



Agents to Control Bleeding Show Promise

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Orlando—Recent clinical trials point to novel therapies to prevent bleeding in individuals at high risk of venous thrombolism who are treated with anticoagulant therapy and in patients with thrombocytopenia. As reported in December at the annual meeting of the American Society of Hematology, various alternatives to current treatments may someday make their way into the clinic.

NEW ANTICOAGULANTS

Every year, thousands of patients develop deep vein thrombosis (DVT) and are at risk of pulmonary embolism after undergoing surgeries, particularly orthopedic procedures in the hips and legs. Although low-molecular-weight heparin is considered the standard therapy for DVT and other forms of venous thromboembolism, it is far from an ideal anticoagulant. Its drawbacks include the need for daily injections, adverse interactions with many types of drugs, and a wide variation in patient response. Researchers have therefore continued to search for alternative therapies.

A phase 2 randomized, open-label trial funded by Sanofi-Aventis assessed the potential of idraparinux for preventing DVT and pulmonary embolism. This anticoagulant, which targets a molecule in the coagulation cascade, can be taken less often than low-molecular-weight heparin.

In the study, 2904 patients with a previous DVT episode were randomized to receive idraparinux by subcutaneous injection once a week or standard treatment, including daily injections of low-molecular-weight heparin. After 3 months of therapy, idraparinux proved to be as

effective as the standard treatment in preventing venous clot recurrence (2.9% vs 3.0% recurrence respectively). Severe bleeding, a potential adverse effect of anticoagulants, occurred in 4.5% of patients taking idraparinux and in 7.0% of those receiving standard therapy.



New agents are being tested to prevent the blood clots and abnormal pooling of blood that occur during deep vein thrombosis.

The results were not as promising when idraparinux was compared with standard therapy in 2215 patients who had experienced a pulmonary embolism and were at risk for developing another venous thromboembolism. The incidence of blood clot recurrence after 3 months was higher (3.4%) in the idraparinux group compared with those receiving standard therapy (1.6%). “This is a surprising finding,” said lead author Harry Buller, MD, of the Academic Medical Center in Amsterdam, the Netherlands. “The frequency [of recurrence] observed in the idraparinux arm was exactly what we expected, but the

big surprise was the very low rate in the comparison arm.” Additional studies are under way to reassess idraparinux’s potential for the prevention of venous thromboembolism in patients who have experienced a pulmonary embolism.

A new oral anticoagulant, a thrombin inhibitor called dabigatran etexilate, was tested in a phase 3 randomized, double-blind, active-controlled trial funded by Boehringer Ingelheim for the prevention of venous thromboembolism following total knee replacement surgery. In the trial, an international team of researchers randomized 2076 orthopedic patients to 3 treatment groups: either 150 or 220 mg/d of dabigatran etexilate starting 1 to 4 hours after surgery or 40 mg/d of subcutaneous enoxaparin (a low-molecular-weight heparin) starting 12 hours before surgery.

Venous thromboembolism events and death rates were comparable in the 3 groups over 3 months of follow-up, occurring in 40.5%, 36.4%, and 37.7% of patients receiving 150 or 220 mg dabigatran etexilate and 40 mg enoxaparin, respectively. There also was no significant difference in the rate of major bleeding among the 3 groups (1.3%, 1.5%, and 1.3%, respectively).

In addition to being as safe and effective as low-molecular-weight heparin, dabigatran etexilate demonstrated additional benefits, said lead investigator Bengt Eriksson, MD, PhD, of the Sahlgrenska University Hospital/Östra, in Gothenburg, Sweden. “It’s an oral drug, there is no need for blood sample monitoring, and the same dose can be given to all patients irrespective of weight or age,” he explained. Eriksson added that dabigatran etexilate also elicits predictable antithrombotic effects with little risk of drug interactions.



STIMULATING PLATELETS IN ITP

Strides are also being made in the treatment of patients with thrombocytopenia, particularly those with immune thrombocytopenic purpura (ITP), a rare autoimmune condition. "In ITP, patients make antibodies that recognize their own platelets as being foreign, and this causes the platelets to be destroyed and predisposes the patient to bleeding," said Nancy Berliner, MD, professor of medicine and genetics at the Yale University School of Medicine, in New Haven, Conn. While individuals normally have platelet counts of $150 \times 10^9/L$ to $450 \times 10^9/L$ of blood, patients with ITP often have less than $30 \times 10^9/L$.

Although it has been assumed that patients with ITP rev up production of platelets in an attempt to compensate for losses, researchers have recently hypothesized that impaired production of platelets in the bone marrow may also contribute to the clinical features of the disease. "This has led to some successful efforts to develop drugs for ITP by inducing the patient to make more platelets," said Berliner.

One such effort has produced the drug eltrombopag, an oral agent that binds to and stimulates the thrombopoietin receptor on bone marrow cells, coaxing them to differentiate into platelets. In a recent randomized, double-blind, placebo-controlled phase 2 trial funded by GlaxoSmithKline, 117 patients with chronic, previously treated ITP and low platelet levels received placebo or eltrombopag once daily at 30 mg, 50 mg, or 75 mg for 6 weeks and were followed up for an additional 6 weeks.

Individuals treated with 50 mg or 75 mg of eltrombopag showed a substantial increase in platelet number and a decrease in bleeding. "More than 70% of the patients at the 50 mg dose and 80% of the patients at the 75 mg dose met the primary response criteria of the study—after 6 weeks of therapy they had a platelet count greater than $50 \times 10^9/L$ after starting at a platelet count less than $30 \times 10^9/L$," said lead author James Bussel, MD, of Weill Cornell Medical Center, in New York City.

Median platelet counts increased progressively with drug dose and by the

end of treatment ranged from $16 \times 10^9/L$ in the placebo group to $183 \times 10^9/L$ in the 75 mg eltrombopag group. Incidence of bleeding events during treatment decreased at the 2 highest dosages, reaching 10%, 16%, 3%, and 4% in the placebo, 30 mg, 50 mg, and 75 mg groups, respectively. Bleeding events also decreased in these groups during follow-up, and were 14%, 13%, 10%, and 7% in the respective groups.

Another oral agent that binds to the thrombopoietin receptor, called AKR-501, has also generated positive results in an early phase 1 study. AKR-501 binds to a different spot on the thrombopoietin receptor than thrombopoietin does and is therefore not competitive with this platelet-stimulating growth factor. "This is important because people with low platelet counts have compensated for that by raising their levels of thrombopoietin, so the ability to have an effect above and beyond that may turn out to be important," said lead author Robert Desjardins, MD, of the drug development company AkaRx Inc, in Paramus, NJ.

In healthy volunteers, investigators evaluated the safety and efficacy of AKR-501 administered in single and multiple doses, with the goal of evoking at least a 50% increase in platelet count. In the single-dose arm, 63 individuals were randomly assigned to receive placebo or AKR-501 in a dose ranging from 1 to 100 mg. In the multiple-dose arm, 45 individuals received placebo or AKR-501 in a dose ranging from 3 to 100 mg, administered daily for up to 2 weeks.

At least a 50% increase in platelet count was achieved in 5 of 6 individuals given a single dose of 100 mg of drug and in all 6 individuals given daily doses of 10 mg for 14 days or 20 mg for 10 days. AKR-501 was well tolerated in all groups with no serious drug-related adverse events reported at any dosage. Desjardins and colleagues have now initiated a phase 2 study of AKR-501 in patients with ITP, and they are interested in testing the drug's potential for treating patients with thrombocytopenia due to other causes, such as chemotherapy and hepatitis.

HALTING PLATELET DESTRUCTION

Researchers have also been attempting to increase platelet counts in patients with ITP by reducing autoimmune-mediated platelet destruction. Previous research has suggested that some patients with chronic ITP respond to rituximab, an antibody directed against the CD20 antigen on T cells and approved to treat non-Hodgkin lymphoma. However, most of these studies were retrospective in nature, included patients with heterogeneous treatment histories, and had limited follow-up, according to Bertrand Godeau, MD, of the Henri Mondor Hospital, in Creteil, France.

To better assess rituximab's potential, Godeau and colleagues initiated a phase 2 multicenter prospective trial partially funded by Laboratoire Roche to determine whether treatment with rituximab could enable patients with chronic ITP to avoid removal of the spleen, which is the main site of platelet destruction. However, Godeau noted, "splenectomy is an invasive procedure, patients run the risk of sepsis and pneumococcal infection, and its long-term efficacy is not so good."

During the trial, 60 patients with ITP with an average duration of disease of 4.8 years and mean platelet count of $16 \times 10^9/L$ were given 4 weekly intravenous infusions of rituximab. One year after the first infusion, success, defined as a platelet count of $50 \times 10^9/L$ or higher with at least a 2-fold increase from the patient's initial count, was achieved in 24 patients (40%). Two other patients had an incomplete response but did see their count double over the 1-year period, while 34 patients (57%) failed to respond.

"Our study suggests that rituximab can be an alternative to splenectomy for adults with chronic ITP and low platelet count; however, there are several questions that need to be answered," said Godeau. For example, investigators do not know the long-term outcome for patients on this drug, the ideal dose has yet to be determined, and the patient characteristics that play a role in response are unknown. □