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Complications of Treatment

# Defibrotide for the management of sinusoidal obstruction syndrome in patients who undergo haemopoietic stem cell transplantation

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ABSTRACT

Sinusoidal obstruction syndrome, previously known as veno-occlusive disease (VOD/SOS), is a complication in patients undergoing haemopoietic stem cell transplantation (HSCT). Severe VOD/SOS, including progression to multi-organ failure, has resulted in a mortality of greater than 80%. Defibrotide's varying pharmacological actions, particularly on endothelial cells, make it is a useful agent to consider for prophylaxis and treatment of VOD/SOS. Barriers to its routine use include the high acquisition cost and the fact that neither the oral or parenteral formulations are licensed products in many countries at this time. This review summarises available literature on the use of defibrotide in the management of VOD/SOS. Publications consist predominantly of single centre cohort studies and case series. Available evidence indicates that defibrotide is effective in the management of VOD/SOS. Using defibrotide prophylaxis should also be considered, especially in the paediatric setting, where there are available results from a large, open label, randomized controlled trial. Patient outcome data from the larger studies and compassionate programs can inform consensus recommendations on dosing regimen and criteria for the treatment of VOD/SOS with defibrotide in the adult population. The reviewed literature indicates an effective and safe dose for treatment is 25 mg/kg/day, continued for at least 14 days or until complete response is achieved. Further studies are required to determine the optimal dose and duration of treatment in both paediatric patients and adults. Recent recommendations and a phase 3 trial using historical controls indicate that defibrotide should be included as a pharmacotherapy option in protocols guiding management of VOD/SOS.



## Introduction

### *Sinusoidal obstruction syndrome*

Sinusoidal obstruction syndrome, previously known as veno-occlusive disease (VOD/SOS), is an established complication in patients undergoing haemopoietic stem cell transplantation (HSCT). VOD/SOS is associated with the intensity of conditioning regimens used in HSCT but has also been reported in patients receiving standard chemotherapy [1–3]. It has been reported that there is a higher incidence of VOD/SOS associated with allogeneic transplant compared to autologous transplant, even when the conditioning regimens are similar [4]. Allogeniecity itself has also been shown to impact the incidence of VOD/SOS. Even when reduced intensity conditioning was used, if non-sibling donors were the transplant cell source, the incidence of VOD/SOS was similar to those receiving a myeloablative regimen [5]. The chemotherapy regimens damage the sinusoidal endothelium and small hepatic venules leading to the activation of the coagulation cascade [1,2,6]. The result is hypercoagulation and blockage of these small hepatic vessels [1,2,6]. Some cases resolve spontaneously but in many patients this occlusion will result in significant hepatic dysfunction and multi-organ failure affecting the kidneys and lungs [1,2,6].

VOD/SOS is diagnosed predominantly on clinical signs and symptoms, usually based on either the modified Seattle [7] or Baltimore [8] criteria (Table 1). Patients with moderate to severe VOD/SOS can present with some or all of the following: raised bilirubin and jaundice, weight gain, hepatomegaly, right upper quadrant pain and ascites. Other organ systems being affected can present as increase in serum creatinine, need for supplemental oxygen

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**Table 1**
Criteria for diagnosis of SOS and severity of SOS [5,6].

| Diagnosis | |
|---|---|
| Modified Seattle | Baltimore |
| At least two of the following, occurring **within 20 d**[a] of transplantation:<br>Serum bilirubin >34 μmol/L (>2 mg/dL)<br>Hepatomegaly with right upper quadrant pain<br>> 2% weight gain from baseline due to fluid retention | Serum bilirubin >34 μmol/L (>2 mg/dL) within 21 d of transplantation AND at least two of the following:<br>Hepatomegaly<br>>5% weight gain from baseline<br>Ascites |
| Severity (Seattle Criteria) | |
| *Mild*<br>No adverse effects of liver disease, AND<br>No medications required for diuresis or hepatic pain, AND<br>All symptoms, signs and laboratory features reversible | |
| *Moderate*<br>Adverse effects of liver disease present, AND<br>Sodium restriction or diuretics required, OR<br>Medication for hepatic pain required, AND<br>All symptoms, signs and laboratory features reversible | |
| *Severe*<br>Adverse effects of liver disease present, AND<br>Symptoms, signs or laboratory features not resolved by day +100, OR<br>Death | |

[a] The specification '**within 20 days**' is what differentiates the modified Seattle criteria from the original Seattle Criteria.

and delirium [1,2]. Ultrasound imaging and liver biopsy, if possible, can be useful in excluding other diagnoses and confirming the presence of VOD/SOS [1,3,6].

VOD/SOS develops predominantly within the first 35 days of HSCT [1]. Even though the incidence of VOD/SOS is reported as less than 5% in patients receiving an autologous HSCT, rates of up to 60% in allogeneic HSCT have been described in the literature [5,9,10]. A large review of published data from 1979–2007, calculated an overall mean incidence of VOD/SOS of 13.7% in patients having undergone an autologous or allogeneic HSCT without defibrotide prophylaxis [10]. Severe VOD/SOS, which includes progression to multi organ failure, resulted in a mortality rate of 84.3% [10]. The higher incidence in allogeneic HSCT is reflective of the higher intensity conditioning regimens used. The incidence between studies does vary, most likely due to the diagnostic criteria being used and that many studies are single centre with select groups of patients [9]. Overall the mean incidence in the allogeneic HSCT group seems to have decreased over the last couple of decades, most likely due to earlier recognition and treatment of VOD/SOS and the introduction of reduced intensity conditioning regimens (RIC) into practice [5].

### *What is defibrotide?*

As described by Prescador et al. "defibrotide is a mixture of 90% single-stranded phosphodiester oligonucleotides (length, 9–80mer; average, 50mer; average molecular mass 16.5 ± 2.5 kDa) and 10% double stranded phosphodiester oligonucleotides derived from the controlled depolymerisation of porcine intestinal mucosal DNA" [11]. Many pharmacological actions have been studied and identified including anti-thrombotic, anti-inflammatory and anti-ischemic properties [11–13].

Defibrotide's varying pharmacological actions, particularly on endothelial cells and in the setting of HSCT indicate that it is a useful agent to consider in both prophylaxis and treatment of VOD/SOS [11–13]. Allogeneic and autologous HSCT has been shown to cause endothelial damage [12,13]. The causes of this damage are inherent in the HSCT process and include the chemotherapy and radiation regimen, immune system responses to damaged tissue and engraftment processes [12]. In an in vitro study, endothelial cell lines were exposed to the immunosuppressive agents cyclosporin, tacrolimus and sirolimus, all commonly used in allogeneic HSCT and known to cause endothelial damage [12,13]. This study reported protective anti-inflammatory and antithrombotic effects of defibrotide on endothelial cell lines exposed to these immunosuppressive agents [12].

Over the last two decades, defibrotide has been increasingly used and studied in the management of VOD/SOS in adult and paediatric patients undergoing HSCT. Although the weight of evidence in the paediatric setting is favourable towards defibrotide's role both in prophylaxis and treatment of VOD/SOS, this is not as clear in the adult setting. Even in the presence of guidance and recommendations on its use [2], barriers to the routine use of defibrotide include the high acquisition cost and the fact that neither the oral or parenteral formulations are licensed products in many countries at this time.

## Evidence in paediatrics

### *Prophylaxis*

One of the largest studies undertaken to investigate defibrotide in HSCT was in the paediatric setting. This study was an open-label, phase 3 randomised controlled trial which recruited 356 paediatric patients [14]. It was conducted at multiple sites across Europe. The study investigated if defibrotide prophylaxis would reduce the incidence of VOD/SOS at day 30 post HSCT. Diagnosis of VOD/SOS was determined by a masked, independent review panel using Seattle criteria [7]. To be included, patients had undergone either an allogeneic or autologous HSCT preceded by myeloablative conditioning. To be eligible, patients also had to have one further risk factor for VOD/SOS such as but not limited to, pre-existing liver disease, previous HSCT or conditioning with busulphan [14]. The patients randomised to the treatment arm received defibrotide intravenously 25 mg/kg per day in divided doses, commencing on the day of conditioning, during the stem cell or bone marrow transplantation (Day 0) and continuing until day 30. If discharge occurred before day 30, the defibrotide was administered for at least 14 days. A placebo could not be formulated so the study was open label and the control arm received no treatment [14]. From the 180 patients randomised to the active arm, 22 (12%) developed VOD/SOS by day 30, compared to 35 of 176 controls (20%). The investigators used a competing risk analysis showing that the risk difference in developing VOD/SOS was −7.7% ($p = 0.048$) in favour of the defibrotide arm [14]. Rates of VOD/SOS associated mortality at day 100 was low in both groups and the difference not statistically significant, 2% in the defibrotide arm compared to 6% in the control group. Day 180 non-relapse mortality was similar in both groups. There were no safety concerns associated with defibrotide in this study. These results as reported by the authors look favourable towards, and compliment earlier studies which also described, the activity of defibrotide as prophylaxis in this setting [14–18]. This study was reviewed by a Cochrane analysis [19]. The results when re-analysed by this review did not indicate any statistical significance between the treatment and control groups for incidence of VOD/SOS or overall survival. There was also no difference within subgroups analysed such as infants and adolescents. It was also noted that outcome data at the pre-determined day 180 endpoint was only available for 48% of participants. These conflicting results reported in the Cochrane review make it difficult to make conclusive assertions from the Corbacioglu study, for the use of defibrotide in the setting