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TMGあさか医療センター
倫理委員会 委員長 殿

申請者（研究責任者）

所 属： 血液内科

役 職： 医師

申請者： 渡邊 純一

I) 研究課題名

『重症再生不良性貧血に対するウマ ATG とウサギ ATG の有効性、安全性の比較』

II) 研究の種類

☐ 疫学研究

☐ 臨床研究 観察研究

☐ 臨床研究 介入あり

☐ その他

III) 研究代表者の氏名・所属・職名

研究代表者：渡邊 純一

所 属：血液内科

職 名：血液内科部長

Ⅳ) 研究の概要（何がどこまで明らかにされているか）

(1) 研究の目的

再生不良性貧血(AA)は100万人あたり8名程度と稀な造血器疾患で、血液難病の1つである。重症例に対して若年では同種造血幹細胞移植が行われるが、40歳以上の患者では免疫抑制療法が優先される。免疫抑制療法では抗胸腺細胞グロブリン(ATG)とシクロスポリン(CsA)とトロンボポエチン受容体作動薬(TPO-RA)の3剤併用が標準治療とされている。ATGには2008年以降ウサギATGが使用されていたが、2008年以前はウマATGが使用されていた。2023年8月に新規ウマATGであるアトガムが発売され、現在使用されているが、稀な疾患のため実臨床での有効性・安全性は不明である。

(2) 研究の対象及び方法

・当院で2020年8月から2026年3月までに通院、治療を行なったAA患者31名を対象とする。特にウマATGを使用した7名の臨床経過、有効性、安全性について後方視的に検討する。また、ウサギATGを使用している患者、他の治療法を行なっている患者の有効性、安全性についても検討する。

(3) 実施場所

・TMG あさか医療センター 6B病棟、及び外来

(4) 研究期間

西暦 倫理委員会承認 ～ 2026年 12月 31日

Ⅴ) 研究における倫理的配慮について

(1) 研究対象となる個人の人権擁護

・本研究は、治療介入を伴わない後方視的研究であるため、新たに採取する試料はない。本研究は当院単独研究であり、外部に情報を持ち出すことがないため匿名化は不要である。

(2) 研究対象となる個人への理解を求め、同意を得る方法

・本研究は侵襲を伴わず、治療介入を一切行わない後方視的研究であるため、「人を対象とする医学系研究に関する倫理指針」によると、患者個人に対しての同意取得は必要ないものとする。ただし、TMG あさか医療センターのホームページ上で、本研究が実施されていることを通知または公開し拒否機会の保障を確保する。

(3) 生じうる個人の利益及び不利益並びに危険性の予測

・本研究は治療介入を伴わない後方視的研究のため、研究に参加することによる不利益および危険性はない。利益についても後方視的研究のため直接的な利益はない。

(4) その他（判断能力の乏しい対象者への対処など）

・成人に対しての後方視的研究でありホームページ上での公開で対応する。

VI) 引用文献・その他参考文献など

1, Scheinberg P, et al. *Horse versus Rabbit Antithymocyte Globulin in Acquired Aplastic Anemia. N Engl J Med* 2011;365:430-8.

2, Kanda Y, et al. *Efficacy and safety of equine anti-thymocyte immunoglobulin (eATG) in three Japanese patients with moderate to very severe aplastic anemia: a case series. International Journal of Hematology* (2023) 117:37–43

ORIGINAL ARTICLE

Horse versus Rabbit Antithymocyte Globulin in Acquired Aplastic Anemia

Phillip Scheinberg, M.D., Olga Nunez, R.N., B.S.N., Barbara Weinstein, R.N.,
Priscila Scheinberg, M.S., Angélique Biancotto, Ph.D., Colin O. Wu, Ph.D.,
and Neal S. Young, M.D.

ABSTRACT

BACKGROUND

From the Hematology Branch (P.S., O.N., B.W., P.S., N.S.Y.) and Office of Biostatistics Research (C.O.W.), National Heart, Lung, and Blood Institute; and the Trans-NIH Center for Human Immunology, Autoimmunity, and Inflammation, National Institutes of Health (A.B., N.S.Y.) — both in Bethesda, MD. Address reprint requests to Dr. Scheinberg at 10 Center Dr., Bldg. 10 CRC, Rm. 3E-5140, MSC 1202, Bethesda, MD 20892-1202, or at scheinbp@mail.nih.gov.

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In severe acquired aplastic anemia, hematopoietic failure is the result of immune-mediated destruction of bone marrow stem and progenitor cells. Immunosuppressive therapy with antithymocyte globulin (ATG) plus cyclosporine is an effective alternative to stem-cell transplantation and improves blood counts and survival. Although horse ATG is the standard therapy, rabbit ATG is more potent in depleting peripheral blood lymphocytes and is preferred in other clinical circumstances.

METHODS

From December 2005 through July 2010, we performed a randomized trial comparing these two ATG formulations in conventional regimens. Patients were treated at a single facility. The primary outcome was hematologic response at 6 months, as determined by blood counts. The study was designed to enroll 60 patients each for the rabbit-ATG and horse-ATG groups and was powered to detect a difference of 25 percentage points in the response rate.

RESULTS

A large, unexpected difference was observed in the rate of hematologic response at 6 months in favor of horse ATG (68%; 95% confidence interval [CI], 56 to 80) as compared with rabbit ATG (37%; 95% CI, 24 to 49; $P<0.001$). Overall survival at 3 years also differed, with a survival rate of 96% (95% CI, 90 to 100) in the horse-ATG group as compared with 76% (95% CI, 61 to 95) in the rabbit-ATG group ($P=0.04$) when data were censored at the time of stem-cell transplantation, and 94% (95% CI, 88 to 100) as compared with 70% (95% CI, 56 to 86; $P=0.008$) in the respective groups when stem-cell-transplantation events were not censored.

CONCLUSIONS

In a randomized study, rabbit ATG was inferior to horse ATG as a first treatment for severe aplastic anemia, as indicated by hematologic response and survival. (Funded by the Intramural Research Program of the National Institutes of Health; ClinicalTrials.gov number, NCT00260689.)

AQUIRED APLASTIC ANEMIA IN ITS severe form is fatal without treatment. The disease is characterized pathologically by an “empty” bone marrow, in which hematopoietic precursor cells are replaced by fat, resulting in pancytopenia.¹ Severe aplastic anemia was first definitively treated with the development of stem-cell transplantation in the 1970s. The serendipitous observation of autologous marrow reconstitution in a few patients with rejected grafts suggested that the conditioning agents required for transplantation might themselves be therapeutic.² Purposeful immunosuppression induced by the infusion of antithymocyte globulin (ATG), polyclonal antibodies generated in animals by inoculation with human thymocytes, proved to be effective, with long-term survival that was similar to the results of stem-cell transplantation from a histocompatible sibling.^{3,4} An immune mechanism of hematopoietic cell destruction was inferred from the success of ATG, and subsequent research in the laboratory and in animal models confirmed that progenitor and stem cells were targeted by immune effector cells and cytokines.¹ Cyclosporine added to ATG improved the response rate and survival, as compared with ATG alone,⁵ a finding that is consistent with the pathophysiological features of the disorder.

In the 1980s and 1990s, most formal studies of the efficacy of ATG therapy in patients with severe aplastic anemia that were conducted in Europe, Japan, and the United States used horse ATG, with hematologic responses observed in about two thirds of cases.^{6–9} An ATG made in rabbits has been available in the United States since 1999, when it was approved for the treatment of acute renal-allograft rejection. In our experience, horse ATG as a first therapy for severe aplastic anemia has yielded a hematologic response rate of 60 to 65%,^{10–12} and we wished to improve this rate.

We hypothesized that rabbit ATG would result in a higher response rate than horse ATG as a first treatment, for several reasons. First, in comparison trials, rabbit ATG was superior to horse ATG in preventing and reversing acute renal-allograft rejection.^{13,14} Second, in patients with severe aplastic anemia, rabbit ATG has been effective as salvage therapy for refractory disease or relapse after initial therapy with horse ATG.^{15,16} Third, in comparison with horse ATG, rabbit ATG more efficiently depletes lymphocytes *in vivo* and is more cytotoxic on a weight basis *in vitro*.¹⁷

Fourth, and possibly relevant to its mechanism of activity, rabbit ATG but not horse ATG induces the development of regulatory T cells from normal T cells in tissue culture, which should be beneficial in suppressing a harmful immune response.^{18,19}

On the basis of these observations, rabbit ATG has been administered as a first therapy for severe aplastic anemia. However, its effectiveness for this condition has not been prospectively tested. We report on a randomized trial comparing horse ATG with rabbit ATG in patients with severe aplastic anemia who have not previously received treatment.

METHODS

STUDY PATIENTS AND OVERSIGHT

Consecutive patients older than 2 years of age who had severe aplastic anemia were enrolled from December 2005 through July 2010 at the Mark O. Hatfield Clinical Research Center of the National Institutes of Health, in Bethesda, Maryland. Patients (or their legal guardians) provided written informed consent according to a protocol approved by the institutional review board at the National Heart, Lung, and Blood Institute and available with the full text of this article at NEJM.org. The study was monitored by an external data and safety monitoring board (for details, see the Methods section in the Supplementary Appendix, available at NEJM.org). This government-sponsored study had no commercial support.

STUDY DESIGN

This original study design is shown in Figure 1 in the Supplementary Appendix. Assignment of treatment was performed with the use of a block randomization scheme in a 1:1 ratio, with the assignment probability remaining fixed over the course of the trial. The randomization schedule was based on a table of random numbers developed by the pharmacy department at the clinical center.

The study's primary end point was hematologic response at 6 months, defined as no longer meeting the criteria for severe aplastic anemia; this end point strongly correlates with transfusion independence and long-term survival.^{6,12} Secondary end points included robustness of hematologic recovery, relapse, response rate at 3 months and yearly, clonal evolution, and overall survival.

Table 1. Characteristics of the Patients.*

Characteristic	Horse ATG (N = 60)	Rabbit ATG (N = 60)	P Value
Age			
Mean — yr	37.4±2.7	31.2±2.6	0.09
<18 yr — no. (%)	12 (20)	18 (30)	0.20
Male sex — no. (%)	34 (57)	37 (62)	0.58
Cause of disease — no. (%)			
Idiopathic	58 (97)	55 (92)	0.24
Hepatitis	2 (3)	5 (8)	0.24
Cell counts			
Absolute reticulocyte count/mm ³	22,100±2,584	18,072±2,283	0.24
Absolute lymphocyte count/mm ³	1,291±71	1,220±79	0.50
Absolute neutrophil count			
Mean/mm ³	408±50	356±46	0.44
<200/mm ³ — no. (%)	23 (38)	26 (43)	0.58
Platelet count/mm ³	16,317±4,689	12,650±1,138	0.45
PNH clone — no. (%)			
<1%	35 (58)	41 (68)	0.25
≥1%	25 (42)	19 (32)	0.25

* Plus–minus values are means ±SE. ATG denotes antithymocyte globulin, and PNH paroxysmal nocturnal hemoglobinuria.

Relapse was defined as any requirement for further immunosuppression (cyclosporine or another course of ATG) because of decreased blood counts.¹² Clonal evolution was defined as a new clonal cytogenetic abnormality or characteristic dysplastic or leukemic changes in the bone marrow.

IMMUNOSUPPRESSIVE REGIMENS

Horse ATG (ATGAM, Pfizer) was administered at a dose of 40 mg per kilogram of body weight per day for 4 days and rabbit ATG (Thymoglobulin, Genzyme) at a dose of 3.5 mg per kilogram per day for 5 days, as previously described.^{12,16} Cyclosporine was administered at a dose of 10 mg per kilogram per day (15 mg per kilogram per day for children under 12 years of age), given in divided doses every 12 hours from day 1 and continued for at least 6 months in both the horse-ATG and rabbit-ATG groups, with the dose adjusted to maintain trough blood levels of 200 to 400 ng per milliliter (for details, see the Methods section in the Supplementary Appendix).

STATISTICAL ANALYSIS

The sample size was calculated on the basis of a 6-month response rate (primary end point) of 60%

with standard horse ATG plus cyclosporine (control group).¹² On the basis of a group sequential trial design, with a two-sided test at a 5% significance level, 80% power, and one interim analysis (to be performed when data for half the total estimated number of enrolled participants per group were available for evaluation of the primary end point), we calculated that enrollment of 60 patients per group would be required to detect a difference of 25 percentage points between groups in the 6-month response rate (for details, see the Methods section in the Supplementary Appendix).

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 120 consecutive patients, 2 to 77 years of age, were randomly assigned to horse ATG or rabbit ATG (60 in each group) (Fig. 2 in the Supplementary Appendix). Characteristics of the patients are shown in Table 1; there were no significant differences in demographic or clinical characteristics between the groups. The median follow-up was 839 days (28 months) (range, 2 to 1852 days) for all patients and 891 days (30 months) (range, 185 to 1852 days) for surviving patients.

HEMATOLOGIC RESPONSE AND RELAPSE

The hematologic response rate at 6 months was 68% (95% confidence interval [CI], 56 to 80) with horse ATG and 37% (95% CI, 24 to 49) with rabbit ATG ($P<0.001$) (Table 2). The response rates at 3 and 6 months with horse ATG plus cyclosporine observed in this study were in accord with our experience with this regimen at our institution.^{6,10-12} The majority of patients had a response within 3 months, and only four patients in the horse-ATG group and two in the rabbit-ATG group had a response between 3 and 6 months. Among patients with a response, the increments in blood counts were similar between the two groups (Fig. 1). When only patients who could be evaluated at 6 months were analyzed, the response rate with horse ATG was 71% (95% CI, 59 to 83) as compared with 43% (95% CI, 29 to 57) with rabbit ATG ($P=0.003$). The subsequent treatment of patients who did not have a response at 6 months is shown according to treatment group in Figure 3 in the Supplementary Appendix.

The cumulative incidence of relapse at 3 years (calculated with the use of Kaplan–Meier estimates) did not differ significantly between the two groups: 28% (95% CI, 9 to 43) with horse ATG and 11% (95% CI, 0 to 25) with rabbit ATG ($P=0.35$); the relatively small number of patients with a response at 6 months, especially in the rabbit-ATG group, resulted in wide confidence intervals and loss of statistical power (Fig. 4A in the Supplementary Appendix). All patients who had a relapse (nine in the horse-ATG group and two in the rabbit-ATG group) received additional immunosuppressive therapy.

CLONAL EVOLUTION AND SURVIVAL

The cumulative incidence of clonal evolution at 3 years (in all patients, those with and those without a response) was 21% (95% CI, 7 to 33) in the horse-ATG group and 14% (95% CI, 1 to 25) in the rabbit-ATG group ($P=0.69$) (Fig. 4B in the Supplementary Appendix). Among patients treated with horse ATG, one each had deletion 3, deletion 5q, deletion 13q, deletion 20q, and leukemia, and four had monosomy 7. In two patients, monosomy 7 was preceded by t(12;13) and deletion 13q. In the rabbit-ATG group, five patients had monosomy 7, and one had deletion 13q.

The overall survival rate at 3 years differed significantly between the two regimens: 96% (95% CI, 90 to 100) in the horse-ATG group as compared with 76% (95% CI, 61 to 95) in the rabbit-ATG

Table 2. Hematologic Response at 3 and 6 Months to Horse ATG and Rabbit ATG.

Response	Horse ATG (N=60)	95% CI	Rabbit ATG (N=60)	95% CI	P Value
	no. (%)		no. (%)		
At 3 mo	37 (62)	49–74	20 (33)	21–46	0.002
At 6 mo	41 (68)	56–80	22 (37)	24–49	<0.001

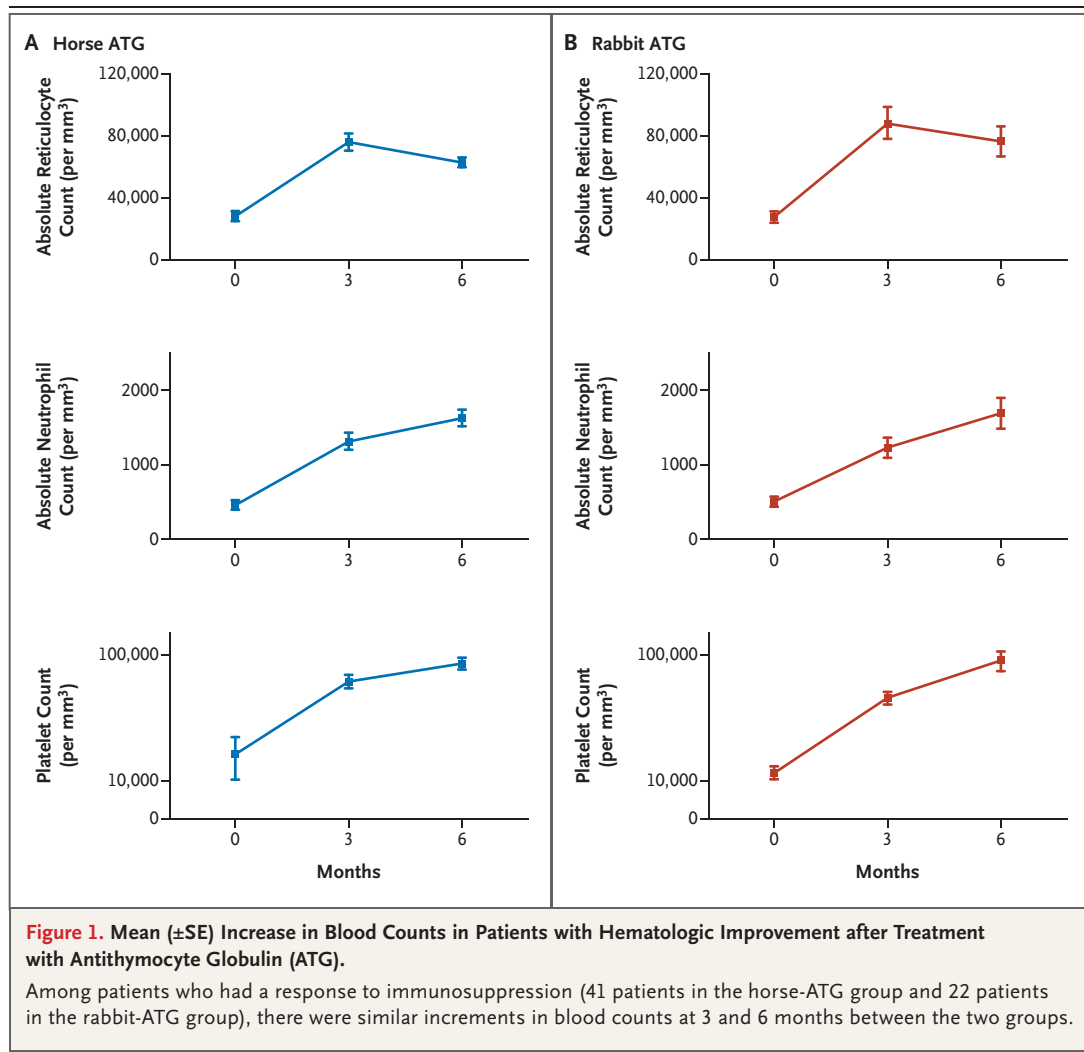
group ($P=0.04$), when data were censored at the time of stem-cell transplantation (Fig. 2A), and 94% (95% CI, 88 to 100) and 70% (95% CI, 56 to 86; $P=0.008$) in the two groups, respectively, when data were not censored at the time of stem-cell transplantation (Fig. 2B). Of the 4 deaths in the horse-ATG group, 1 each resulted from intracranial hemorrhage, sepsis, and lung cancer, and 1 occurred after stem-cell transplantation (from a sibling donor). Of the 14 deaths in the rabbit-ATG group, 2 resulted from intracranial hemorrhage and 3 from infection (1 from pneumonia, 1 from septicemia, and 1 from necrotizing fasciitis), 6 occurred after stem-cell transplantation (3 from a sibling donor and 3 from an unrelated donor), 1 was due to a traffic accident, and 2 were from unknown causes.

IN VIVO ALTERATIONS IN LYMPHOCYTE NUMBERS AND SUBPOPULATIONS

ATGs, which are polyclonal in serum, contain antibodies that recognize various antigens on cell-surface membranes, and they are cytotoxic to lymphocytes in vitro. Rapid depletion of lymphocytes occurred with both agents, but lymphopenia was more protracted after treatment with rabbit ATG, a finding that is consistent with previous reports (Fig. 3A).¹⁷ There were strikingly lower levels of CD4+ T cells for virtually the entire 6 months before assessment of the primary end point in patients treated with rabbit ATG than in patients who received horse ATG (Fig. 3C and 3D). The numbers of regulatory T cells (defined as CD4+CD25+CD127– for this analysis)²⁰ were much lower in the weeks after treatment with rabbit ATG, as would be expected, given the markedly lower levels of CD4+ T cells in this group (Fig. 3E and 3F). Smaller differences were noted in the kinetics of CD8+ T cell depletion and reconstitution (Fig. 3G and 3H).

ADVERSE EVENTS

Serious adverse events are summarized in Table 1 in the Supplementary Appendix. As expected in



this population, the most prevalent complications were infectious. Two patients in the horse-ATG group and nine in the rabbit-ATG group could not be evaluated at 6 months because of death or progressive disease (Fig. 2 in the Supplementary Appendix).

DISCUSSION

Immunosuppression with ATG and cyclosporine is often the first therapy administered for severe aplastic anemia, since most patients lack a histocompatible sibling donor or are not suitable candidates for stem-cell transplantation because of age, coexisting conditions, or lack of access to this treatment modality. Most published experience has involved the horse formulation of the polyclonal antibody. In the past decade, rabbit ATG plus cy-

closporine has gained in popularity because of its activity in relapsed and refractory severe aplastic anemia. In some centers in the United States, rabbit ATG has been used as the first therapy, and in Europe, Japan, and Latin America, rabbit ATG is the only formulation currently available.

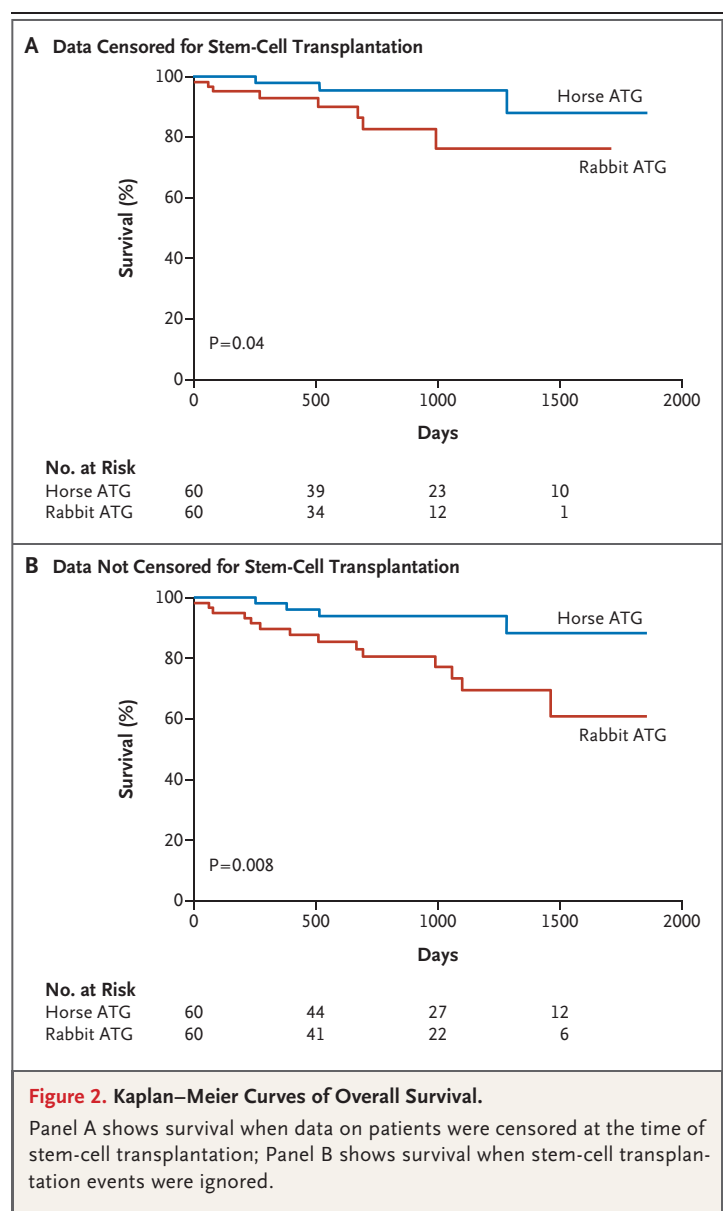
The reported experience with rabbit ATG plus cyclosporine as initial therapy for severe aplastic anemia is limited to retrospective studies, with conflicting results. In a phase 2 study in the United States involving 13 patients with severe aplastic anemia, a response to rabbit ATG was observed in 12 patients (92%) at about 3 months after therapy.²¹ In contrast, a retrospective analysis conducted in Brazil involving 71 patients showed a higher response rate at 6 months among those who had received horse ATG (60%) than among those treated with rabbit ATG (35%), with a sur-

vival benefit noted in the patients receiving horse ATG. In addition, use of rabbit ATG was an independent predictor of death in a multivariate analysis in this study.²² In a recent retrospective study from Europe, no significant difference was seen in the overall response rate between horse ATG (49%) and rabbit ATG (45%) when administered as a first-line therapy,²³ but the response rate of 49% with horse ATG was markedly lower than reported response rates of 60 to 70% with this agent in large prospective studies in the United States, Europe, and Japan.¹

In our randomized, prospective trial, rabbit ATG plus cyclosporine was inferior to horse ATG plus cyclosporine when administered as a first-line treatment. The hematologic response rate with rabbit ATG was about half that with horse ATG, which translated into about a 25% lower survival rate at 3 years. Despite a relatively short period of follow-up, the rates of relapse and clonal evolution did not differ significantly between the two groups.

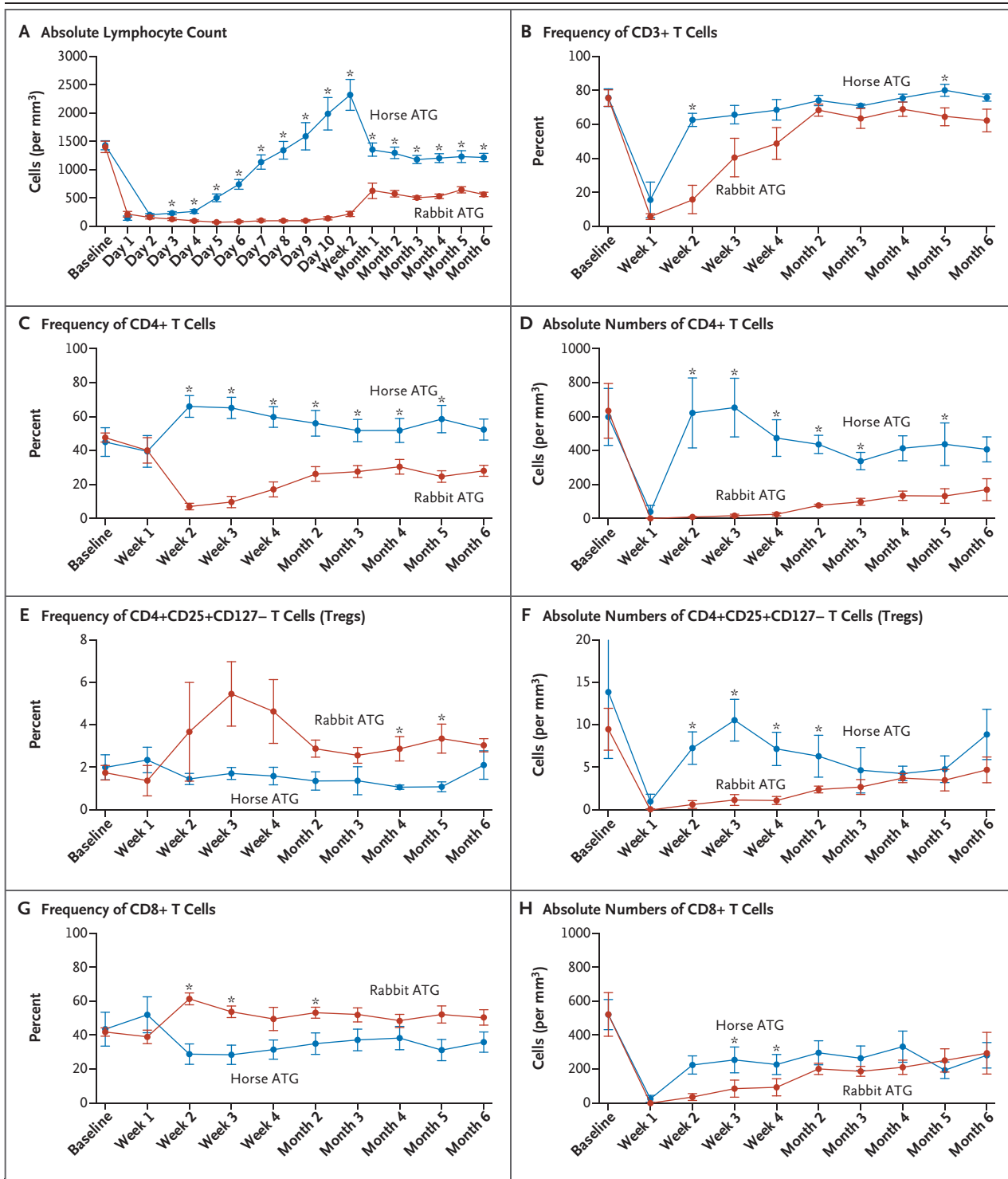
These results were unanticipated, given the success of rabbit ATG in treating relapsed and refractory severe aplastic anemia and the superiority of this agent in protecting kidney allografts.¹³⁻¹⁶ The use of rabbit ATG as a first-line treatment for severe aplastic anemia was logical because it is more immunosuppressive than is horse ATG¹⁷; thus, a higher response rate and improved survival were anticipated. Our study was originally designed to test this hypothesis and was powered to detect a difference of 25 percentage points between the two groups. Because of the large clinical difference between the groups, the response and survival rates crossed statistical boundaries of significance at the conclusion of the study, with confidence intervals between groups that did not overlap for hematologic response and survival.

Our data raise questions about the mechanism by which hematopoiesis is restored after ATG administration in patients with severe aplastic anemia. Although the horse and rabbit preparations of ATG undergo apparently similar manufacturing processes, there are marked differences in vitro and in vivo between the two preparations. In human peripheral-blood mononuclear cells cocultured with different ATGs, an increase in the frequency of regulatory T cells was observed with rabbit ATG but not with horse ATG.¹⁸ Furthermore, a marked difference in gene-expression profile was shown in human cells cultured with



either horse or rabbit ATG.¹⁸ In humans, more prolonged lymphopenia follows rabbit ATG administration, and patterns of viral reactivation have been shown to differ between these two agents.¹⁷

Lot-to-lot variability among ATGs is unlikely to explain the large observed differences in outcomes. First, laboratory testing has not shown marked or consistent dissimilarity in cytotoxicity or antigen-binding specificities among multiple lots of horse and rabbit ATGs^{24,25} nor among commercially available ATGs.²⁶ Second, in our clinical experience over a period of several decades, the



response rates with horse ATG in sequential protocols among patients with previously untreated aplastic anemia have been nearly identical, at an average of 62% (including the current study).¹⁰⁻¹² Response rates with rabbit ATG among patients

with refractory severe aplastic anemia have also appeared to be stable in separate studies conducted over a period of 10 years at our institution, at about 33%.^{16,27} Third, because the preparation of rabbit ATG involves many animals, less variability would

Figure 3 (facing page). Mean ($\pm$ SE) Depletion of Lymphocytes after ATG Administration.

The initial decrease in the absolute lymphocyte count was similar in the horse-ATG and rabbit-ATG groups, but lymphocyte counts remained lower longer after the use of rabbit ATG (Panel A). T cells (CD3+CD45+) decreased rapidly in both groups, with reconstitution in subsequent weeks (Panel B). There was a large difference in the kinetics of CD4+ T-cell depletion between the two groups, with a much lower frequency and lower absolute numbers after the use of rabbit ATG (Panels C and D). The frequency of regulatory T cells (Tregs; defined as CD4+CD25+CD127– for this analysis) was higher after the use of rabbit ATG, but absolute numbers were markedly lower because of more potent depletion of CD4+ T cells, as compared with depletion after the use of horse ATG (Panels E and F). The difference in depletion kinetics of CD8+ T cells was less striking between the two groups, as compared with the difference in CD4+ T cells (Panels G and H). Panel A shows data for all 120 patients. Panels B through H show data for 14 patients (7 from each group). Asterisks denote significant differences between the groups ($P < 0.05$ on the basis of paired t-tests). For details on flow cytometric analysis, see the Methods section in the Supplementary Appendix.

be expected in this formulation. Fourth, the kinetics of lymphocyte depletion with either agent were consistent among the patients. Finally, secular trends in the response observed in the current study remained steady, and there were no significant differences in response rates among patients treated with different lots of ATG (data not shown).

Other, more plausible explanations probably account for our results. Horse and rabbit ATGs led to a similar depletion of CD8+ cytotoxic T cells, but there was a more profound depletion of CD4+ T cells after the use of rabbit ATG (Fig. 3). One possible inference is that the depletion of CD8+ T cells is linked to the success of treatment with ATG (horse or rabbit), as expected from the pathophysiology of aplastic anemia, but that the loss of CD4+ T cells after the use of rabbit ATG may

be detrimental. The CD4+ cell compartment is phenotypically and functionally heterogeneous. Contained within the large CD4+ cell population are regulatory T cells, which modulate immune responses. In the current study, the frequency of regulatory T cells was higher after the use of rabbit ATG than after the use of horse ATG (as predicted from tissue-culture experiments),^{18,19} but this effect was negated by the more potent depletion of CD4+ T cells (Fig. 3E and 3F). CD4+ cells have other positive effects on hematopoiesis, and they may be important for hematologic recovery as well as for the promotion of tolerance in severe aplastic anemia (as after stem-cell transplantation).²⁸ In addition, horse serum might contribute to the recovery of hematopoiesis by stimulatory effects in the bone marrow.^{29,30} More prolonged lymphopenia after the use of rabbit ATG might impair marrow recovery, because stimulatory cytokines derived from T cells are depleted.³¹

It is unclear whether further intensification of immunosuppression will yield superior outcomes among patients with severe aplastic anemia.³² The addition of mycophenolate mofetil¹⁰ or sirolimus¹¹ to horse ATG plus cyclosporine has not achieved this goal, and the use of more potent lymphocytotoxic agents (rabbit ATG and alemtuzumab²⁷) in place of horse ATG has had inferior results. Although horse ATG is not available in many countries outside the United States, this agent combined with cyclosporine appears to be the most effective first-line immunosuppressive regimen for severe aplastic anemia.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Efficacy and safety of equine anti-thymocyte immunoglobulin (eATG) in three Japanese patients with moderate to very severe aplastic anemia: a case series

Yoshinobu Kanda¹ · Takehiko Mori^{2,3} · Atsushi Narita⁴ · Kevin D. Wolter⁵ · Hiroki Yoshimatsu⁶ · Kazuma Nishimura⁶

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Abstract

Aplastic anemia results from lymphocyte-mediated destruction of hematopoietic stem cells. Immunosuppressive therapy with anti-thymocyte globulin (ATG) and cyclosporine is the standard front-line treatment for patients with severe aplastic anemia who are not suitable candidates for stem cell transplants. PF-06462700 is a potent equine ATG that targets T-lymphocytes and has been approved as a treatment for aplastic anemia outside of Japan for over 30 years. Due to the high medical need for PF-06462700, the Ministry of Health, Labor and Welfare requested its development for Japanese patients with aplastic anemia. In this case series, the efficacy and safety of PF-06462700, administered intravenously at 40 mg/kg/day for 4 days, were assessed over a 24-week period. This was as an open-label, single-arm, multicenter clinical study designed to enroll a minimum of three Japanese participants with aplastic anemia. Two participants met the primary outcome of hematologic response at week 12 and improvements in disease severity were observed. No deaths or serious adverse events were reported. The efficacy results from this case series suggest that administration of PF-06462700 is generally well-tolerated and produces a hematologic response in Japanese patients with aplastic anemia, which should be further evaluated in real-world studies. ClinicalTrials.gov identifier: NCT04350606.

Keywords Equine anti-thymocyte immunoglobulin · Aplastic anemia · Hematologic response · eATG · Safety

Introduction

Aplastic anemia is mainly caused by immune-mediated destruction of hematopoietic stem cells by lymphocytes, resulting in pancytopenia [1]. The global incidence of aplastic anemia varies: between 2004 and 2012 there was

an estimated incidence of 8.2 cases of aplastic anemia per 1,000,000 person-years in Japan [2], which is considerably higher than the estimated incidence of 2.34 cases per million person-years in a European population study [3]. Standard front-line treatments for aplastic anemia include hematopoietic stem cell transplantation [4] or immunosuppressive therapy with anti-thymocyte globulin (ATG) and methylprednisolone plus cyclosporine (the latter for patients who are not suitable candidates for stem cell transplants) [5]. As part of their treatment strategy, patients with aplastic anemia also receive crucial supportive care, which includes transfusions of red blood cells and platelets, and prophylaxis with antimicrobials to prevent potentially fatal infections [1].

Equine ATG (eATG; PF-06462700) is an immunosuppressant that targets T-lymphocytes and has been available for over 30 years outside of Japan for the treatment of moderate-to-severe aplastic anemia [6]. Rapid depletion of lymphocytes with PF-06462700 was observed in a previous clinical study in patients with aplastic anemia [7]. eATG had better efficacy as a first-line treatment for severe aplastic anemia than rabbit ATG (rATG), as demonstrated by a

✉ Yoshinobu Kanda
ycanda-tky@umin.ac.jp

¹ Division of Hematology, Department of Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-Shi, Tochigi-Ken 329-0498, Japan

² Division of Hematology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan

³ Department of Hematology, Tokyo Medical and Dental University, Tokyo, Japan

⁴ Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan

⁵ Pfizer Inc, New York, NY, USA

⁶ Pfizer R&D Japan, Tokyo, Japan

significantly higher hematologic response rate following treatment with eATG compared with rATG, which subsequently translated into a higher survival rate [7]. In preclinical studies, PF-06462700 also stimulated both the growth of erythroid progenitor cells and the release of hematopoietic growth factors in vitro [8, 9]. It is possible that these activities also contribute to the therapeutic effect of PF-06462700 in aplastic anemia [8].

In October 2018, the 36th Meeting of the Study Group on Unapproved and Off-label Drugs of High Medical Need evaluated PF-06462700 as a drug with high medical need for aplastic anemia in Japan, and its development was requested by the Research and Development Division, Health Policy Bureau, Ministry of Health, Labor and Welfare in November 2018. PF-06462700 was designated as an Orphan Drug in Japan on March 11, 2021. A previous clinical study indicated the usefulness of two doses of PF-06462700 (10–20 mg/kg/day for 8 days) in 50 Japanese patients with aplastic anemia [10]; however, additional clinical data are required to support further development of PF-06462700 40 mg/kg/day for 4 days for use in Japan. This case series, conducted as an open-label, single-arm, multicenter clinical study, with design agreed by the Pharmaceuticals and Medical Devices Agency, assessed the efficacy and safety of PF-06462700 40 mg/kg/day for 4 days in Japanese patients with moderate and above aplastic anemia.

Methods

Participants

A minimum of three patients with aplastic anemia was planned for this non-statistically powered case series, based on the high medical need for PF-06462700 in Japan and the feasibility of the study in this rare disease, as agreed between the sponsor and the Pharmaceutical and Medical Devices Agency. Participants eligible for inclusion were males or females aged ≥ 2 years who had a clinical diagnosis of aplastic anemia based on either bone marrow aspiration and biopsy findings, magnetic resonance imaging, or both. Eligible participants also met criteria for moderate or above aplastic anemia (Stage 2b or worse) based on the diagnosis criteria established by the Japanese Study Group on Idiopathic Hematopoietic Disorders [11].

Exclusion criteria included: patients who were eligible and willing to have a sibling allogeneic stem cell transplantation; evidence of a myelodysplastic syndrome (except for refractory cytopenia in children) or other primitive marrow diseases; history or suspicion of congenital aplastic anemia; history of malignant tumors with active disease within 5 years; infection with hepatitis B or C virus, human immunodeficiency virus, or human T-cell leukemia virus type 1;

hypersensitivity after the skin test of the study drug; severe hepatic, renal, or cardiac failure, or any other life-threatening concurrent (aspartate aminotransferase, alanine aminotransferase, or total bilirubin values $> 5 \times$ upper limit of normal [ULN], and/or creatinine values $> 2 \times$ ULN); uncontrolled severe infection; vaccination with a live vaccine or live attenuated vaccine within 6 weeks of the first dose of study drug; prior stem cell transplant; or prior immunosuppressive therapy with lymphocyte-depleting agents/therapies, including both non-B-cell-selective and B-cell-depleting agents.

Study design

Participants were enrolled across three sites in Japan between 2020 and 2021. Following a screening period of up to 4 weeks, patients received intravenous PF-06462700 (Pfizer Inc, Michigan, USA) at 40 mg/kg/day for 4 days, with a 24-week follow-up period. Infusion time ranged from 4 to 24 h. Concomitant use of granulocyte-colony stimulating factor, eltrombopag, romiplostim, and anabolic steroids was permitted only if necessary; however, lymphocyte-depleting agents, ATGs (other than study drug), and immunosuppressants (except for cyclosporine and corticosteroids), were not permitted. The study protocol was reviewed and approved by the Institutional Review Board and/or Independent Ethics Committee at each study site, and the study was registered with Clinicaltrials.gov (NCT04350606). The study was conducted in accordance with international guidelines, including the Declaration of Helsinki, the Council for International Organizations of Medical Sciences International Ethical Guidelines, and the International Council for Harmonisation Good Clinical Practice Guidelines, along with local laws and regulations. Signed and dated informed consent was obtained from each participant before any study-specific activity was performed.

Efficacy outcomes

The primary endpoint was hematologic response at week 12, defined as meeting ≥ 2 of the following criteria (independently of administration of growth factors or transfusion): absolute neutrophil count $\geq 500/\mu\text{L}$; platelet count $\geq 20,000/\mu\text{L}$; and reticulocyte count $\geq 60,000/\mu\text{L}$. Secondary efficacy endpoints were hematologic response at week 24; hematologic test values (absolute neutrophil, platelet, and reticulocyte counts) at day 4 and at weeks 1, 2, 4, 6, 8, 10, 12, and 24; survival status; and transfusion independence at weeks 12 and 24, based on absence of any record of transfusion after the first dose of PF-06462700 to the day of the week 12 visit (inclusive) for week 12, and from the day after the week 12 visit to the week 24 visit (inclusive) for week 24. For patients with aplastic anemia Stage 2b/3 at screening or

baseline, an improvement in disease stage was also required to meet the hematologic response criteria.

Safety outcomes

Safety was monitored throughout the study based on treatment-emergent adverse events (TEAEs), serious adverse events, adverse events leading to discontinuation, vital signs, physical examination, 12-lead electrocardiograms (ECG), and clinical safety laboratory assessments. Adverse events were classified according to Medical Dictionary for Regulatory Activities, version 24.0.

Statistical analyses

Efficacy analyses were conducted on the full analysis set. The full analysis set and the safety analysis set included all participants who received ≥ 1 dose of PF-06462700. No statistical testing and inference were planned. Efficacy analyses were conducted without imputation for missing data, and all observations were included regardless of prohibited concomitant medication. Efficacy and safety data were reported for individual participants.

Results

Participants

Three Japanese participants aged 14–47 years, one male and two female with severe or very severe disease at baseline (Stage 4 or 5) were enrolled in this study. Prior to the start of the study, all three participants received transfusions of red blood cells and platelets. In addition, one participant had previously received medication for aplastic anemia rATG, cyclosporine, eltrombopag, and filgrastim. All three participants received concomitant cyclosporine and filgrastim and one participant received romiplostim during the study. All three participants enrolled in the study completed the treatment and follow-up periods.

Efficacy

Two of the three participants achieved hematologic response at week 12 with PF-06462700, which was accompanied by improvements in disease severity from Stage 4 to Stage 1, and from Stage 5 to Stage 3 (Table 1). The remaining participant also met the defined response criteria for all cell types at week 12. However, the counts were deemed to be dependent upon the administration of romiplostim during the study; therefore, the participant's hematologic response was classified as "not effective". This participant demonstrated an improvement in disease severity from Stage 5 to Stage 1.

At week 24, the hematologic response was consistent with that observed at week 12 (Table 1). In addition, increases in absolute neutrophil, platelet, and reticulocyte counts from baseline through week 24 were observed in all three participants (Fig. 1). Following treatment with PF-06462700 40 mg/kg/day for 4 days, all three participants remained transfusion-dependent at week 12 (i.e., all participants required transfusion within the 12 weeks prior to evaluation). However, two of the participants were transfusion-independent at week 24. For all participants, the frequency of blood transfusions decreased over time (Supplementary material, Table S1).

Safety

A total of 42 TEAEs were reported in the three participants. All three participants experienced ≥ 1 TEAE, most of which resolved during the study. The most common all-causality TEAEs observed in ≥ 2 participants were abdominal pain, nausea, hyperglycemia, and hypertension. All TEAEs were mild or moderate in severity. Moderate TEAEs were abdominal pain, nausea, hypogammaglobulinemia, staphylococcal infection, increased C-reactive protein, decreased oxygen saturation level, insomnia, and nail bed inflammation (each reported in one participant).

A total of 10 TEAEs were reported to be treatment-related, all of which were mild in severity. All three participants reported ≥ 1 treatment-related TEAE (Table 2). With regard to infectious complications, two participants developed cytomegalovirus (CMV) reactivation, with one reported as CMV infection, which was controlled by antivirals, and the other reported as CMV viremia, which did not require antiviral treatment. Decreases in white blood cells and lymphocytes were each reported once. There were no incidences of Epstein–Barr virus reactivation, deaths or serious TEAEs reported during the study. No clinically significant changes in laboratory parameters, vital signs, or ECG were reported.

Discussion

This case series, conducted as an open-label, single-arm, multicenter clinical study, assessed the efficacy and safety of PF-06462700 in Japanese patients with aplastic anemia. Although the number of enrolled participants was small, this was inline with anticipated recruitment numbers based on the rarity of aplastic anemia in Japan. Baseline disease characteristics and use of prior therapies were as expected for patients with severe aplastic anemia. All participants received concomitant immunosuppressive therapy with cyclosporine throughout the study participation period, which has been shown to improve response to ATGs [5]

Table 1 Hematologic response at weeks 12 (primary endpoint) and 24 (full analysis set)

Subject	Hematologic response ^a	Severity of aplastic anemia (stage)			Absolute neutrophil count		Platelet count		Reticulocyte count		
		BL	Week 12	Week 24	(per μL)	Improvement depends on transfusion	Improvement depends on hematopoietic growth factor	(per μL)	Improvement depends on transfusion	Improvement depends on hematopoietic growth factor	
Week 12											
1	Effective	4	1	–	2300	No	No	77,000	No	84,300	No
2	Effective	5	3	–	450	No	No	47,000	No	69,000	No
3	Not effective	5	1	–	5330	No	Yes	88,000	No	261,200	Yes
Week 24											
1	Effective	4	–	1	2700	No	No	139,000	No	53,760	No
2	Effective	5	–	1	750	No	No	58,000	No	85,000	No
3	Not effective	5	–	2A	1755	No	Yes	16,000	No	57,600	Yes

BL baseline

^aEffective defined as meeting ≥ 2 of the following criteria: absolute neutrophil count $\geq 500/\mu\text{L}$; platelet count $\geq 20,000/\mu\text{L}$; reticulocyte count $\geq 60,000/\mu\text{L}$. Improvement in counts that were dependent upon exogenously administered growth factors or transfusion were not considered as fulfilling response criteria. For subjects with Stage 2b or 3 at baseline/screening, hematologic response was defined as “effective” when 2 or more of the above-mentioned criteria were met and stage was improved

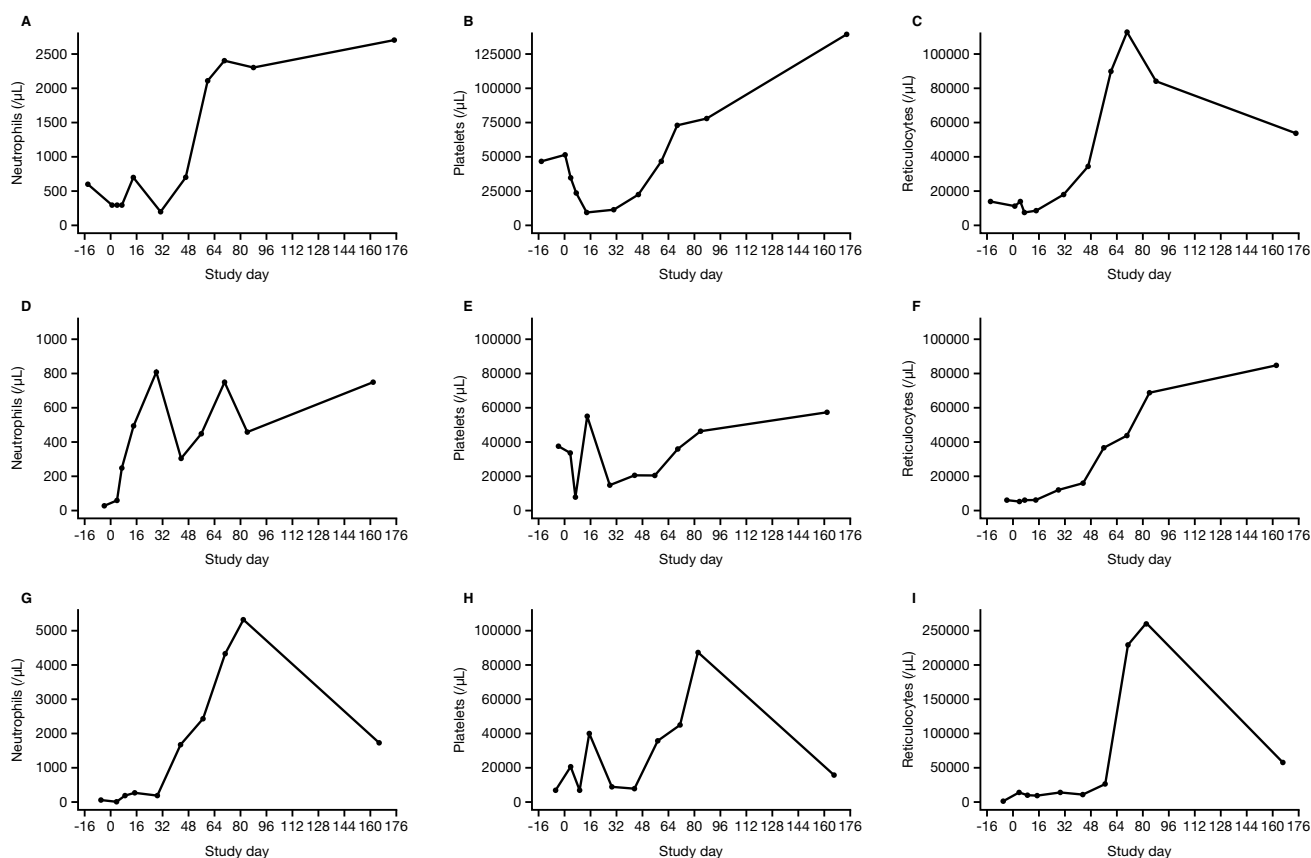


Fig. 1 Hematologic cell counts for absolute neutrophils, platelets, and reticulocytes in individual study participants. Participant 1 (A–C), participant 2 (D–F), and participant 3 (G–I)

and is recommended in combination with ATG therapies in Japanese guidelines [11].

An effective hematologic response was documented for two of the three participants while improvements in stage of disease from baseline was observed in all three participants by week 12. Similar findings were reported in previous non-Japanese studies, with a hematologic response rate of 50–62% for 3 months and 50–68% at 6 months observed following treatment with 40 mg/kg/day of eATG for 4 days plus cyclosporine, in patients with severe aplastic anemia [7, 12]. In addition, a retrospective analysis of real-world use of eATG reported an overall response rate at 12 months of 69.2% following eATG treatment in patients with moderate-to-severe aplastic anemia [13].

Two participants were transfusion-independent by week 24, and there was an overall gradual reduction in the frequency of blood transfusions for all three participants. The participant who remained transfusion-dependent at week 24 had Stage 5 disease at baseline and did not meet the criteria for hematologic response at weeks 12 or 24. Despite cell counts meeting the criteria for “effective”, the investigator judged the response to be “not effective” in this participant, since these counts might have been related to administration

of romiplostim, a thrombopoietin receptor-agonist that can stimulate erythrocyte, neutrophil, and platelet production in patients with aplastic anemia [14]. The same participant had previously received, and was refractory to, a combination of eltrombopag and rATG, and thus the efficacy of PF-06462700 as a second-line treatment was suggested but requires further investigation.

Our results suggest that intravenous administration of PF-06462700 at 40 mg/kg/day for 4 days is well-tolerated in Japanese patients, as no serious TEAEs or new safety signals were identified. Based on initial results from a previous clinical trial, PF-06462700 could be used in combination with the thrombopoietin receptor-agonist eltrombopag, as higher response rates were observed following treatment with standard immunosuppressive therapy (eATG and cyclosporine) and eltrombopag, compared with standard treatment alone [15].

Only three participants were enrolled in this case series. As planned, the results were not statistically verified, which may limit the ability of the study to draw definite conclusions. Hence, results should be interpreted with caution. A further limitation was the open-label, single-arm study design.

Table 2 Overview of treatment-related TEAEs by MedDRA System Organ Class and Preferred Term (safety analysis set)

System organ class	PF-06462700
Preferred term	40 mg/kg/day (<i>N</i> = 3)
Any treatment-related TEAE	3 ^a
Gastrointestinal disorders	1
Abdominal pain	1
General disorders and administration site conditions	2
Feeling abnormal	1
Infusion site extravasation	1
Edema	1
Immune system disorders	1
Serum sickness	1
Infections and infestations	2
Cytomegalovirus infection	1
Cytomegalovirus viremia	1
Investigations	2
Blood creatinine increased	1
Lymphocyte count decreased	1
White blood cell decreased	1

Data shown are number of subjects with individual TEAE; subjects could have had more than one TEAE in the same System Organ Class
MedDRA medical dictionary for regulatory activities, version 24.0,
TEAE treatment-emergent adverse event

^aA total of 10 events were recorded

The results presented suggest that intravenous administration of PF-06462700 40 mg/kg/day is well-tolerated and produces an effective hematologic response in Japanese patients with aplastic anemia. The efficacy and safety of PF-06462700 in Japanese patients was comparable with findings in previous clinical studies in Western participants. Due to the small sample size, the efficacy and safety of PF-06462700 in Japanese patients should be further investigated in real-world studies with larger patient populations.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12185-022-03496-5>.

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Author contributions Study design: YK, TM, AN, KDW, HY, KN. Study execution: YK, TM, AN, KN. Data analysis and interpretation: KDW, HY, KN. Edit and review of the manuscript: YK, TM, AN, KDW, HY, KN.

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Data availability Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

Declarations

Conflict of interest YK, TM, and AN have no conflicts to declare. KDW is an employee and shareholder of Pfizer Inc. KN is an employee and shareholder of Pfizer R&D Japan. HY is an employee of Pfizer R&D Japan.

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