Best Practice & Research Clinical Haematology 27 (2014) 288–292

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha

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The new thrombopoietic agenda: Impact on leukemias and MDS

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Keywords:
thrombopoeitin receptor agonists
romiplostim
eltrombopag
myelodysplastic syndromes
MDS
acute myeloid leukemia
AML
immune thrombocytopenia
ITP
TPO

The two generations of thrombopoietin (TPO) receptor (R) agonists have had utility in a number of hematologic conditions. However their use has often been surprisingly complex and drawbacks have been revealed in certain conditions more than in others. The first-generation megakaryocyte growth and development factor (MGDF) was discontinued due to the production of antibodies against it that cross-reacted with native TPO. Nonetheless it was tested in a wide variety of thrombocytopenic conditions and showed unequivocal efficacy in increasing the number of platelets in certain ones. As a result of lessons learned with MGDF, second-generation TPO-R agonists romiplostim and eltrombopag were initially tested and have been approved for the treatment of chronic immune thrombocytopenia (ITP), thrombocytopenia in hepatitis C, and recently aplastic anemia. These agents have had more mixed outcomes in diseases such as acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). Results of several studies will be discussed.

Introduction

Thrombopoietin (TPO) is unequivocally the key player in driving megakaryopoiesis [1]. To what degree thrombopoietin drives megakaryocytes to make platelets is not quite as certain. However, if there are many megakaryocytes in the marrow, platelet numbers almost always will increase. Thrombopoietin levels are dependent on the number of TPO receptors in the circulation, including

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http://dx.doi.org/10.1016/j.beha.2014.10.012
1521-6926/

progenitor cells in the marrow. Several studies have shown that if there are megakaryocytes in the marrow, even in the setting of profound thrombocytopenia, TPO levels will be low; conversely, if megakaryocytes are absent from the marrow, TPO levels will be high. In contrast, blood levels of erythropoietin (EPO) are based on peripheral blood oxygen delivery (hemoglobin) as determined by renal sensors. Levels of granulocyte colony-stimulating factor (GCSF) are regulated in the same way as levels of TPO are regulated: they are based on the number of receptors in the circulation, which includes myeloid progenitor cells in the marrow.

The first generation of TPO-R agonists was generated not long after the cloning of thrombopoietin in 1994. However, immunologic reactivity to them after multiple exposures, with antibodies forming that cross-reacted with endogenous thrombopoietin, caused these two agents to go out of development. Before the studies ended, megakaryocyte growth and development factor (MGDF) and "recombinant thrombopoietin" were used in about 500–1000 patients across a number of indications. Some highly pertinent data were acquired from this first set of agents, even though they are not currently in use.

It is important to note that these TPO agents were clinically ineffective in myeloablative states, like that resulting from myeloablative chemotherapy in adults with acute myeloid leukemia (AML). In order to produce a platelet response with TPO agents, there need to be precursors in the bone marrow. If there are only stem cells or early progenitors, a response to TPO agents could occur but might require weeks to more than 1 month. In addition, if there are abnormal precursor cells in the marrow, TPO stimulation may induce leukemia. Therefore, the new generation agents were initially developed for immune thrombocytopenic purpura (ITP) and still have not been fully explored in chemotherapy-induced thrombocytopenia (CIT). Table 1 lists the diseases or situations in which TPO-RA are likely to be useful.

Approved TPO agonists

The approved TPO-receptor agonists include romiplostim (AMG531 or Nplate) and eltrombopag (Promacta in the U.S. or Revolade outside of the U.S.). Both agents have been licensed since 2008 for ITP in the U.S. and are now each licensed in more than 80 countries. Eltrombopag is also licensed for hepatitis C. The utility of romiplostim and more recently eltrombopag have been studied extensively in myelodysplasia. These agents are also likely to be useful for certain inherited thrombocytopenias, acquired bone marrow aplasia, and (in the future) platelet donation.

Romiplostim has four identical TPO agonist peptides, identified by screening of thousands of peptides, to allow dimerization of the thrombopoietin receptor required for its activation [2]. Romiplostim also has glycine bridges to connect the peptides to each other and to the Fc carrier domain backbone to increase its half-life. There is no sequence homology to endogenous TPO to avoid cross reactive antibodies and thus far these have not been seen. Romiplostim is given subcutaneously once a week, and its mechanism of action is thought to be similar to that of thrombopoietin itself, directly binding to the site on the thrombopoietin receptor and initiating the signaling pathways.

In contrast, eltrombopag is a small molecule that is given orally once a day. Eltrombopag is a nonpeptide thrombopoeitin receptor agonist that does not compete with TPO for binding to the TPO receptor and has a low immunogenic potential. While native thrombopoietin has a molecular weight of 64,000 Da, eltrombopag has a molecular weight of 442 Da. One issue with eltrombopag is the contraindication of taking it within 2 h of eating or 4 h of ingesting supplemental calcium or iron because eltrombopag is a potent chelator and will become inactive if bound with calcium. Most

Table 1
Disease or situations in which TPO agents will likely be useful.

Disease/situation	Comments
Immune thrombocytopenia	ITP
Hepatitis C	Treated with PEG interferon
Myelodysplasia (MDS)	In adults
Congenital thrombocytopenias	Several
Platelet donation	
Bone marrow aplasia	Being studied
Chemotherapy-induced thrombocytopenia (CIT)	Non-myeloablative to preserve dose intensity
Ex vivo platelet production	