Defitelio (Defibrotide Sodium): First Drug Approved for Patients with Hepatic Veno-Occlusive Disease

By Laura Morgan

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome, is a rare and life-threatening liver condition that is characterized by rapid weight gain, ascites, painful hepatomegaly, and jaundice. It is often observed in patients after allogeneic or autologous hematopoietic stem-cell transplantation (HSCT), and has also been reported during the treatment of Wilms tumor, rhabdomyosarcoma associated with actinomycin D, and acute lymphoblastic leukemia.

Hepatic VOD is thought to be caused by damage to sinusoidal endothelial cells and hepatocytes in the area surrounding the central veins. The pathogenesis of hepatic VOD involves cytokine release, endothelial injury, hemostatic activation, and hepatic drug detoxification through the glutathione pathway. Hepatocellular necrosis, fibrosis, and vascular occlusion lead to liver failure, hepatorenal syndrome, multiorgan failure, and death.

A liver biopsy is the gold standard for diagnosing hepatic VOD; however, the majority of cases are diagnosed clinically because of the invasive nature of a biopsy. Hepatic VOD is more common after allogeneic HSCT than after autologous HSCT, and is usually triggered by the administration of conditioning therapy for HSCT. It has been reported in ≤60% of patients after HSCT, ranging in severity from a mild, reversible disease to a severe syndrome associated with a high mortality rate and progression to multiorgan failure; however, there is no consensus on how to evaluate the severity of hepatic VOD. Overall, <2% of patients have severe hepatic VOD, and approximately 80% of these patients do not survive.

The primary goal of treating hepatic VOD is to normalize the flow in the sinusoidal vessels and veins by controlling the vasculitis and fibrin deposition. Although no specific treatment modality has been recognized for patients with VOD, several methods have been used to normalize flow in sinusoidal blood vessels and veins, including low-dose tissue plasminogen activators to increase fibrin degradation, antithrombin III replacement, and antithrombin III in combination with heparin and low-dose tissue plasminogen activators. Other anticoagulant therapies have also been used, but yielded mixed results.

FDA Approves Defitelio for Hepatic VOD

On March 30, 2016, the US Food and Drug Administration (FDA) approved defibrotide sodium (Defitelio; Jazz Pharmaceuticals) for the treatment of adults and children with hepatic VOD with renal or pulmonary dysfunction after HSCT. Defibrotide sodium is the first therapy to receive FDA approval for patients with severe hepatic VOD.

The FDA approval was based on 3 clinical trials showing its treatment benefits in 528 patients with severe hepatic VOD and with liver or kidney abnormalities after HSCT. The studies measured the percentage of patients who were still alive 100 days after undergoing HSCT.

“The approval of Defitelio fills a significant need in the transplantation community to treat this rare but frequently fatal complication in patients who receive chemotherapy and HSCT,” said Richard Pazdur, MD, Director of the FDA’s Office of Hematology and Oncology Products.

Defibrotide sodium was approved under the FDA’s priority review status, which enables the FDA to expedite the review of certain drugs because of their potential to benefit patients with serious conditions. In addition, defibrotide sodium received an orphan drug designation.

Mechanism of Action

Although its mechanism of action is not fully understood, defibrotide sodium has been shown to enhance the enzymatic activity of plasmin to hydrolyze clots of fibrin. Defibrotide sodium increases tissue plasminogen activator and thrombomodulin expression, and decreases expression of von Willebrand factor and plasminogen activator inhibitor-1 in endothelial cells, leading to the reduction of endothelial-cell activation and increased endothelial-cell–mediated fibrinolysis. In addition, defibrotide sodium protects endothelial cells from damage associated with chemotherapy, tumor necrosis factor-α, serum starvation, and perfusion.

Dosing and Administration

Defibrotide sodium is administered for 2 hours via a continuous intravenous infusion; defibrotide sodium should be diluted before infusion. The recommended dosage is 6.25 mg/kg every 6 hours; the dose should be...
Defibrotide sodium should be administered for a minimum of 21 days, and continued until the signs and symptoms of VOD have resolved, or up to a maximum of 60 days. Defibrotide sodium is available in a 200-mg/2.5-mL (80-mg/mL) single-use vial, containing light yellow to brown, sterile, preservative-free solution.

Defibrotide Sodium Distribution

Defibrotide sodium is distributed through McKesson Plasma and Biologics. Institutions should verify they have a contract with this distributor or set up a contract before ordering the drug, according to the drug manufacturer (https://defitelio.com).

Clinical Trials

The approval of defibrotide sodium for the treatment of adults and children with hepatic VOD and renal or pulmonary dysfunction after HSCT was based on the results of 3 clinical trials. Survival rates reported with defibrotide sodium in the 3 studies are outlined in Table 1.

Study 1: Phase 3 Trial

In the first study, a phase 3, prospective clinical trial, investigators evaluated the efficacy and safety of defibrotide sodium in 134 patients with hepatic VOD and multiorgan failure. Patients in the treatment group (N = 102) received defibrotide sodium 25 mg daily, and the control group (N = 32) comprised historical-control patients who underwent HSCT and were identified from 6867 medical charts.

The primary outcome measure was the difference in survival rate at day 100 or more (100+) after HSCT between the treatment group and the control group; the secondary outcome measures were (1) the difference in the complete response rate at 100+ days after HSCT in the treatment group versus the control group, and (2) survival at 180+ days after HSCT.

The survival rate at 100+ days after HSCT was 38.2% in the treatment group versus 25% in the control group (P = .0109). The complete response rate at the same time point was 25.5% in the defibrotide sodium group, and 12.5% in the control group (P = .0160; Table 1).

Study 2: Phase 2 Trial

The second study was a phase 2, dose-finding clinical trial in which investigators prospectively evaluated adult and pediatric patients with hepatic VOD and multiorgan dysfunction after HSCT. Overall, 75 patients received defibrotide sodium 6.25 mg/kg, and 74 patients received defibrotide sodium 10 mg/kg infused every 6 hours for ≥14 days or until the signs of hepatic VOD resolved. The survival rate at 100+ days after HSCT was 44% for patients who received the 6.25-mg/kg dose, and 39% for patients who received the 10-mg/kg dose (P = .619). In addition, the complete response rate was 49% in the 6.25-mg/kg group, and 43% in the 10-mg/kg group (P = .613; Table 1).

Study 3: Expanded Access Trial

The third study was an expanded access analysis in 351 adult and pediatric patients with hepatic VOD and renal or pulmonary dysfunction after HSCT who received 6.25-mg/kg infusions of defibrotide sodium every 6 hours. The survival rate at day 100+ after HSCT was 45% (Table 1).

Adverse Reactions

The safety of defibrotide sodium was evaluated in 176 patients who participated in the 3 clinical trials. The most common (≥10%) adverse reactions of any grade reported with defibrotide sodium were hypotension (37%), diarrhea (24%), vomiting (18%), nausea (16%), and epistaxis (14%). The most common serious adverse events were hypotension (7%) and alveolar hemorrhage (11%). Table 2 lists grade 4 or 5 adverse events occurring in 3% of the patients.

Data from 102 patients with VOD showed that 34% of patients had adverse events that resulted in the permanent discontinuation of defibrotide sodium. Adverse events that led to the permanent discontinuation of de-

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Table 1. Survival Rates with Defibrotide Sodium After HSCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Study description</th>
<th>Patients receiving defibrotide sodium, N</th>
<th>Survival rate 100+ days after HSCT, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>Phase 3 prospective</td>
<td>102</td>
<td>38 (95% CI, 29-48)</td>
</tr>
<tr>
<td>Study 2</td>
<td>Phase 2 prospective</td>
<td>75</td>
<td>44 (95% CI, 33-55)</td>
</tr>
<tr>
<td>Study 3</td>
<td>Expanded access</td>
<td>351</td>
<td>45 (95% CI, 40-51)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HSCT, hematopoietic stem-cell transplantation. Sources: References 14-17.

Table 2. Grade 4 or 5 Adverse Reactions in ≥3% Patients

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Grade 4 or 5, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Pulmonary alveolar hemorrhage</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Graft versus host disease</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Lung infiltration</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (3)</td>
</tr>
</tbody>
</table>

Source: Reference 14.
Defibrotide sodium included pulmonary alveolar hemorrhage (5%), pulmonary hemorrhage (3%), hypotension (3%), catheter-site hemorrhage (3%), multiorgan failure (3%), cerebral hemorrhage (2%), and sepsis (2%).

**Contraindications**

The use of defibrotide sodium concomitantly with systemic anticoagulants or fibrinolytic therapy is contraindicated. In addition, defibrotide sodium is contraindicated in patients with a hypersensitivity to any of its excipients.

**Warning and Precautions**

**Bleeding.** Defibrotide sodium should not be used in patients with persistent, severe or potentially life-threatening bleeding. Increased activity of fibrinolytic enzymes may increase the risk for bleeding in patients with VOD after HSCT. Patients should be monitored for the signs of bleeding, and defibrotide sodium should be permanently discontinued in patients with recurrent, significant bleeding. The risk for bleeding may be increased with the concomitant use of defibrotide sodium and a systemic anticoagulant or fibrinolytic therapy.

**Hypersensitivity reactions.** Hypersensitivity reactions, including rash, urticaria, and angioedema, have occurred in <2% of patients who received defibrotide sodium; anaphylactic shock was reported in 1 patient who had received defibrotide sodium. Patients should be monitored for hypersensitivity reactions, especially if they have been exposed to defibrotide sodium; the drug should be discontinued if a hypersensitivity reaction occurs.

**Use in Specific Populations**

**Pediatric patients.** The safety and efficacy of defibrotide sodium have been established in pediatric patients aged 1 month to 17 years, and were consistent across pediatric and adult patients in the clinical trials.

**Pregnant or lactating women.** The safety and efficacy of defibrotide sodium therapy have not been established in pregnant patients. It is advised that women should not receive defibrotide sodium while breast-feeding.

**Geriatric patients.** Insufficient data were collected in older patients (aged ≥65 years) to determine whether they respond differently to defibrotide sodium compared with younger patients.

**Conclusion**

Defibrotide sodium is the first treatment to receive FDA approval in the United States for patients with severe hepatic VOD, a rare but life-threatening condition occurring in patients who receive chemotherapy after HSCT. Evidence from 3 clinical trials shows that this new medication is generally safe and well-tolerated, and is an effective treatment option for patients with hepatic VOD associated with renal or with pulmonary dysfunction after HSCT.

**References**