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Are Tpo agonists an option for ITP in pregnancy?

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In this issue of *Blood*, Michel and colleagues provide a multi-institutional, retrospective, and observational study on the use of thrombopoietin receptor agonists (Tpo-RAs) in the management of severe thrombocytopenia in pregnant immune thrombocytopenia (ITP) women refractory to standard therapies.[1]

The approved Tpo-RAs for the treatment of patients with ITP (romiplostim, eltrombopag, avatrombopag) are highly effective and safe in adult ITP. However, pregnant animal studies document transfer to the fetus and presence in mother's breast milk. Because of these observations, the Food and Drug Administration approved caution labels against their use in pregnancy and in breast-feeding mothers. Without randomized trials to validate the efficacy and safety of Tpo-RA in pregnancy, under what circumstances could a clinician consider the use of a Tpo-RA in pregnancy and/or in the postpartum period?

The finding of significant thrombocytopenia with a platelet count of $\leq 50 \times 10^9$/L in an apparently healthy pregnant woman is most often associated with a diagnosis of ITP. In a 20-month prospective cohort study of 1 296 963 pregnancies by the UK Obstetric Surveillance System (UKOSS), 107 pregnancies were identified in women with clinically significant ITP (0.083 per 1000 pregnancies, 95% confidence interval: 0.068 to 1.00).[2] In this cohort, 62 (58%) pregnancies were in women with a previous diagnosis of ITP and 47 (42%) were diagnosed during the pregnancy.[2]

A pregnancy in a woman with ITP, although infrequent, raises several important questions for the hematologist and obstetrician. What is the minimum safe platelet count during gestation and delivery with its theoretical risk of life-threatening postpartum hemorrhage (PPH)? What platelet count is needed for epidural anesthesia? Because ITP is a disorder associated with antiplatelet antibodies that can be transferred to the fetus, what are the risks of thrombocytopenia in the neonate and intracranial hemorrhage (ICH) during birth trauma?

The composite of contemporary clinical experience has proposed some answers to these questions. A platelet count of $\geq 30 \times 10^9$/L appears safe for most vaginal deliveries, and platelet count of $\geq 50 \times 10^9$/L appears safe for a cesarean section performed for obstetrical reasons.[3] Current obstetrical recommendations for epidural anesthesia are a platelet count of $\geq 80 \times 10^9$/L.[4] The risk of ICH with vaginal delivery is low at $<1.5\%$.[2,5,6]

Corticosteroids and intravenous immunoglobulin (IVIG) are the accepted first-line and generally safe treatments for ITP in pregnancy. In a retrospective study, each alone has a platelet response of ~40%.[7] Platelet increases with the combination may be greater. Their use in combination is often limited to late trimester in preparation for vaginal delivery with epidural anesthesia.

How effective are prednisone and IVIG in the community setting? The UKOSS cohort study[2] found the median platelet count at time of delivery was 64×10^9/L (12 to 218×10^9/L) for the cohort. However, using standard definitions of PPH, 56/107 (52%) had PPH (≥500 mL in the first 24 hours), and 22/107 (20.6%) had severe PPH (≥1000 mL in the first 24 hours). Although there were no maternal deaths, 1 mother needed a hysterectomy to stop her postpartum bleeding. The median platelet count for women with PPH was 58×10^9/L (range: 12 to 148×10^9/L) compared with a median platelet count of 132×10^9/L (range: 94 to 170×10^9/L) in women without PPH. It is obvious that we need another effective treatment in this patient population.

In 2017, there was a report on the use of a novel recombinant thrombopoietin (rTpo) for management of refractory ITP in pregnancy in *Blood*.[8] Thirty-one patients with ITP refractory to first-line therapy with platelet counts $<30 \times 10^9$/L received the rTpo. Twenty-three of 31 (74%) responded. Ten patients (32%) achieved a platelet count $>100 \times 10^9$/L. The therapy was well tolerated with no reported maternal or neonate complications. In their commentary on the study, Bussel and Lee agreed that a safe new ITP therapy for use in pregnant patients was needed.[9] However, they questioned the safety of the 2 approved Tpo-RA medications, romiplostim and eltrombopag, for use in pregnancy.

The study by Michel et al presents outcome results of 15 pregnant women with ITP after 17 pregnancies. This was a highly refractory cohort with a median platelet count prior to starting Tpo-RA of 10×10^9/L (range: 1 to 55×10^9/L). Bleeding manifestations were present in 13 (76.5%) pregnancies prior to Tpo-RA treatment. Eight women received eltrombopag and 7 women received romiplostim. The median Tpo-RA exposure was 4.4 weeks (1 to 39 weeks) and Tpo-RA treatment was used in 10 (58%) women in preparation for delivery. It is notable that 3 women were taking eltrombopag at the start of their pregnancies. Platelet response was seen in 12/16 (77%) pregnancies. There were no thrombotic events in the mothers or reported postpartum hemorrhages. Neonatal complications occurred in 9 pregnancies, inclusive of twins in 1 mother. Six neonates had thrombocytopenia but were without findings of ICH. There was 1 grade 1 intraventricular hemorrhage in a premature infant with a favorable outcome. There was 1 neonate with thrombocytosis from a mother taking eltrombopag who continued to take the drug after delivery and breast-fed the child.

In view of the severity of the ITP in this multinational cohort of pregnant women, the outcome for the 17 pregnancies appears quite good. However, the small number of patients in this report were treated with 2 different Tpo-RA; therefore, outcome results do not provide us with sufficient clinical data to determine if there were response or safety differences between the 2 agents. Also, 7 of the

10 responders received other concomitant ITP medications. Although the majority of eltrombopag-treated patients received 50 mg/d, others received doses up to 100 mg. The romiplostim dosing was also high, with 4/7 receiving greater than 7 μg/kg weekly.

Although this report is an important contribution toward allowing a clinician to consider the use of a Tpo-RA in a pregnant treatment refractory ITP patient, I would still caution against its routine use. It will take a prospective trial inclusive of clearly defined refractory patients using a single Tpo-PA agent with a defined dosing algorithm to know the overall safety and efficacy of Tpo-RA drugs in this patient population.

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TRANSPLANTATION

Comment on Myllymäki et al, page 3070

Telomere length in hematopoietic cell transplant

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In this issue of *Blood*, Myllymäki et al[1] evaluated the role of pretransplant leukocyte telomere length (LTL) on survival outcomes in patients with myelodysplastic syndrome (MDS). The authors found associations between recipient short LTL and poor overall survival and high risk of nonrelapse mortality (NRM) after unrelated donor hematopoietic cell transplant (HCT).

Telomeres are long tandem $(TTAGGG)_n$ nucleotide repeats and linked protein complexes that cap the end of chromosomes to maintain genomic stability. They shorten with each cell division and therefore are markers for cellular replicative capacity and biological aging.[2] Germline pathogenic variants in telomere biology genes result in short telomere length (TL; <10th percentile for age) and cause a spectrum of illnesses called telomere biology disorders (TBDs). Patients with dyskeratosis congenita, the prototypical TBD, have a mucocutaneous phenotype and a high risk of bone marrow failure, MDS, acute myeloid leukemia, and other cancers, as well as pulmonary, liver, and other multisystem manifestations.[3] Allogeneic HCT is a curative therapy for severe hematologic diseases, including MDS, but the associated mortality and morbidity risk are high. Finding biomarkers that would precisely identify patients who will benefit the most from HCT has the potential to improve patient outcomes. Recipients and donor TL have been at the center of such investigations with early studies showing significant TL attrition in transplanted donor hematopoietic stem cells in the first year after transplantation. This telomere shortening is primarily a consequence of the extensive cell proliferation needed to achieve immune reconstitution. Telomere shortening in recipient nonhematopoietic cells is also expected due to intense HCT conditioning regimens, and the graft-versus-host disease inflammatory state. Post-HCT TL shortening in donor or recipient cells may explain, at least in part, the high risk of age-related diseases in HCT recipients (reviewed in Gadalla and Savage[4]; see figure).

Myllymäki et al used the high-throughput widely used quantitative polymerase chain reaction (qPCR) assay to measure pre-HCT relative LTL and correlated it with survival outcomes in 1267 patients with MDS who received HCT at age ≥40 years. The authors showed that short LTL was associated with higher risk of NRM that corresponded with an overall survival disadvantage; this was independent of MDS somatic mutation profiles, known markers of MDS severity, or other known clinical factors affecting outcomes in those patients. The relationship between LTL and NRM, but not overall survival, was modified by the type of HCT conditioning regimen, with associations between LTL and NRM restricted to patients receiving myeloablative or fludarabine/melphalan-based conditioning regimens.[1] These findings are similar to those reported in patients receiving HCT for bone marrow failure due to dyskeratosis congenita where myeloablative regimens increase patient risk of toxicity.[5]

Short LTL in patients with MDS can reflect markers of disease severity, such as high frequency of marrow blasts and cytogenetic abnormalities,[6] or potentially identify a subset of patients with unrecognized TBDs. In Myllymäki et al, the presence of unrecognized TBD is likely because short LTL was not associated with frequency of blasts, but significant associations were noted with pre-HCT pulmonary and hepatic dysfunction. In line with that, a recent HCT study in severe aplastic anemia showed that patients with LTL < 10th percentile for age, but not those with longer telomeres, were at high risk of poor survival.[7] The relationship between short LTL and NRM was previously reported in 178 patients who received HCT for different indications