RESEARCH LETTER

blood advances

TO THE EDITOR:

Long-term efficacy and safety of romiplostim in refractory aplastic anemia: follow-up of a phase 2/3 study

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Romiplostim is an Fc-peptide fusion protein that activates intracellular transcriptional pathways via the thrombopoietin receptor,[1] resulting in stimulation of hematopoietic stem and progenitor cells, as well as megakaryocytes. We previously conducted a 52-week, open-label, phase 2/3 study to assess the efficacy and safety of weekly romiplostim at an initial dose of 10 μg/kg that was up-titrated to a maximum of 20 μg/kg for patients with aplastic anemia (AA) refractory to immunosuppressive therapy.[2] At weeks 27 and 53, 26 of 31 (84%) and 25 of 31 (81%) of patients, respectively, achieved any (ie, platelet, neutrophil, or erythrocyte) hematologic response.[3] However, long-term efficacy and safety data of romiplostim for refractory AA beyond 53 weeks remain scarce. To clarify this, we prospectively evaluated clinical courses of patients with AA who continued romiplostim for up to 3.5 years including the first 53 weeks of treatment (supplemental Figure 1).

Twenty-seven patients who completed the week 53 assessment of the first study (evaluation study) and gave written informed consent were enrolled in this extension study (supplemental Figure 2). Further details of the study methods can be found in the supplemental Methods. The main characteristics of the 27 patients at enrollment in the evaluation study and hematologic parameters at the beginning of this extension study are summarized in supplemental Table 1. Seven (25.9%) and 3 (11.1%) of the 27 patients had severe and very severe AA, respectively. Twenty-one (77.8%) and 4 (14.8%) patients required transfusions at the beginning of the evaluation and extension studies. Twenty-three, 7, and 6 patients remained in this study at 104, 156, and 182 weeks, respectively. The median duration of romiplostim treatment was 137.1 (range, 16.0 to 191.3) weeks. The median cumulative dose was 1690.0 (range, 180. to 3695.0) μg/kg, and the dose per week was 15.9 (range, 1.3 to 19.3) μg/kg from the beginning of the evaluation study. The changes in weekly doses administered to patients from the start of the evaluation period until the end of the extension period are shown in supplemental Figure 3.

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All data including study participant data, data dictionary, statistical analysis plan, and informed consent will not be shared.

The protocol is available on reasonable written request from the corresponding author, Shinji Nakao (snakao8205@staff.kanazawa-u.ac.jp).

The full-text version of this article contains a data supplement.

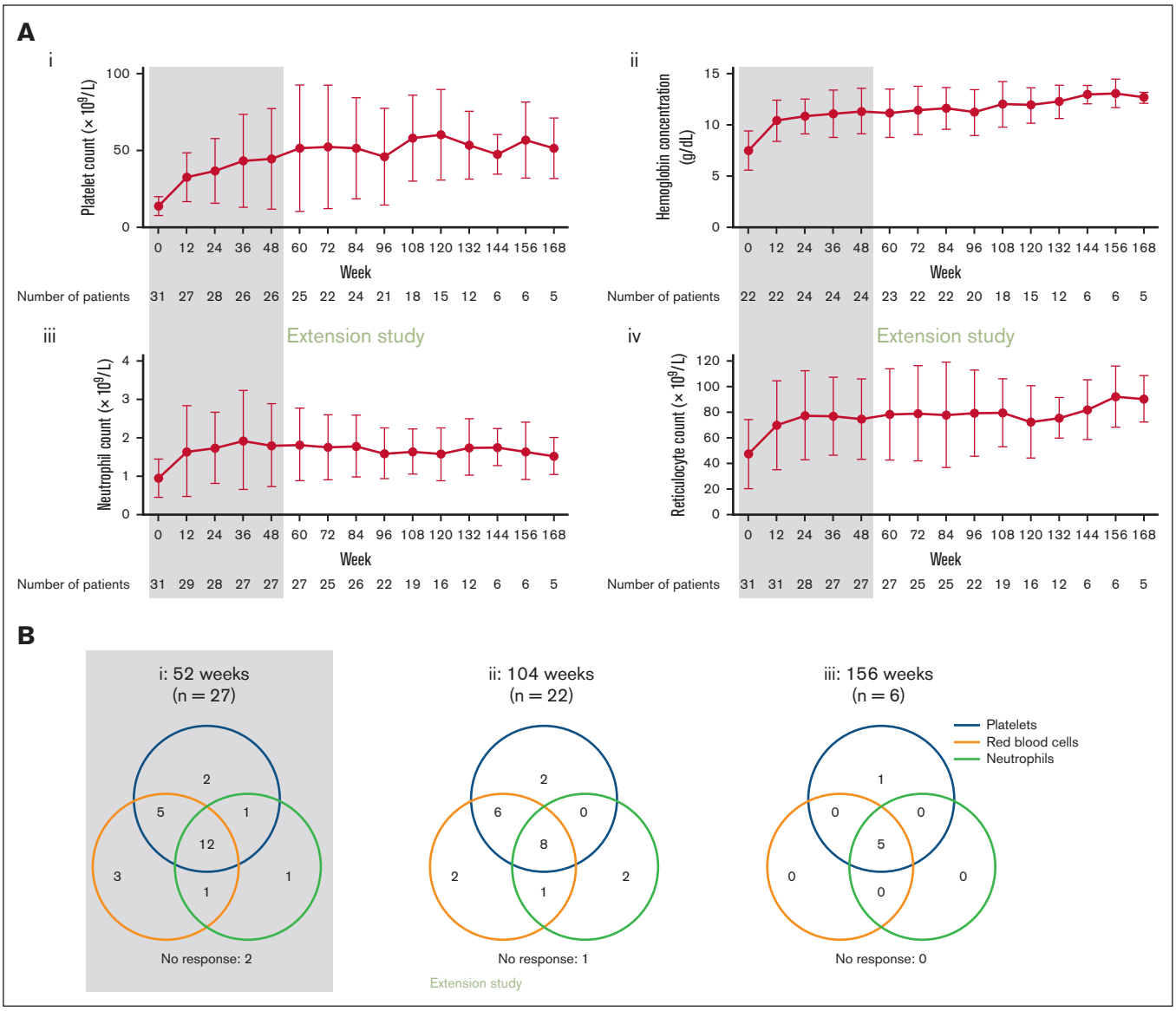

Figure 1. Long-term efficacy of romiplostim. (A) Change in hematologic parameters during the entire period; (i) platelet count, (ii) hemoglobin concentration, (iii) neutrophil count, and (iv) reticulocyte count. (B) Hematologic responses to romiplostim at (i) 52 weeks, (ii) 104 weeks, and (iii) 156 weeks. The numbers of cases with missing data were 5 at 104 weeks and 21 at 156 weeks. Of the patients for whom data could be collected, no response was 1 at 104 weeks and 0 at 156 weeks.

Figure 1A shows the changes in platelet counts, hemoglobin concentration, neutrophil counts, and reticulocyte counts from the start of the evaluation study until the end of the extension study. After entering the extension study, all blood cell counts continued to increase, whereas neutrophil counts remained relatively stable until the end of the extension period (42 months). Further details of the changes in the blood cell counts can be found in the supplemental Results.

The numbers of hematologic responses during the entire study are shown in Figure 1B. Of the 23 patients who remained in the study after 2 years (104 weeks; at 1 year of the extension study), 22 were evaluable for response. Remarkably, 21 patients showed responses to romiplostim in at least 1 lineage of cells. Four of the 7 patients who had not achieved a response in platelets, 2 of the 6 patients in red blood cells, and 2 of the 2 patients in any of the 3 lineages of cells at week 53 obtained their respective responses during the extension study. The Kaplan-Meier curve of trilineage response during the entire period of the study (supplemental Figure 4) increased up to 1 year from baseline and remained stable thereafter until the end of the study, with a cumulative incidence of 55%. Supplemental Figure 5 illustrates details of patients with trilineage response, including the onset of each hematologic response. The changes in the proportion of patients dependent on platelet and/or red blood cell transfusion throughout the evaluation and extension studies are highlighted in supplemental Figure 6.

The proportion of patients dependent on transfusion decreased from 23 of 23 (100%) at baseline to 4 of 21 (19.0%) at 1 year during the evaluation study but increased to 5 of 19 (26.3%) at 2

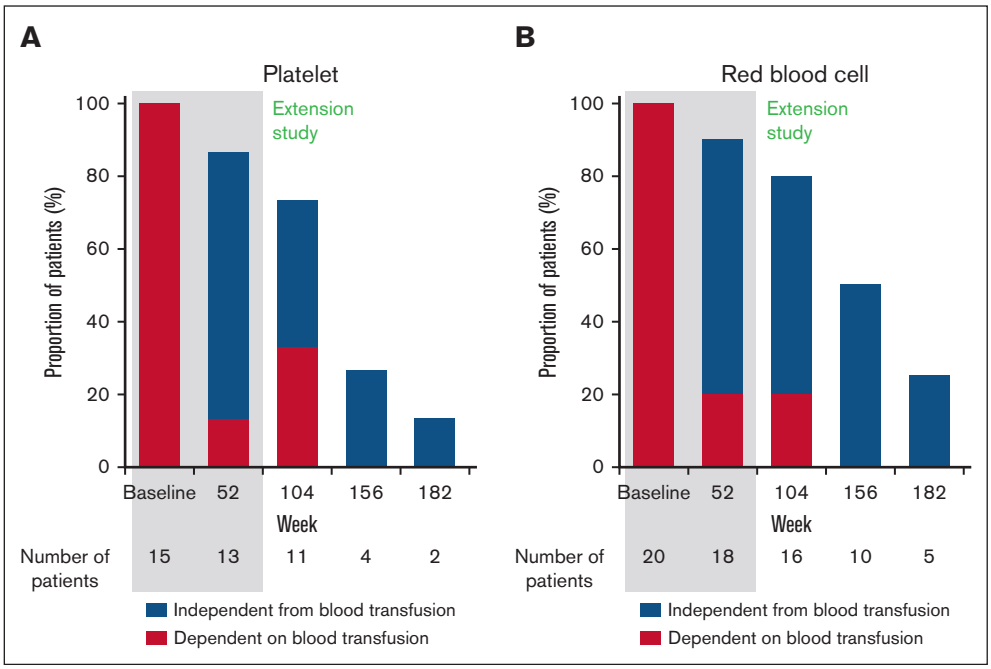

Figure 2. Proportion of transfusion-dependent patients based on the type of transfusion during the entire period. (A) Platelet and (B) red blood cell.

years. Nevertheless, by week 156 of the extension study, all patients achieved independence from blood transfusion, which persisted until week 182. The changes in the proportions of patients dependent on red blood cell transfusion and platelet transfusion are depicted in Figure 2. No differences were observed in the red blood cell or platelet transfusion rates.

Of note, 4 patients achieved any sustained hematologic response, which lasted for 29 to 111 weeks until the end of the extension study, after discontinuation of romiplostim at week 51 to week 121. The relevant background factors of these patients at the beginning of the evaluation study are summarized in supplemental Table 2. Among baseline blood cell counts, the median reticulocyte counts (69.9×10^9/L; range, 50.2×10^9/L to 93.8×10^9/L) of these patients tended to be higher ($P = .087$) than those of the remaining 23 patients (45.80×10^9/L; range, 2.7×10^9/L to 114.7×10^9/L) who obtained a platelet response at least once but required romiplostim to maintain the response until the end of the extension study.

Five patients (18.5%) with AA showed a response once but lost the response under the continuous administration of romiplostim with the maximum dose of 20 μg/kg for >8 weeks (relapse on romiplostim, n = 4) or upon the discontinuation of romiplostim without responding to reinitiation with the maximum dose (failure to respond to second romiplostim, n = 1). The characteristics of these patients with secondary refractoriness are shown in supplemental Table 3. In these patients, the platelet count was in the minimum and maximum range of 5 to 36×10^9/L and 18 to 114×10^9/L, respectively, and the hemoglobin concentration was in that of 5.0 to 7.0 g/dL and 7.9 to 12.5 g/dL during the entire period of the study. All 5 patients discontinued romiplostim because of a lack of response from baseline until weeks 72 to 129.

The main adverse events (AEs) that occurred in the extension study are listed in supplemental Table 4. According to the investigator's judgment, 10 AEs in 7 patients were possibly related to romiplostim, whereas 2 AEs in 2 patients were considered related to romiplostim. The most commonly encountered side effects of romiplostim included headache in 2 patients (7.4%). The incidence of grade 3 AEs was 3.7% (1 weight increase event in 1 patient), and no grade 4/5 AEs were observed.

Development of cytogenetic abnormality in 1 patient led to the discontinuation of romiplostim. G-banding analysis of bone marrow cells revealed chromosomal abnormalities in 2 patients during the extension study (supplemental Table 5). One patient developed t(11;17)(q23;q12) or t(11;17)(q23;q21) (5 metaphases among 20) at week 108. Although the patient did not show any morphological signs of transformation to myelodysplastic syndromes or acute myeloid leukemia, the administration of romiplostim was stopped at week 137 because the abnormal clone was expanded (16 of 20 metaphases) at week 134. The other patient showed trilineage hematologic response to romiplostim and developed add(10)(p11.2) (1 metaphase among 20) at week 134 but continued the treatment until the end of the study (week 153). No patients, including the 2 patients with chromosomal abnormalities, progressed to myelodysplastic syndrome or acute myeloid leukemia during the extension period.

The overall response rate to romiplostim in our cohort at any given time (77.8%) appears to be superior to the response observed with eltrombopag (50.0%) in 40 patients diagnosed with severe AA, as demonstrated by Winkler et al.[4] However, it is essential to note that the majority (63.0%) of our patient cohort consisted of patients with nonsevere AA. Consequently, it would be inappropriate to draw indirect comparisons of effectiveness between different thrombopoietin receptor agonists in AA.

In conclusion, long-term administration of romiplostim up to 3.5 years in length of time was found to be effective and tolerable in adults with AA refractory to, or ineligible for, antithymocyte globulin. A

considerable proportion of patients eventually achieved a response by continuing the administration for more than 1 year, demonstrating the presence of late responders to romiplostim. Beneficial effects were maintained or augmented by prolonged administration of romiplostim, and some patients achieved any sustained hematologic response even after the discontinuation of romiplostim.

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