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Clinical benefits of granulocyte colony-stimulating factor therapy after hematopoietic stem cell transplant in children: results of a prospective randomized trial

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Background and Objectives. Hematopoietic stem cell transplantation (HSCT) is associated with profound neutropenia and significant morbidity and mortality. To evaluate the safety and efficacy of non-glycosylated recombinant human granulocyte colony-stimulating factor (rHuG-CSF) in accelerating myeloid recovery and its influence on infections, supportive therapy, and transplant-related mortality we carried out a randomized study in pediatric patients receiving HSCT.

Design and Methods. Two hundred and twenty-one consecutive children, recipients of an allogeneic or autologous bone marrow (BM) or peripheral blood progenitor cell (PBPC) transplant, were randomized to either receive rHuG-CSF 10 μg/kg (n=110) or not (n=111).

Results. Myeloid engraftment was faster in the treated arm (14 vs 20 days, p=0.0001). Neutrophil recovery was accelerated both in the BM subgroups (allogeneic and autologous, p=0.002) and in the PBPC group (p=0.0005). All the other evaluated variables showed an advantage in favor of rHuG-CSF treated patients that was significant for platelet transfusion independence and time to discharge (p=0.02 and p=0.04, respectively) only in the BM subgroup.

Interpretation and Conclusions. We conclude that faster neutrophil recovery in BM recipients receiving rHuG-CSF led to clinical benefits, while, in the PBPC subgroup, it did not translate into clinical advantages.

Key words: rHu G-CSF, bone marrow transplantation, children.

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High dose chemo-radiotherapy followed by either allogeneic or autologous hematopoietic stem cell transplantation (HSCT) is the treatment of choice for an increasing number of congenital and acquired diseases of childhood.[1] One of the major drawbacks of this procedure is the prolonged post-transplant period of profound neutropenia, which may cause significant morbidity and mortality.[2]

During the last decade hematopoietic growth factors have been increasingly used after HSCT. Although several phase II and phase III studies on adult patients proved that recombinant human granulocyte colony-stimulating factor (rHuG-CSF) accelerates neutrophil recovery,[3,4] the actual clinical benefits of rHuG-CSF in children remain a controversial point requiring controlled studies.[4-8]

It is well-known that children frequently recover faster than adults after HSCT and suffer less from life-threatening side effects, and this holds true even for severe infections.[9]

Moreover, the kinetics of stem cell proliferation, the hematopoietic reservoir, and the profile of the effects of rHuG-CSF may be quite different from those observed in adult patients. Indeed, in two recent retrospective studies on pediatric patients we obtained controversial results regarding the clinical benefits of G-CSF following allogeneic bone marrow transplant.[10,11]

We now report on a large randomized phase III trial carried out to evaluate the safety and the efficacy of non-glycosylated rHuG-CSF in accelerating myeloid engraftment in children undergoing HSCT. Moreover, we analyze whether acceleration of neutrophil recovery translates into secondary benefits regarding infections, supportive therapy, hospitalization, and transplant-related mortality (TRM).

Design and Methods

Selection of patients

Patients younger than 18 years and undergoing allogeneic (HLA-matched sibling or unrelated donor) or autologous [bone marrow (BM) or peripheral blood progenitor cell (PBPC)] transplant were eligible for the study. Autologous BM transplant was given mostly to children with hematologic malignancies and autologous PBPC transplant was given to children with solid tumors grafted since January 1996. All allogeneic transplants used bone marrow as the source of progenitor cells. Parents of all children gave written informed consent and understood the experimental nature of the protocol. The study was approved by the Institutional Review Board at each of the participating Institutions. Patients were centrally randomized by a computer generated random list, stratified according to type of transplant (allogeneic: sibling or unrelated donor; autologous: BM or PBPC), and disease risk, as shown in Table 1.

From January 1995 to June 1998, 221 consecutive patients aged 0.16 to 17.9 years (median 6.6 years) were enrolled in 9 Italian centers affiliated to the *Italian Association of Pediatric Hematology and Oncology* (AIEOP). The characteristics of the patients, divided according to treatment group, are reported in Table 1.

rHuG-CSF treatment

Children randomized into the treament arm received rHuG-CSF in 100 mL saline as a 2-hour intravenous infusion daily at a dose of 10 μg/kg body weight. Treatment started on day +5 and lasted for 25 consecutive days, or until the absolute neutrophil count (ANC) reached 0.5×10^9/L for 3 consecutive days, whichever occurred first.

Clinical monitoring

Children were kept in positive pressure rooms equipped with HEPA filters and were together with one of their parents. Blood cell counts with differential and blood chemistries were monitored daily. Children were transfused on a routine basis when the hematocrit was below 30%, and received platelet transfusions for counts below 20×10^9/L or in the presence of hemorrhage. Total parenteral nutrition (TPN) was given to maintain calorie intake over 50% of the daily requirement. Blood components were irradiated and filtered to reduce contaminating leukocytes. Febrile episodes were classified according to the European Organization for Research and Treatment of Cancer criteria.[12] When patients developed fever or any sign of infection they were treated with broad-spectrum antibiotics according to the Center's policy. Graft-versus-host disease (GvHD) prophylaxis included cyclosporin A (CSA) in children receiving HSCT from a sibling donor, CSA associated with short-term methotrexate (MTX) and antilymphocyte globulin (ALG) in children transplanted from an unrelated donor (UD). The severity of acute GvHD was scored weekly using standard criteria.[13] Pretransplant preparative regimens were assigned according to institutional protocols, on the basis of the underlying disease and phase, as well as on the recipient's age. Patients were discharged when they were afebrile and off parenteral antibiotics and antimycotics for at least

Table 1. Characteristics of patients divided according to treatment group.

	TG (n=110)	*CG (n=111)*	*p*
Type of transplant			ns#
Autologous			
BM	34	32	
PBPC	33	31	
Allogeneic			
Sibling	23	30	
Unrelated	20	18	
Age at transplant (yrs)			ns$
median	6.7	6.7	
range	1.2–17,9	0.16–17,9	
Diagnosis-transplant interval (months)			ns$
median	10	9.8	
range	1-119	1-135	
Gender			ns#
Male/Female	68/42	65/46	
Primary diagnosis			ns#
Standard risk	110	99	
AL 2nd CR	34	43	
CML 1st CP	5	4	
Non-Hodgkin's lymphoma 1st CR	6	7	
SAA	1	1	
RA	–	1	
Congenital diseases	5	4	
Solid tumors	49	39	
Advanced risk	10	12	
AL 3rd CR	7	6	
CML >1st CR	1	1	
Non-Hodgkin's lymphoma >1st CR	1	5	
SAA >3 months	1	1	
Conditioning regimen			ns#
TBI + chemotherapy	43	52	
Chemotherapy alone	64	58	
Not known	5	–	
Mononuclear cells infused (10^8/kg)			ns$
Median	3.3	3	
Range	0.3–20.9	0.03– 61	

Abbreviations: TG, treated group; CG, control group; #two-tailed Fisher's exact test; BM, bone marrow; PBPC, peripheral blood progenitor cell; $Wilcoxon's rank sum test and t-test; AL, acute leukemia; CR, complete remission; CML, chronic myelogenous leukemia; CP, chronic phase; SAA, severe aplastic anemia; RA, refractory anemia; TBI, total body irradiation.

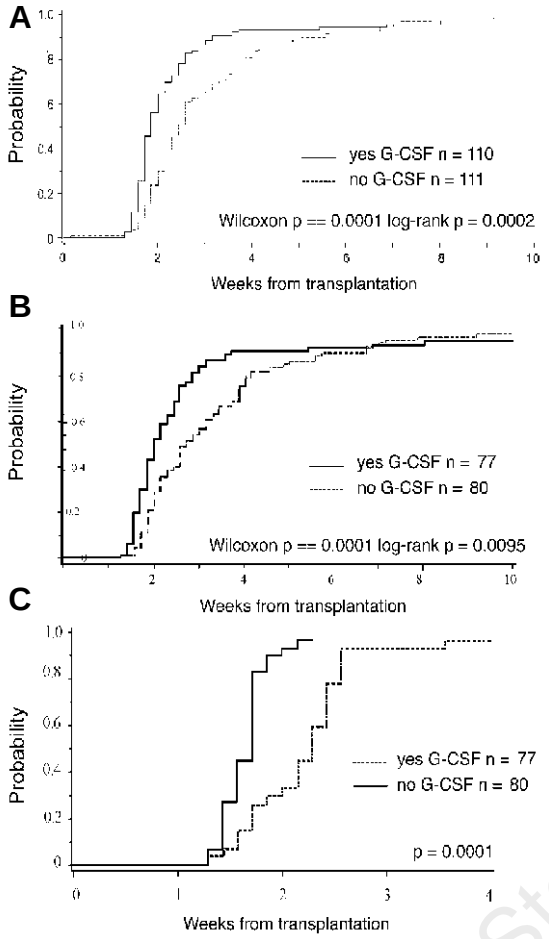

Figure 1. A. Granulocyte engraftment by randomization: all patients. B. Granulocyte engraftment by randomization; autologous and allogeneic bone marrow transplantation. C. Granulocyte engraftment by randomization: autologous PBPC transplant.

72 hours, their oral intake provided more than 60% of the daily calorie requirement, and in the absence of diarrhea.

Statistical analysis

All data were stored in a central data base (AIEOP–BMT Registry), organized at the AIEOP Operation Office.[14] Demographic and clinical characteristics of the two groups of patients were compared using the two-tailed Fisher's exact test for categorical variables (gender, disease, type of transplant, and conditioning regimens), the Wilcoxon's rank sum test and the t-test for continuous variables (age, diagnosis - HSCT interval, and marrow cell dose).[15] The primary end-point of this study was to evaluate neutrophil recovery, defined as the first of three consecutive days with an ANC of at least 0.5×10^9/L. Other variables evaluated included time to the last platelet transfusion, time to the last red blood cell transfusion, number of febrile days, days on intravenous antibiotic therapy, duration of TPN, duration of hospitalization after infusion, incidence of grade ≥ II acute GvHD, TRM and event-free survival (EFS), and incidence of relapse.

In order to understand the role of rHuG-CSF better, all variables were separately analyzed according to transplant type. Subsequently, we carried out the same statistical analysis gathering the three bone marrow subgroups (autologous and allogeneic-familial and unrelated), but excluding PBPC. The effects of treatment in terms of neutrophil recovery, TRM, EFS and relapse rate (RR) were examined in unvariate analysis according to the Kaplan-Meier method.[16] The generalized Wilcoxon test[17] and the log-rank test were applied for comparing the outcome of the randomized groups. A Cox regression model was applied to estimate treatment effect adjusting for covariates.[18] All analyses were performed according to the intention-to-treat principle. The study had an 80% power to detect a 20% difference in neutrophil recovery, considering a baseline 15-day neutrophil recovery probability for the control group of 0.75 and $\alpha = 0.05$ (two-sided), resulting from a minimum sample size of 53 patients per arm. Since 60 autologous and 50 allogeneic BMT were expected per year, two years' accrual made it possible to evaluate the primary end point both in allogeneic and autologous subgroup analyses. The SAS package (SAS Institute, Cary, NC, USA) was used for analysis of the data.

Results

From January 1995 to June 1998 221 patients were randomly assigned to the group treated with rHuG-CSF (n=110) or to the control group (n=111). Treated children and controls were comparable in terms of clinical characteristics (Table 1). rHuG-CSF was well tolerated, no side effects or hepatic or renal abnormalities potentially related to the drug were reported, and no children in the treated arm required treatment discontinuation, and no children in the control group received rHuG-CSF.

Blood cell recovery and transfusion

Two hundred and sixteen out of 221 (98%) patients reached myeloid engraftment at a mean of 17 days (range: 8-63; 95% confidence interval-CI: 16-18). The five patients who did not (3 undergoing autologous BMT, 1 allogeneic sibling and 1 UD BMT) died of infections on days 8-53 (median 31 days).

Table 2. Hematologic parameters in the two groups, expressed as means (95% confidence interval).

Type of transplant	*Auto PBPC*			*Auto BMT*			*Allo Sib. BMT*			*Allo UD BMT*			*Auto + Allo BMT*		
	TG	*CG*	*p#*	*TG*	*CG*	*p#*	*TG*	*CG*	*p#*	*TG*	*CG*	*p#*	*TG*	*CG*	*p#*
N. of patients	33	31		34	32		23	30		20	18		77	80	
Days to ANC* >0.5×10⁹/L	11 (10-12)	14 (12-16)	0.0005	18 (14-21)	28 (22-32)	0.002	11 (10-12)	18 (12-24)	ns	13 (12-14)	19 (15-23)	0.004	15 (13-17)	22 (19-25	0.002
Time to last RBC* transfusion (days)	21 (10-31)	53 (5-100)	ns	38 (23-53)	55 (28-82)	ns	28 (13-43)	61 (27-95)	ns	64 (31-97)	64 (41-87)	ns	52 (33-71)	60 (43-77)	ns
Time to last PLT* transfusion (days)	27 (11-43)	31 (7-56)	ns	39 (25-54)	63 (34-91)	ns	21 (13-29)	58 (23-93)	ns	33 (22-44)	57 (34-80)	ns	36 (27-45)	59 (41-77)	0.02

Abbreviations: Auto: autologous; PBPC: peripheral blood progenitor cell transplant; pts: patients; BMT: bone marrow transplant; Allo: allogeneic; Sib: sibling; UD: unrelated donor; TG: treatment group; CG: control group; #t-test; ANC: absolute neutrophil count; RBC: red blood cell; PLT: platelet; ns, not significant.

Three were in the treated group and two were in the control group. The mean time to ANC >0.5×10⁹/L was significantly shorter in patients treated with rHuG-CSF than in the control group: 14 (95% CI: 13-15) vs 20 (95% CI: 18-22) days, respectively; p=0.0001 (Figure 1A). Subgroup analysis confirmed the faster kinetics of neutrophil recovery in autologous PBPC transplants (p=0.0005), and in BMT (allogeneic and autologous) (p=0.002) recipients (Table 2 and Figures 1B and 1C).

The mean day of the last red cell transfusion was comparable in the two randomization arms. The mean day of the last platelet transfusion was 36 (95% CI: 27-45) for rHuG-CSF treated patients undergoing BMT (autologous and allogeneic) and 59 (95% CI: 41-77) days for the controls (p=0.02), whereas there was no difference in favor of the rHuG-CSF group in patients undergoing PBPC transplant (Table 2).

Supportive care

A trend towards shorter antibiotic treatment, shorter TPN duration, and fewer days of fever was observed in the rHuG-CSF-treated patients. In some subgroups of patients a significant difference in favor of the treatment group was observed (Table 3).

Hospitalization

The duration of hospitalization after BMT (autologous and allogeneic) was shorter (p<0.04) in rHuG-CSF treated patients (37 days; 95% CI: 31-43) than in controls (46 days; 95% CI: 39-53), whereas there was no difference between the two arms in patients undergoing autologous PBPC transplant (Table 3).

Other management issues

In the allogeneic BMT setting no differences were observed in the incidence of grade II-IV acute GvHD (25/43 and 27/48 patients at risk in the treated and control groups, respectively) and of extensive chronic GvHD (8/11 and 9/17, respectively). In all subgroups the actuarial probabilities of EFS, relapse, and TRM at 100 days and at 48 months after HSCT were comparable in treated patients and controls. In patients with malignancies, the relapse rate did not differ significantly in the two groups (Table 4).

Discussion

Several clinical studies have addressed the issue of the benefits of using hematopoietic growth factors following HSCT.[3-8] Most of these studies were performed on adults, while few trials were performed on children. The 1998 recommendations of a European committee on the use of colony-stimulating factors (CSF) in children[19] stated that rHuG-CSF should be used routinely as an adjuvant in autologous, but not in allogeneic BMT, or in autologous PBPC transplants and suggested that prospective studies were required to draw evidence-based guidelines. *In vitro* studies on T-cells derived from allogeneic BMT recipients showed decreased ability to produce CSFs, which may account for an increased susceptibility to infections.[20] A large placebo-controlled phase III trial evaluated the role of glycosylated rHuG-CSF in a group of 315 patients, including 46 children, receiving either autologous or allogeneic BMT. rHuG-CSF therapy in all patients, including children, was associated with a faster ANC recovery, fewer febrile-neutropenic days, fewer days of TPN, fewer microbiologically documented infections, and a shorter period of hospitalization.[4] To our knowledge, our study is the largest phase III trial reported to date analyzing the use of hematopoietic CSF in children. Our study demonstrated the reproducibility of results reported in adults on a large number of transplanted patients below 18 years of age. Ninety-eight percent of the patients successfully reached myeloid engraftment. The drug

Table 3. Other clinical variables evaluated in the two groups, expressed as means (95% confidence interval).

Type of transplant	*Auto PBPC*			*Auto BMT*			*Allo Sib. BMT*			*Allo UD BMT*			*Auto + Allo BMT*		
	TG	*CG*	*p#*	*TG*	*CG*	*p#*	*TG*	*CG*	*p#*	*TG*	*CG*	*p#*	*TG*	*CG*	*p#*
N. of patients	33	31		34	32		23	30		20	18		77	80	
N. of febrile days*	5 (4-6)	6 (4-7)	ns	9 (4-11)	10 (6-13)	ns	9 (5-13)	9 (7-11)	ns	10 (7-13)	12 (9-15)	0.04	9 (7-11)	11 (9-13)	ns
Days on antibiotic therapy	13 (10-16)	14 (12-16)	ns	18 (15-21)	19 (16-23)	ns	15 (12-18)	22 (18-26)	0.03	20 (17-23)	23 (20-26)	ns	19 (17-21)	22 (20-24)	ns
Duration of TPN (days)	17 (14-20)	16 (14-18)	ns	20 (17-24)	27 (22-32)	0.03	21 (17-25)	30 (25-35)	0.03	31 (24-38)	32 (27-37)	ns	26 (22-30)	30 (26-34)	ns
Duration of hospitalization (days)	22 (18-25)	22 (18-26)	ns	27 (24-31)	34 (29-39)	0.02	32 (25-29)	46 (12-180)	ns	46 (37-55)	54 (55-64)	ns	37 (31-43)	46 (39-53)	0.04

Abbreviations: Auto: autologous; PBPC: peripheral blood progenitor cell transplant; pts: patients; BMT: bone marrow transplant; Allo: allogeneic; Sib: sibling; UD: unrelated donor; TG: treatment group; CG: control group; #: t-test; MDI: microbiologically documented infections; TPN: total parenteral nutrition; ns, not significant.

was very well tolerated by the children, and no adverse effects were reported. Compared to the control group, rHuG-CSF accelerated myeloid engraftment after autologous PBPC transplant as well as after autologous and allogeneic BMT. The difference reached a statistical significance in all subgroups except that of patients receiving an allogeneic sibling HSCT, probably due to the low number of patients in this group. In addition to the effect on hematopoietic recovery, this study attempted to prospectively determine the effect of rHuG-CSF treatment on some clinical parameters. The results demonstrated that the faster myeloid engraftment in pediatric patients undergoing autologous and allogeneic BMT resulted in a somewhat reduced post-transplant morbidity. This led to a decrease in the duration of hospitalization which was significant in the overall allogeneic + autologous population and in the autologous BMT subgroup. The difference did not reach a statistical difference in allogeneic BMT, probably due to the low number of patients. A trend towards shorter antibiotic treatment, shorter TPN, and fewer days of fever was observed in rHuG-CSF-treated patients. This difference was not statistically significant when compared to controls, possibly due to the limited sample size. In keeping with the results reported by Kawano *et al*.[8] rHuG-CSF appeared to provide limited benefits when used after autologous PBPC transplant in a pediatric population. Two factors may explain this difference from results of adult studies: the potentially higher cell dose infused in lower weight patients, and the possibly more efficient hematopoiesis in children than in adults.[8] Furthermore, it must be noted that, as previously

Table 4. Clinical outcome.

	Auto PBPC pts			*Auto + Allo BMT pts*		
	TG %(SE)	*CG %(SE)*	*p#*	*TG %(SE)*	*CG %(SE)*	*p#*
TRM at 100 days	0	6.7 (4.6)	ns	10.5 (3.5)	8.8 (3.2)	ns
TRM at 48 months	3.6 (3.5)	14.5 (7.0)	ns	21.0 (4.9)	18.7 (4.6)	ns
RR at 48 months	61.5 (9.0)	67.1 (9.2)	ns	42.1 (6.1)	30.3 (5.6)	ns
EFS at 48 months	36.8	26.7 (8.1)	ns	44.1 (5.7)	55.5 (5.6)	ns

Abbreviations: Auto, autologous, PBPC, peripheral blood progenitor cells; pts, patients; Allo, allogeneic; BMT, bone marrow transplant; TG, treated group; CG, control group; #log-rank test; SE, standard error; TRM, transplant-related mortality; RR, relapse rate; EFS, event-free survival; ns, not significant.

reported,[21] all the measured variables showed lower toxicity and faster recovery in patients undergoing autologous PBPC transplant than in patients undergoing autologous BMT, regardless of the use of rHuG-CSF. As shown by Kawano *et al*.,[8] further benefits induced by growth factor administration cannot be achieved. The clinical benefit of the reinfusion of large numbers of earlier engrafting committed progenitor cells[22] led most study groups to shift from the use of BM to PBPC, especially in the setting of solid tumors. Recently, some investigators have hypothesized that the administration of growth factors after transplantation may be detrimental to platelet recovery.[8,23,24] In addition, conflicting data have been reported on the impact of growth factors following allogeneic BMT on the incidence of acute GvHD.[23,25,26] The results of our

study showed that the use of rHuG-CSF was associated with a favorable effect on the time to independence from platelet transfusion in children undergoing allogeneic or autologous BMT. This was not observable in children undergoing PBPC transplant, in keeping with the results reported by Kawano *et al*.[8] In our study, time to last platelet transfusion was four days later in the PBPC subgroup receiving rHuG-CSF, possibly influencing duration of hospitalization and costs. The reasons for these different results need to be clarified and further investigation on this point is required. There was no evidence in the present study that the rHuG-CSF regimen had any effect on the incidence or severity of GvHD, or on the incidence of relapse.

Schriber *et al*.[27] observed a higher than expected early mortality in patients receiving rHuG-CSF after BMT from a matched unrelated donor. In our study TRM at 100 days and survival did not differ between the two randomization arms, regardless of the type of stem cells or donor used.

In our study rHuG-CSF administration was started on day +5 in order to avoid the possible negative influence of early administration and to save costs.[29] Recently, it has been shown that postponing treatment with rHuG-CSF from day 1 to day 5 or even later after HSCT had no significant effect on hematopoietic engraftment and furthermore, delaying rHuG-CSF treatment was associated with a significant saving in costs.[30,31,32] Moreover, it has been reported that early administration of rHuG-CSF was associated with a higher frequency of veno-occlusive disease[27] and with a significant drop in plasma antithrombin levels.[29] In our study we administered rHuG-CSF at a daily dose of 10 μg/kg body weight, although we cannot exclude that a different dose may be equally effective.[19,31,33]

In conclusion, on the basis of our results the administration of rHuG-CSF in children at a dose of 10 μg/kg/day from day 5 following allogeneic and autologous BMT was safe and effective because it accelerated myeloid engraftment and significantly decreased the period spent in hospital. The observed trend in favor of the treated group, in terms of antibiotic and TPN requirements, was probably responsible for the earlier discharge. On the other hand we confirmed that the use of rHuG-CSF provided marginal clinical benefits to children undergoing autologous PBPC transplantation.

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Disclosures

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PEER REVIEW OUTCOMES

Manuscript processing

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What is already known on this topic

Recombinant human granulocyte colony-stimulating factor (rHuG-CSF) accelerates neutrophil recovery after HSCT in adults, but the actual clinical benefits of rHuG-CSF in children remain controversial.

What this study adds

This prospective randomized phase III trial demonstrates that although faster neutrophil recovery was observed in both BM and PBPC rHuG-CSF treated groups, significant clinical benefits were only observed in BM recipients.

Potential implications for clinical practice

As in adults, rHuG-CSF administration in children at a dose of 10 μg/kg/day from day 5 of SCT is safe and effective, leading to clinical benefits at least in patients submitted to allogeneic or autologous BMT. On the other hand, other trials are required to clarify the clinical usefulness of the systematic use of rHuG-CSF in children undergoing autologous PBPC transplantation.

Josep Maria Ribera, Associate Editor
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