



New Options for Medical Management of ITP

Introduction

Thrombocytopenia is a condition of reduced platelets. This can occur either through increased destruction of platelets, decreased production, or both. Standard management of adult ITP may include corticosteroids, IVIG, anti-D immunoglobulin, splenectomy, rituximab and combinations of these treatments. A new approach to modulating the balance of platelets is stimulation of platelet production by thrombopoietin (TPO) agonists.

TPO Agonist Efficacy

Platelets are formed from precursor cells in the bone marrow. TPO stimulates the production and differentiation of megakaryocytes and thus increases the number of platelets. Drugs that act like TPO or enhance its effects have been sought for several years, and there are now a variety of promising agents.

Romiplostim (AMG-531, Nplate™) is a protein drug delivered by weekly injection under the skin. In a 24-week clinical evaluation, more than 80% of patients given romiplostim showed an overall platelet response rate, compared with less than 10% of patients given placebo (Kuter 2008). Romiplostim was approved by the FDA in 2008 for treatment of ITP.

Eltrombopag (SB497115, Promacta®) is an orally active drug with similar therapeutic effects to romiplostim. In one clinical study, patients received either placebo or eltrombopag pills once daily for 6 weeks. At the study's end, 16% of placebo-treated patients and 59% of eltrombopag-treated patients had reached the primary endpoint (Bussel 2007). Since the study designs are different and these agents have not been assessed in head-to-head trials, the numerical results of different drug trials should not be compared. Eltrombopag is under Priority Review by the FDA, which is expected to act on the drug application early in 2009.

AKR-501 is an orally active drug under development for the treatment of ITP, and was found to increase platelet counts in healthy volunteers. Subjects who received AKR-501 for 14 days experienced a 2.8-fold increase in average peak platelet count. Clinical studies of AKR-501 in ITP are now underway. Two phase 2 studies are recruiting patients with ITP to gather preliminary safety and efficacy data and determine the optimal dose for phase 3 trials.

LGD4665 is another orally active TPO enhancer. It is currently being evaluated in a phase 2 trial for platelet count and bleeding score in 24 patients with ITP. Recruitment is ongoing for some of these trials. More information can be obtained at <http://www.clinicaltrials.gov>.

TPO Agonist Side Effects

About 1/3 of patients taking romiplostim in clinical trials experienced headache, but approximately the same proportion taking placebo did as well. The rate of side effects in the groups receiving romiplostim exceeded the rate in the placebo group by 5% to 20% for the following symptoms: pain in joints, muscles, limbs, abdomen, or shoulder; dizziness; sleep disorder; indigestion; and a feeling of "pins and

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needles.” Patients experiencing these effects should consult their doctor. Eltrombopag was associated with an increased risk of bone marrow fibrosis. Weekly and then monthly blood monitoring is necessary for patients receiving romiplostim.

About 1/5 of the patients receiving 75 mg per day eltrombopag in clinical trials experienced headache, similar to the number receiving placebo.

Safety information on AKR-501 and LGD4665 will be available after the details of their clinical evaluation are published.

Conclusions

A new class of drugs to treat ITP is emerging. The first thrombopoietin agonist to be approved by the FDA is romiplostim, and a decision on eltrombopag is expected in 2009. Several other synthetic TPO agonists are in clinical development. Clinical experience with these drugs will determine how they can be used best in the management of patients with ITP.

References

Kuter DJ. New drugs for familiar therapeutic targets: thrombopoietin receptor agonists and immune thrombocytopenic purpura. *Eur J Haematol*. 2008;80(S69):9-18.

Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med*. 2007;357:2237-2247.

For clinical trial information: <http://www.clinicaltrials.gov>. Accessed November 2008.

For more information on romiplostim: <http://www.nplate.com>. Accessed November 2008.