



# AAMDSIF

## **Aplastic Anemia Research Summary** *from the* 2017 AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING

*Summary of Selected Scientific Abstracts for Patients with Aplastic Anemia and Their Caregivers*

### DIAGNOSIS

**2468**

#### **Genetic Sequencing of Children with Bone Marrow Failure Syndromes**

*Hideki Muramatsu, MD, PhD, Yusuke Okuno, MD, PhD, Kenichi Yoshida, MD, PhD, Yuichi Shiraishi, PhD, Sayoko Doisaki, Atsushi Narita, MD, PhD, Hirotochi Sakaguchi, MD, PhD, Nozomu Kawashima, MD, PhD, Xinan Wang, PhD, MD6, Yinyan Xu, Kenichi Chiba, Hiroko Tanaka, Asahito Hama, Masashi Sanada, MD, Yoshiyuki Takahashi, MD, PhD, Hitoshi Kanno, MD, PhD, Hiroki Yamaguchi, MD, PhD, Shouichi Ohga, Atsushi Manabe, MD, PhD, Hideo Harigae, MD, Shinji Kunishima, PhD, Eiichi Ishii, MD, PhD, Masao Kobayashi, MD, PhD, Kenichi Koike, MD, PhD, Kenichiro Watanabe, MD, PhD, Etsuro Ito, MD, PhD, Minoru Takata, MD, PhD, Miharu Yabe, Seishi Ogawa, MD, PhD, Satoru Miyano, PhD, Seiji Kojima, MD, PhD*

In bone marrow failure syndromes, the bone marrow stops making enough healthy blood cells. These diseases can be inherited from the patient's parents, but most cases aren't inherited. It's important for doctors to diagnose bone marrow syndromes accurately because different syndromes require different types of treatment.

A team from Japan assessed genetic information from 347 children, including 166

with inherited bone marrow failure syndromes and 164 with non-inherited syndromes (MDS and aplastic anemia). The inherited bone marrow failure syndromes included Fanconi anemia, Diamond-Blackfan anemia, congenital dyserythropoietic anemia, severe congenital neutropenia, and dyskeratosis congenita.

#### **Key findings:**

- The investigators were able to diagnose 86 patients (25%) based on genetic mutations.
- The diagnosis rate was higher, at 36%, for patients with inherited bone marrow failure syndromes.
- 10 patients (6%) who had been diagnosed with aplastic anemia had inherited genetic mutations.
- The research team identified somatic mutations, or changes in genes that happened after conception, in another 10 patients with aplastic anemia as well as 6 patients (35%) with MDS.

#### **Conclusions:**

- Genetic sequencing resulted in a satisfactory rate of accurate diagnoses.
- The results show the effectiveness of sequencing many genes to diagnose both inherited and non-inherited bone marrow failure syndromes.

# STEM CELL TRANSPLANTATION

**1184**

## **Donor Telomere Length and Outcomes of Stem Cell Transplantation in Aplastic Anemia**

*Aruna Barade, MTech, Anu Korula, MD, DM, Nisham PN, MD, DM, Kavitha M Lakshmi, MSc, Uday Prakash Kulkarni, MD, DM, Anup Devasia, MD, DM, Aby Abraham, MD, DM, Alok Srivastava, MD, Vikram Mathews, MD, DM, Eunice Sindhuvi Edison, PhD, Biju George, MD, DM*

Telomeres, located at the ends of chromosomes, help keep chromosomes stable. As people age, their telomeres become shorter, and this shortening is fastest in the first 20 years of life. Some research suggests that the telomere length of stem cell donors can affect outcomes of stem cell transplantation in patients with aplastic anemia.

A research team from the Christian Medical College in Vellore, India, studied the effects of the telomere length of stem cell donors on outcomes in 170 patients with aplastic anemia (median age 22) who underwent stem cell transplantation. Most patients had severe aplastic anemia (70%) or very severe aplastic anemia (18%). Of these patients, 137 received cells from a sibling, 9 had an unrelated donor whose blood HLA markers matched theirs, and 24 had haploidentical donors (the donor's HLA markers matched half the patient's HLA markers).

### **Key findings:**

- Time to engraftment (when the transplanted cells reached the bone marrow and began making healthy blood cells) was shorter with donors who had longer telomeres.
- Donor telomere length was not associated with risk of graft-versus-host disease in patients.
- The transplanted cells didn't engraft in 19% of patients whose donor was related and had short telomeres, compared with 11% of all patients with a related donor.
- Long donor telomeres were associated with better outcomes.

### **Conclusions:**

- The donor's telomere length plays an important role in the engraftment of transplanted stem cells in patients with aplastic anemia.
- Telomere length also affects the likelihood that the transplanted cells won't engraft and how long patients survive after receiving donated cells from a relative.

# NON-TRANSPLANTATION TREATMENTS

**777**

## **Eltrombopag for Severe Aplastic Anemia**

*Thomas Winkler, MD, James N. Cooper, MD, Danielle M. Townsley, MD, MSc, Phillip Scheinberg, MD, Sophia Grasmeyer, RN, Colin Wu, PhD, Jennifer Lotter, Marie J. Desierto, MS, Ronan Desmond, MD, Matthew J. Olnes, MD, PhD, Katherine R Calvo, MD, PhD, Neal S. Young, MD, Cynthia E. Dunbar, MD*

The U.S. Food and Drug Administration approved eltrombopag (Promacta) for the treatment of severe aplastic anemia in 2014. This approval was based on a Phase I/II clinical trial of 50 to 150 mg eltrombopag per day for 12 weeks.

The investigators of that trial conducted a follow-up Phase II study of 150 mg eltrombopag for 6 months in 39 patients with severe aplastic anemia that had not responded or had stopped responding to other treatments.

### **Key findings:**

- 19 patients (49%) responded to eltrombopag treatment at 6 months.
- 18 of these patients continued eltrombopag treatment, and 13 (72%) were able to stop eltrombopag treatment because they had robust responses after an average of 12 months.
- 3 of the 13 patients who stopped eltrombopag because of a strong response started taking it again after they had a relapse, and all 3 responded to this second treatment course.
- Of 83 participants in both clinical trials, disease progressed in 16 patients (18%), usually within 6 months.

### **Conclusions:**

- A fixed dose of 150 mg eltrombopag daily for 6 instead of 3 months increased the likelihood of responding in some patients with severe aplastic anemia.
- After the treatment ended, most patients maintained robust responses.

# NON-TRANSPLANTATION TREATMENTS

**1183**

## **Tacrolimus for Aplastic Anemia**

*Victor Chiu, MD, Ilene Ceil Weitz, MD, David J. Hermel, MD*

Immunosuppressive therapy (IST) with cyclosporine and horse antithymocyte globulin (ATG) is the standard treatment for patients with aplastic anemia who aren't eligible for stem cell transplantation. These drugs weaken the patient's immune system and stop it from attacking the bone marrow.

But cyclosporine has problematic side effects, such as gum disease and excessive body hair. Tacrolimus (Prograf) has less severe side effects than cyclosporine, but its use as an alternative to cyclosporine hasn't been studied.

A research team from the University of Southern California analyzed data on 23 patients with moderate, severe, or very severe aplastic anemia treated with tacrolimus and horse ATG. On average, they were 40 years old at diagnosis, 65% were female, 48% were Latino, and 35% were Caucasian.

### **Key findings:**

- After 3 months of treatment, 75% responded, and 100% did so by 12 months.
- Among those with severe aplastic anemia, the overall response rates were 75% at 3 months and 27% at 12 months. Two of these patients eventually had stem cell transplantation.
- 11 patients were treated with tacrolimus after they stopped cyclosporine because they had side effects or an incomplete response.
- Among patients who had severe or very severe AA treated with cyclosporine before, 55% responded to tacrolimus at 3 months and 45% did so at 12 months. But all responders had moderate aplastic anemia.

### **Conclusions:**

- First-line treatment with tacrolimus and ATG for aplastic anemia is safe.
- Second-line treatment with tacrolimus in patients previously treated with cyclosporine can achieve significant responses if their aplastic anemia is moderate.

# NON-TRANSPLANTATION TREATMENTS

**1186**

## **Outcomes of Long-Term Calcineurin Inhibitor Treatment in Severe Aplastic Anemia**

*Steven D. Green, MD, Joyatee M. Sarker, PhD, Erica B. Bernhardt, MD, Muhammad Khawaja, MBBS, MPH, Robert P. Nelson Jr., MD*

Standard treatment for aplastic anemia is stem cell transplantation or immunosuppression treatment (IST) with antithymocyte globulin (ATG) and a calcineurin inhibitor (either tacrolimus or cyclosporine). These ISTs weaken the patient's immune system and stop it from attacking the bone marrow. Guidelines call for stopping calcineurin inhibition treatment after 4–6 months.

The purpose of this study was to compare outcomes of IST for longer than 6 months to stem cell transplantation outcomes in 24 patients with severe aplastic anemia. Fifteen patients were treated with IST for longer than 6 months, and 9 underwent stem cell transplantation.

### **Key findings:**

- Patients who underwent stem cell transplantation had greater improvements than those treated with IST in white blood cell counts for up to 15 months, hemoglobin counts for up to 7 months, and platelet counts for up to 48 months.
- But beyond these times, the difference in outcomes between the two groups was not significant.
- 88% of those treated with IST survived until the end of the study (an average of 34 months), compared with 89% of those who underwent stem cell transplantation.
- Patients treated with calcineurin inhibitors for longer than 6 months had a significant improvement in their hemoglobin counts starting at 30 months.

### **Conclusions:**

- Stem cell transplantation improved blood cell counts more than calcineurin inhibitors at first, but the difference eventually disappeared.
- Patients treated with calcineurin inhibitors for longer than 6 months showed a consistent increase in blood cell counts, but this increase wasn't statistically significant (except, maybe, for hemoglobin) compared with counts at 6 months.

**2456**

## **Aplastic Anemia Treatment with Extracellular Vesicles from Mesenchymal Stem Cells**

*Sicheng Wen, MD, PhD, Mark S Dooner, Elaine Papa, Michael Del Tatto, Mandy Pereira, Yan Cheng, Laura R Goldberg, MD, PhD, Peter J. Quesenberry, MD*

Mesenchymal stem cells (MSCs) are immature cells that can become different types of cells. Like other cells, when mesenchymal stem cells die, they release molecules known as “vesicles” into the surrounding, or extracellular, environment. Vesicles from MSCs can help heal many different types of cells.

A research team from Rhode Island Hospital evaluated the ability of extracellular vesicles (EVs) from MSCs to reverse bone marrow failure in a mouse breed with aplastic anemia.

### **Key findings:**

- Infusions of human MSC EVs significantly prolonged survival in the mice.
- Although half the treated mice died within 30 days, only 30% of treated mice died within this time.
- Bone marrow stem cell counts were significantly higher in treated than non-treated mice.
- The MSC EV treatment also partially or completely reversed some of the RNA damage associated with aplastic anemia.

### **Conclusions:**

- MSC EV treatment partially and quickly reversed bone marrow failure in mice.