Thrombopoietins Take Platelets to New Heights

By Margaret Ragni, MD

Several new agents that influence thrombopoietin (TPO) or its receptor are changing management of thrombocytopenias. The most common thrombocytopenia is idiopathic (immune) thrombocytopenia (ITP). In this condition, platelet production is inadequate in as many as two-thirds of individuals. The early platelet growth factors, so-called thrombopoietins, were complicated by the development of platelet antibodies, and, thus, recent efforts have been directed at generating recombinant thrombopoietins with no sequence homology to endogenous thrombopoietins. Among the first such agent in clinical trials is the *subcutaneous* recombinant thrombopoietin AMG 531 (NEJM 2006; 355:1672-81), which shows safety and preliminary efficacy in increasing platelet counts in ITP.

An international phase II randomized, double-blind placebo-controlled trial of the *oral* platelet thrombopoietin receptor agonist, eltrombopag, abstract #475, was presented by James Bussel, MD, Cornell, in yesterday's simultaneous session on immune thrombocytopenic purpura (ITP) and its treatment. The drug was given daily for six weeks to 117 adults with previously treated ITP and platelets below 30,000/uL, who were randomly assigned to placebo, 30-, 50-, or 75-mg dose levels. The drug was safe and significantly increased platelet counts above 50,000/uL at the two higher dose levels. There was a trend toward reduced bleeding, as measured by the WHO bleeding scale, in the two higher dose levels. Based on its preliminary safety and efficacy, a phase III study of eltrombopag has been initiated.

The results of a phase I study of the oral thrombopoietin receptor agonist, AKR-501 (YM477), abstract #477, was presented by Robert Desjardins, MD, and colleagues at AkaRx Inc. and Massachusetts General Hospital, at the Disorders of Platelet Number or Function Session on Monday. When given to healthy volunteers daily for 14 days in both single and multiple doses, ranging up to 100 mg, there was a 50 percent increase in platelet count in five of six volunteers given a single dose of 100 mg, and in six of six given 10 mg daily for 14 days. The drug, which acts by stimulating megakaryocyte proliferation and differentiation, was well tolerated. There was a linear correlation between dose and platelet change.

Another phase I study of the oral platelet growth factor SB-559448 in healthy subjects, abstract #1072, was reported by Dr. Sheng-Fang Su, GlaxoSmithKline, Collegeville, PA. In this randomized, single-blind placebo-controlled study, the drug, a non-peptide small-molecule thrombopoietin receptor agonist, was given for 10 days at doses ranging from 160 mg to 640 mg. There was good tolerance, safety, and oral bioavailability with pharmacokinetic studies supporting once-daily dosing. A dose-dependent increase in platelet counts was observed at all doses when given for 10 days.

An interesting quality-of-life study performed as an extension study in ITP subjects enrolled in the AMG531 trial, poster #3292, reported by Dr. James George, University of Oklahoma, showed improvement in physical health and emotional health that was significantly greater among those with durable platelet responses (a 50 percent increase over baseline) as compared to those without a durable response.