

## EDITORIALS



## Immune Thrombocytopenic Purpura — From Agony to Agonist

Robert S. Schwartz, M.D.

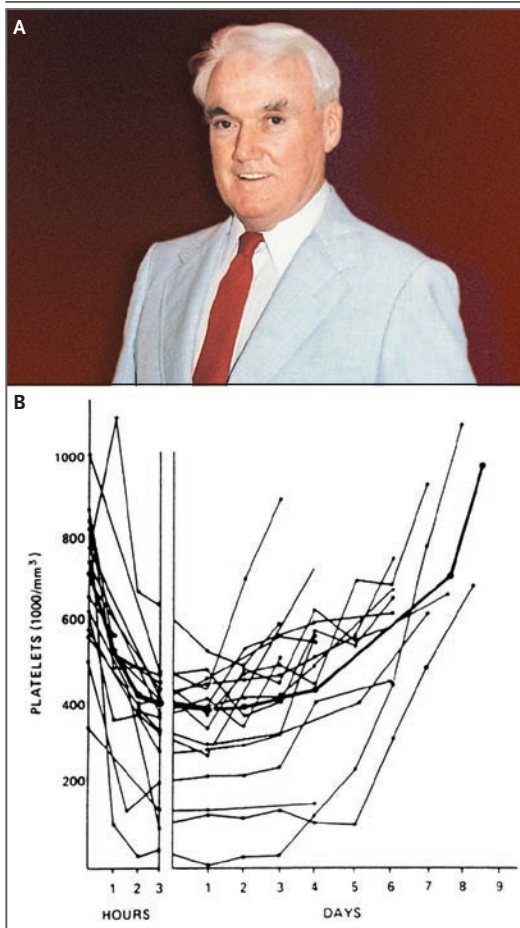
In the summer of 1950, two hematology fellows working at the Barnes Hospital in St. Louis — William J. Harrington and James W. Hollingsworth — hatched a plan to test their idea that the cause of the idiopathic thrombocytopenic purpura (ITP) in a woman under their care was a factor in the blood that destroyed platelets. They decided that of the two fellows, the one whose blood type matched the patient's would receive 500 ml of her blood. In a flip of the genetic coin, Harrington matched.

Within a few hours after receiving the woman's blood, Harrington's platelet count dropped precipitously, and he had a major seizure. For 4 days, his platelet count hovered at dangerously low levels, and bruises and petechiae were evident. Reprieve occurred on the fifth day, when the platelet count began to return to normal. Examination of Harrington's bone marrow, obtained by means of sternal puncture before and after the transfusion, showed no visible changes in megakaryocytes, indicating an effect not on the marrow but on the circulating platelets. Subsequently, all suitable members of the Hematology Division of the Barnes Hospital, including its head, Dr. Carl V. Moore, received plasma from a patient with ITP, and in each recipient the platelet count plunged within 3 hours (Fig. 1).<sup>1</sup>

This experiment, one of the most important ever to be performed in the field of hematology, established that ITP is caused by a circulating factor. The thrombocytopenic factor has since been definitively identified as a cluster of IgG antibodies with specificity for one or more platelet glycoproteins.<sup>2</sup>

The Harrington–Hollingsworth experiment changed the meaning of the “I” in ITP from idiopathic to immune, but “immune” in this case means “autoimmune,” because the antibodies

bind to and cause the destruction of the patient's own platelets. Molecular studies of the antiplatelet antibodies in patients with ITP indicate that



**Figure 1. The Harrington–Hollingsworth Experiment.**

Panel A shows William J. Harrington (1924–1992). Panel B shows rapid development of thrombocytopenia, followed by a return to normal platelet levels, in healthy volunteers who received plasma from patients with idiopathic thrombocytopenic purpura (from Harrington et al.<sup>1</sup>).

they have the genetic marks of antibodies made in response to a persistent antigenic stimulus, but what drives the process is unknown.<sup>3</sup>

The Fc region of the IgG antibodies on the surface of the platelet in patients with ITP binds to Fcγ receptors displayed by macrophages. This encounter triggers the phagocytosis of an antibody-coated platelet by a macrophage. In the presence of high-affinity IgG antiplatelet autoantibodies, the lifespan of a platelet that enters the blood is only a few hours, whereas normally, the lifespan is 10 days. Thrombocytopenia occurs because the rapid rate of destruction exceeds the rate of production of platelets by megakaryocytes in the marrow. Most of the macrophages that ingest antibody-coated platelets reside in the spleen and liver, but there are many other macrophages elsewhere.<sup>4</sup>

This understanding of the mechanism of ITP underlies the major principles of the treatment of the disease: the inhibition of autoantibody formation; removal of the major platelet-destroying organ, the spleen; and interference with the uptake of antibody-coated platelets by phagocytic cells. The American Society of Hematology has endorsed guidelines for the treatment of chronic ITP, which make the important point that therapy is not indicated for an asymptomatic patient with a platelet count of 30,000 or more per cubic millimeter unless there are risk factors for bleeding.<sup>5</sup> Below that level, the standard recommendations — now more than 10 years old, yet still valuable — include initial treatment with corticosteroids, and if a sustained remission cannot be induced or if intolerability or adverse events occur, the remaining major choices are splenectomy, intravenous IgG therapy, or the use of immunosuppressive drugs. Intravenous administration of anti-Rh antibodies is also an option in Rh-positive patients (the antibody-coated erythrocytes compete with antibody-coated platelets in the phagocytic system). There are yet other possibilities for treatment; none of them have proven efficacy, but they are worth trying after all else has failed in a patient covered with ecchymoses and petechiae.

Recently, the idea has arisen that clearance of circulating antibody-coated platelets by phagocytosis is not the only mechanism of thrombocytopenia in patients with ITP. There is also evidence of impaired platelet production, probably due to an attack by autoantibodies against mega-

karyocytes in the bone marrow.<sup>6</sup> Indeed, signs of dying megakaryocytes and even megakaryocytes that have undergone phagocytosis have been observed in bone-marrow specimens from patients with ITP.<sup>7</sup> It may be surprising that plasma levels of thrombopoietin, the principal regulator of platelet production, are usually normal in patients with ITP, whereas they are considerably increased in those with aplastic anemia or other types of thrombocytopenia associated with bone-marrow failure.<sup>8</sup> These contrasting findings indicate that the liver, the principal source of thrombopoietin, is unable to produce sufficient amounts of the growth factor to keep pace with the platelet destruction.

It seems logical, in light of these recent observations, to evaluate the efficacy of thrombopoietin therapy, which is available as a recombinant polypeptide, in patients with ITP in whom conventional treatment has failed. There are, however, major drawbacks to such an investigation: one is the development of fibrosis in the marrow, and the other is the production of antibodies against the recombinant polypeptide that also neutralize the recipient's native thrombopoietin. The resulting thrombopoietin-induced thrombocytopenia can be severe and was the principal reason for stopping clinical trials of recombinant thrombopoietin.<sup>9</sup>

More recently, small molecular mimics of thrombopoietin, which act as agonists when they bind to the thrombopoietin receptor on megakaryocytes yet have no sequences in common with the native growth factor, have been developed. One of these agonists, AMG 513, is a “peptibody” that consists of a pair of identical short peptides, each linked to the Fc region of IgG, which acts as a carrier. Its half-life in humans is more than 4 days, and it increases the platelet count in normal volunteers. In a phase 1 study of AMG 513 in 28 patients with chronic ITP who did not have a response to at least one previous type of treatment, the platelet count rose to more than 50,000 per cubic millimeter in 17. The durability of the response and the long-term safety of this peptide mimic are unknown.<sup>10</sup>

In this issue of the *Journal*, Bussel et al. report on the clinical activity of another mimic, eltrombopag — a simple chain of four carbon-based rings with various side chains.<sup>11</sup> This agonist binds to the thrombopoietin receptor at a point different from the binding site of thrombopoi-

etin, stimulates the growth of thrombopoietin-dependent cell lines in vitro, and raises the platelet count in normal volunteers. In this phase 1 trial of eltrombopag in patients with chronic ITP who did not have a response to at least one previous type of treatment, the drug raised the platelet count to 50,000 or more per cubic millimeter in 21 of 26 patients who received 75 mg per day, in 19 of 27 who received 50 mg per day, and in 8 of 29 who received 30 mg per day. As with AMG 531, the durability of the response and the long-term safety of the compound are unknown. In a companion paper in this issue of the *Journal*, McHutchison et al. report their results regarding eltrombopag in the treatment of thrombocytopenia associated with cirrhosis due to hepatitis C infection.<sup>12</sup> In this small trial, treatment with eltrombopag raised the platelet count to 100,000 or more per cubic millimeter in most patients who received the highest dose of the compound, thereby enabling the initiation of antiviral therapy. Notably, during the 12-week period of antiviral treatment, platelet counts fell despite the continuation of eltrombopag therapy, but the levels remained above the baseline. Whether this observation has implications for the durability of the response to eltrombopag in patients with ITP is not known.

The results reported for thrombopoietin-receptor agonists are too preliminary for any definitive statement about applications in clinical practice, but they surely encourage further work in this direction. Hematologists everywhere are thwarted by patients with ITP in whom every available treatment has failed to improve the platelet count.

A new, safe way of treating the disease would be a considerable advance.

- Harrington WJ, Minnich V, Hollingsworth JW, Moore CV. Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura. *J Lab Clin Med* 1951;38:1-10.
- Tomer A, Koziol J, McMillan R. Autoimmune thrombocytopenia: flow cytometric determination of platelet-associated autoantibodies against platelet-specific receptors. *J Thromb Haemost* 2005;3:74-8.
- Roark JH, Bussel JB, Cines DB, Siegel DL. Genetic analysis of autoantibodies in idiopathic thrombocytopenic purpura reveals evidence of clonal expansion and somatic mutation. *Blood* 2002;100:1388-98.
- Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med* 2002;346:995-1008.
- George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 1996;88:3-40.
- McMillan R, Wang L, Tomer A, Nichol J, Pistillo J. Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. *Blood* 2004;103:1364-9.
- Houwerzijl EJ, Blom NR, van der Want JLL, et al. Ultrastructural study shows morphologic features of apoptosis and paraptosis in megakaryocytes from patients with idiopathic thrombocytopenic purpura. *Blood* 2004;103:500-6.
- Emmons RV, Reid DM, Cohen RL, et al. Human thrombopoietin levels are high when thrombocytopenia is due to megakaryocyte deficiency and low when due to increased platelet destruction. *Blood* 1996;87:4068-71.
- Li J, Yang C, Xia Y, et al. Thrombocytopenia caused by the development of antibodies to thrombopoietin. *Blood* 2001;98:3241-8.
- Bussel JB, Kuter DJ, George JN, et al. AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. *N Engl J Med* 2006;355:1672-81. [Erratum, *N Engl J Med* 2006;355:2054.]
- Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 2007;357:2237-47.
- McHutchison JG, Dusheiko G, Shiffman ML, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med* 2007;357:2227-36.

Copyright © 2007 Massachusetts Medical Society.

## Statins for Ischemic Systolic Heart Failure

Frederick A. Masoudi, M.D., M.S.P.H.

Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) represent one of the most important pharmacologic advances in the prevention of cardiovascular disease in decades. Since the publication of the Scandinavian Simvastatin Survival Study in 1994,<sup>1</sup> several trials have demonstrated important benefits of statins in patients with established coronary disease. These findings have resulted in strong recommendations for the use of statins in clinical-practice guidelines.<sup>2</sup> Statins

are one of the few classes of drugs that are embedded in clinical-performance measures for coronary artery disease, which indicates that clinicians should be considered remiss if they do not prescribe these agents for all their eligible patients.<sup>3</sup>

In the context of the strong evidence base and recommendations supporting the use of statins for secondary prevention of cardiovascular disease, in this issue of the *Journal* Kjekshus et al.<sup>4</sup>