

# Treatment of inherited thrombocytopenias

Carlo L. Balduini

Ferrata-Storti Foundation and University of Pavia, Pavia, Italy

## Correspondence:

Carlo L. Balduini  
[carlo.balduini@unipv.it](mailto:carlo.balduini@unipv.it)

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## Abstract

The new techniques of genetic analysis have made it possible to identify many new forms of inherited thrombocytopenias (IT) and study large series of patients. In recent years, this has changed the view of IT, highlighting the fact that, in contrast to previous belief, most patients have a modest bleeding diathesis. On the other hand, it has become evident that some of the mutations responsible for platelet deficiency predispose the patient to serious, potentially life-threatening diseases. Today's vision of IT is, therefore, very different from that of the past and the therapeutic approach must take these changes into account while also making use of the new therapies that have become available in the meantime. This review, the first devoted entirely to IT therapy, discusses how to prevent bleeding in those patients who are exposed to this risk, how to treat it if it occurs, and how to manage the serious illnesses to which patients with IT may be predisposed.

## Introduction

Until a few years ago, a review entirely dedicated to the therapy of inherited thrombocytopenias (IT) would have been unthinkable because the therapeutic armamentarium was extremely limited and no clinical studies were available to evaluate the efficacy of different treatments. On the other hand, very few forms of IT were known and, consequently, the series of patients with these diseases were also very small. In the last 20 years, the number of well-defined forms has rapidly increased, passing from a handful of diseases to almost 50 different forms. In addition, case series with reports on hundreds of patients have appeared in the literature. It was, therefore, possible to learn more about these diseases and identify new treatments. These advances now allow me to write a review entirely dedicated to IT.

Being a niche topic, I think it is useful to devote a few lines to what is the current vision of IT. In addition, I believe it useful to include a table reporting the essential characteristics of the diseases mentioned in the paper (Table 1). For a detailed description of IT, the reader is invited to refer to the exhaustive reviews that have recently appeared in the literature.<sup>1-3</sup>

## The changing view of inherited thrombocytopenias

Until twenty years ago, IT were considered extremely rare, and were almost always characterized by a severe hemorrhagic diathesis. In 2012, their prevalence was estimated to be around 2.7 in 100,000, similar to that of severe hemophilia A and myelofibrosis with myeloid metaplasia. In the last 10 years, many new forms of IT have been discovered, and therefore the rate calculated 10 years ago very probably underestimates the real prevalence of these diseases. IT are, therefore, although rare, not so rare as originally thought. Today, we also know that most of the affected subjects have a moderate, mild or even absent spontaneous bleeding diathesis, although bleeding may occur during hemostatic challenges, such as surgery, childbirth, or taking medications that further hinder hemostasis. From this point of view, the clinical phenotype is, therefore, less serious than previously thought. However, an unpleasant surprise has emerged from the analysis of large case series: many IT predispose to the development of additional diseases, including hematological malignancies, bone marrow aplasia, and severe non-hematological illnesses, which strongly influences the prognosis of af-

**Table 1.** Essential features of the inherited thrombocytopenias mentioned in this review.

| Disease (abbreviation, OMIM entry)   | Freq. <sup>1</sup> | Gene                                       | Peculiar features  |
|--|--------------------|--|--|
| <b>FORMS WITH ONLY THROMBOCYTOPENIA</b>  |                    |  |  |
| Bernard-Soulier syndrome, biallelic form (bBSS, 231200)  | ++++               | <i>GP1BA</i><br><i>GP1BB</i><br><i>GP9</i> | Severely defective platelet function.  |
| Bernard-Soulier syndrome, monoallelic form (mBSS, 153670)  | +++                |  |  |
| Gray platelet syndrome (GPS, 139090)   | ++                 | <i>NBEAL2</i>                              | Defective platelet function. Development of progressive bone marrow fibrosis and splenomegaly. Platelet count decreases over time.   |
| <i>ITGA2B/ITGB3</i> -related thrombocytopenia ( <i>ITGA2B/ITGB3</i> -RT, 187800)   | ++                 | <i>ITGA2B</i><br><i>ITGB3</i>              | Defective platelet function.   |
| <i>SLFN14</i> -related thrombocytopenia ( <i>SLFN14</i> -RT, 616913)   | +                  | <i>SLFN14</i>                              | Defective platelet function.   |
| <i>FLI1</i> -related thrombocytopenia  | +                  | <i>FLI1</i>                                | Defective platelet function.   |
| <b>SYNDROMIC FORMS</b>   |                    |  |  |
| Jacobsen syndrome (JBS, 147791), Paris-Trousseau thrombocytopenia (TCPT, 188025)   | ++++               | Deletions in 11q23                         | Physical growth delay, intellectual disability and various malformations. Defective platelet function.   |
| Thrombocytopenia with absent radii (TAR, 274000)   | +++                | <i>RBM8A</i>                               | Bilateral radial aplasia +/- other upper and lower limb bone abnormalities. Platelet count spontaneously increases over time.  |
| Wiskott-Aldrich syndrome (WAS, 301000)   | ++++               | <i>WAS</i>                                 | Severe immunodeficiency leading to early death. Eczema. Increased risk of malignancies and autoimmunity.   |
| X-linked thrombocytopenia (XLT or THC1, 313900)  |                    |  | Mild immunodeficiency. Mild and transient eczema. Increased risk of malignancies and autoimmunity.   |
| <b>FORMS PREDISPOSING TO ADDITIONAL DISEASES</b>   |                    |  |  |
| <i>MYH9</i> -related disease ( <i>MYH9</i> -RD, 155100)  | ++++               | <i>MYH9</i>                                | Most patients develop extra-hematological manifestations, i.e., sensorineural deafness, nephropathy evolving into kidney failure, and/or cataracts.  |
| <i>ANKRD26</i> -related thrombocytopenia ( <i>ANKRD26</i> -RT or THC2, 188000)   | +++                | <i>ANKRD26</i>                             | Propensity to acquire myeloid malignancies (about 10% of reported patients).   |
| Familial platelet disorder with propensity to acute myelogenous leukemia (FPD-AML, 601399)                                   | +++                | <i>RUNX1</i>                               | Propensity to acquire myeloid malignancies (over 40% of reported patients). Increased risk of T-cell acute lymphoblastic leukemia. Defective platelet function.  |
| <i>ETV6</i> -related thrombocytopenia ( <i>ETV6</i> -RT or THC5, 616216)   | ++                 | <i>ETV6</i>                                | Propensity to acquire hematological malignancies (about 30% of reported patients), especially childhood B-cell acute lymphoblastic leukemia.   |
| Congenital amegakaryocytic thrombocytopenia (CAMT, 604498)   | +++                | <i>MPL</i>                                 | Evolution to bone marrow aplasia during infancy or childhood.  |
| Congenital amegakaryocytic thrombocytopenia variant due to biallelic <i>THPO</i> mutation (na, na)                           | +                  | <i>THPO</i>                                | Evolution to bone marrow aplasia during infancy or childhood.  |
| <i>MECOM</i> -associated syndrome, including radioulnar synostosis with amegakaryocytic thrombocytopenia 2 (RUSAT2, 616738). | ++                 | <i>MECOM</i>                               | Evolution to bone marrow aplasia during infancy or childhood. Bilateral radioulnar synostosis is frequent. Possible other skeletal anomalies, cardiac and/or renal malformations, and/or sensorineural deafness. |

Continued on following page.

|  |   |               |  |
|--|---|---------------|--|
| Radioulnar synostosis with amegakaryocytic thrombocytopenia 1 (RUSAT1, 605432) | + | <i>HOXA11</i> | Possible evolution to marrow aplasia during infancy or childhood. Bilateral radioulnar synostosis and other skeletal abnormalities and/or sensorineural deafness |
| <i>GNE</i> -related disorder ( <i>GNE</i> -RD, na)                             | + | <i>GNE</i>    | Biallelic mutations can cause thrombocytopenia and late-onset muscle disorder while monoallelic mutations cause sialuria   |
| <i>DIAPH1</i> -related disorder ( <i>DIAPH1</i> -RD, 124900)                   | + | <i>DIAPH1</i> | Patients develop progressive sensorineural deafness during infancy or childhood. Recurrent mild neutropenia in some cases.                                       |

The presence of clinically relevant defect of platelet function is in red. In these cases the bleeding risk is higher than predicted by the platelet count and patient management must take into account this evidence. <sup>1</sup>Freq.: frequency; +: less than 10 reported families; ++: more than 10 reported families; +++: more than 50 reported families; ++++: more than 200 reported families.

ected subjects (Table 1). Altogether, the prevalence of IT predisposing to other diseases is near 50% of the known forms (Figure 1). The most feared risk for subjects with IT is, therefore, no longer that of bleeding, but of developing potentially fatal diseases (Figure 2). This has become even truer in recent years due to the identification of treatments capable of increasing the number of platelets and/or reducing the bleeding risk in many IT (Table 2).

**Platelet transfusion**

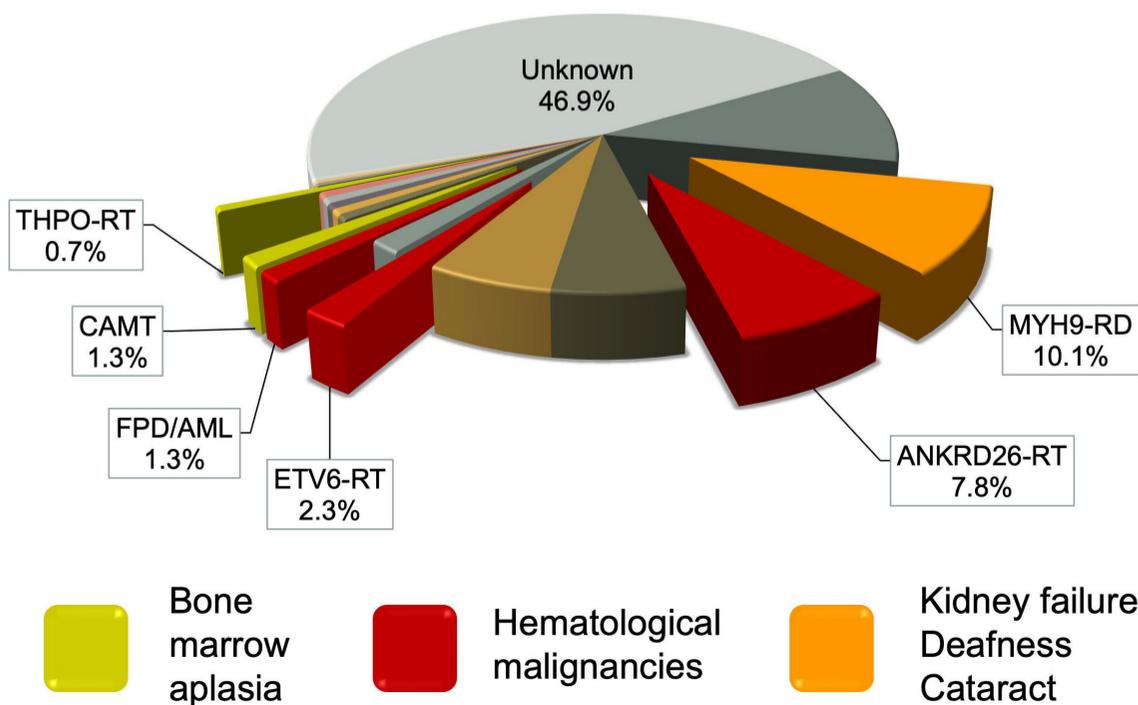
Platelet transfusions are the most effective therapeutic intervention to stop bleeding in people with IT. However, the risk of acute reactions, transmissions of infectious agents, transfusion-associated graft-versus-host disease (TA-GvHD) and alloimmunization with consequent refractoriness to subsequent platelet transfusions is intrinsic to this treatment.<sup>4,6</sup> The formation of antibodies against donor HLA antigens is a highly detrimental event in IT patients because most of them are destined to remain thrombocytopenic for life, and alloimmunization could compromise the efficacy of future platelet support and put their lives at risk. The use of platelet transfusions should, therefore, be limited to bleeding that cannot be controlled with localized measures, to life-threatening hemorrhages, or to bleeding at critical sites.

When platelet transfusion is essential, the risk of alloimmunization can be significantly reduced by two approaches: 1) leukoreduced platelet concentrates; and 2) HLA-matched donors.<sup>7</sup> Although clinical studies in patients with IT are not available, experience in other clinical conditions provides useful indications.

**Treatments to stop hemorrhages**

**Bleeding from accessible sites**

Localized measures are often successful for mucocutaneous hemorrhages.<sup>4,5</sup> Nasal packing and/or endoscopic cauterization may be effective for stopping epistaxis. Suturing often stops hemorrhages from accidental or surgical wounds (e.g., bleeding after tooth extraction). Compression and application of gelatin sponges or gauzes soaked in tranexamic acid can help stop bleeding from superficial wounds. Mouthwash with tranexamic acid may be useful for gum bleeding.

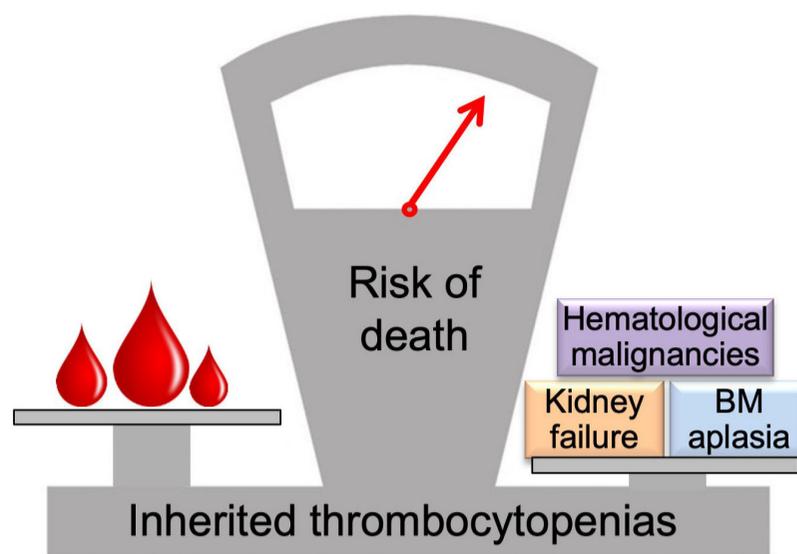


**Figure 1. Inherited thrombocytopenias (IT) predisposing to other disorders.**

Based on personal experience (303 consecutive families with IT), 45% of patients with known IT have one of the forms that predispose to additional disorders, including glomerulonephritis, bone marrow aplasia, leukemia and myelodysplastic syndromes. Recognizing patients with the IT highlighted in the figure is important because they need a specific follow-up and can benefit from effective treatments. The prevalence of the forms of IT mentioned in this manuscript are given in Table 1.

A clinical study performed many years ago showed that leukoreduction decreased alloimmunization from 45% to 17%, and refractoriness from 13% to 3%.<sup>8</sup> A more recent study demonstrated that even better results were obtained by the combined use of ABO-identical transfusion (platelets expressing ABO antigens) and leukoreduction.<sup>9</sup> The advantage of using HLA-match donors to prevent alloimmunization in this system is obvious; but this is not practically feasible in the case of unforeseen serious bleeding. In the case of patients who have already developed alloantibodies, crossmatch-compatible platelet units should be used.<sup>10</sup>

Although rare, TA-GvHD is an important complication of platelet transfusion because it is almost always fatal. TA-GvHD develops: 1) when there are differences in histocompatibility between recipient and donor; 2) in the presence of immunocompetent T cells in the blood component; and 3) when the recipient is unable to reject the immunocompetent cells.<sup>11</sup> In practice, newborns and children in the first year of life, patients with immunodeficiency and after bone marrow transplantation, as well as those receiving HLA-matched platelets or products from first- or second-degree relatives are at risk of this complication. Since  $\gamma$  or X irradiation results in the inactivation of T lymphocytes, irradiated platelet concentrates should be administered to these categories of patients. More recent studies suggested that some techniques used for the reduction of pathogens in platelet



**Figure 2. Risk of death in hereditary thrombocytopenias (IT).**

The collection of large series of patients with IT revealed that the majority of patients have modest to no bleeding diathesis. In addition, available therapies are often able to reduce the risk of bleeding in those with severe forms of IT. The greatest risk is, therefore, that deriving from the possible development of further diseases to which some IT predispose; BM: bone marrow.

concentrates achieve similar, or even better, results.<sup>12</sup> Patients with the classical, biallelic form of Bernard Soulier syndrome (bBSS) who completely lack the platelet GPIb/IX/V complex often develop isoimmunization against this complex. In this case, immunosuppression and/or plasmapheresis may restore the efficacy of platelet transfusions.<sup>13</sup>

**Table 2.** Summary of the most relevant treatments for inherited thrombocytopenias.

|   | Indications   | Comments  |
|---|---|---|
| Platelet transfusions                   | All inherited thrombocytopenias. To stop bleedings when local measures failed. To prepare patients for surgery  | Leukoreduction of platelet concentrates and HLA-matched donors reduce the risk of alloimmunization and refractoriness to platelet transfusion |
| Splenectomy                             | -Wiskott–Aldrich syndrome<br>-X-linked thrombocytopenia   | Increases platelet count but also the already high risk of infections   |
| TPO-receptor agonists                   | Preparation for hemostatic challenges of patients with:<br>- <i>MYH9</i> -related disease<br>- Wiskott–Aldrich syndrome/X-linked thrombocytopenia<br>- monoallelic Bernard-Soulier syndrome<br>- <i>ANKRD26</i> -related thrombocytopenia | Efficacy in other conditions to be tested<br>The efficacy and safety of long-term treatments (life-long?) remain to be demonstrated           |
|   | Variant of congenital amegakaryocytic thrombocytopenia ( <i>THPO</i> mutation)  | Restore entire hemopoiesis  |
| Hematopoietic stem cell transplantation | -Wiskott–Aldrich syndrome<br>-Congenital amegakaryocytic thrombocytopenia ( <i>MPL</i> mutation)<br>-Severe Bernard-Soulier syndrome<br>- <i>MECOM</i> -associated syndrome   | Can cure patients and is the first-line treatment for patients with poor prognosis  |
| Gene therapy                            | -Wiskott–Aldrich syndrome   | Can cure patients. Efficacy in other conditions not yet tested  |

### Other treatments for stopping hemorrhages

As for the preparation for hemostatic challenges (see below), the efficacy of systemic administration of tranexamic acid in helping to stop bleeding in the general population has been demonstrated in numerous studies.<sup>14</sup> Even without clear evidence of its effectiveness in IT, many authors use this drug for stopping bleeding also in these conditions.<sup>4,5,15</sup> Particular caution should be used in the case of hematuria because clot formation in the urinary tract has been reported in some patients.<sup>16</sup>

Also recombinant activated factor VII (rFVIIa) has been used successfully to stop bleeding in a few patients with bBSS.<sup>17,18</sup> Due to the potential severe side effect of thromboembolic events,<sup>19</sup> this drug should be considered in IT only if platelet transfusions have not proved effective.

## Treatments to prevent bleeding

As already discussed, most patients with IT have mild, moderate, or even absent spontaneous bleeding, and intervention is required only on the occasion of hemostatic challenges.

### Simple and cheap general measures can effectively reduce the risk of bleeding in everyday life

Preventing hemostatic challenges is an important general recommendation to be given to patients with IT. They need to know that many drugs inhibit platelet function and facilitate bleeding. Aspirin and non-steroidal anti-inflammatory agents should certainly be avoided, but many other frequently used drugs, e.g., some antibiotics and antidepressants, can also affect platelet function.<sup>20</sup> Patients with IT should, therefore, consult their physician before taking any medication and discuss the risk-to-benefit ratio of each treatment.

Oral contraceptives are usually effective in preventing or controlling menorrhagia and their use should be considered in women with heavy menstruation.<sup>21</sup> In case they develop iron deficiency anemia, this must be corrected with iron administration, not only to improve their quality of life, but also because it has been suggested that anemia facilitates bleeding. In fact, *in vitro* studies showed that red blood cells push the platelets towards the vessel wall and facilitate their hemostatic effect.<sup>22</sup>

Dental interventions are among the most frequent hemostatic challenges, and maintaining good oral hygiene with regular dental visits are simple measures to prevent the need for these invasive procedures. Moreover, adherence to screening programs for early cancer detection is particularly recommended, as thrombocytopenia can be a major obstacle to the treatment of advanced malignancies. Finally, activities such as contact sports should be discouraged in patients with severe thrombocytopenia

(<20x10<sup>9</sup> platelets/L) or with bleeding episodes following even minor trauma. Fortunately, this is only rarely required.

### Prophylactic treatments are effective in reducing the risk of bleeding on the occasion of hemostatic challenges

When a hemostatic challenge can be programmed, the need for therapeutic measures to improve hemostasis must be carefully evaluated. Two large retrospective clinical studies provided useful information on the bleeding risk of patients with IT on the occasion of two common hemostatic challenges: childbirth and surgery.

The first study analyzed the course of pregnancy and the outcome of childbirth in 181 women with 13 different forms of IT who had 339 pregnancies.<sup>23</sup> There was no difference in gestation to that of healthy subjects in terms of miscarriages, fetal bleeding, and pre-term births, while the frequency of delivery-related maternal bleeding was increased. Of note, 46 women received spinal or epidural anesthesia without bleeding complications. No significant differences were found between vaginal and cesarean delivery in terms of maternal bleeding. Regarding the risk of bleeding in the newborn, fatal cerebral hemorrhages were observed in only two infants, both born by vaginal delivery to two mothers with *MYH9*-related disease (*MYH9*-RD): one infant had *MYH9*-RD and was severely thrombocytopenic, the other was not tested. The risk of hemorrhage for newborns therefore appears to be small, but the low number of observed events does not allow us to recommend a preferred method for delivery. However, it is worth mentioning here an old study that enrolled 162 pregnant women with immune thrombocytopenia (ITP).<sup>24</sup> No intracranial hemorrhage was observed in 71 newborns (at risk of maternal antibody-induced thrombocytopenia) delivered by cesarean section, while intracranial hemorrhages were reported in 2 of 17 newborns after vaginal delivery. Both the IT and ITP studies therefore seem to suggest that cesarean delivery is safer than vaginal delivery when the newborn is at risk of being thrombocytopenic. While awaiting further data to provide statistically significant evidence, my personal suggestion is to take advantage of the observation that the number of platelets of newborns with IT is similar to that of the mother who transmitted the disease.<sup>25</sup> Therefore, if the mother has severe thrombocytopenia, I suggest a cesarean section; in other cases, the type of delivery will be suggested by obstetric considerations.

The search for parameters predicting delivery-related bleeding in the mother suggested that hemorrhages requiring blood transfusion were more frequent in women with a history of severe bleedings before pregnancy and with platelet count <50x10<sup>9</sup>/L. A surprising finding was the similar incidence of bleeding at delivery in those mothers receiving and those not receiving prophylactic platelet transfusions. However, platelet count was lower in women

given transfusions, and this suggests that prophylactic platelet infusions were effective in reducing the frequency of hemorrhages.

The second study analyzed 829 surgical procedures carried out in 423 patients with well-defined forms of inherited platelet disorders, including 185 subjects with IT.<sup>15</sup> Also in this context, bleeding was more frequent in IT than in healthy subjects, and a platelet count  $<68 \times 10^9/L$ , as well as a history of previous hemorrhages, predicted these events. The presence of functional platelet defects associated with thrombocytopenia (Table 1) also had a negative prognostic value. As in the study on pregnancy, platelet transfusions were given more frequently to patients with severe thrombocytopenia, and this is probably the reason why bleeding was similar in those subjects receiving and those not receiving this prophylactic treatment. Of note, this study also suggested that prophylactic treatments other than platelet transfusions were effective in reducing bleeding at surgery (see below).

#### *Recommended use of platelet transfusions*

The recommendations for the safe level of platelets on the occasion of hemostatic challenges derive from retrospective and observational studies, expert opinion or clinical practice reviews, and are, therefore, based on low-quality evidence. Furthermore, the only studies conducted in patients with IT are the two described above on pregnancy<sup>23</sup> and surgery<sup>15</sup>; however, even these are retrospective and therefore do not provide any concrete evidence. Having said that, prophylactic platelet transfusion is recommended in preparation for surgery and childbirth in IT patients with  $<70$  and  $<50 \times 10^9$  platelets/L, respectively. For surgeries where bleeding can have more serious consequences (e.g., neurosurgery or posterior eye surgery), it is reasonable to achieve higher platelet counts (at least  $100 \times 10^9/L$ ).<sup>25,26</sup> Higher platelet counts are also required for spinal epidural anesthesia ( $<70 \times 10^9/L$ ) because of the theoretical risk of hematoma formation and neurological damage.<sup>27</sup>

On the occasion of scheduled hemostatic challenges, a platelet count much higher than  $50 \times 10^9/L$  may be indicated also in subjects with platelet functional defects associated with thrombocytopenia, such as bBSS, gray platelet syndrome (GPS), *ITGA2B/ITGB3*-related thrombocytopenia (*ITGA2B/ITGB3-RT*), *SLFN14*-related thrombocytopenia, Jacobsen syndrome/Paris-Trousseau thrombocytopenia, *FLI1*-related thrombocytopenia, and familial platelet disorder with propensity to acute myelogenous leukemia (FPD/AML) (Table 1).

The recommendations already provided for platelet concentrates to stop bleeding also apply to preparing patients for hemostatic challenges that can be programmed. In this case, however, there is time to search for an HLA donor who offers the greatest compatibility possible to reduce the risk of alloimmunization.

Prophylactic administration of platelets is not required for the many IT patients who have platelet counts above those levels required for the invasive procedure, although it is prudent to ensure the immediate availability of platelet concentrates should unexpected excessive bleeding occur.

Platelet count is not the only parameter to consider when deciding whether to administer platelet transfusions; the patient's medical history also plays an important role. In fact, subjects who had severe bleeding in the past are more at risk of hemorrhagic complications at the programmed hemorrhagic challenge than those without.<sup>15,23</sup> If a patient has a safe platelet level but had a major bleeding event in the past, they should be evaluated further to identify any other condition that may explain this discrepancy.

#### *Short-term treatment with thrombopoietin receptor agonists is an attractive alternative to platelet transfusion in preparation to surgery*

Two thrombopoietin receptor agonists (TPO-RA) have been used in IT: eltrombopag and romiplostim. Eltrombopag is a small, non-peptide molecule given orally (on an empty stomach), while romiplostim is a recombinant protein requiring subcutaneous injection. Both bind to the TPO receptor of megakaryocytes (although the binding site is different for the two drugs) and stimulate platelet production. Eltrombopag also acts as a calcium chelator, but the clinical results of this action are still little known.<sup>28</sup>

Eltrombopag is currently approved for ITP, HCV-related thrombocytopenia, and aplastic anemia,<sup>29</sup> but recent studies showed that it was able to increase platelet count in all the forms of IT in which it was tested. In two, small, non-randomized clinical trials,<sup>30,31</sup> 36 patients with *MYH9-RD*, *ANKRD26*-related thrombocytopenia (*ANKRD26-RT*), X-linked thrombocytopenia/Wiskott-Aldrich syndrome (XLT/WAS), and monoallelic BSS (mBSS) received a 3- to 6-week course of eltrombopag. Treatment was well tolerated and the vast majority of patients achieved a platelet count higher than the values required for safe surgery (Figure 3). Based on these results, a monocentric, prospective study evaluated the ability of eltrombopag to replace platelet transfusion in preparation for 11 surgeries of 5 consecutive patients with severe *MYH9-RD* and high bleeding risk.<sup>32</sup> A safe platelet count was obtained in 10 of 11 cases, and patients underwent invasive procedures without the need for platelet support and without any bleeding complications. Of note, eltrombopag caused a durable increase in platelet count throughout the peri-operative period and allowed patients to receive standard antithrombotic prophylaxis. Finally, eltrombopag was effective in preparing for hip arthroplasty a patient with *DIAPH1*-related disorder (*DIAPH1-RD*) and severely reduced platelet count who had developed multiple anti-

HLA immunoglobulin G alloantibodies and platelet refractoriness because of previous platelet transfusions.<sup>33</sup>

Experience in IT with romiplostim (a drug currently approved for ITP) is more limited and relates to its efficacy in 67 patients with WAS >15 years of age.<sup>34</sup> Patients received the drug at a dose of 9 µg/kg weekly for at least four weeks and 60% of them had an increase in platelet count. In particular, 33% of patients had a complete response, and platelet count increased from a median of  $30 \times 10^9/L$  pretreatment to a peak median value of  $247 \times 10^9/L$  by the third week. Twenty-seven percent achieved partial responses, with the average platelet count rising from  $17 \times 10^9/L$  to  $73 \times 10^9/L$  by the second week. Even if none of these patients underwent surgery, the platelet values achieved would have been sufficient for the most common surgical interventions.

Due to the high cost of clinical trial registration and the small number of IT patients who could use this drug, eltrombopag and romiplostim have not yet been approved for any IT, and future approval remains unlikely. Nevertheless, it seems reasonable to propose that short-term administration of TPO-RA is regarded as the first-line option to cover elective surgery in those IT where it has been shown to be effective. Moreover, the use of TPO-RA should be considered in other forms of IT without a clinically relevant defect in platelet function (Table 1) and with no contraindication to this drug. TPO-RA are not expected to work in congenital amegakaryocytic thrombocytopenia

(CAMT) because the TPO receptor (MPL) is defective in this condition.

As for eltrombopag, the drug for which there is more experience in IT, I suggest that patients start treatment with 50 mg/day three weeks before the scheduled surgery (Figure 4) and, depending on platelet count, continue this treatment for 3-7 days after the intervention. If the platelet count does not rise sufficiently after two weeks, eltrombopag can be increased to 75 mg/day. If the desired platelet count has still not been achieved, the patient should receive alternative prophylactic treatment.

#### *Does short-term treatment with thrombopoietin receptor agonists or thrombopoietin represent an alternative to platelet transfusion in preparation for childbirth?*

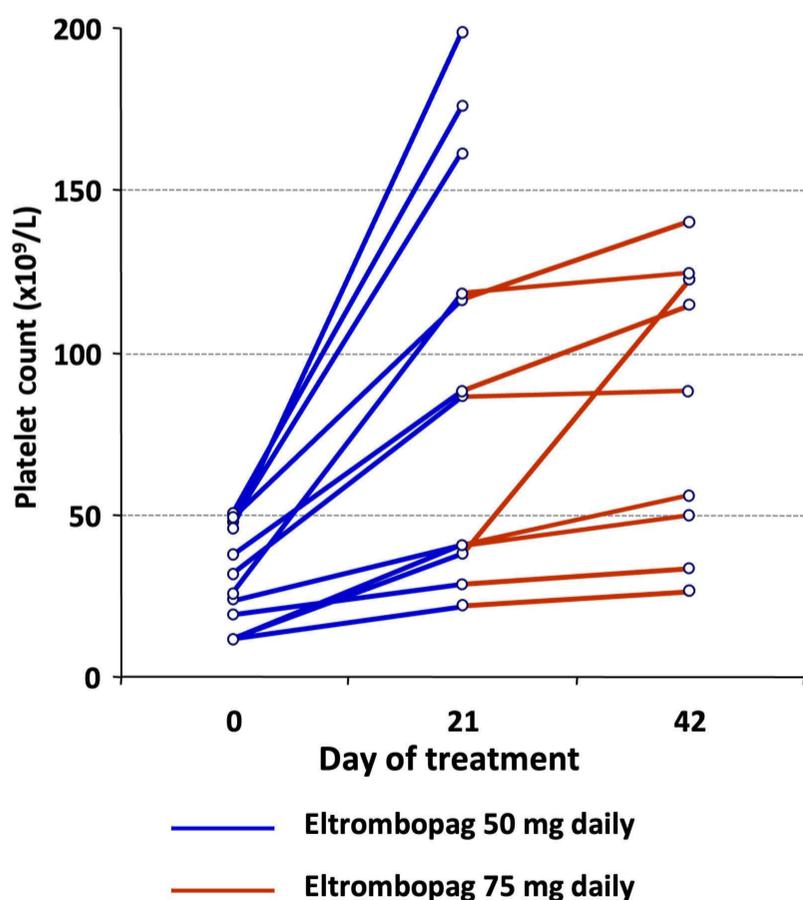
Since TPO-RA pass the placental barrier, the possible harmful effects on the fetus have so far discouraged their use in pregnant women with thrombocytopenia. However, a recent, small, retrospective study assessed the safety and efficacy of eltrombopag and romiplostim in 15 pregnant women (17 pregnancies) with chronic ITP who had not responded to 2-7 previous treatment lines.<sup>35</sup> In 58% of pregnancies, TPO-RA were given in the third trimester in preparation for delivery. Most patients responded to treatment and neither the mothers nor the neonates had serious complications, except for transient thrombocytosis in one neonate. Case reports and small series have also not reported malformation in newborns of ITP mothers who had taken TPO-RA. Instead, low birth-weight infants were sometimes observed.<sup>36</sup>

Concerning IT, the only evidence from literature is that eltrombopag was successfully used to prepare a woman with *MYH9*-RD for cesarean delivery, without consequences for the newborn.<sup>37</sup>

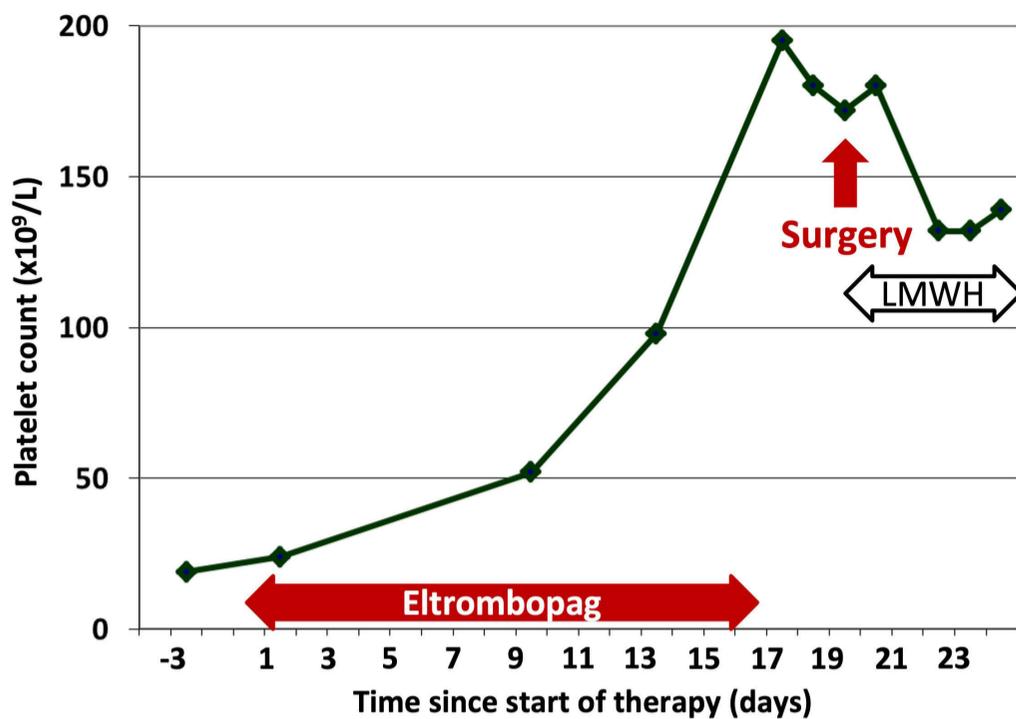
Available data are, therefore, not yet sufficient to recommend the use of TPO-RA before delivery for women with acquired or inherited thrombocytopenia, even if the results reported so far seem promising in terms of safety for both the mother and the fetus.

While eltrombopag and romiplostim pass through the placenta, the full-length recombinant human thrombopoietin (rhTPO), approved by the China State Food and Drug Administration for the treatment of refractory chronic ITP, is not expected to do so. This should eliminate doubts about its possible toxicity to the fetus. A prospective study in which 31 pregnant women with ITP received rhTPO in the second or third trimester of gestation demonstrated the absence of any congenital disease or developmental delays of newborns during a median follow-up of 53 weeks.<sup>38</sup> Furthermore, rhTPO was well tolerated by the mothers and increased their platelet count. Results were, therefore, good, but the study was too small in size to be able to state that rhTPO can be safely used in pregnant women. Furthermore, the drug is only available in China.

In conclusion, TPO-RA should not be routinely used as a



**Figure 3. First clinical study with eltrombopag in inherited thrombocytopenias.** This figure shows the effect of eltrombopag in 12 patients with *MYH9*-related disease. Most of them had a clinically relevant increase in platelet count after a few weeks of treatment. (From Pecci *et al.*<sup>30</sup> with permission.)



**Figure 4. Eltrombopag for preparation for surgery in IT patients.** Thrombopoietin receptor agonists is an advantageous alternative to platelet transfusions in the preparation for surgery of patients with forms of IT who respond to this treatment. The figure shows the trend of the number of platelets in one representative patient reported in the study by Zaninetti *et al.*<sup>31</sup> who used eltrombopag to prepare for 11 surgical interventions. This was an adult subject with severe *MYH9*-related disease who received eltrombopag in preparation for orthopedic surgery and a rapid normalization of platelet count was achieved. This avoided excessive bleeding during surgery and safe administration of antithrombotic prophylaxis. (From Zaninetti *et al.*<sup>31</sup> with permission.) LMWH: low molecular weight heparin.

substitute for platelet transfusions in preparation for delivery outside of clinical trials. In case of refractoriness to platelet transfusions, however, their utilization should be considered.

#### Other hemostatic treatments in preparation for hemostatic challenges

Only one study has investigated the efficacy of prophylactic treatments other than platelet transfusions in preparation of IT patients for hemostatic challenges, and concluded that antifibrinolytic agents were associated with a lower post-surgical bleeding frequency.<sup>15</sup> However, this is low-quality evidence because the study was retrospective and few patients received this type of treatment. In this regard it is worth mentioning that the efficacy of antifibrinolytics in IT is supported by a few case reports describing the success of tranexamic acid in major surgery.<sup>39,40</sup> Moreover, the use of tranexamic acid in IT is made plausible by its documented efficacy in the general population in preventing bleeding in a variety of major surgical procedures, especially cardiac surgery and major orthopedic operations.<sup>14</sup> Lastly, the Network for the Advancement of Patient Blood Management, Hemostasis and Thrombosis (NATA) recommended intravenous administration of tranexamic acid for women at increased risk of postpartum hemorrhage.<sup>41</sup> Since tranexamic acid is not burdened with significant side effects (in particular, it does not appear to increase thrombotic risk),<sup>42</sup> its prophylactic use in IT can be considered when proven treatments are not available.

Another drug to be considered is desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]), which promotes the release of von Willebrand factor from endothelial cells and enhances the procoagulant activity of platelets.<sup>43</sup> Desmopressin is approved for mild hemophilia A and type 1 von Willebrand disease, and a few case reports have suggested that it was effective in preventing

surgery-related bleeding also in some IT.<sup>44,45</sup> Furthermore, a retrospective study (see above) disclosed that prophylactic administration of DDAVP was associated with a lower incidence of surgical bleeding in subjects with inherited functional platelet defect isolated or associated with thrombocytopenia.<sup>15</sup> When considering the use of DDAVP, it should be borne in mind that it rarely results in hypotension, tachycardia, fluid retention, or hyponatremia, and is contraindicated in ischemic heart disease or congestive heart failure, infancy, and pregnancy.

rFVIIa promotes hemostasis by activating the extrinsic pathway of the coagulation cascade, and is approved in hemophilia A or B with inhibitors, congenital factor VII deficiency, acquired hemophilia, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions. A few thromboembolic events have been reported. rFVIIa has been successfully used to cover major or minor surgery in a few patients with bBSS<sup>17</sup> and in one subject with thrombocytopenia and absent radii (TAR)<sup>46</sup> with an administration schedule similar to that recommended for Glanzmann thrombasthenia.<sup>47</sup> Given the unproven efficacy in IT and possible side effects, rFVIIa should only be considered when other prophylactic treatments are not possible.

## Treatments to stably increase platelet count in subjects with severe bleeding diathesis

Although rare, some patients have a severe bleeding diathesis that interferes with normal daily activities and significantly reduces their quality of life. In addition, the repeated platelet transfusions required by their frequent bleeding episodes can result in alloimmunization and refractoriness to platelet transfusion. It would, therefore, be

desirable in these cases to avoid platelet transfusions by steadily increasing the platelet count. In very rare cases, splenectomy achieves this, while TPO-RA could, theoretically, be effective in a higher number of patients.

### Splenectomy

Several patients with IT underwent splenectomy because they were misdiagnosed with ITP (for instance, personal experience indicates that 15% of subjects with *MYH9*-RD, the most frequent IT, received this treatment); but the removal of the spleen had no favorable effect.

Notable exceptions are WAS and X-linked thrombocytopenia (XLT), a mild form of WAS. In these IT, splenectomy often increases platelet count up to normal levels and maintains levels stable, but unfortunately the procedure aggravates the immunodeficiency typical of these diseases. Splenectomy, therefore, reduces the high risk of dying from bleeding, but increases the already high risk of dying from infections. Concerning WAS, an old retrospective study of 42 patients concluded that the advantages outweigh the disadvantages, as splenectomy increased survival.<sup>48</sup> A more recent retrospective study of 173 patients (41 splenectomized) concluded that the advantage of the increase in the number of platelets was counterbalanced by the increase in infections, which were especially frequent in patients not receiving antibiotic prophylaxis.<sup>49</sup> The net result was that splenectomy did not modify patients' survival. We now know that hematopoietic stem cell transplantation (HSCT) is the treatment of choice for WAS and one of the therapeutic options for XLT (see below). Moreover, gene therapy has been given successfully in a few cases (see below). Thus, splenectomy should be considered only when more effective treatments are not possible. Once splenectomy has been performed, lifelong antibiotic therapy is essential to reduce the risk of infections. Splenectomy should be avoided in patients who are candidates for HSCT, or who have already been treated with HSCT, as it increases the incidence of serious post-transplant infections.<sup>50</sup>

### Life-long thrombopoietin receptor agonists: a credible option?

Thrombopoietin receptor agonists are proving effective in preparing patients with some forms of IT for hemostatic challenges. Why not administer them as chronic treatment to patients with severe bleeding diathesis?

Results of a few studies support the long-term effectiveness of TPO-RA in IT. In a prospective trial, 4 patients (2 with *MYH9*-RD, one with WAS, and one with *ITGA2B/ITGB3*-RT) with mucosal hemorrhages WHO grade 2 or 3 received eltrombopag for 19-22 weeks and obtained a stable increase in platelet count and remission of bleeding symptoms.<sup>31</sup> Two patients achieved these results with the dosage of 25 mg/day and the other 2 with 50 mg/day. The

WAS patient experienced worsening of a pre-existing cutaneous eczema and the drug was prudently discontinued. No other adverse events were recorded.

A retrospective study analyzed 8 patients with XLT/WAS and severe thrombocytopenia (6 children and 2 adults) who received eltrombopag for 22-209 weeks. Five patients achieved a platelet response and experienced significant improvement in bleeding symptoms. No major adverse events were observed.<sup>51</sup> Moreover, a case report described a 2-year-old male with WAS and life-threatening bleeding episodes with secondary anemia who received eltrombopag for 32 weeks as a 'bridge' therapy to HSCT.<sup>52</sup> With 50-75 mg/day of eltrombopag, the number of platelets went from baseline values between 10 and 20x10<sup>9</sup>/L to values around 30x10<sup>9</sup>/L. This small increase was enough to greatly reduce bleeding and abolished the need for platelet transfusions. Treatment was well tolerated.

Romiplostim has also been administered successfully for prolonged treatments in some cases of IT. A study already mentioned above retrospectively evaluated 67 young WAS patients receiving this drug for 1-12 months while they were waiting for HSCT.<sup>34</sup> Most short-term responders (38/40) had a sustained response to romiplostim over several months and no clinically relevant side effects were observed.

Romiplostim was also used to treat 5 children affected with the congenital amegakaryocytic thrombocytopenia (CAMT) variant caused by *THPO* gene mutations (a form of IT with TPO deficiency and propensity to develop bone marrow aplasia).<sup>53,54</sup> In most of these children, treatment was started when symptoms of bone marrow aplasia were already present (transfusion-dependent hyporegenerative anemia and/or neutropenia with frequent infections). In all cases, romiplostim greatly increased platelet count. Notably, it induced a trilineage hematological response with improvement not only of platelet count, but also of hemoglobin concentration and neutrophil count. The response was maintained throughout the follow-up period (from 13 months to 6.5 years) (Figure 5). Lastly, successful long-term use of romiplostim has been observed in a case of *MYH9*-RD who had previously been diagnosed as ITP.<sup>55</sup> In conclusion, the few available data seem to indicate that TPO-RA maintain efficacy even for very prolonged treatments without causing relevant side effects. However, this does not exclude the possibility that the side effects that have been hypothesized in other diseases may occur in IT patients who have been receiving TPO-RA for many years. The disease for which there is more experience of prolonged administration of TPO-RA is ITP, and some studies have shown an increase in thrombotic events in treated patients while others did not. The most recent and largest meta-analysis, including both eltrombopag- and romiplostim-treated patients, looked at 11 trials with a total of 740 patients enrolled in the intervention group and 352 in the

control group.<sup>56</sup> More thromboembolic events were noted in the TPO-RA group (n=25) than in the control group (n=4), but this difference did not reach statistical significance.

Another hypothesized risk of TPO-RA is that of facilitating the onset of acute leukemia in subjects with other pathologies that in themselves predispose to hematological malignancies. This hypothesis is particularly alarming for subjects with IT, because three frequent forms predispose to acute leukemia.

A large and recent meta-analysis investigated the results of 8 randomized studies including 707 patients with different forms of myelodysplastic syndrome (MDS), who are at high risk of leukemic transformation.<sup>57</sup> The authors concluded that neither romiplostim nor eltrombopag promoted progression to leukemia (Risk Ratio: 1.08 and 1.12, respectively).

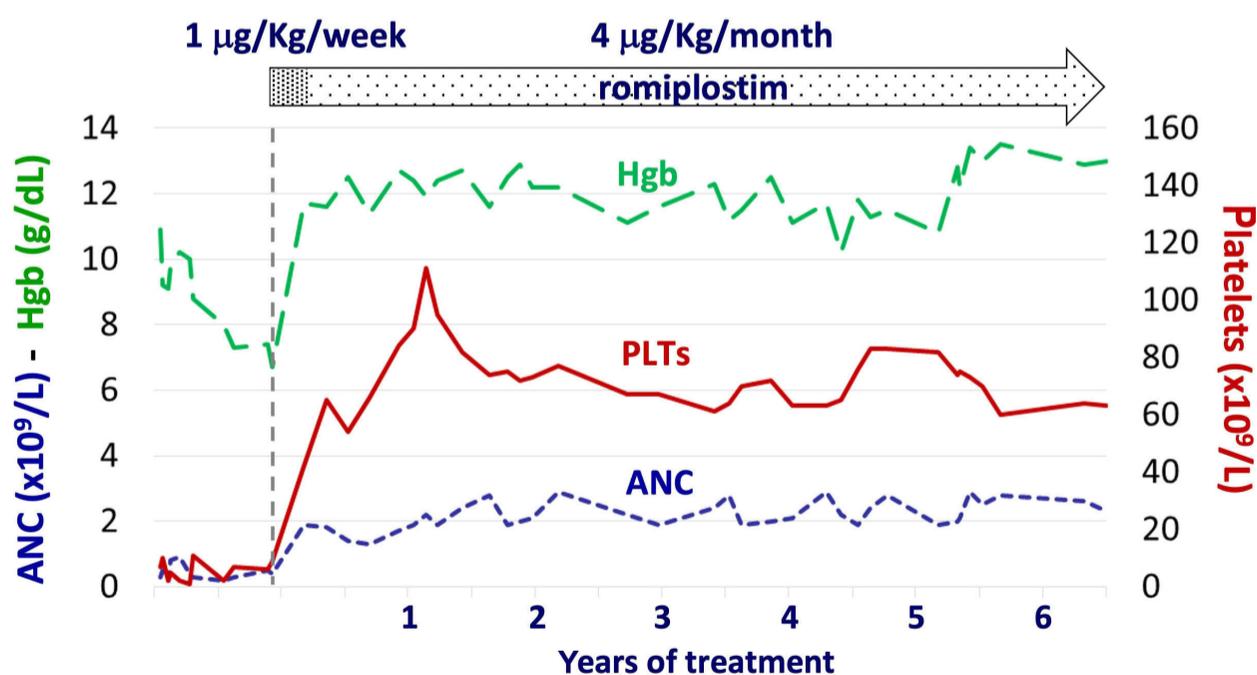
The few studies in patients with IT, and the broader evidence obtained in ITP and MDS, seem to indicate that, overall, prolonged treatment with TPO-RA maintains efficacy for a very long time, do not expose the patient to the risk of leukemia, and appear to result in an insignificant increase in the risk of thrombosis. Obviously, these reassurances refer to the prolonged use of these drugs and not to their lifelong administration. In conclusion, lifelong TPO-RA administration is a credible and attractive option for most severe forms of IT, but the efficacy and safety of this approach remain unproven. Furthermore, TPO-RA are not approved for any form of IT, and they are expensive, and these are serious obstacles to their use in chronic treatments.

## Treatments to cure inherited thrombocytopenias

All IT are potentially curable with HSCT or by replacing hematopoietic progenitors carrying the mutation with gene-corrected autologous cells (gene therapy). The single exception is the form of CAMT caused by loss-of-function mutations in the gene for TPO, which is produced primarily in the liver, and does not benefit from replacing the patient's hemopoietic progenitors. In just a few IT, however, the risk:benefit ratio is in favor of these treatments.

### Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation is the treatment of choice in CAMT, WAS and MECOM-associated syndrome because they almost always lead to death if left untreated. A recent study analyzed data of 86 patients with CAMT receiving HSCT collected by the Center for International Blood and Marrow Transplant Research from 2000 to 2018.<sup>58</sup> In most cases, transplant was from HLA matched or mismatched unrelated donors; the remaining were from HLA-matched sibling and HLA-mismatched relative. The predominant graft types were bone marrow and cord blood. The 5-year overall survival was 86%, with mortality and graft failure higher with HLA mismatched donor. The 5-year incidence of chronic graft-versus-host disease was 33%, and in the vast majority of cases it occurred after transplant from an unrelated donor. Better results in term of survival were obtained in patients transplanted before the age of three years and within 12 months of diagnosis.



**Figure 5. Romiplostim in patients with a form of inherited thrombocytopenia due to mutation in the gene for thrombopoietin (congenital amegakaryocytic thrombocytopenia [CAMT] variant due to *THPO* mutation).** The figure is from an article reporting an Egyptian family with 4 siblings suffering from this recently identified form of inherited thrombocytopenia. The patient described in the figure is the one with the most severe clinical manifestations. He was born with thrombocytopenia but later developed pancytopenia from bone marrow aplasia. The administration of small doses of romiplostim rapidly increased the values of platelets, neutrophils and hemoglobin. The infections and bleeding stopped, and the patient no longer needed red blood cell transfusions. Of note, the treatment was still effective and well tolerated after 7 years. (From Pecci *et al.*<sup>53</sup> with permission.) ANC: absolute neutrophil count; Hgb: hemoglobin; PLT: platelets.

Thus, early transplant from an HLA-matched donor offers the best chance of survival; but even in the absence of these characteristics, HSCT is indicated in CAMT patients who are otherwise not destined to reach adulthood.

Improved prophylactic antimicrobials and immunoglobulin supplementation increased the survival of patients with the severe syndrome induced by WAS mutations, but nevertheless they are doomed to die from infection or bleeding in early adulthood.<sup>59</sup> In one old study, the 20-year probability of overall survival was 0% for patients who fail to express WAS protein, while it was 92% for those expressing normal-sized protein.<sup>60</sup> Thus, HSTC (or gene therapy; see below) is mandatory in subjects with WAS mutations and the composite phenotype of severe thrombocytopenia and immunodeficiency with autoimmunity. A scoring system can help identify patients who need to undergo this procedure.<sup>59</sup> It uses five parameters: thrombocytopenia, the severity of eczema, infections, development of autoimmunity, and malignancy. HSCT (or gene therapy; see below) is recommended with a score  $\geq 3$ , which indicates a severe phenotype.

HSCT outcome in WAS has improved over time, and what we can expect today from this procedure is exemplified by a recent study that has taken into consideration 197 patients transplanted at European Bone Marrow Transplantation centers between 2006 and 2017.<sup>61</sup> After a median follow-up of 44.9 months, 176 patients were alive, with a 3-year overall survival of 88.7%, and chronic GvHD-free survival of 81.7%. Conditioning regimen and donor type were unrelated to overall survival, whereas age  $< 5$  years at HSCT was associated with a more favorable outcome. Similar results have been obtained in a previous study evaluating the outcome of HSCT in 129 patients transplanted at 29 Primary Immune Deficiency Treatment Consortium centers from 2005 through 2015 (Figure 6).<sup>62</sup>

Hematopoietic stem cell transplantation is indicated also in *MECOM*-associated syndrome (RUSAT2), a rare form with amegakaryocytic thrombocytopenia due to *MECOM* mutation variably associated with other somatic defects and evolving to bone marrow failure during infancy or childhood.<sup>63</sup> Four different reports described the outcome of HSCT in a total of 20 patients (median age: 9.5 months); 76.5% had a good outcome while the remaining 23.5% died.<sup>64-67</sup> Although the results are less positive than in CAMT and WAS, HSCT must be considered in this rare disease.

Patients with radioulnar synostosis with amegakaryocytic thrombocytopenia 1 (RUSAT1) caused by *HOXA11* mutation have a phenotype similar to RUSAT2, but evolution to bone marrow aplasia is less frequent and HSCT may not be required.<sup>68</sup>

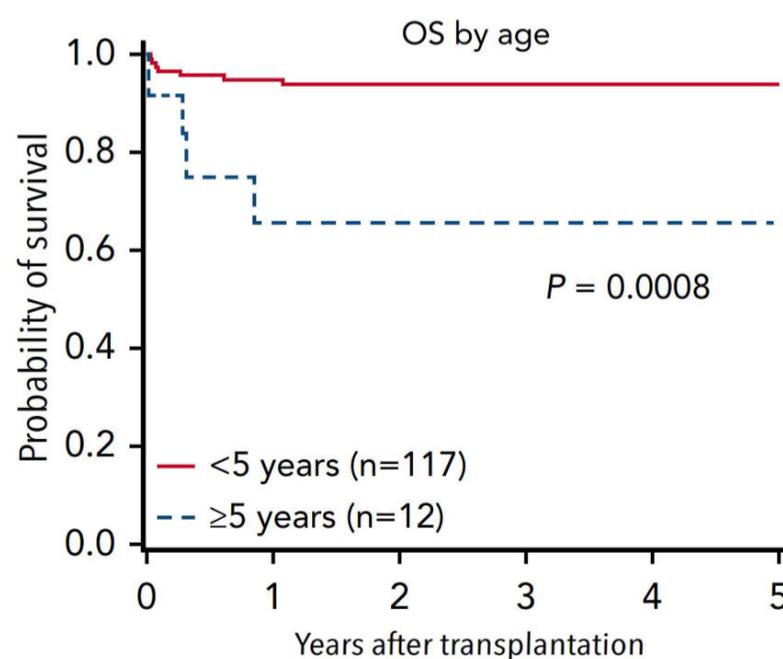
In rare cases, HSCT can be considered in IT other than CAMT, WAS and *MECOM*-associated syndrome when the patient has a severe bleeding diathesis and does not respond to any treatments. This was the case of 3 patients

with bSS<sup>69,70</sup> and one with thrombocytopenia with TAR<sup>71</sup> who successfully received HSCT from HLA-identical siblings because they had life-threatening hemorrhages and had become refractory to platelet transfusions. In one subject with GPS and severe pancytopenia due to the development of myelofibrosis, HSCT corrected both the myelofibrosis and the platelet defect.<sup>72</sup> Finally, HSCT in a young girl with *GNE*-related disorder (*GNE*-RD) and severe bleeding tendency resulted in a successful outcome.<sup>73</sup>

### Gene therapy

Autologous hematopoietic stem cell (HSC) gene therapy is an attractive alternative to HSCT, addressing as it does the needs of patients who lack appropriate donors. In the field of IT, it has only been used up to now in WAS, in which it promises to correct not only thrombocytopenia but also severe immunodeficiency. Moreover, it has the advantages over HSCT of bearing a low risk of rejection or GvHD and not requiring immunosuppression or fully myeloablative conditioning, which further increase the already high risk of infection. However, the first clinical trial yielded very alarming results. It used a  $\gamma$ -retroviral vector in which the WAS gene was under the control of a strong viral promoter. Treatment corrected blood cell defects in most cases, but 7 of 9 evaluable patients developed leukemia as a consequence of insertions of the retroviral vector in proto-oncogenes and overexpression of these genes.<sup>74</sup>

Thereafter, a self-inactivating lentiviral vector in which the WAS complementary DNA is under the control of a human WAS promoter was used to address the insertional mutagenesis risk.<sup>75</sup> A recent paper reported the outcome of this approach in 8 WAS children after a median follow-up of 7.6



**Figure 6. Hematopoietic stem cell transplantation (HSCT) in Wiskott-Aldrich syndrome (WAS).** Patients with WAS on average die in early adulthood from infections or bleeding. HSCT cures this disease in the vast majority of cases. The best results are obtained when the procedure is performed early. (From Burroughs *et al.*<sup>62</sup> with permission.) OS: overall survival.

years.<sup>76</sup> The gene-corrected cells were engrafted and were stable, and no serious treatment-related side effects occurred. However, one patient not analyzed in this study died 7 months after gene therapy from pre-existing complications of infection.<sup>77</sup> Expression of WAS protein was increased and great benefit in terms of recurrent infections, autoimmunity and eczema were observed. In addition, bleeding episodes were less frequent and no patient required platelet transfusions. However, platelet count normalized in only 3 subjects, in 2 of them after splenectomy. Interestingly, an accurate investigation of patients' platelet counts concluded that gene therapy only partially corrected the platelet compartment because structure and function remained defective. Similar clinical benefit was described after a 3.5-year follow-up in another series of 8 children receiving the same therapeutic approach.<sup>78</sup>

The good results obtained by these two studies in children open up the possibility of treating adult patients for whom allogeneic HSCT would be associated with high risk; the successful lentiviral gene therapy in a 30-year-old patient with severe WAS supports this hypothesis.<sup>79</sup>

## Management of the manifestations that add to thrombocytopenia

When the diagnosis of an IT with predisposition to hematological malignancies (FPD-AML, *ETV6*-RT, or *ANKRD26*-RT) is made, blood cell count, examination of blood smear, and physical examination are recommended. Some authors advise a baseline bone marrow study to rule out malignancy and for future comparative use, after which, follow-up evaluations, including basic blood investigation, and physical examination, should be carried out every 6-12 months.<sup>80,81</sup> In cases in which patients develop a hematological malignancy, they are treated as patients with *de novo* forms. When HSCT is considered, it is imperative to avoid choosing as the donor a relative carrying the familial germline mutation, as this results in a high risk of donor-derived malignancies and/or poor engraftment. Thus, the potential related donors should be investigated by molecular testing because a normal platelet count does not exclude the possibility that they have the same mutation as the patient.<sup>82-84</sup>

As already discussed, HSCT is required for patients with bone marrow aplasia diagnosed with CAMT and *MECOM*-associated syndrome. It is important to remember that subjects with the rare variant of CAMT caused by *THPO* mutation do not respond to this treatment.<sup>53,54</sup>

Patients with *MYH9*-RD and mutations at high risk of developing glomerulonephritis<sup>85</sup> should be monitored every 6-12 months for the occurrence of proteinuria. Should signs

of initial kidney damage appear, patients have to receive angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers, because these drugs have been reported to have a beneficial effect.<sup>86,87</sup>

A retrospective analysis of 10 *MYH9*-RD patients revealed that cochlear implantation was highly effective in restoring hearing function in patients who developed severe deafness. Better results were obtained when this procedure was performed early.<sup>40,88</sup> Standard surgery for cataracts should be carried out when indicated in *MYH9*-RD subjects who have developed this complication.

In patients with IT associated with congenital limb deformities (TAR, RUSAT), reconstructive orthopedic surgery may allow children to resume most daily activities.<sup>46,89</sup>

## Future directions

Despite the great advances, there is still plenty of room for improving IT treatment.

*Genotype/phenotype correlation* - the ability to accurately define the prognosis in each single patient would be especially beneficial in IT with a predisposition to other diseases. For example, knowing the risk of an individual patient with *RUNX1*, *ANKRD26* or *ETV6* mutations of developing hematological malignancies could allow HSCT to be performed before onset. This is expected to reduce the risks associated with the procedure.

*Platelet transfusion* - the scarcity of donors and the risk of developing alloimmunization limit the use of this important therapeutic support. *In vitro* production of poorly immunogenic human platelets and development of 'artificial' platelets could solve the problem. Platelets obtained *in vitro* from induced pluripotent stem cell (iPSC) have already been successfully used in one patient with aplastic anemia<sup>90</sup> and this gives rise to the hope that genetic engineering can be used to create universal HLA class-I depleted platelets with very low immunogenicity. On the other hand, 'synthetic platelet' nanoparticles have already been manufactured and have been proved capable of supporting hemostasis in animal models.<sup>91</sup>

*TPO-RA* - these drugs increased platelet count in some forms of IT, but they are probably effective in many others as well; large, collaborative clinical studies are required to test this hypothesis. Clinical trials to test the safety of these drugs in pregnancy are also highly desirable.

*Gene therapy* - genetic engineering has been shown to be effective in WAS, but other severe forms of IT could benefit from this approach when HSCT is not possible.

## Disclosures

*No conflicts of interest to disclose*

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