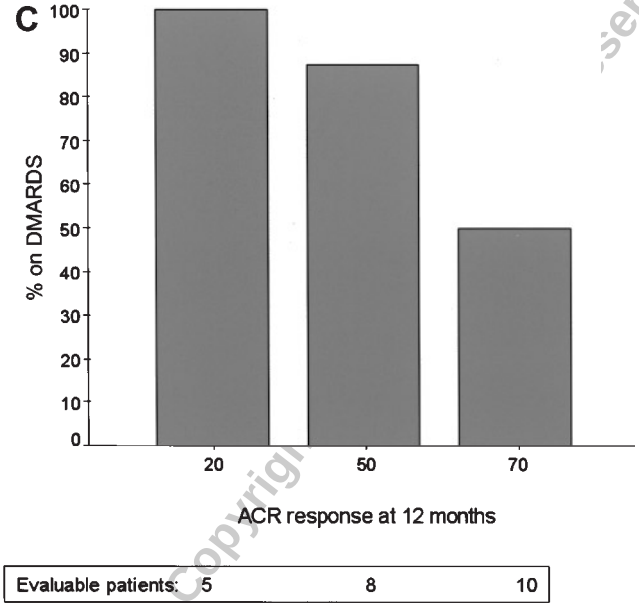
It was not possible to analyze certain data collected, i.e., joint counts and RF concentrations, because contributing centers had used different types of scales. However, relative changes in these variables are incorporated in the reported ACR response criteria.

Comparison of high and low responders. In order to look for factors that might influence response to treatment, the groups were divided into low and high responders depending on whether they achieved at least an ACR 50 at any point in their followup post-transplant. Chi-squared tests were used to test for significant differences. The following groups were analyzed according to response: duration of disease (< 100 months or not), RF positive or not, HLA-DR4 present or not, previous types of DMARD < 4 or not, mobilization with chemotherapy and G-CSF or G-CSF alone, and any graft manipulation performed or not.

Numbers of patients in each group are summarized in Table 2. The only factor significantly related to response was the presence of RF. The analysis suggests that the response is significantly better for RF negative patients compared with RF positive patients ($p = 0.02$).

Based on the evaluable patient data, 14% of seronegative patients were receiving DMARD at 6 months post-transplant in contrast to 69% of seropositive cases ($p = 0.01$,





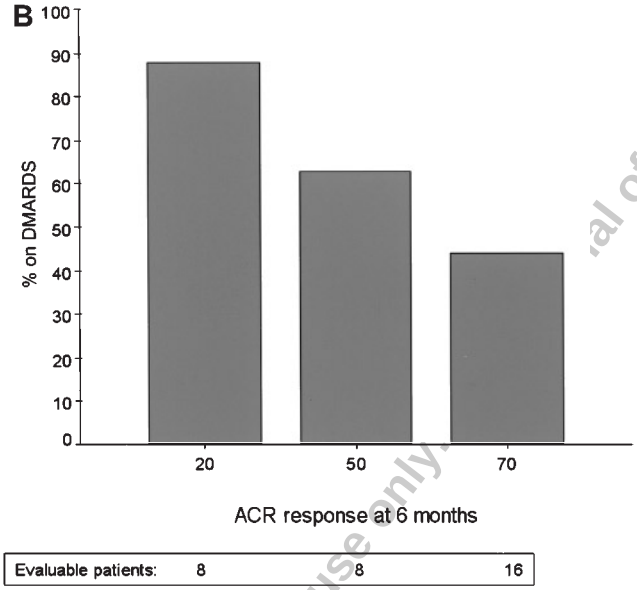


Figure 1. A. ACR responses expressed as percentage of evaluable patients at certain time points post-ransplant. B. Percentage of evaluable patients taking DMARD at 6 months post-transplant with respect to ACR response. C. Percentage of evaluable patients taking DMARD at 12 months post-transplant with respect to ACR response.

Fisher's exact test). This probably reflects their generally better responses to transplantation.

There were insufficient data to compare responses between the high dose regimens, although the surviving patient (with seronegative RA from adolescence) who received the BuCYC regimen remains in complete remission at 58 months.

DISCUSSION

Our study represents almost the entire world experience of high dose therapy and autologous HSCT in patients with severe resistant RA. It is a retrospective analysis with relatively short term followup in which data have been collected from a number of transplant centers using different treatment protocols. Notwithstanding, it is by far the largest analysis of patients with severe RA treated with this novel intensive approach, and provides important information that is not available from smaller studies.

Our study gives an indication of the safety of this approach in severe RA. The treatment related mortality (TRM) is low compared with, for example, lymphoma (6%) and autoimmune disease in general (9%)[5], and may relate to

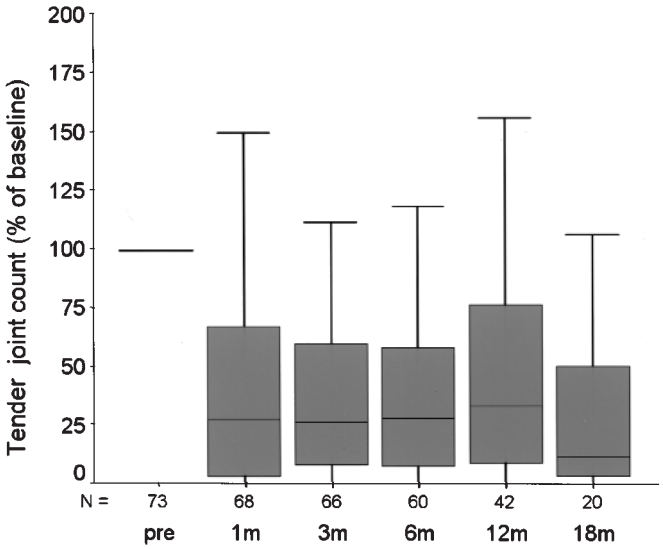


Figure 2. Response in terms of relative reduction in tender joint count. It is emphasized that responses follow autologous transplantation and, in the majority of patients, the subsequent reintroduction of DMARD ($p = 0.0001$ at all time points).

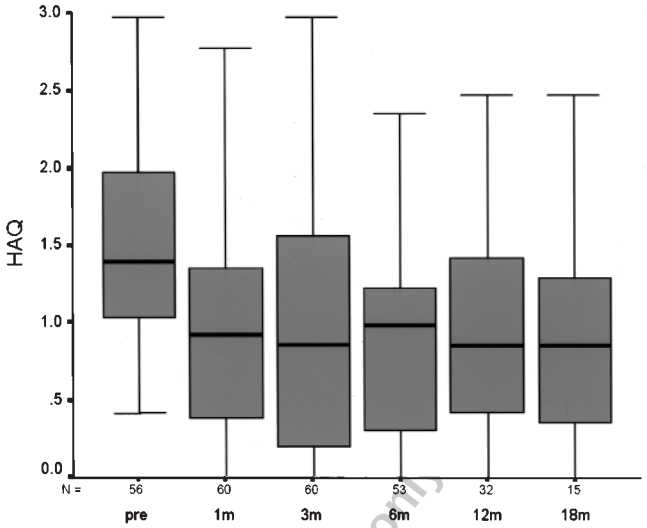


Figure 3. Response in terms of HAQ score. It is emphasized that responses follow autologous transplantation and, in the majority of cases, the subsequent reintroduction of DMARD ($p < 0.005$ at all time points).

the ability to select patients with good vital organ function. It is notable that there were no deaths in 62 patients who received CYC 200 mg/kg. It would therefore seem appropriate to regard CYC 200 mg/kg as a safe regimen for use in future studies. The responses following the BuCYC regimen were profound[11,12], with one case still in remission at 58 months. As this patient had seronegative RA from adolescence, it is not possible to predict whether myeloablative regimens will produce similar results in other patients. In the first instance, further phase I data should be made available before this regimen is used more widely for RA.

Employing the widely used ACR response criteria, this analysis has been able to provide an overall estimate of efficacy. Given the resistant nature of the RA in this group of patients, significant responses were achieved in the majority of patients, with 67% achieving at least ACR 50 at some point following transplant. In addition, significant reductions in tender joint counts and HAQ score were also observed. Responses were apparently sustained over 18 months, although, given a gradual reduction in total numbers over time, the possibility of a reporting bias should be considered in the interpretation of these data. In addition, progressively more patients over time required reintroduction of DMARD to maintain such responses (Figures 1B and 1C).

In the majority of patients, disease flare occurred eventually and reintroduction of DMARD was necessary in most by 6 months. Based on this and other studies, it is clear that autologous HSCT using non-myeloablative regimens, such as CYC 200 mg/kg used in the majority of patients, does not represent a cure for RA. However, in many cases, the patient appeared to respond to a DMARD that they had previously failed. The responses support a "debulking of inflammation" and/or a "resetting" of the immune system, which reenables disease control with DMARD[14-19]. Introduction of post-transplant maintenance therapy with DMARD may provide longterm reduction in disease activity, although this needs to be formally answered in carefully designed prospective clinical trials.

A simple analysis to look for a relationship between patient- and treatment-related factors and response was performed. The analysis suggested that patients with seronegative RA respond better to this type of treatment, with all patients achieving at some point post-transplant an ACR 50 or greater. This may be explained by seronegative arthritis having a better prognosis and response to treatment generally[23,24], although clearly such patients had received HSCT as their disease had been resistant to many conventional agents. Otherwise there appeared to be no trends. In particular, other factors considered to be predictive of response such as earlier and less heavily treated disease[25] and HLA-DR typing[26] did not seem to influence outcome. T cells are known to be important in the pathogenesis of RA[27], but, similar to a recent randomized controlled study[19], this study failed to support the hypothesis that T cell depletion of the autologous graft might improve the outcome[28], at least with non-myeloablative regimens, such as CYC 200 mg/kg. However, it remains possible that lymphocyte depletion might be clinically advantageous if used in conjunction with lympho-myeloablative regimens, such as the BuCYC regimen.

It is important to recognize that most of the patients were treated in the "pre-TNF blocker era" of rheumatology, with only 4 out of 73 patients having received anti-TNF agents before HSCT. The introduction of these drugs has repre-

Table 2. Summary of subgroup analysis.

Best ACR response	Low Responder (ACR 0/20)	High Responder (ACR 50/70/CR*)	p
Duration of disease			
< 100 months	5 (21%)	19 (79%)	0.22
> 100 months	10 (39%)	16 (61%)	
Previous DMARD			
< 5	7 (26%)	20 (74%)	0.43
≥ 5	16 (38%)	26 (62%)	
Rheumatoid factor			
Positive	22 (37%)	37 (63%)	0.02
Negative	0 (0%)	10 (100%)	
HLA-DR 4			
Present	9 (33%)	18 (67%)	0.72
Absent	3 (25%)	9 (75%)	
Mobilization			
G-CSF alone	15 (37%)	26 (63%)	0.62
G-CSF + chemotherapy	9 (29%)	22 (71%)	
T cell depletion of graft			
No	8 (28.6%)	20 (71.4%)	0.61
Yes	16 (35.6%)	29 (64.4%)	

G-CSF: granulocyte-colony stimulating factor. * Complete remission.

sented a major therapeutic advance in the treatment of resistant RA with relatively low toxicity. Clearly, given its potential morbidity and mortality, autologous HSCT can now only be considered within the estimated 25% of patients who fail TNF antagonists as well as conventional DMARD[29]. It remains to be seen whether lower response rates will be seen in patients failing anti-TNF treatment.

In summary, analysis of this relatively large number of cases has confirmed high dose therapy and autologous HSCT to be relatively well tolerated and that, at least in the short term, profound responses can be achieved in a majority of patients. Responses have been significant, with ACR 50–70 responses being frequent. Unfortunately, reactivation of disease activity is common. Along with other reports, the survey suggests a renewed sensitivity of RA to DMARD therapy. However, the followup is relatively limited and we cannot exclude mere induction of a short-lived response without modification of the longterm prognosis. Further clinical trials are necessary to answer basic questions regarding the utility of autologous HSCT in RA. The ASTIRA (Autologous Stem cell Transplantation International Rheumatoid Arthritis) trial commenced in early 2002. The aim is to prospectively evaluate the efficacy of CYC 200 mg/kg with autologous HSCT followed by maintenance treatment in patients with severe RA resistant to conventional therapies and TNF blockade. Potentially, other trials investigating the benefit of further dose intensification of autologous transplantion as well as allogeneic transplantation may become available[30,31]. Results of such studies may not only provide an effective treatment option for resistant RA, but also provide insights into pathogenesis. Patients so treated should be included in prospective randomized controlled trials.

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