Defibrotide for the treatment and prophylaxis of hepatic veno-occlusive disease

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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All authors and reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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Content

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LIST OF ABBREVIATIONS

AE..... adverse event
CCT..... controlled clinical trial
CHMP..... Committee for Medicinal Products for Human Use
CI..... confidence interval
CR ..... complete response
DNA..... deoxyribonucleic acid
EMA ..... European Medicines Agency
FDA..... U.S. Food and Drug Administration
GRADE..... Grading of Recommendations Assessment, Development and Evaluation
GVHD ..... graft-versus-host-disease
HCT ..... hematopoietic cell transplantation
HSCT ..... hematopoietic stem cell transplantation
ICAM-1 ..... intercellular adhesion molecule 1
IQR..... interquartile range
IU ..... international unit
LBI-HTA ..... Ludwig Boltzmann Institut für Health Technology Assessment
MOF..... multi-organ failure
MOH ..... Ministry of Health
NA ..... data not available
p..... p value
RCT..... randomised controlled trial
SOS..... sinusoidal obstruction syndrome
TBI ..... total body irradiation
t-PA ..... tissue-plasminogen activator
UDCA ..... ursodeoxycholic acid
US..... ultrasound
VOD ..... veno-occlusive disease

Summary

Introduction

This systematic review evaluates the following research questions:

- Is defibrotide for the prophylaxis of veno-occlusive disease (VOD) for patients undergoing haematopoietic stem cell transplantation (HSCT) in comparison to no prophylaxis, placebo or other experimental options in adult and paediatric patients more effective and safe concerning overall and disease-specific mortality, incidence of VOD, quality of life and adverse events?
- Is defibrotide for the treatment of severe veno-occlusive disease (VOD) after oncologic therapy or after haematopoietic stem cell transplantation (HSCT) in comparison to no treatment, placebo or other experimental options in adult and paediatric patients more effective and safe concerning overall and disease-specific mortality, resolution of VOD, quality of life and adverse events?

VOD is a rare disease, often associated with conditioning regimens prior to HSCT

VOD is a rare disease most often occurring as a result of a conditioning treatment administered prior to HSCT; hepatic sinusoidal endothelial cell lesions are deemed to be the primary cause. Characteristic symptoms are painful hepatomegaly, right upper quadrant pain, jaundice and ascites; VOD is diagnosed by either the Seattle criteria or the Baltimore criteria. For patients undergoing HSCT, varying estimates for the frequency of VOD are given. The mean incidence reported from a study evaluating the incidence of VOD in patients undergoing HSCT across 135 studies ranged between 0 and 62.3%, with a mean incidence of 13.7%. However, in the majority of studies (130/135), the variation in incidence ranged from 0 to 40%. The natural course of the disease depends on its severity, which is based on clinical features that can be assigned only retrospectively. Severe VOD is associated with a high mortality rate of 84.3% and progression to multi-organ failure (MOF) in most of these patients.

defibrotide: antithrombotic, profibrinolytic and anti-inflammatory disease

Defibrotide is a large, single-stranded deoxyribonucleotide with antithrombotic, profibrinolytic and anti-inflammatory effects; the precise mechanism of action is unclear. For the treatment of VOD, defibrotide is indicated in patients with severe VOD at a dosage of 25 mg/kg per day (same dosage for children and adults), divided into four doses for a minimum of 21 days, and should be continued until the symptoms and signs resolve. For the prophylaxis of VOD in adults and children undergoing allogeneic stem cell transplantation with risk factors (pre-existing hepatic disease, second myeloablative transplant, allogeneic transplant for leukemia beyond second relapse, conditioning with busulfan-containing regimens, prior treatment with gemtuzumab ozogamicin, diagnosis of primary haemophagocytic lymphohistiocytosis, adrenoleukodystrophy or osteopetrosis), the recommended dosage of defibrotide is 6.25 mg/kg i.v. four times daily.

In September 2013, the European Medicines Agency (EMA) granted marketing authorisation for Defitelio® "for the *treatment* of severe VOD also known as sinusoidal obstructive syndrome (SOS) in HSCT therapy". The market authorisation was granted "under exceptional circumstances", and Defitelio® is under additional monitoring. Defibrotide is not approved for the prophylaxis of VOD.

no standard therapy for VOD prevention available

For the prophylaxis of VOD after HSCT therapy, no standard therapy exists. UDCA and low-dose heparin are in clinical use, but they are not approved for this indication. The British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation recommend defibrotide at a dose of 6.25 mg/kg i.v. four times daily for children (level of recommendation is 1A = strong recommendation with high quality of evidence) and for adults (level of recommendation is 2B = weak recommendation based on moderate quality of evidence) undergoing allogeneic SCT who additionally have any of the following risk factors: pre-existing hepatic disease, second myeloablative transplant, allogeneic transplant for leukaemia beyond second relapse, conditioning with busulfan-containing regimens, prior treatment with gemtuzumab ozogamicin, diagnosis of primary hematophagocytic lymphohistiocytosis, adrenoleucodystrophy or osteopetrosis. Also for the treatment of VOD, the committee recommends defibrotide for both adults and children (level of recommendation is 1B = strong recommendation based on moderate quality of evidence).

mainstay of VOD therapy is supportive care

For the treatment of VOD no standard therapy is available; the mainstay of VOD therapy is supportive care. Tissue plasminogen activator (t-PA), N-acetylcysteine or methylprednisolone are other agents which have been used in clinical practice.

Methods

To evaluate the effectiveness and safety of defibrotide for the treatment and prophylaxis of VOD, a systematic literature search in four databases was conducted in December 2014 and a Scopus search in January 2015. Furthermore, the market authorisation holder was contacted to submit relevant publications.

Two review authors independently selected the literature. In addition, one review author extracted data from the included studies and a second review author checked the extracted data regarding completeness and accuracy. In cases of disagreement, consensus was achieved through discussion or by involving a third person. The risk of bias and the strength of evidence (according to GRADE) were assessed.

Results

Prophylaxis of VOD

three prevention studies included

For evaluating the effectiveness and safety of defibrotide for VOD prophylaxis, three studies with a total of 563 patients were included overall: one randomised controlled trial (RCT) conducted in a paediatric study population and two historical controlled trials (one trial included children only; the other trial included both adults and children). The RCT compared defibrotide to no prophylaxis of VOD in overall 356 patients. Both groups received treatment with defibrotide once VOD had developed and about one third in each group received ursodeoxycholic acid (UDCA) as concomittant prophylactic therapy. In the historic controlled trials, patients in the control group received either UDCA or tinziparin as prophylaxis or low-dose heparin was compared to low-dose heparin in combination with defibrotide.

All three studies assessed overall mortality at 100 days after transplant. The RCT did not find a statistically significant difference between the two groups (both 10%), but this outcome may have been biased due to the administration of therapeutic defibrotide after development of VOD in both groups of

the trial; additionally, one-third of the patients in each group received concomitant UDCA. One of the historical controlled trials also calculated the statistical significance between their groups and showed no significantly reduced mortality rate for defibrotide (p=.07).

All three prophylaxis studies calculated the incidence of VOD (the incidence of VOD by 30 days after HSCT was the primary endpoint of the RCT), ranging from 0–12% in the intervention groups to 7–20% in the control groups. In the RCT, the incidence of VOD was 12% in the intervention group and 20% in the control group closely reaching statistical significance. In one of the historical controlled studies the difference was with 0% in the defibrotide group in comparison to 19% in the control group also statistically signficant. According to two studies, disease-specific mortality was 0–2% in the defibrotide group and 6% in the control groups which was not statistically significant. These results have to be interpreted against the background of different criteria used for the diagnosis of VOD.

Results of the RCT showed that the incidence of acute graft-versus-host-disease (GVHD) by day +30 was 34% in the defibrotide arm compared to 52% in the control arm (p=.0057). By day + 100, the incidence was 47% in the defibrotide group and 65% in the control group (p=.0046). The incidence of chronic GVHD did not differ between the groups by 180 days. In one of the historically controlled trials, the incidence of acute GVHD grade ≥II was 34% in the study group versus 38% in the control group (p=.58). Authors of the other historically controlled trial reported the occurrence of GVHD in two patients of the defibrotide group, no information was provided for the occurrence of GVHD in the control group.

In terms of safety, both historical controlled studies did not provide exact data on the occurrence of overall adverse events (AEs). Results from the RCT showed that 87–88% patients had AEs and 37% had severe AEs. However, treatment-related AEs were reported in only 6% of patients receiving defibrotide and in 4% of patients in the control group. Severe treatment-related AEs (Grade 3) occurred in 2% of defibrotide arm patients and in 3% of control arm patients. However, these numbers have been measured after defibrotide treatment was administered in both study arms to all patients who had developed VOD.

strength of evidence for defibrotide prophylaxis: very low-moderate

Treatment of VOD

The results based on the currently available evidence for defibrotide treatment of VOD (one dose-finding RCT and one prospective case series with overall 239 patients) showed similar rates for overall mortality on day +100 (58–65%). For disease-specific mortality + 100 days, results were only available from the dose-finding RCT (28–29%). A complete response of VOD was reported in 36–46% of patients.

defibrotide treatment: two studies included

Data on AEs were only provided in the dose-finding study. High rates of AEs were reported from both treatment arms; comparing the two different dosages, no statistically significance was reported (p=.367). However, treatment-related AEs occurred in 8% of patients overall, of which 3% were of grade 3–4. No grade 5 treatment-related AE occurred and no treatment-related deaths were reported. Treatment-related bleeding of grade 3–4 was reported in 1% of all treated patients.

No evidence was found on the effect of defibrotide on patients' quality of life. Regarding the fact that VOD is a potential life-threatening disease and that patients suffering from severe VOD are critically ill, the outcome for this endpoint is relevant, but might be secondary.

Upcoming evidence

One parallel, randomised study, evaluating the efficacy and safety of defibrotide for the prophylaxis of VOD was identified.

Two defibrotide treatment studies, both single-arm, are ongoing.

Reimbursement

defibrotide treatment: costs of € 80,514 per treatment cycle

According to the submission documents received from the Ministry of Health (MoH), defibrotide is currently not included in the Austrian catalogue of benefits. Assuming an average body weight of 70 kg for adults, 1,750 mg defibrotide are needed per day (i.e., 6.25 mg/kg every six hours). Defibrotide is available in vials containing 200 mg, costing € 426. For the administration of 1,750 mg, nine vials would be needed, corresponding to daily treatment costs of € 3,834. Assuming a treatment duration for a minimum of 21 days, costs of € 80,514 would occur.

The costs for defibrotide for VOD prophylaxis are hard to calculate due to the unclear duration of administration. In the included RCT patients who were allocated to the intervention group received defibrotide for VOD prophylaxis for a median of 35 days (range 4–71 days). Thus, assuming a duration of 35 days for VOD prophylaxis, costs of € 134,190 would occur.

According to information submitted by the applicants, defibrotide was used in Austria off-label for over ten years in patients who developed VOD after high-dose chemotherapies with consecutive autologous or allogeneic HSCT. For many years, defibrotide was available as Prociclide® (approved for the treatment of deep vein thrombosis) for approximately € 350 per treatment cycle. Later, the marketing authorisation was withdrawn in the context of a prospective approval study (indication: VOD). The EMA approval (under exceptional circumstances) of Defitelio® for the treatment of VOD was associated with a substantial price increase of the drug.

Discussion

Currently, the evidence for both possible indications of defibrotide is scarce. Due to the rarity of disease, RCTs, foremost for defibrotide therapy,are difficult to conduct. A search in two databases was conducted and two defibrotide treatment studies (both single-arm), and one study, evaluating the efficacy and safety of defibrotide for the prophylaxis of VOD (parallel, randomised) were identified (see Appendix Section “Ongoing research”. The paucity of evidence leaves several questions unanswered:

- Drug administration: Different dosages were used for prophylaxis as well as for the treatment of VOD, ranging from 10 mg/kg/day – over 25 to 60 mg/kg/day. According to the British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation, defibrotide is recommended at a dose of 6.25 mg/kg four times daily for the prevention and treatment of VOD in children and adults. However, the guidelines mention that further work is required to investigate the optimal dose of defibrotide. Furthermore, the duration of administration differed. Thus, the optimal duration and the optimal dosage remain unknown, even though there are some indications that lower doses are associated with fewer adverse events. In addition, defibrotide is also available as oral therapy, even though this route of administration was not used in any of the studies. How these differ-

ent applications affect outcomes has not been assessed. In addition, no information on differences concerning oral versus intravenous administration was found.

- Different criteria (Baltimore- or modified Seattle criteria) were used for the diagnosis of VOD. Depending on the criteria used, a different set of patients at different stages of disease will be identified.
- A further question concerns whether defibrotide therapy should be preferred over VOD prophylaxis. Foremost, since younger age has been identified as a risk factor for the development of VOD, the prophylaxis with defibrotide may yield better outcomes than therapy in this age cohort. Concerning prophylaxis, guidelines recommend defibrotide for high-risk patients only. The effectiveness of defibrotide prophylaxis remains unknown in children at low risk and in an adult population.
- Besides age, several further risk factors for the development of VOD have been characterised. Thus, the reduction of risk factors and risk stratification for VOD are keys to minimise VOD occurrence.
- Currently, no long-term data on safety is available for defibrotide.

Conclusion

Defibrotide for VOD prophylaxis

Overall, the strength of evidence for the effectiveness and safety of defibrotide for the prophylaxis of VOD was very low to moderate.

VOD prophylaxis: not recommended

Even though there are indications that the prophylaxis of VOD with defibrotide reduces the incidence of VOD, a life-threatening disease, at least in children at high risk and few adverse events are associated with this therapy, an inclusion in the catalogue of benefits for an off-label indication cannot be recommended.

A re-evaluation is recommended when the licensing status of the drug changes.

Defibrotide for VOD treatment

Overall, the strength of evidence for the effectiveness and safety of defibrotide for the treatment of VOD is very low.

VOD treatment: recommendation with restrictions

The current evidence is not sufficient to evaluate the effectiveness and safety of defibrotide for the treatment of VOD. Since VOD is a rare and life-threatening disease with no other therapeutic options available, defibrotide offers a new therapeutic approach for patients with severe VOD and meets an area of high unmet clinical need. Therefore, an inclusion in the catalogue of benefits is recommended with restrictions.

The proper assessment of risk factors and, whenever possible, the avoidance of factors contributing to the development VOD have to be ensured. Data on outcomes, foremost on long-term safety, should be collected in a prospective patient registry. Re-evaluation is recommended once these data become available. Thus, EMA website surveillance is also recommended to identify any change in the licensing status. Risk-sharing agreements are also indicated.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Ziel: Sicherheit und Wirksamkeit von Defibrotid Therapie und Prophylaxe von veno-okklusiver Erkrankung zu evaluieren

Ziel dieses systematischen Reviews ist, die Wirksamkeit und Sicherheit von Defibrotid (Defitelio®) für zwei verschiedene Indikationen zu evaluieren:

- Ist Defibrotid für die Prophylaxe der hepatischen veno-okklusiven Erkrankung (VOD) für PatientInnen nach Stammzelltransplantation (HSCT) verglichen mit keiner Prophylaxe, Placebo oder experimentellen Möglichkeiten bei Erwachsenen und Kindern wirksamer und sicherer hinsichtlich der Gesamtsterblichkeit, der krankheitsspezifischen Sterblichkeit, der Inzidenz der VOD, der Lebensqualität und Nebenwirkungen?
- Ist Defibrotid für die Therapie der hepatischen VOD für PatientInnen nach onkologischer Therapie oder HSCT verglichen mit keiner Prophylaxe, Placebo oder experimentellen Möglichkeiten bei Erwachsenen und Kindern wirksamer und sicherer hinsichtlich der Gesamtsterblichkeit, der krankheitsspezifischen Sterblichkeit, der Rückbildung der VOD, der Lebensqualität und Nebenwirkungen?

Beschreibung der Technologie

Defibrotid antithrombotisch, profibrinolytisch und antientzündlich

Defibrotid wird durch kontrollierte Depolymerisation von Desoxyribonucleinsäure (DNA) aus der Darmschleimhaut von Schweinen hergestellt. Defibrotid weist antithrombotische, profibrinolytische und antientzündliche Eigenschaften auf, der genaue Wirkmechanismus ist jedoch noch ungeklärt.

VOD ist seltene Erkrankung

hauptsächlich durch Konditionierungstherapie vor Stammzelltransplantation

Die hepatische VOD zählt zu den seltenen Erkrankungen und kann Erwachsene und Kinder betreffen. Als primäre Ursache der VOD wird eine Schädigung von Lebersinusoiden angenommen, welche in weiterer Folge zum Verschluss kleiner Lebervenen führt. Am häufigsten wird die Erkrankung durch Konditionierungstherapien im Vorfeld von HSCT ausgelöst. Seltenere Ursachen können vorangegangene Chemotherapien, hochdosierte Strahlentherapien, die Aufnahme von toxischen Alkaloiden sowie Lebertransplantationen sein.

Charakteristische Symptome der Lebervenen-Verschlusskrankheit sind Schmerzen im Oberbauch (rechter oberer Quadrant), schmerzhafte Lebervergrößerung, Ikterus und Ascites.

Inzidenz schwankt stark, im Durchschnitt bei ca 14 %
Schwere VOD hohe Letalität

Die in Studien angegebenen Inzidenzen variieren stark. Eine Untersuchung der Inzidenzen der VOD in 135 Studien (die PatientInnen hatten sich einer HSCT unterzogen) ergab eine mittlere Inzidenz von 13,7 % (0–62,3 %), wobei in 130 der insgesamt 135 Studien die Inzidenz zwischen 0 und 40 % variierte. Die Erkrankung kann in verschiedenen Schweregraden verlaufen, wobei die schwere VOD mit einer Mortalitätsrate von 84,3 % assoziiert ist und zu Multiorganversagen führen kann.

Risikofaktoren Lebererkrankung, Art der Konditionierungstherapie, Alter, diverse Grunderkrankungen

Risikofaktoren für die VOD sind vorbestehende Lebererkrankungen, die Art der Konditionierungstherapie (höheres Risiko bei der Anwendung von Cyclophosphamiden oder hochdosierter Strahlentherapien), die Art des Transplantates (Risiko höher bei allogenen Transplantaten), das Alter der PatientInnen (Kinder <7 Jahren erkranken häufiger), schlechter Zustand der PatientInnen bei Behandlungsbeginn, vorangegangene abdominale Strahlentherapie, Erkrankungen wie Osteopetrosis, primäre hämophagozytische Lym-

phozytose oder Adrenoleukodystropie sowie Therapien zur Prophylaxe der Graft-versus-Host-Reaktion (GvHR).

Diagnosestellung mittels unterschiedlicher Kritieren

Die Diagnosestellung der VOD kann entweder basierend auf den Seattle-Kriterien oder den Baltimore-Kriterien gestellt werden. Differentialdiagnostisch sollten Erkrankungen, die ebenfalls zu Leberversagen führen können (z. B. Budd-Chiari Syndrom, akute GvHR, hepatische Infektionen oder Arzneimitteltoxizität) ausgeschlossen werden.

Therapie mit bestmöglichen supportiven Maßnahmen

Ein wichtiger Faktor bei der Behandlung der VOD ist, unabhängig vom Schweregrad der Erkrankung, bestmögliche supportive Behandlungsmaßnahmen zu ergreifen. Dabei wird besonderes Augenmerk auf den Flüssigkeitshaushalt, das intravaskuläre Volumen und die Nierenperfusion gelegt, um die Ansammlung freier Flüssigkeit einzuschränken. Außerdem sollte die Anwendung potentiell leberschädigender Substanzen vermieden werden.

Orphan Designation in Europa

zunächst keine Zulassung

2013: positive Entscheidung unter „außergewöhnlichen Umständen" für Therapie von VOD

Defibrotid erhielt 2004 von der EMA eine Orphan Drug Designation für die Therapie der hepatischen VOD. Im März 2013 erfolgte eine negative Stellungnahme des Committee for Medicinal Products for Human Use (CHMP) zu Defibrotide für die Therapie und die Prophylaxe der VOD aufgrund methodologischer Mängel der bereitgestellten Evidenz sowie Mangel an Daten bei PatientInnen mit eingeschränkter Nierenfunktion. Im September 2013 erteilte die EMA für Defitelio® für die Therapie schwerer venookklusiver Erkrankung bei HSCT nach einem erneuten Zulassungsantrag aber die Markzulassung. Die Marktzulassung erfolgte unter „außergewöhnlichen Umständen", außerdem unterliegt das Arzneimittel einer zusätzlichen Überwachung. Defitelio® ist, nachdem der Hersteller seinen Zulassungsantrag für die VOD Prophylaxe zurückgezogen hatte, nicht für diese Indikation zugelassen.

In den USA erhielt Defitelio® von der FDA keine Marktzulassung, ist aber im Rahmen eines „expanded access" Protokolls erhältlich. Defibrotid erhielt 2003 für die Therapie und 2007 für die Prävention der hepatischen VOD eine Orphan Drug Designation von der FDA.

keine Standardtherapie für VOD Therapie …

Für die Behandlung der hepatischen VOD gibt es derzeit keine Standardtherapie, die Erkrankung kann mit den bestmöglichen supportiven Behandlungsmaßnahmen und Defibrotid behandelt werden. Für diese Indikation wird Defibrotid in einer Dosierung von 6,25 mg/kg i. v. alle 6 Stunden (25 mg/kg/Tag) für mindestens 21 Tage verabreicht, bis sich die Symptome der schweren VOD auflösen. Die Dosierung ist für Erwachsene und Kinder gleich. In klinischem Gebrauch sind außerdem der gewebespezifische Plasminogenaktivator (t-PA), N-Acetycstein sowie Methylprednisolon.

… oder Prophylaxe

Defibrotid für Prophylaxe und Therapie von Guideline empfohlen

Für die Prophylaxe der hepatischen VOD gibt es derzeit keine Standardtherapie. Zwei Substanzen (beide nicht für diese Indikation zugelassen) sind in klinischem Gebrauch: Ursodesoxycholsäure (UDCA) und niedrig dosiertes Heparin. Die Anwendung der beiden Arzneimittel wird durch Ergebnisse aus randomisierten Studien unterstützt. Das British Committee for Standards in Haematology und die British Society for Blood and Marrow Transplantation empfehlen Defibrotid in einer Dosierung von 6,25 mg/kg 4 mal täglich für Kinder (Grad der Empfehlung ist 1A = starke Empfehlung mit hoher Qualität der Evidenz) und für Erwachsene (Grad der Empfehlung ist 2B = schwache Empfehlung basierend auf mäßiger Qualität der Evidenz), die sich einer allogenen HSCT unterzogen hatten und Risikofaktoren (z. B. eine vorbestehende Lebererkrankung, Konditionierungstherapien mit Busulfan, Osteopetrosis) aufweisen. Auch die Therapie der VOD mit Defibrotid, wird von dem Kommittee sowohl für Kinder als auch für Erwachsene empfohlen (Grad der Empfehlung 1B = starke Empfehlung basierend auf mäßiger Qualität der Evidenz).

Methoden

Klinische Wirksamkeit und Sicherheit

wesentliche Outcomes

Zur Evaluierung der klinischen Wirksamkeit der VOD Prophylaxe mittels Defibrotid wurden folgende Outcomes als wesentlich erachtet: die Gesamtsterblichkeit, die krankheitsspezifische Sterblichkeit, die Inzidenz von VOD sowie die Lebensqualität der PatientInnen. Um die klinische Wirksamkeit von Defibrotid für die Therapie der VOD zu evaluieren, wurden die Outcomes Gesamtsterblichkeit, krankheitsspezifische Sterblichkeit, das Abklingen der Symptome der VOD und die Lebensqualität der PatientInnen als ausschlaggebend erachtet.

Zur Evaluierung der Sicherheit von Defibrotid für die VOD Prophylaxe und Therapie wurden das Auftreten von schwerwiegenden Nebenwirkungen und mit der Behandlung im Zusammenhang stehenden Nebenwirkungen als wesentlich erachtet.

systematische Suche in 4 Datenbanken

Relevante Informationen wurden durch eine im Dezember 2014 durchgeführte systematische Literatursuche in 4 Datenbanken (Medline via Ovid, Embase, The Cochrane Library and CRD) gewonnen und durch eine Scopus-Suche (Jänner 2015) ergänzt. Auch der Hersteller wurde kontaktiert.

Relevante Daten für die Wirksamkeit und Sicherheit von Defibrotide für die Therapie und Prophylaxe wurden in Extraktionstabellen (siehe Tabellen A1-1 bis A1-3) dargestellt. Die Beurteilung der internen Validität der inkludierten Studien ist in den Tabellen A2-1 bis A2-3 ersichtlich. Die Qualität der vorliegenden Evidenz wurde anhand der GRADE-Methode beurteilt.

Ergebnisse

Prophylaxe von VOD

3 Studien für Prophylaxe eingeschlossen
1 RCT, 2 historisch kontrollierte Studien

Um die Wirksamkeit von Defibrotid für die Prophylaxe von VOD zu evaluieren, wurden 3 Studien inkludiert: eine randomisierte, kontrollierte Studie (RCT) und 2 historisch kontrollierte Studien mit insgesamt 563 inkludierten PatientInnen (alle PatientInnen hatten sich einer HSCT unterzogen). An zwei der Studien nahmen ausschließlich PatientInnen unter 18 Jahren teil, in der dritten Studie hatten die StudienpatientInnen ein mittleres Alter von etwa 37 Jahren. Die meisten PatientInnen hatten eine allogene HSCT erhalten, davor war Busulfan in 15–59 % der PatientInnen verabreicht worden. 12–34 % der PatientInnen wiesen eine vorbestehende Lebererkrankung auf. PatientInnen konnten am RCT teilnehmen, wenn zumindest ein Risikofaktor für VOD vorlag.

Insgesamt wurden 279 PatientInnen mit Defibrotid behandelt. Die Dosierungen variierten zwischen 10 und 25 mg/kg pro Tag für 20–30 Tage nach der Transplantation.

Die 284 PatientInnen der Kontrollgruppe (176 PatientInnen im RCT, 56 bzw. 52 PatientInnen in den beiden historisch kontrollierten Studien) erhielten kein Defibrotid zur VOD Prophylaxe (n=228), erhielten jedoch dieselbe Begleitmedikation wie die PatientInnen der Interventionsgruppe. Dies waren, je nach Studie, entweder niedrig dosiertes Heparin, UDCA, oder UDCA und Tinziparin (als VOD Prophylaxe für HochrisikopatientInnen in einer der historisch kontrollierten Studien).

VOD wurde in zwei Studien (RCT und historisch kontrolliert) unter der Verwendung der modifizierten Seattle-Kriterien diagnostiziert, in der dritten Studie (historisch kontrolliert) wurden die Baltimore-Kriterien zur Diagnose angewandt. Die Nachbeobachtungsdauer betrug (falls berichtet) 180 Tage beziehungsweise 57 Monate.

unterschiedliche Kriterien für VOD Diagnose, unterschiedliche Patientengruppen und Vergleichstherapien

Der RCT inkludierte insgesamt 356 PatientInnen unter 18 Jahren mit mindestens einem Risikofaktor für VOD. Die PatientInnen wurden entweder der Interventionsgruppe (n=180) oder der Kontrollgruppe (n=176) zugeteilt. Die PatientInnen der Interventionsgruppe erhielten Defibrotid (25 mg/kg/Tag), vom ersten Tag der Konditionierungstherapie bis 30 Tage nach der Transplantation oder, im Fall der Entlassung aus dem Krankenhaus vor Erreichen der 30 Tage, für mindestens 14 Tage. Die PatientInnen der Kontrollgruppe erhielten keine VOD Prophylaxe. 68 % der PatientInnen der Interventionsgruppe hatten sich einer allogenen HSCT unterzogen, bei 29 % (Interventionsgruppe) und 31 % (Kontrollgruppe) der PatientInnen wurde eine autologe HSCT durchgeführt. Der primäre Endpunkt, die Inzidenz von VOD war mit 12 % in der Interventionsgruppe und 20 % in der Kontrollgruppe gerade statistisch signifikant (p=.0488). Hinsichtlich der Gesamtsterblichkeit und der VOD-assoziierten Mortalität konnten keine Unterschiede zwischen PatientInnen mit prophylaktisch angewandtem Defibrotide und PatientInnen ohne Prophylaxe festgestellt werden. Allerdings erhielten PatientInnen beider Gruppen bei Auftreten einer VOD Defibrotid als Therapie, wodurch die Möglichkeit der Verzerrung der Studienergebnisse besteht. Zusätzlich erhielt etwa ein Drittel der PatientInnen in beiden Gruppen UDCA als Begleitmedikation. Eine der beiden historisch kontrollierten Studien, in welche auch Erwachsene inkludiert wurden, zeigte eine verminderte Inzidenz von VOD, während in der zweiten historisch kontrollierten Studie kein statistisch signifikanter Unterschied festgestellt werden konnte. In einer der historisch kontrollierten Studien wurde die Mortalitätsrate im Vergleich beider Gruppen mit p=.07 als nicht statistisch signifikant berechnet.

RCT mit 356 paediatrischen PatientInnen mit Risikofaktoren für VOD

Inzidenz von VOD statistisch signifikant niedriger in Defibrotidgruppe

keine Unterschiede hinsichtlich Gesamtmortalität oder VOD-assoziierten Mortalität

Verzerrung durch therapeutische Defibrotidgabe in beiden Gruppen

Die Inzidenz der akuten GvHD war im RCT sowohl an Tag 30, als auch an Tag 100 nach der HSCT in der Defibrotidgruppe statistisch signifikant niedriger. Keinen Unterschied gab es hinsichtlich der Inzidenz der chronischen GvHD an Tag 180 nach der HSCT. In einer der historische kontrollierten Studien wurde die Inzidenz der akuten GvHD (Grad ≥ 2) mit 34 % in der Defibrotidgruppe und 38 % in der Kontrollgruppe angegeben (p=.58). In der zweiten historisch kontrollierten Studie trat die GvHD bei zwei PatientInnen der Defibrotidgruppe auf, zum Auftreten der GvHD in der Kontrollgruppe wurden keine Angaben gemacht.

Die Studien wiesen verschiedene Einschränkungen auf: Unklare Follow-up Zeitpunkte, unklare Begleitmedikationen und fehlende Daten bezüglich Patientencharakteristika und deren Unterschiede zu Studienbeginn. Weitere Einschränkungen bezüglich der Studienqualität ergaben sich in zwei Studien durch die geringe Anzahl an PatientInnen und den Vergleich mit historischen Kontrollgruppen.

Einschränkungen der Studien: unklares Follow-up und Begleitmedikation, Unterschiede in Patientencharakteristika

kaum Angaben zu Nebenwirkungen in historisch kontrollierten Studien

In den beiden historisch kontrollierten Studien wurden keine exakten Daten zum Auftreten von Nebenwirkungen genannt. Ergebnisse des RCT zeigten das Auftreten von Nebenwirkungen in 87–88 % der PatientInnen, 37 % hatten schwerwiegende Nebenwirkungen. Allerdings wurden Nebenwirkungen, welche im Zusammenhang mit der Behandlung standen, bei nur 6 % der Defibrotidgruppe im Vergleich zu 4 % der Kontrollgruppe ohne Prophylaxe beobachtet. Schwerwiegende (Grad 3) mit der Behandlung in Zusammenhang stehende Nebenwirkungen traten bei 2 % der PatientInnen der Defibrotidgruppe und 3 % der PatientInnen der Kontrollgruppe auf. Die mit der Behandlung in Zusammenhang stehen Nebenwirkungen wurden gemessen, nachdem PatientInnen beider Studiengruppen bei Auftreten von VOD Defibrotid zur Behandlung erhalten hatten.

RCT: Nebenwirkungen in 87 %, Behandlungsbedingte Nebenwirkungen nur in 6 % in der Defibrotidgruppe und 4 % in Kontrollgruppe

Therapie von VOD

keine komparativen Studien für Therapie

Für die Beurteilung der Wirksamkeit von Defibrotid für die Therapie der hepatischen VOD konnten keine komparativen Studien gefunden werden. Als beste verfügbare Evidenz wurden eine prospektive Fall-Serie und eine randomisierte Dosisfindungsstudie inkludiert. Insgesamt wurden 239 PatientInnen (Erwachsene und Kinder), die sich einer HSCT unterzogen hatten und bei welchen eine hepatische VOD klinisch diagnostiziert wurde, inkludiert. Die PatientInnen waren im Mittel 34–35 Jahre alt (das Alter variierte zwischen 0 und 63 Jahren). 68–87 % der PatientInnen hatten allogene Transplantate, 42–53 % vor der HSCT Busulfan und 75–80 % Cyclophosphamide erhalten. 33–46 % der PatientInnen hatten sich einer Ganzkörperbestrahlung unterzogen.

ähnliche Mortalitätsraten: 58–65 %

In beiden Publikationen wurden ähnliche Raten der Gesamtsterblichkeit (an Tag 100) gemessen (58–65 %). Die krankheitsspezifische Mortalität an Tag 100 wurde nur in der Dosierungsfindungsstudie gemessen (28–29 %). Ein komplettes Ansprechen auf die Defibrotid Therapie war bei 36–46 % der PatientInnen zu beobachten.

Therapie bedingte Nebenwirkungen in 8 %, davon 3 % schwerwiegende

Nebenwirkungen wurden in der Dosierungsfindungsstudie beschrieben, hier waren insgesamt 97 % aller PatientInnen von Nebenwirkungen betroffen, wovon 89 % Nebenwirkungen von Grad 3 oder 4 waren. Mit der Therapie in Verbindung stehende Nebenwirkungen traten allerdings bei nur 8 % aller Behandelten auf (7 % in der Gruppe mit geringerer Dosierung, 10 % in der Gruppe mit höherer Dosierung). Davon waren 3 % der Nebenwirkungen von Grad 3 oder 4. Blutungen (Grad 3–4), welche mit der Therapie in Verbindung standen wurden in 1 % der PatientInnen berichtet. Es gab keine mit der Therapie assoziierten Todesfälle.

Laufende Studien

3 laufende Studien, 1 zu Prophylaxe, 2 zu Therapie

Die Suche in entsprechenden Datenbanken (siehe Kapitel 10.5) zeigte, dass es derzeit zwei einarmige Studien über die Behandlung der VOD mit Defibrotid gibt. Eine weitere Studie (parallel, randomisiert) evaluiert die Wirksamkeit und Sicherheit von Defibrotid für die Prophylaxe von VOD.

Kostenerstattung

Defibrotid derzeit nicht im Erstattungskodex

Derzeit ist Defibrotid nicht im Leistungskatalog des Österreichischen Gesundheitsministeriums enthalten. Für die Therapie der VOD würden, ausgehend von einem durchschnittlichen Körpergewicht eines Erwachsenen von 70 kg, pro Tag 1.750 mg Defibrotid benötigt werden (6,25 mg/kg alle 6 Stunden). Defibrotid ist in Einheiten zu je 200 mg erhältlich, diese kosten jeweils

Kosten für 21 Tage: € 80.000

€ 426. Für die Verabreichung von 1.750 mg Defibrotid würden 9 Einheiten benötigt werden und Behandlungskosten von € 3.834 pro Tag entstehen. Ausgehend von einer Behandlungsdauer von mindestens 21 Tagen würden sich die Kosten für einen Behandlungszyklus auf € 80.514 belaufen.

unklare Behandlungsdauer von Prophylaxe

Aufgrund der noch ungeklärten optimalen Anwendungsdauer von Defibrotid für die VOD Prophylaxe sind die genauen Kosten schwierig zu berechnen. Im inkludierten RCT wurden die PatientInnen der Interventionsgruppe, welche Defibrotid für die Prophylaxe der VOD erhielten, im Mittel 35 Tage lang (zwischen 4 und 71 Tagen) behandelt. Ausgehend von einer Behandlungsdauer der VOD Prophylaxe von 35 Tagen würden Kosten von € 134.190 entstehen.

„off-label" Defibrotid bereits lang in Verwendung

Defibrotid wurde über viele Jahre „off-label", für die Behandlung von PatientInnen, welche im Rahmen einer Hochdosistherapie mit autologer oder allogener HSCT eine VOD entwickelten, verwendet. Die Substanz war unter dem Handelsnamen Prociclide® für die Behandlung der tiefen Beinvenenthrombose zugelassen, die Kosten beliefen sich auf etwa € 350 pro Behandlungszyklus. Im Kontext einer prospektiven Zulassungsstudie wurde Prociclide von Markt genommen. Als Defibrotid unter dem Handelsnamen Defitelio® für die Behandlung der VOD zugelassen wurde, war dies mit einer starken Preissteigerung verbunden.

Diskussion

wenig Evidenz

Derzeit ist die Evidenz für beide mögliche Indikationen von Defibrotid rar. Durch die Seltenheit der Erkrankung ist die Durchführung von RCTs – vorallem für die Therapie von VOD, schwierig. Aktuell werden zwei einarmige Studien zur Behandlung der VOD mit Defibrotid und eine weitere Studie (parallel, randomisiert,) zur Evaluierung der Wirksamkeit und Sicherheit von Defibrotid für die Prophylaxe der VOD durchgeführt. Durch den derzeit bestehenden Evidenzmangel bleiben einige Fragen unbeantwortet:

ungeklärte Fragen: Dauer, Dosierung, oral vs iv

- Optimale Dosierung/Dauer: In den inkludierten Studien wurden verschiedene Dosierungen (zwischen 10 und 25 mg/kg/Tag für die Prophylaxe und zwischen 10 und 60 mg/kg/Tag für die Therapie) verwendet. Das British Committee for Standards in Haematology und die British Society for Blood and Marrow Transplantation empfehlen Defibrotid für die in einer Dosierung von 6,25 mg/kg 4 mal täglich für Kinder und Erwachsene. Allerdings sind laut Guideline weitere Studien nötig, um die optimale Dosierung von Defibrotid zu ermitteln. Ebenfalls ungeklärt ist die optimale Dauer der Behandlung (in den inkludierten Studien waren die Behandlungszeiträume unterschiedlich lange). Für Defibrotid gibt es auch die Möglichkeit der oralen Verabreichung, diese wurde jedoch in keiner der inkludierten Studien angewandt. Es bleibt unklar, ob die Art der Verabreichung Einfluss auf die Outcomes hat.

unterschiedliche Diagnosekriterien

- Diagnosestellung: in den inkludierten Studien wurden unterschiedliche Systeme (Baltimore- oder modifizierte Seattle-Kriterien) angewandt. Dadurch wird die Erkrankung bei betroffenen PatientInnen in unterschiedlichen Stadien diagnostiziert, dies kann zu Unterschieden hinsichtlich der Outcomes führen.

Guidelines empfehlen VOD Prophylaxe nur für Hochrisiko-patientInnen

- Prophylaxe versus Therapie: es ist fraglich, ob die Therapie mit Defibrotid der Prophylaxe vorgezogen werden sollte. Da jüngere PatientInnen ein höheres Risiko für VOD aufweisen, könnten durch VOD

Prophylaxe gerade in dieser Altersgruppe bessere Ergebnisse erzielt werden als mit der Therapie. Von Guidelines wird die Prophylaxe von VOD nur für HochrisikopatientInnen empfohlen.

- Population: im inkludierten RCT wurde die Defibrotid Prophylaxe ausschließlich an Hochrisikopatienten unter 18 Jahren untersucht. Aufgrund der mangelhaften Evidenzlage bleibt die Wirksamkeit von Defibrotid bei Erwachsenen und Kindern mit niedrigem VOD-Risiko ungeklärt.
- Neben dem Alter der PatientInnen wurden noch einige andere Risikofaktoren für die Entwicklung der VOD festgestellt. Die Reduktion von Risikofaktoren und die Riskostratifikation sind daher Schlüsselfaktoren um das Auftreten der VOD zu reduzieren.
- Langzeitdaten: es gibt keine Langzeitdaten über die Sicherheit der Anwendung von Defibrotid.

Empfehlung

Defibrotid Prophylaxe

Qualität der Evidenz sehr niedrig-mäßig

Insgesamt ist die Qualität der Evidenz für die Wirksamkeit und Sicherheit von Defibrotid zur VOD Prophylaxe mit „sehr niedrig“ bis“ mäßig“ zu bewerten.

aufgrund fehlender Zulassung kann Aufnahme in Leistungskatalog derzeit nicht empfohlen werden

Obwohl es Hinweise darauf gibt, dass die Prophylaxe mittels Defibrotid die Inzidenz von VOD bei Kindern mit hohem VOD-Risiko reduziert, kann die Aufnahme eines Medikaments in den Leistungskatalog ohne entsprechende Zulassung für diese Indikation nicht empfohlen werden.

Eine erneute Evaluierung bei Änderung des Zulassungsstatus wird empfohlen.

Defibrotid für die Therapie von VOD

Qualität der Evidenz sehr niedrig

Die Qualität der Evidenz für die Wirksamkeit und Sicherheit von Defibrotid für die Behandlung der VOD wurde mit „sehr niedrig“ eingestuft.

Aufgrund fehlender Therapieoptionen und oft lebensbedrohlichem Verlaufs wird Aufnahme in Leistungskatalog mit Einschränkungen empfohlen

Die derzeit verfügbare Evidenz ist nicht ausreichend um die Wirksamkeit und Sicherheit von Defibrotid zur Therapie der hepatischen VOD zu belegen. Da die VOD aber eine lebensbedrohliche Erkrankung darstellt, für die es keine andere Therapie gibt, stellt Defibrotid für PatientInnen mit schwerer VOD eine Therapieoption dar. Daher wird die Aufnahme in den Leistungskatalog mit Einschränkungen empfohlen.

Die Ermittlung von Risikofaktoren und, falls möglich, die Vermeidung von Faktoren welche die Entwicklung einer VOD begünstigen, sollte sichergestellt werden. In einem PatientInnenregister sollten Behandlungsresultate, vor allem Langzeitdaten bezüglich der Sicherheit von Defibrotid gesammelt werden. Sobald diese Daten verfügbar sind, ist eine erneute Evaluierung empfohlen. Weiters wird die Beobachtung des Zulassungsstatus von Defibrotid empfohlen, Risikoteilungsvereinbarungen werden als notwendig erachtet.

1 Scope

1.1 Research questions

PICO questions

Is defibrotide for the prophylaxis of veno-occlusive disease (VOD) for patients undergoing haematopoietic stem cell transplantation in comparison to no prophylaxis, placebo or other experimental options in adult and paediatric patients more effective and safe concerning overall and disease-specific mortality, incidence of VOD, quality of life and adverse events?

Is defibrotide for the treatment of severe veno-occlusive disease (VOD) after oncologic therapy or after haematopoietic stem cell transplantation in comparison to no treatment, placebo or other experimental options in adult and paediatric patients more effective and safe concerning overall and disease-specific mortality, resolution of VOD, quality of life and adverse events?

1.2 Inclusion criteria

inclusion criteria

Inclusion criteria for relevant studies are summarised in Table 1.2-1.

Table 1.2-1: Inclusion criteria

Population	**Prophylaxis** Adult patients, adolescents, children and infants over one month of age undergoing allogeneic or autologous stem cell transplantation **Treatment** Adult patients, adolescents, children and infants over one month of age with severe hepatic VOD after oncologic therapy or after allogeneic or autologous stem cell transplantation **MeSH terms**: Hepatic veno-occlusive disease [C06.552.360], Haematopoietic Stem Cell Transplantation [E04.936.225.687.500]; Liver Diseases [C06.552] **ICD:** K76.5; I82.0, Z94.8
Intervention	**Prophylaxis** Defibrotide (Defitelio®) is administered intravenously at a dosage of 10–25 mg/kg/day. **Treatment** Defibrotide (Defitelio®) intravenously at a dosage of 25 mg/kg/day for a minimum of 21 days and should be continued until the symptoms and signs of severe VOD resolve. **MeSH terms:** Platelet Aggregation Inhibitors [D27.505.954.502.780]; Fibrinolytic Agents [D27.505.519.421.750]
Control	**Prophylaxis** • No prevention • Placebo • Other experimental agents for prophylaxis (e.g., ursodeoxycholic acid) **Treatment** • No therapy • Placebo • Other experimental agents for the treatment (e.g., methylprednisolone, N-acetylcystein)

Outcomes	
Efficacy	**Prophylaxis** ✵ Overall mortality ✵ Disease-specific mortality ✵ Incidence of VOD ✵ Quality of life ✵ Severity of VOD ✵ Incidence of GVHD **Treatment** ✵ Overall mortality ✵ Disease-specific mortality ✵ Resolution of VOD ✵ Quality of life
Safety	✵ Severe adverse events ✵ Treatment-related mortality
Study design	
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials
Safety	Randomised controlled trials Prospective non-randomised controlled trials Any prospective study design

1.3 Literature search

systematic literature search in databases and websites

The systematic literature search was conducted on the 30th of December, 2014 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA).

Search filters were applied in Medline and Embase to limit the results to clinical trials and systematic reviews. After deduplication, 151 citations overall were included. The specific search strategy employed can be found in the Appendix.

overall 270 publications identified

The manufacturer (Gentium SpA) submitted seven publications of which two had already been identified by the systematic search, therefore resulting in five new citations. A Scopus search of two reference articles identified an additional n=114 references, resulting in 270 hits overall.

1.4 Flow chart study of selection

Literaturauswahl

Overall, 151 hits were identified. The references were screened by two independent researchers. In case of disagreement, a third researcher was involved to solve the differences. The selection process is displayed in Figure 1.4-1:

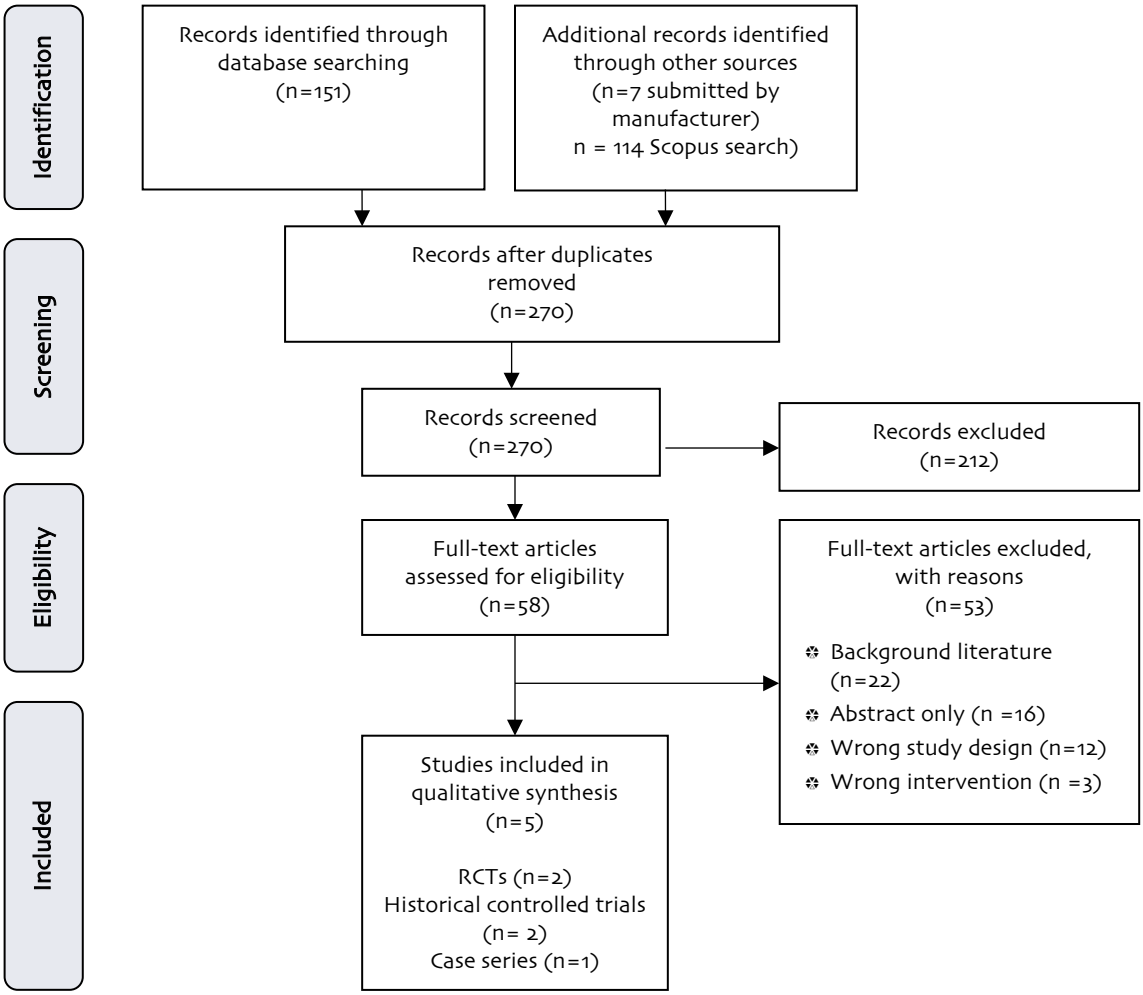

Figure 1.4-1: Flow chart of study selection (PRISMA Flow Diagram)

2 Description and technical characteristics of technology

2.1 Methods

Research questions

Element ID	Research question	Importance 2 = critical 1 = optional
B0001a	What is defibrotide?	2
B0001b	What is the comparator for the prophylaxis of VOD?	2
B0001c	What is the comparator for the treatment of VOD?	2
A0020	For which indications has defibrotide received marketing authorisation?	2
B0002	What is the claimed benefit of defibrotide in relation to the comparators?	1
B0004	Who administers defibrotide and the comparators and in what context and level of care are they provided?	1
B0009	What supplies are needed to use defibrotide and the comparators?	1
A0021	What is the reimbursement status of defibrotide?	2

Sources

The basic search was used to answer most of the research questions. In addition, websites of the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) were searched for information on the licensing status.

2.2 Results

Features of the technology and comparators

B0001a – What is defibrotide?

Defibrotide is a large, single-stranded deoxyribonucleotide. It is obtained from porcine intestinal mucosa and prepared by controlled depolymerisation of deoxyribonucleic acid (DNA) [1].

antithrombotic, profibrinolytic and anti-inflammatory effects

While in vitro data supports a role for defibrotide in endothelial cell protection by antithrombotic, profibrinolytic and anti-inflammatory effects, there are no established pharmacodynamic effects in vivo [2, 3]. Thus, the precise mechanism of action still remains unknown. However, by interaction with various receptors (e.g., adenosine receptors A1 and A2) which are located on the vascular endothelium, the expression of certain adhesion molecules (e.g., intercellular adhesion molecule 1 [ICAM-1]) is reduced and thereby the influx of inflammatory mediators [3]. By this means, the narrowing of hepatic sinusoids, which is typically associated with VOD, is reduced. Further, it assists

precise mechanism of action unclear

in partial revascularisation; it activates the fibrinolytic system (increases the function of tissue plasminogen activator (t-PA), decreases the plasminogen activator inhibitor-1), reduces the activation of the extrinsic coagulation pathway and exerts anti-inflammatory effects by stimulating prostaglandin production [3]. Through the combination of these effects, defibrotide is thought to help maintain the hepatic sinusoidal integrity.

In terms of graft-versus-host disease (GVHD), defibrotide is expected to work by reducing formation of blood clots and increasing their breakdown in the blood; furthermore it may protect the cells lining blood vessels, which are damaged in patients undergoing stem-cell transplantation [4].

B0001b – What is the comparator for the prophylaxis of VOD?

no standard therapy for VOD prophylaxis

No standard therapy is available for the prophylaxis of VOD in transplant recipients, but several experimental agents have been tested, including heparin, low-dose heparin, danaparoid, ursodeoxycholic acid or glutamine [5]. Of these, the clinical use of two agents, i.e., ursodeoxycholic acid (UCDA) and low-dose heparin, is supported by randomised trials. They are applied depending on the type of hematopoietic stem cell transplantation (HSCT) regimen [6]:

2 agents in clinical use: UDCA and low-dose heparin

- UDCA for patients undergoing allogeneic HSCT. It is administered at a daily dosage of 12 mg/kg (in two doses) from the day preceding the preparative regimen and is continued for the first three months of transplantation.
- Low-dose heparin for patients undergoing autologous HSCT. Patients receive heparin at a dosage of 100 units/kg per day (continuous intravenous infusion) from the first day of the preparative regimen until hematopoietic engraftment.

B0001c – What is the comparator for the treatment of VOD?

supportive care is the mainstay of VOD therapy

For the treatment of VOD no standard therapy is available. The mainstay of VOD therapy is supportive care, including fluid restriction and diuretics, and avoidance of hepatotoxic medications [7]. Other agents which have been used in clinical practice include tissue plasminogen activator (t-PA), N-acetylcysteine or methylprednisolone [8].

A0020 – For which indications has defibrotide received marketing authorisation?

since 2013 approved by the EMA for treatment of severe VOD in HSCT therapy

In 2004, defibrotide received orphan designation by the European Commission for the treatment of hepatic VOD. In November 2013, the EMA granted orphan designation for defibrotide for the prevention of GVHD [9].

In September 2013, the European Medicines Agency (EMA) granted marketing authorisation for Defitelio® "for the *treatment* of severe VOD also known as sinusoidal obstructive syndrome (SOS) in hematopoietic stem-cell transplantation (HSCT) therapy" [1].

not approved for VOD prevention

Prior to this decision, EMA's Committee for Medicinal Products for Human Use (CHPM) adopted a negative opinion concerning the licensing of Defitelio® for the *treatment* and *prophylaxis* of VOD in March 2013. The Committee noted for both indications that the evidence provided by the manufacturer suffered from methodological flaws. Another concern which subsequently led to a refusal of market authorisation was the lack of data for patients with comprised kidney function [10].

approval "under exceptional circumstances" and additional monitoring

The manufacturer requested a re-examination restricting the indications to the treatment of patients with *severe* VOD and the prevention of VOD only in *patients at high risk*. The manufacturer withdrew their application for prophylaxis prior to a final decision of the CHMP, which ultimately led to the market authorisation for the *treatment* of severe VOD only [10]. However, the market authorisation was granted "under exceptional circumstances" and Defitelio® is under additional monitoring, meaning that it is monitored even more intensively than other medicines [11].

Defitelio® is available in Germany, Italy (under special law 648/96), France, the UK, Sweden, the Netherlands, Denmark, Norway, Finland and, since the 24th of March, 2014, in Austria [12].

in the U.S. available under expanded-access protocol

In the U.S., Defitelio® has not been approved by the FDA, but it is available under an expanded-access protocol [13]. This protocol, sometimes also labelled "compassionate use", is intended for investigational medical products for serious diseases or conditions for which no comparable or satisfactory alternative therapy exists. If patients cannot be enrolled into clinical trials or if there are no ongoing trials, patients can get access to investigational products even outside of trials. Defibrotide also received orphan drug designation from the FDA for the treatment of hepatic VOD (in 2003) and for the prevention of hepatic VOD (in 2007) [14].

B0002 – What is the claimed benefit of defibrotide in relation to the comparators?

no approved drugs for prophylaxis of VOD available

For the prevention of VOD, no approved drugs are available. Since VOD therapy is unsuccessful in most instances, routine prophylactic therapies are commonly administered in transplant centres to avoid the occurrence of VOD. However, in the absence of standard therapies, regimens administered vary considerably across centres [5]. Defibrotide would thus be a new option for the prophylaxis of VOD.

defibrotide is the only approved drug for VOD treatment

VOD is a potentially life-threatening disease with a high mortality. Of the patients receiving HSCT, about 70% develop VOD, resulting in death in about 84% of severe cases despite therapy [7]. Even though several agents have been used for the treatment of VOD, defibrotide is currently the only approved drug for it. Defibrotide is thus a new treatment option for VOD.

Administration, investments, personnel and tools required to use the technology and the comparators

B0004 – Who administers defibrotide and the comparators and in what context and level of care are they provided?

administration by specialised physicians in university hospitals or transplant centres

Defibrotide and other available pharmaceutical therapeutic options have to be administered by specialised physicians experienced in the diagnosis and treatment of the complications of HSCT [2]. Defibrotide treatment requires in-patient care at university hospitals or transplant centres. In the case of severe VOD development with progression to multi-organ failure (MOF), affected patients need to be treated in an intensive care unit.

B0009 – What supplies are needed to use defibrotide and the comparators?

Defibrotide is marketed under the name Defitelio®. It is available in single-use glass vials of 2.5 mL. One mL contains 80 mg of defibrotide, corresponding to 200 mg in one 2.5 mL vial [2]. Defibrotide has to be diluted with 5% glucose solution or sodium chloride 9 mg/mL (0.9%) solution and is subsequently administered by an intravenous infusion over two hours. Contraindications listed are hypersensitivity for defibrotide or any of the excipients (sodium citrate, dihydrate, hydrochloric acid, sodium hydroxide, water for injection) and the concomitant use of thrombolytic therapy [2].

defibrotide dosage: 25 mg/kg/day (in four divided doses) for a minimum of 21 days

For the treatment of patients with severe VOD, defibrotide plus supportive care can be administered [6, 8], which is indicated in adults, adolescents, children and infants over one month of age. Defibrotide is administered at a dosage of 6.25 mg/kg body weight every six hours (25 mg/kg/day) i.v. for a minimum of 21 days and should be continued until the symptoms and signs of severe VOD resolve. The dosage for children (from one month of age up to 18 years) is the same as for adults. It is not recommended to administer doses above 25 mg/kg per day due to limited efficacy and safety data on doses above this level [2].

For the prophylaxis of VOD, the recommended dosage is 6.25 mg/kg i.v. four times daily in children undergoing allogeneic SCT with the following risk factors: pre-existing hepatic disease, second myeloablative transplant, allogeneic transplant for leukaemia beyond second relapse, conditioning with busulfan-containing regimens, prior treatment with gemtuzumab ozogamicin, diagnosis of primary haemophagocytic lymphohistiocytosis, adrenoleukodystrophy or osteopetrosis. For adults under the same conditions, the suggested dosage to prevent VOD is also 6.25 mg/kg i.v. four times daily [8].

The administration of defibrotide requires an intravenous infusion set and sodium chloride 9 mg/mL (0.9%) or 5% glucose solution for dilution prior to use. An intravenous infusion set is required for heparin administration, whereas UDCA is administered orally.

Regulatory & reimbursement status

A0021 – What is the reimbursement status of defibrotide?

defibrotide currently not included in the catalogue of benefits

According to the submission documents received from the Ministry of Health (MoH), defibrotide is currently not included in the Austrian catalogue of benefits. Assuming an average body weight of 70 kg for adults, 1,750 mg defibrotide are needed per day (i.e., 6.25 mg/kg every six hours). Defibrotide is available in vials containing 200 mg, costing € 426. For the administration of 1,750 mg, nine vials would be needed, corresponding to daily treatment costs of € 3,834. Assuming a treatment duration for a minimum of 21 days, costs of € 80,514 would occur.

The costs for defibrotide for VOD prophylaxis are hard to calculate due to the unclear duration of administration. In the included RCT [15] patients who were allocated to the intervention group received defibrotide for VOD prophylaxis for a median of 35 days (range 4–71). Thus, assuming a duration of 35 days for VOD prophylaxis, costs of € 134,190 would occur. According to information submitted by the applicants, defibrotide was used in Austria off-label for over ten years in patients who developed VOD after high-dose chemotherapies with consecutive autologous or allogeneic HSCT. For many years,

defibrotide was available as Prociclide® (approved for the treatment of deep vein thrombosis) for approximately € 350 per treatment cycle. Later, the marketing authorisation was withdrawn in the context of a prospective approval study (indication: VOD). The EMA approval (under exceptional circumstances) of Defitelio® for the treatment of VOD was associated with a substantial price increase of the drug.

3 Health problem and current use

3.1 Methods

Research questions

Element ID	Research question	Importance 2 = critical 1 = optional
A0002	What is VOD?	2
A0001	For which health conditions and for what purposes is defibrotide used?	2
A0003	What are the known risk factors for hepatic VOD?	2
A0004	What is the natural course of VOD?	2
A0024	How is VOD currently diagnosed according to published guidelines and in practice?	2
A0025a	How is VOD prophylaxis currently managed according to published guidelines and in published guidelines and in practice?	2
A0025b	How is VOD therapy currently managed according to published guidelines and in practice?	2
A0007	What is the target population in this assessment?	2
A0023	How many people belong to the target population?	2
A0011	How much is defibrotide utilised?	1

Sources

The basic search was used to answer the research questions.

3.2 Results

Overview of the disease or health condition

A0002 – What is VOD?

VOD often caused by conditioning treatment prior to HSCT

VOD, also termed hepatic sinusoidal obstruction syndrome (SOS), most often occurs as a result of a conditioning treatment administered prior to HSCT [8]. HSCT is indicated in patients suffering from malignant but also non-malignant diseases such as thalassaemia who have received chemotherapy that has destroyed, besides malignant cells, normal blood-forming cells in the bone marrow. By transplanting haematopoietic stem cells, the ability of the patient to produce blood cells should be restored. Allogeneic transplants can be distinguished from autologous transplants. For allogeneic HSCT, cells are harvested from a donor other than the transplant recipient, whereas for autologous transplants the patient's own cells are used [16].

Allogeneic HSCT replaces the affected immune system and is used to to exploit the graft versus tumour effect of allogeneic cells [17]. For the conditioning therapy, traditional myeloablative conditioning regimens, reduced-intensity- and non-myeloablative regimens are available [18], regimens with a reduced incidence of VOD.

Previous expositions to chemotherapeutic agents or high-dose radiation therapy, ingestion of alkaloid toxins or liver transplantation are less common causes for VOD [19].

hepatic sinusoidal endothelial cell lesion are deemed to be primary cause

Hepatic sinusoidal endothelial cell lesions are deemed to be the primary cause of VOD, leading to the non-thrombotic occlusion of the hepatic veins with concentric subendothelial thickening associated with oedema and fibrosis [20]. VOD occurs most commonly within the first three weeks after performing HSCT, but it can generally occur at any time after HSCT treatment [19].

VOD symptoms: hepatomegaly, right upper quadrant pain, jaundice and ascites

Characteristic symptoms of VOD are painful hepatomegaly, right upper quadrant pain, jaundice and ascites [19]. Functional renal insufficiency is common and coagulopathy and hepatic encephalopathy may indicate hepatic insufficiency [20].

VOD is a rare disease

VOD is classified as a rare disease affecting children and adults [20]. The incidence between studies varies widely, depending on the type of transplant, the applied conditioning regimen and the diagnostic criterions used.

The GVHD is a further potential complication occurring after haematopoietic cell transplant. The disease develops when immune cells transplanted from a non-identical donor recognise the transplant recipient as foreign, thereby initiating an immune reaction that causes disease in the transplant recipient [21].

A0001 – For which health conditions and for what purposes is Defitelio® used?

In Europe, the licensed indication of defibrotide is:

- the treatment of severe hepatic VOD in HSCT in adults, adolescents, children and infants over one month of age.

In addition, based on the submission documents received, coverage in the catalogue of benefits is also sought:

- for the treatment of VOD after chemotherapy,
- for the prophylaxis of VOD in patients undergoing HSCT.

A0003 – What are the known risk factors for hepatic VOD?

risk factors

Risk factors for developing VOD include:

- pre-existing liver disease (characterised by elevation of the liver enzyme aspartate aminotransferase)
- type of conditioning regimen (higher when cyclophosphamide or high doses of radiation are used)
- source of graft (allogeneic greater than autologous)
- age of patients (children <7 years are more often affected)
- a poor performance status at baseline
- prior abdominal radiation therapy,
- diagnosis of osteopetrosis, primary haemophagocytic lymphocytosis or adrenoleukodystrophy [13].
- graft-versus-host disease (GVHD) prophylaxis regimens [22].

Depending on the absence or presence of one or more of these risk factors, patients at high risk for developing VOD are identified [8].

A0004 – What is the natural course of VOD?

natural course of VOD depends on severity of disease

The natural course of VOD depends on the severity of the disease. Severity is based on clinical features which can only be assigned retrospectively [8]. No commonly accepted criteria are used for assessing the severity of VOD [23]. Some authors suggest that patients with mild VOD can be defined as those who do not require therapy; patients who need best supportive care to alleviate pain from hepatomegaly are considered as having had moderate VOD, whereas patients who die from VOD or with illness that persists >100-day post-HSCT are considered to have had severe VOD [8, 19].

Due to the lack of unified criteria, the evolution of MOF has been proposed as a better predictor of severity and outcome [24]. Accordingly, in the European Public Assessment Report by the EMA, severe disease is defined as VOD in the presence of multi-organ failure (MOF), pulmonary dysfunction (with an oxygen requirement with an oxygen saturation of <90% on room air and/or ventilator dependence), and/or renal dysfunction (defined as the doubling of baseline creatinine and/or dialysis dependence), and/or encephalopathy.

Of the patients developing VOD, there are indications that about one-quarter of those with VOD progress to severe disease [25]. The mortality rate from severe VOD has been reported at 84.3% when treated with supportive care alone [6, 24], in comparison to about 20% for patients with moderate VOD [13]. Patients usually do not die due to VOD, but rather of liver failure. Progressive MOF with consecutive lethal renal and cardiopulmonary complications are typically the main causes of death [1]. As predictions for developing severe VOD, the early development of jaundice and weight gain after transplant and MOF are mentioned.

Current clinical management of the disease or health condition

A0024 – How is VOD currently diagnosed according to published guidelines and in practice?

2 systems for diagnosis: Seattle criteria and Baltimore criteria

For the diagnosis of VOD, two systems based on clinical diagnostic criteria are established [19]:

- According to the modified Seattle criteria, VOD is diagnosed when (within 20 days of HCT) two or more of the following occur:
  - Serum bilirubin >2 mg/dL
  - Hepatomegaly or right upper quadrant pain
  - Weight gain (>2 percent of baseline body weight) caused by fluid accumulation.
- The Baltimore criteria define VOD by bilirubin concentration greater than 2 mg/dL within 21 days of HCT and the occurrence of two or more of the following:
  - Hepatomegaly
  - Ascites
  - Weight gain >5%, measured against body weight before HCT.

For the purpose of differential diagnosis, other diseases leading to hepatic failure, e.g., Budd-Chiari syndrome, acute GVHD, hepatic infections and drug toxicity, need to be excluded by Doppler ultrasonography and serologies. Both VOD and acute GVHD can cause abdominal pain and a rising serum bilirubin. The most definitive method to distinguish the diseases is biopsy, which is rarely performed due to the bleeding risk [19].

severity can only be assessed retrospectively

These clinical criteria are used for assessing the severity of VOD, but they can only be assigned retrospectively. When patients are followed up for the first 100 days after HSCT, but do not require therapy despite liver biochemical abnormalities and other clinical features of the disease, they are considered to have mild VOD. Patients requiring sodium restriction and diuretics for fluid retention and/or medications to alleviate pain from hepatomegaly are considered to have moderate VOD, whereas patients who die within 100 days post-transplant or have persistent hepatic dysfunction lasting more than 100 days have severe VOD [8].

A0025a – How is VOD prophylaxis currently managed according to published guidelines and in practice?

no standard therapy for prevention of VOD

No standard management scheme exists for preventing the occurrence of VOD in patients receiving chemotherapy and HSCT. An assessment of risk factors for individual patients, which is aimed at reducing the likelihood of developing VOD, is currently recommended. For example, the administration of a reduced intensity conditioning treatment or treatment with treosulfan instead of a busulfan conditioning therapy have been shown to reduce the risk of VOD especially in paediatric patients [8].

Even though defibrotide can be administered as a prophylaxis for all patients undergoing HSCT, another option is to restrict defibrotide prophylaxis to those patients at a particularly high risk of developing VOD [5, 8]. The British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation recommend the regimen for children (level of recommendation is 1A = strong recommendation with high quality of evidence) and for adults (level of recommendation is 2B = weak recommendation based on moderate quality of evidence) undergoing allogeneic stem cell transplantation who additionally have any of the following risk factors: pre-existing hepatic disease, second myeloablative transplant, allogeneic transplant for leukaemia beyond second relapse, conditioning with busulfan-containing regimens, prior treatment with gemtuzumab ozogamicin, diagnosis of primary hematophagocytic lymphohistiocytosis, adrenoleucodystrophy or osteopetrosis [8].

Besides defibrotide, the guidelines *suggest* only UDCA for the prophylaxis of VOD [8].

A0025b – How is VOD therapy currently managed according to published guidelines and in practice?

supportive care is a key factor in VOD therapy

Regardless of the severity of the disease, a key factor in managing affected patients is supportive care focussed on fluid balance and maintaining intravascular volume and renal perfusion while limiting third space fluid collection. Substances which potentially induce liver injury need to be avoided [6].

In patients with mild or moderate VOD, supportive care might be a sufficient therapy. Nevertheless, it is important to reassess severity every day to recognise changes [6].

The British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation recommends the use of defibrotide in the treatment of VOD in adults and children (level of recommendation is 1B = strong recommendation with moderate quality of evidence). Methylprednisolone may be considered for use in the treatment of VOD with the appropriate caveats of caution regarding infection [8]. Experimental treat-

ment approaches recommended within this guideline are surgical treatment options, that is, a transjugular intrahepatic portosystemic shunt or hepatic transplantation.

Target population

A0007 – What is the target population in this assessment?

The target population in this assessment consists of adults, adolescents, children and infants over one month of age for the treatment of severe VOD and for the prophylaxis of VOD.

A0023 – How many people belong to the target population?

VOD is an orphan disease; estimated number of patients in Austria: 4,250

Since VOD is an orphan disease, the number of patients affected is low; no more than five in 10,000 people in the European Union are affected [2]. With an overall population of 8.5 million in Austria, a maximum of 4,250 people would be affected by VOD.

For patients undergoing HSCT, varying estimates for the frequency of VOD are given. One study calculated the overall mean incidence of VOD in patients undergoing HSCT across 135 studies performed between 1979 and 2007. The mean incidence was 13.7% (with absolute values ranging from 0 to 62.3%) across age groups with differences for adults and children; however, in the majority of studies (130/135) the variation in incidence ranged from 0 to 40%. Only five studies reported an incidence of VOD over 40%; all of them included high-risk patient groups. The mortality rate from severe VOD was 84.3%; both prevention studies and studies evaluating the treatment of VOD were included in this review [24]. A mean incidence of about 25% was reported for children [26]. Lee et al. reported an incidence of VOD in the paediatric transplant population ranging from 11–31%, with an associated death rate of up to 50% [27]. Of patients developing VOD, there are indications that about one-quarter of those with VOD progress to severe disease [28].

Estimating the number of patients who would qualify for VOD prophylaxis is more difficult, since it depends on the qualification criteria: i.e., whether every transplant patient may be treated with prophylaxis or the treatment is restricted to patients at high risk only.

Estimates of the incidence of VOD will also depend on the set of diagnostic criteria used (see also A0024 and C0007).

A0011 – How much are the technologies utilised?

estimated number of utilisation per year in Austria: 500–5,000

Based on the submission files received from the MoH, the actual number of current interventions delivered ranged from 60–380, depending on the size of the hospital submitting the application. The indicated number of estimated annual utilisation rates ranged from 500–5,000. According to information submitted by the applicants, defibrotide was used off-label for over ten years in patients who developed VOD after high-dose chemotherapies with consecutive autologous or allogeneic SCT.

4 Clinical effectiveness

4.1 Methods

Research questions

Element ID	Research question	Importance 2 = critical 1 = optional
D0001a	What is the expected beneficial effect of defibrotide prophylaxis of VOD on overall mortality?	2
D0001b	What is the expected beneficial effect of defibrotide treatment of VOD on overall mortality?	2
D0001c	What is the expected beneficial effect of defibrotide prophylaxis on disease-specific mortality?	2
D0001c	What is the expected beneficial effect of defibrotide treatment on disease-specific mortality?	2
D0005a	How does defibrotide prophylaxis affect the incidence of VOD?	2
D0005b	How does defibrotide therapy affect the resolution of VOD?	2
D0005c	How does defibrotide therapy affect the severity of VOD?	2
D0005d	How does defibrotide prophylaxis affect the incidence of GVHD?	2
D0012	What is the effect of defibrotide on generic health-related quality of life?	1
D0013	What is the effect of defibrotide on disease-specific quality of life?	1

The following *crucial* outcomes for prophylaxis with defibrotide were used as evidence to derive a recommendation:

- Overall mortality
- Disease-specific mortality
- Incidence of VOD
- Quality of life.

The following *crucial* outcomes for defibrotide treatment were used as evidence to derive a recommendation:

- Overall mortality
- Disease-specific mortality
- Resolution of VOD
- Quality of life.

ultimate aim for treatment and prophylaxis is prolongation of life

Since VOD is a life-threatening disease, the ultimate aim of prophylaxis or treatment with defibrotide is to prolong life. Health-related quality of life is a relevant secondary outcome measure [29]. Avoidance of the occurrence of VOD is also deemed to be of critical relevance for the assessment of the effectiveness of a prophylactic regimen. For therapy with the agent, the resolution of VOD goes hand in hand with a reduced morbidity; therefore, it can also be considered as an outcome relevant for patients.

Sources

The information for this chapter was retrieved by a systematic literature search in four databases: Medline via Ovid, Embase, The Cochrane Library and CRD (DARE, NHS-EED, HTA), complemented by a Scopus search.

Analysis

To evaluate the effectiveness of defibrotide for the treatment and prevention of VOD, data from the included studies were extracted in evidence tables provided in the Appendix (A1-1, A1-2 and A1-3). No further analysis was performed. The internal validity of the included studies was assessed in Tables A2-1, A2-2 and A2-3 based on criteria used in the Internal Manual of the LBI-HTA [30] and in the Risk of Bias tool for randomised controlled trials from the Cochrane Collaboration [31] as provided in the Guidelines of EUnetHTA [32]. The strength of evidence of effectiveness was assessed according to the GRADE methodology [33].

Synthesis

The research questions were answered in plain text format, based on the results presented in evidence Tables A1-1, A1-2 and A1-3.

4.2 Results

Included studies

Prophylaxis of VOD

3 prevention studies with overall 563 patients were included

For assessing the effectiveness of prophylaxis of VOD with defibrotide, three studies overall were included [15, 34, 35]. The studies comprised one randomised controlled trial (RCT) [15] and two historically controlled prospective studies [34, 35]. Overall, 563 patients, all undergoing HSCT, were included. In two trials [15, 34] the study population consisted of children and adolescents (≤18 years), whereas the third publication did not apply any age limit, resulting in a median age of about 37 years [35]. In contrast to the non-randomised studies, the presence of at least one risk factor for VOD determined eligibility for the RCT. Most of the HSCT were allogeneic transplants (53–100%), a conditioning treatment containing busulfan was used in 15–56% and a pre-existing liver disease was present in 12–34% [15, 34, 35]. Different risk groups were formed in the two non-randomised studies based on varying criteria (see Table A1-2).

dosage ranged from 10–25 mg/kg/day

patients received defibrotide when developing VOD

Overall, 279 patients had been treated with defibrotide. The dosage of defibrotide ranged from 10 mg [35] over 20 mg [34] to 25 mg/kg/day [15] for 20–30 days after transplantation. When patients developed a VOD, dosage was either increased to 40–60 mg/kg/day [34] or patients who had previously not received defibrotide were treated for VOD with the same dosage as the intervention group [15].

The 284 patients who served as controls had received no defibrotide for VOD prophylaxis (n=228), but received the same concomitant therapies like the intervention group, which consisted either of low-dose heparin [35], UDCA [15] or, in one study, patients received UDCA and tinziparin for those considered as high risk [34] as VOD prophylaxis (n=56).

VOD assessment was done in two studies [15, 34] according to the modified Seattle criteria and, in the third study, based on the Baltimore criteria [35]. Follow-up, if reported, ranged from 180 days [15] to 57 months [35].

Study characteristics and results of included studies are displayed in Tables A1-1, and A1-2.

Treatment of VOD

2 studies included for assessing defibrotide for VOD treatment with 239 patients overall

No prospective comparative studies were identified for the assessment of effectiveness. As best available evidence, two studies were included: one prospective case series [36] and one randomised dose-finding study [37]. Due to the comparison of two different dosages of defibrotide, the comparator was not relevant for the study question and the study was therefore treated as single-arm study.

Overall, 239 adult and paediatric patients who had undergone HSCT and were clinically diagnosed with hepatic VOD were included. Patients had a median age of 34–35 years, with a wide age range from 0 to 63 years. Most of the transplants were allogeneic (68–87%); previously, 42–53% of patients had been treated with busulfan; in 75–80% of patients the conditioning regimen consisted of cyclophosphamide. 33–46% of patients had undergone total body irradiation.

total daily dosages from 10–60 mg/kg

In the dose-finding trial, the clinical diagnosis of VOD was defined as the presence of jaundice (total serum bilirubin ≥2 mg/dL) and at least two associated signs (ascites, weight gain >5% from baseline, hepatomegaly or right upper quadrant pain, by day + 35 post HSCT + US to confirm diagnosis) [37]. In the prospective case series, patients were considered having severe VOD when jaundice (bilirubin ≥34.2 μM), hepatomegaly and/or right upper quadrant pain, and ≥5% weight gain from admission, with or without ascites were diagnosed. Patients who met at least two criteria and had a liver biopsy and patients not addressed by the Bearman model were eligible if VOD was considered their major clinical problem and organ failure was present in at least one other organ system. Patients with a concurrent, potential confounding cause of liver dysfunction such as GVHD or inconsistent findings evident on ultrasound imaging were required to have biopsy-proven VOD to be considered eligible [36]. According to the Bearman model, the risk of developing severe VOD is related to the degree of weight gain, the rise in bilirubin and the day of transplant when these changes occur [8].

Overall, 239 patients were treated with defibrotide. In the dose-finding trial [37], the starting dose was 10 mg/kg, increased to 25 mg/kg/day in arm A, and to 40 mg/kg/day in arm B for a minimum of 14 days or until the achievement of complete remission, or until the progression of VOD, unacceptable toxicity (recurrent grade 3/4 adverse events (AEs) considered likely or definitely related to defibrotide), or comorbidities precluded further treatment. In the prospective case series [36], patients received defibrotide 10 mg/kg/day as four divided doses; the dose was increased incrementally to a maximum potential total daily dose of 60 mg/kg for a minimum of 14 days.

Study characteristics and results of included studies are displayed in Table A1-3.

Mortality

D0001a – What is the expected beneficial effect of defibrotide prophylaxis of VOD on overall mortality?

overall mortality: no significant difference between the two treatment groups

All three studies assessed overall mortality at 100 days after transplant. In the defibrotide groups 0–10% patients died in comparison to 4–19% in the control groups. The RCT did not find a statistically significant difference between the two groups (both 10%), but this outcome may have been biased due to the administration of therapeutic defibrotide after the development of VOD in both groups of the trial (I 13% vs. C 20%). In addition, 31% of patients in the intervention group and 32% in the control group respectively received concomitant UDCA. Chalandon et al. also calculated the statistical significance between their groups and showed no significantly reduced mortality rate for defibrotide (p=.07).

D0001b – What is the expected beneficial effect of defibrotide treatment of VOD on overall mortality?

In the dose-finding RCT and the prospective case series, overall mortality on day +100 was 58% to 65% [36, 37].

D0001c – What is the expected beneficial effect of defibrotide prophylaxis on disease-specific mortality?

disease-specific mortality: no significant difference shown in the RCT

Two prophylaxis studies presented results for disease-specific mortality for 460 patients overall [15, 35]. 0–2% in the intervention groups and 6% in the control group respectively died due to VOD. With 2% in the defibrotide group and with 6% in the no prophylaxis group, the RCT found no statistically significant difference. However, these numbers may have been compromised due to defibrotide therapy after VOD occurrence in both groups. The second study did not calculate statistical significance [35].

D0001d – What is the expected beneficial effect of defibrotide treatment on disease-specific mortality?

Results on disease-specific mortality + 100 days were provided only in the dose-finding RCT and were 28%–29%, depending on the dosage administered [37].

Morbidity

D0005a – How does defibrotide prophylaxis affect the incidence of VOD?

incidence of VOD: different diagnosis criteria used among studies

All three prophylaxis studies calculated the incidence of VOD, ranging from 0–12% in the intervention groups to 7–20% in the control groups. These results have to be interpreted against the background of usage of different criteria for the diagnosis of VOD. The modified Seattle criteria were used in two studies [15, 34], whereas the third used the Baltimore criteria [35]. The latter criteria are considered more restrictive, resulting in fewer cases diagnosed, but usually at a later stage with more severe cases of VOD. Abdominal ultrasound + Doppler tests were used in all studies to confirm diagnosis.

VOD incidence (assessed according to the modified Seattle criteria) was the primary outcome in the RCT. A cumulative risk approach, which took death not related to VOD, study discontinuation due to an AE or receipt of a sec-

ond transplant into account, was used. A risk difference of -7.7% was found for this analysis, closely reaching statistical significance with a p-value of .0488. According to the Kaplan-Meier method, p was .050.

A second study calculated the difference of incidence and found, with 0% in the intervention group and with 19% in the historical control group receiving heparin, a significant difference [35]. However, it is not clearly evident when the different incidences (0% vs. 19%) were measured. Of note, the dosage of defibrotide was 10 mg/kg/day for patients considered at standard risk (i.e., acute leukaemia in first complete remission, chronic myeloid leukaemia in chronic phase 1) and 25 mg/kg/day for all others considered at high risk.

Dooo5b – How does defibrotide therapy affect the resolution of VOD?

VOD resolution (= complete response, CR) was achieved by 36% of patients in the prospective case series (CR defined as evidence of improvement in VOD-related symptoms and concurrent MOF, and a concomitant or subsequent decrease in bilirubin to less than 34.2 μM) and by 46% of patients in the dose-finding trial (CR defined as total serum bilirubin <2 mg/dL after initiation of defibrotide with resolution of VOD-related MOF).

Dooo5c – How does defibrotide therapy affect the severity of VOD?

Corbacioglu et al. [38] reported an incidence of MOF on day + 100 of 32% (bilirubin not elevated) vs. 60% (elevated bilirubin >2 mg/dL) of patients (p=.0383). Data for VOD severity unrelated to bilirubin levels were not presented.

Dooo5d – How does defibrotide prophylaxis affect the incidence of GVHD?

All included prophylaxis studies evaluated the incidence of GVHD. Results of the RCT showed that patients who received defibrotide prophylaxis had a lower incidence and severity of acute GVHD by 30 days and 100 days than patients of the control group (in which patients received defibrotide for treatment of VOD). Incidence of acute GVHD by day +30 was 34% in the defibrotide arm compared to 52% in the control arm (p=.0057). By day + 100, the incidence was 47% in the defibrotide group and 65% in the control group (p=.0046). The incidence of chronic GVHD did not differ between the groups by 180 days. Corticosteroids (prescribed predominantely for acute GVHD) were used in 37% of defibrotide group patients and in 48% of control group patients [15].

Chalandon et al. reported an incidence of acute GVHD grade ≥II of 34% in the study group versus 38% in the control group (p=.58). All included patients received GVHD prophylaxis, most patients were treated with cyclosporine A and short-course methotrexate with or without other agents [35]. Qureshi et al. reported the occurrence of GVHD in two patients of the defibrotide group (no information was provided for the occurrence of GVHD in the control group) [34].

Health-related quality of life

D0012 – What is the effect of defibrotide on generic health-related quality of life?

no evidence for assessing quality of life

No evidence was found to answer this research question.

D0013 – What is the effect of defibrotide on disease-specific quality of life?

No evidence was found to answer this research question.

5 Safety

5.1 Methods

Research questions

Element ID	Research question	Importance 2 = critical 1 = important
C0008a	How safe is defibrotide for the prophylaxis of VOD in comparison to the comparators?	2
C0008b	How safe is defibrotide for the treatment of VOD in comparison to the comparators?	2
C0002	Are the harms related to the dosage or frequency of applying defibrotide?	2
C0004	How does the frequency or severity of harms change over time or in different settings?	1
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	1
B0010	What kind of data/records and/or registry are needed to monitor the use of the technology and the comparator?	1

The following *crucial* outcomes were used as evidence to derive a recommendation for the prophylaxis and treatment with defibrotide:

- Severe AEs
- Treatment-related mortality.

In order to assess the relative effectiveness of an intervention, balancing harms against benefits is crucial. Serious AEs and treatment-related mortality are of special importance and were thus considered as crucial for assessing the safety of defibrotide [39] .

Sources

The information for this chapter was retrieved by a systematic literature search in four databases: Medline via Ovid, Embase, The Cochrane Library and CRD (DARE, NHS-EED, HTA), and was complemented by a Scopus search.

Analysis

To evaluate the safety of defibrotide for the treatment and prevention of VOD, data from the included studies were extracted in Tables A1-1, A1-2 and A1-3. No further analysis was performed. Internal validity of the included studies was assessed in Tables A2-1, A2-2 and A2-3 according to the Risk of Bias tool from the Cochrane Collaboration [31] for randomised controlled trials and for non-randomised studies according to a checklist used by EUnetHTA. The strength of evidence of safety was assessed according to the GRADE methodology [33].

Synthesis

The research questions were answered in plain text format, based on the results presented in evidence Tables A1-1, A1-2 and A1-3.

5.2 Results

Included studies

For assessing the safety of defibrotide for the prophylaxis and treatment of VOD, the same studies were included as for effectiveness (see Chapter 4.2).

Study characteristics and results of included studies are displayed in Tables A1-1, A1-2 and A1-3. Of note, the numbers of AEs extracted from the RCT have been measured after defibrotide treatment was administered in both study arms to all patients who had developed VOD.

Patient safety

Cooo8a – How safe is defibrotide for the prophylaxis of VOD in comparison to the comparators?

RCT: treatment-related AEs in 6% (treatment group) and 4% (control group) of patients

Only the RCT presented numbers on overall AEs which were observed in 87% (treatment group) and 88% (control group) respectively [15]. 37% of patients in both groups experienced severe AEs (grade 3), whereas the two other studies did report that no grade 3 or 4 AEs occurred [34, 35]. However, treatment-related AEs of any grade which were reported only in the RCT occurred in only 6% in the treatment group and 4% in the control group [15]. Severe treatment-related AEs (Grade 3) occurred in 2% of defibrotide arm patients and in 3% of control arm patients. However, these numbers have been measured after defibrotide treatment was administered in both study arms to all patients who had developed VOD. The most common drug-related AEs were gastrointestinal haemorrhage and epistaxis in the defibrotide group and gastrointestinal haemorrhage and prolonged activated partial thromboplastin time in the control group.

Data on treatment-related mortality was available for 460 patients overall [15, 35]. In one study [35], treatment-related mortality was 14% in the study group and 28% in the control group; in the RCT 1% died in the defibrotide group and 0% in the control group (measured after defibrotide was administered in both study arms for the treatment of all patients who had developed VOD).

Cooo8b – How safe is defibrotide for the treatment of VOD in comparison to the comparators?

dose-finding trial: treatment-related AEs in 8%

no treatment-related deaths

In one of the studies with a total of 151 patients, overall AEs were reported in 97% of patients [37]. In 89%, AEs were of grade 3–4 without a difference between the doses used (most common were renal failure, hypotension, hypoxia, and other pulmonary events), 17% of patients experienced grade 5 AEs. Treatment-related AEs were stated in only one publication and occurred in 8% of patients overall, 7% in lower-dose arm and 10% in higher-dose arm [37]. Treatment-related AEs of grade 3–4 were reported in 3% of patients

overall (3% in lower-dose arm and 4% in higher-dose arm). No treatment-related deaths were reported in the same publication. Treatment-related bleeding of grade 3–4 was reported in 1% of all treated patients [37].

From the prospective case series of 88 patients with severe VOD, no exact safety data was reported [36]. At the time of defibrotide initiation, all patients were seriously ill; they were either thrombocytopenic, platelet-transfusion- or plasma product-dependent and/or uremic. The authors noted that "serious grade 3 or 4 AEs that occurred during treatment were those commonly observed in such critically ill patients in the post-transplantation setting (e.g., bacteraemia, acute renal failure and pulmonary oedema) and were not attributed to defibrotide by the treating physicians" [36].

no exact safety data available from prospective case series

C0002 – Are the harms related to the dosage or frequency of applying defibrotide?

Based on the current evidence, no definite conclusions can be drawn concerning any difference in harms in relation to the dosage. AEs were poorly described in some studies; the number of patients treated was overall rather small and patients' characteristics differed considerably to allow any differentiation. However, in the study comparing defibrotide at 25 mg/kg/day to 40 mg/kg/day, the occurrence of AEs did not differ significantly between the two groups, with the exception of hypoxia [37].

harms in relation to dosage: no conclusions can be drawn

C0004 – How does the frequency or severity of harms change over time or in different settings?

No evidence was found to answer this research question.

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of the technology?

Even though treatment-related AEs did not differ between adults and paediatric patients, paediatric patients were more likely to experience bleeding, hypotension and expected AEs in the dose-finding study with 151 patients overall [37].

C0007 – Are defibrotide and comparators associated with user-dependent harms?

No unequivocal tool for the diagnosis of VOD exists. Depending on whether the Baltimore or the Seattle criteria are used, different sensitivities and specificities can be expected [23, 24]. Misdiagnoses will therefore result in either foregoing potentially effective therapies or in putting patients at risk of receiving unnecessary and potentially harmful therapies. However, no evidence was found to answer the questions of whether physician experience and/or the criteria applied have any influence on the harms of defibrotide.

Investments and tools required

B0010 – What kind of data/records and/or registry are needed to monitor the use of the technology and the comparator?

multi-centre, prospective, observational patient registry for severe hepatic VOD

VOD is a rare disease with only a small number of affected patients. Since market authorisation was granted under exceptional circumstances, RCTs are unlikely to be feasible. As stated in the European Assessment Report, the market authorisation holder was required to implement a patient registry prior to launch in order to investigate long-term safety, health outcomes and patterns of utilisation. The EMA requires a multi-centre, multinational and prospective observational disease registry of patients diagnosed with severe hepatic VOD following HSCT and enrol patients treated with defibrotide, other treatments or supportive care [1].

6 Quality of evidence

quality of evidence was rated according to GRADE

The strength of evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [33] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the re commendation of the GRADE Working Group [33]. The ranking according to the GRADE scheme for the research question can be found in Table 6-1 and Table 6-2.

GRADE uses four categories to rank the strength of evidence:

- High = We are very confident that the true effect lies close to that of the estimate of the effect;
- Moderate = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- Low = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- Very low = Evidence either is unavailable or does not permit a conclusion.

Defibrotide for VOD prophylaxis

quality of evidence for defibrotide prophylaxis was very low to moderate

Overall, the strength of evidence for the effectiveness and safety of defibrotide for the prophylaxis of VOD was very low to moderate.

Defibrotide for VOD treatment

the strength of evidence for the effectiveness of defibrotide treatment was very low

Overall, the strength of evidence for the effectiveness and safety of defibrotide for the treatment of VOD is very low.

Table 6-1: Evidence profile: efficacy and safety of defibrotide for the prophylaxis of VOD

No of studies/ patients	Study design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy							
Overall mortality at 100 days, % (I vs. C)							
1/356	RCT	10 vs. 10 p=.9	No serious limitations	Only one study	Major uncertainty (-2)[1, 2]	None	Low
2/207	Historic controls	0–8 vs. 4–19 p=.07	Serious limitations (-1)[3]	No important inconsistency[4]	Direct	None	Very low
Disease-specific mortality, % (I vs. C)							
1/356	RCT	2 vs. 6 p=.1	No serious limitations	Only one study	Major uncertainty (-2)[1, 2]	None	Low
1/104	Historic control	0 vs. 6	Serious limitations (-1)[3]	Only one study	Direct	None	Very low
Incidence of VOD, % (I vs. C)							
1/356	RCT	12 vs. 20 Risk difference: -7.7; z-test p=.048	No serious limitations	Only one study	Direct	Imprecise results (-1)[5]	Moderate
2/207	Historic controls	0–4 vs. 7–19 p=.001	Serious limitations (-1)[3]	No important inconsistency[4]	Direct	None	Very low
Safety							
Averse events grade 3–4, % (I vs. C)							
1/356	RCT	37 vs. 37	No serious limitations	Only one study	Major uncertainty (-2)[1, 2]	None	Low
1/103	Historic control	0	Serious limitations (-1)[3]	Only one study	Direct	None	Very low
Treatment-related mortality, % (I vs. C)							
1/356	RCT	1 vs. 0	No serious limitations	Only one study	Major uncertainty (-2)[1, 2]	None	Low
1/104	Historic control	14 vs. 28 p=.075	Serious limitations (-1)[3]	Only one study	Direct	None	Very low

I= intervention; C= control; RCT= randomised controlled trial; P = p -value

1 = Patients in both groups (I 13% vs. C 20%) received therapeutic defibrotide once VOD occurred; AEs were reported for defibrotide after it was received following diagnosis of VOD.

2 = Concomitant UDCA was administered in both groups.

3 =Historic controls, unclear follow-up, unclear concomitant therapies, missing data on baseline characteristics or differences at baseline

4 = Differences can be explained by different comparators used and by different patient characteristics

5 = Large confidence interval

Table 6-2: Evidence profile: efficacy and safety of defibrotide for the treatment of VOD

No of studies/ patients	Study design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy							
Overall mortality at 100 days, %							
2/239	RCT[1], prospective case series	58–65	Serious limitations (-1)[2, 3]	No important inconsistency	Indirect	None	Very low
Disease-specific mortality, %							
1/151	RCT[1]	28–29	Serious limitations (-1)[2, 3, 4]	Only one study	Indirect	None	Very low
Resolution of VOD, %							
2/239	RCT[1], prospective case series	36–46	Serious limitations (-1)[2, 3, 4]	No important inconsistency	Indirect	None	Very low
Safety							
Averse events grade 3–4, %							
1/151	RCT[1]	89	Serious limitations (-1)[2, 3, 4]	Only one study	Indirect	None	Very low
Treatment-related mortality, %							
1/151	RCT[1]	0	Serious limitations (-1)[2, 3, 4]	Only one study	Indirect	None	Very low

I= intervention; C= control; RCT= randomised controlled trial

1 = Even though this study is a RCT, it was designed as dose-finding study; therefore, the comparator included is not relevant for the study question. The study is therefore treated as single-arm study.

2 = Unclear whether patients were enrolled consecutively.

3 = Lack of (a relevant) comparator does not allow conclusions to be drawn on the effectiveness of the intervention in comparison to other treatment options.

4 = Outcome assessors were not blinded.

7 Discussion

Defibrotide for the prophylaxis of VOD

no standard therapy for VOD prevention available

VOD is a serious and life-threatening disease, but no standard therapy is available for the prophylaxis of VOD. Even though UDCA and low-dose heparin are used in clinical practice, they are not approved. Moreover, defibrotide has not been licensed for this indication, because the manufacturer withdrew the application for the prophylaxis of VOD. However, even though usage of defibrotide in this setting is off-label, the European School of Haematology and European Group for Blood and Marrow Transplantation handbook, as well and the British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation, both recommend defibrotide for the prophylaxis of VOD for children (1A = strong recommendation with high quality of evidence) and for adults (2B = weak recommendation based on moderate quality of evidence) [8, 40].

reduced intensity conditioning regimens and treosulfan treatment could reduce risk of VOD

Several risk factors for the development of VOD have been identified, amongst them age, type of conditioning regimen and previous liver disease. Generally, patients scheduled for HSCT should be assessed for risk factors for VOD. For patients at risk, reduced intensity conditioning regimens or treatment with treosulfan instead of busulfan could reduce the risk of VOD foremost in paediatric patients [8].

different results for overall mortality among included studies

The only RCT found for the prophylaxis of VOD was conducted in children <18 years with at least one risk factor for VOD. With 12% in the intervention group and 20% in the control group, the incidence of VOD was closely reaching statistical significance [15]. Concerning mortality outcomes, no difference was found between defibrotide and no prophylaxis. However, these outcomes may have been biased due to the administration of therapeutic defibrotide to patients in both groups once they had developed VOD. Additionally, one-third of patients in each group received concomitant UDCA.

Two further and historical controlled trials were identified as supportive evidence [34, 35]. VOD incidence was reduced in one of these trials which had also included adults [35], whereas the other did not find a statistically significant difference [34]. Overall mortality at 100 days did not show an advantage for defibrotide prophylaxis in these studies and disease-related mortality was 0% in the intervention group in comparison to 6% in the control group in one study. However, study limitations are attributable to unclear follow-up, unclear concomitant therapies and missing data on baseline characteristics or differences at baseline. Furthermore, in two studies the low number of patients and the matching of intervention group patients with historical controls impact on the confidence in these results.

RCT:
4–6% of patients had treatment-related AEs

In terms of safety, two studies [34, 35] did not provide exact data on the occurrence of overall AEs. Results from the RCT [15] showed that 87–88% of patients included in the RCT had AEs, 37% had severe AEs and treatment-related AEs were reported from 4–6% of patients. Severe treatment-related AEs (Grade 3) occurred in 2% of defibrotide arm patients and in 3% of control arm patients; the low incidences of treatment-related AEs indicate that defibrotide is well-tolerated. However, these numbers have been measured after defibrotide treatment was administered in both study arms to all patients who had developed VOD. Statistical significance was calculated for the incidence of haemorrhage (the most common AE, regarded by the investigator as

possibly, likely or certainly related to defibrotide) and for the incidence of transplant-associated microangiopathy; both p-values were not statistically significant.

Defibrotide for the treatment of VOD

defibrotide approved by the EMA (with restrictions) for VOD treatment

For the treatment of hepatic VOD, a disease with high mortality rates, supportive care is the mainstay of therapy. Defibrotide is currently the only approved drug for the treatment of severe VOD and it is also recommended by different European Societies [8, 40]. The British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation recommend defibrotide for the treatment of VOD in adults and children (level of recommendation is 1B = strong recommendation with moderate quality of evidence) [8].

EMAs licensing decision was based on a phase 3 historical-controlled study including 44 children and 58 adult patients with severe VOD post-HSCT, compared to 32 historical control patients. This study was only published as an abstract and therefore not included in this assessment [1]. Complete responses (i.e., total bilirubin <2 mg/dL and the resolution of MOF) were observed in 24% (24/102) of the patients treated with defibrotide in comparison to 9% (3/32) in the historical control (p=0.013). Day+100 survival rate was 38% (39/102) versus 25.0% (8/32) (p=0.034) [2].

2 included studies: similar rates for overall mortality

Only two studies were included in this assessment [36, 37]. In both, the defibrotide treatment of VOD showed similar rates for overall mortality on day +100 (58–65%). For disease-specific mortality + 100 days, results were only available from the dose-finding RCT (28–29%) [37]. VOD resolution was reported in 36–46% of patients.

AEs were described in one of the studies, the dose-finding trial [37]. Overall, 97% experienced AEs and 89% were of grade 3 or 4. Although 8% of patients were considered as having treatment-related AEs, no treatment-related deaths were observed. Treatment-related AEs of grade 3–4 occurred in 3% of all patients. Considering the low incidences of treatment-related AEs, defibrotide has a favourable safety profile.

included studies not appropriate for assessing effectiveness

Both of the included studies were not appropriate for evaluating the effectiveness of defibrotide treatment due to the lack of a comparator. The RCT [37] was designed as a dose-finding study and, therefore, the included comparator is not relevant for the study question. Furthermore, the outcome assessors were not blinded. In the prospective case series [36], it is unclear whether patients were enrolled consecutively.

General discussion

Currently, the evidence for both possible indications of defibrotide is scarce. However, defibrotide received orphan drug status for both indications and the EMA has granted marketing authorisation "under exceptional circumstances". This market authorisation applies to "products for which the applicant can demonstrate in this application that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- in the present state of scientific knowledge, comprehensive information cannot be provided, or
- it would be contrary to generally accepted principles of medical ethics to collect such information" [41].

Due to the rarity of disease, RCTs, foremost for the therapy with defibrotide, are difficult to conduct. Currently, two defibrotide treatment studies (both single-arm), and one study, evaluating the efficacy and safety of defibrotide for the prophylaxis of VOD (parallel, randomised) are ongoing (see Appendix Section "Ongoing research").

The paucity of evidence also leaves several questions unanswered.

- *Drug administration:* Different dosages were used for prophylaxis as well as for the treatment of VOD, ranging from 10 mg/kg/day – over 25 to 60 mg/kg/day. According to the British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation, defibrotide is recommended at a dose of 6.25 mg/kg four times daily for the prevention and treatment of VOD in children and adults. However, the guidelines mention that further work is required to investigate the optimal dose of defibrotide [8]. Furthermore, the duration of administration differed. Thus, the optimal duration and the optimal dosage remain unknown, even though there are some indications that lower doses are associated with fewer adverse events [3]. In addition, defibrotide is also available as oral therapy, even though this route of administration was not used in any of the studies [8]. How these different applications affect outcomes has not been assessed.
- *Diagnosis:* Different criteria exist for diagnosing VOD. Depending on the criteria used, a different set of patients will be identified. The Baltimore criteria identify more advanced cases of hepatic VOD than the modified Seattle criteria. Since clinical criteria may only become apparent with a delay, the effectiveness of defibrotide may also differ depending on the severity of disease at diagnosis and thus on the initiation of therapy.
- *Prophylaxis versus treatment:* A further question concerns whether defibrotide therapy should be preferred over prophylaxis of VOD [26]. Since younger age has been identified as a risk factor for VOD, prophylaxis in this age cohort may yield better outcomes than therapy [3]. Also, a more preferable safety profile can be expected for patients receiving prophylactic therapy than for those with established severe VOD. In addition, it remains unclear how patients previously treated with defibrotide prophylaxis will respond to defibrotide therapy. In any case, risk stratification and, consequently, the reduction of risk-factors for VOD are keys to minimise the occurrence of VOD [25].

- *Long-term safety:* No long-term safety data are currently available for defibrotide. Especially for young patients and in the light of missing data on the optimal duration of prophylactic therapy with defibrotide, the question concerning long-term safety outcomes is of utmost relevance.
- *Population:* Even though there is no plausible rationale why defibrotide should act differently in an adult and a paediatric population, the RCT on defibrotide prophylaxis has assessed this prophylactic regimen only in children at high risk for VOD. Since age has been identified as a risk factor for the development of VOD and data on side effects for different age groups are scarce, the effectiveness of defibrotide remains unknown in children at low risk and in an adult population [3]. Concerning prophylaxis, guidelines recommend defibrotide for high-risk patients only.

8 Recommendation

In Table 8-1 and Table 8-2 the schemes for recommendations are displayed and the according choices are highlighted.

Defibrotide for VOD prophylaxis

Table 8-1: Evidence-based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The **inclusion** in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion** in the catalogue of benefits is **not recommended.**

Reasoning:

Even though there are indications that the prophylaxis of VOD with defibrotide reduces the incidence of VOD, a life-threatening disease, at least in children at high risk and few AEs are associated with this therapy, an inclusion in the catalogue of benefits for an off-label indication cannot be recommended.

A re-evaluation is recommended when the licensing status of the drug changes.

Defibrotide for VOD treatment

Table 8-2: Evidence-based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
X	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
	The **inclusion** in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion** in the catalogue of benefits is **not recommended.**

Reasoning:

The current evidence is not sufficient to evaluate the effectiveness and safety of defibrotide for the treatment of VOD. However, since VOD is a rare and life-threatening disease with no other therapeutic options available, defibrotide offers a new therapeutic approach for patients with severe VOD and targets an area of high unmet clinical need.

The proper assessment of risk factors and, whenever possible, the avoidance of risk factors have to be ensured in all patients scheduled for HSCT or at risk for developing VOD. Data on outcomes, foremost on long-term safety, should be collected in a prospective patient registry. Re-evaluation is recommended once these data become available. Thus, EMA website surveillance is also recommended to identify any change in the licensing status. Risk-sharing agreements are also indicated.

9 References

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A1-1: VOD prophylaxis – results from RCTs

Author, year, reference number	Corbacioglu et al. [15] (2012)
Country	28 centres in Europe (Austria, France, Germany, Ireland, Israel, Italy, Netherlands, Sweden, Switzerland, United Kingdom)
Sponsor	Gentium SpA, European Group for Blood and Marrow Transplantation
Study design	Multi-centre, phase III, open-label RCT, stratification according to centre and diagnosis of osteopetrosis
Intervention (I)	Defibrotide 25 mg/kg/day, in four divided i.v. infusions of 6.25 mg/kg over two hours Starting with the conditioning treatment and continued for 30 days after transplantation or at least for 14 days if discharged earlier
Comparator (C)	No prophylaxis
Concomitant therapies	UDCA was allowed when patients developed VOD; treatment with defibrotide at 25mg/kg was administered until complete recovery or death in both groups.
Number of pts (I vs. C)	356 (180 vs. 176)
Inclusion criteria	Patients <18 years who had undergone myeloablative conditioning before allogeneic or autologous HSCT and had one or more risk factors for VOD
Exclusion criteria	NA
Patient characteristics (I vs. C)	
Age of patients (median, yrs)	5.1 vs. 4.6
Sex (female), %	39 vs. 43
VOD high-risk criteria, %	
familial macrophage activity/osteopetrosis/adrenoleukodystrophy	6/4/1 vs. 9/3/1
Second myeloablative transplantation	14 vs. 13
Allogeneic HSCT for leukaemia >2nd relapse	9 vs. 6
Pre-existing liver disease	23 vs. 31
Previous abdominal irradiation	5 vs. 5
Previous gemtuzumab treatment	6 vs. 3
Conditioning with busulfan and melphalan/cyclophosphamide	59 vs. 56
Type of donor, %[1]	
Allogeneic HSCT	68 vs. 67
Autologous HSCT	29 vs. 31

[1] Transplant data were unavailable for 3% of patients in the defibrotide group and 2% of patients in the control group.

Author, year, reference number	Corbacioglu et al. [15] (2012)
Additional medication, %	concomitant UDCA: 31 vs. 32 treatment with defibrotide: 13 vs. 20
Evaluation of VOD	Modified Seattle criteria + US + independent review committee to confirm diagnosis
Follow-up after transplantation, days (median)	180 (range 28–1108, IQR 179–185)
Loss to follow-up, n	4 vs. 0
Outcomes (I vs. C)	
Efficacy	
Overall mortality at 100 days, n (%)	18 (10) vs. 17 (10), log-rank test p=0.9
Disease-related mortality at 100 days, n (%)	4 (2) vs. 10 (6) p =0.1
Incidence of VOD by 30 days after HSCT, n (%)	22 (12) vs. 35 (20) (risk difference -7.7, 95% CI -15.3 to -0.1; log-rank test p=0.0507, Z test for competing risk analysis, p=0.0488
VOD in patients with osteopetrosis, n (%)	1/7 (14) vs. 4/6 (67)
VOD by type of donor, n (%)	
Allogeneic HSCT	15/180 (8) vs. 25/176 (14)
Autologous HSCT	7/180 (4) vs. 10/176 (6)
VOD by age distribution, n (%)	
Infants	9/46 (20) vs. 11/41 (27)
Children	10/91 (11) vs. 16/95 (17)
Adolescents	3/43 (7) vs. 8/40 (20)
Severity of VOD up to 100 days post HSCT	p=0.034
Incidence of acute GVHD by day +30, n (%)	42 (34) vs. 61 (52) , p=0.0057
Incidence of acute GVHD by day +100, n (%)	57 (47) vs. 76 (65), p=0.0046
Health-related quality of life	-
Safety	
All AEs, n (%)	154 (87) vs. 155 (88)
AEs (grade 3), n (%)	66 (37) vs. 65 (37)
Treatment-related mortality, n (%)	1 (1) vs. 0 (0)
Treatment-related AEs, n (%)	10 (6) vs. 7 (4)
Treatment-related AEs (grade 3), n (%)	4 (2) vs. 6 (3)

AE= adverse event; CI= confidence interval; GVHD= graft-versus-host disease; HSCT= hematopoietic stem cell transplantation; IQR= interquartile range; i.v. = intravenous; NA= data not available; p= p value; RCT= randomised controlled trial; UDCA= ursodeoxycholic acid; US= ultrasound; VOD= veno-occlusive disease

Table A1-2: VOD prophylaxis – results from non-randomised clinical trials

Author, year, reference number	Qureshi 2008 [34]	Chalandon 2004 [35]
Country	United Kingdom	Switzerland
Sponsor	NA	NA
Study design	Prospective, historically-controlled (consecutive inclusion of intervention group April 2004–December 2005; control group from November 2001–April 2004)	Prospective, historically-controlled (consecutive inclusion of intervention group October 1999–June 2002; controls group from February 1997–September 1999)
Intervention	Defibrotide 20 mg/kg/day from start of condition treatment until day 28 post-stem cell infusion	Defibrotide 200–400 mg (10–25 mg/kg/d in children weighing 30 kg), i.v. over 2 hours 4 times daily starting one day before conditioning treatment to day +20 after transplantation + Low-dose heparin (5000 IU i.v. continuously for 24 hours if weight <70kg or 10000 IU if weight >70 kg)
Comparator	High-risk patients (busulfan conditioning; deranged baseline transaminase levels) received UDCA (15 mg/kg/once daily) and tinziparin (50µ /kg/once daily)	Low-dose heparin (5000 IU i.v. continuously for 24 hours if weight <70kg or 10000 IU if weight >70 kg)
Dose modification	In 4 of 47 patients who developed clinical VOD, defibrotide dose was increased to treatment dose of 40–60 mg/kg/day	Higher risk patient received higher dose (400 mg 4 times daily), standard risk patients received standard doses (200 mg 4 times daily)
Concomitant therapies	NA	antibiotics, liposomal amphotericin B, acyclovir, cytomegalovirus-negative blood products, parenteral nutrition, fungal prophylaxis, foscarnet if required, growth factors
Number of pts (I vs. C)	103 (47 vs. 56)	104 (52 vs. 52)
Inclusion criteria	Children undergoing HSCT from April 2004–December 2005	Patients with hematologic malignancies who underwent allogeneic peripheral blood stem cell or bone marrow transplantation from October 1999–June 2002
Exclusion criteria	NA	NA
Patient characteristics (I vs. C)	Age, % 1–6 y: 47 vs. 34 7–12 y: 30 vs. 43 13–18 y: 23 vs. 23	Median age, years 36.5 (range 5–60) vs. 37 (range 4–60)
Sex (female), %	30 vs. 43	46 vs. 27
Risk factors, %		
Treatment with busulfan/ cyclophosphamide	NA	15 vs. 21/81 vs. 73
Total body irradiation	NA	100 vs. 100
Pre-existing liver disease	30 vs. 34	13 vs. 12
Type of transplant, % (I vs. C)		
Allogeneic	53 vs. 48	100 vs. 100
Autologous	47 vs. 52	0

Author, year, reference number	Qureshi 2008 [34]	Chalandon 2004 [35]
VOD risk status, %	Low risk: 30 vs. 36 Intermediate risk: 51 vs. 46 High risk: 19 vs. 18[2]	Standard risk: 42 vs. 54 High risk: 58 vs. 46[3]
Evaluation of VOD	Modified Seattle criteria + US to confirm diagnosis	Baltimore criteria + US to confirm diagnosis
Follow-up, months	NA	Median: 21 (range 9–41) vs. 57 (range 43–70)
Loss to follow-up, n	NA	NA
Outcomes (I vs. C)		
Effectiveness		
Overall mortality at 100 days, n (%)	0 (0) vs. 2 (4)	NA (8) vs. NA (19); p=0.07
Disease-related mortality, n (%)	NA	0 vs. 3 (6)
Incidence of VOD, n (%)	2 (4) vs. 4 (7)	0 (0) vs. 10 (19) p=0.001
Severity of VOD, n (%)	NA	NA
Incidence of GVHD, n (%)	2 (4) vs. NA	Acute GVHD grade ≥ II: NA (34) vs. NA (38), p=0.58
Health-related quality of life	NA	NA
Safety		
Overall AEs, n (%)	NA	NA
AEs (grade 3–4), n (%)	NA	NA
Treatment-related mortality, n (%)	NA	NA (14) vs. NA (28), p=0.075
Treatment-related AEs, n (%)	NA	NA
Treatment-related AEs grade 3 or 4, n (%)	NA	0

AE= adverse event; GVHD= graft-versus-host disease; IU= international unit; i.v. = intravenous; NA= data not available; p= p value; UDCA= ursodeoxycholic acid; VOD= veno-occlusive disease

[2] Intermediate risk: allogeneic transplant; high risk: abnormal transaminase levels at baseline

[3] High risk: pre-transplantation liver disturbance/abdominal irradiation/previous stem cell transplantation

Table A1-3: Defibrotide for the treatment of VOD – results from uncontrolled trials

Author, year, reference number	Richardson 2010 [37]	Richardson 2002 [36]
Country	USA	USA
Sponsor	Gentium SpA, Orphan Drug Product Grant, Richard Corman Multiple Myeloma Research Fund	Gentium SpA provided defibrotide
Study design	Multi-centre, randomised, dose-finding, open-label phase II	Prospective, case series
Intervention	Defibrotide 25 mg/kg/day and 40 mg/kg/day Starting dose was 2.5 mg/kg every 6 hours for 4 doses (total dose, 10 mg/kg), increased to 6.25 mg/kg every 6 hours (total dose, 25 mg/kg/day) in arm A and to 10 mg/kg every 6 hours (total dose 40 mg/kg/day) in arm B for a minimum of 14 days or until achievement of CR, or until progression of VOD, unacceptable toxicity (recurrent grade 3/4 AEs considered likely or definitely related to defibrotide), or comorbidities precluded further treatment	Defibrotide 10 mg/kg/day as 4 divided doses; dose was increased incrementally to a max. potential total daily dose of 60 mg/kg for a minimum of 14 days.
Comparator	None	None
Additional medication	transfusions	transfusions
Dose modification	NA	Dose was increased incrementally to a maximum potential daily dose of 60 mg/kg
Number of pts	151 (75 25 mg/kg defibrotide vs. 74 40 mg/kg defibrotide)	88
Inclusion criteria	Adult or paediatric patients after HSCT with a clinical diagnosis of hepatic VOD (according to clinical criteria for evaluation of VOD or jaundice + US +1 further diagnostic criterion or biopsy confirmed VOD), with a predicted risk ≥30% according to the Bearman model or if they had MOF	Adult patients and children after HSCT with a clinical diagnosis of VOD[4] treated from March 1995–May 2001 on an emergency use basis
Exclusion criteria	Uncontrolled bleeding, hemodynamic instability, grade B–D GVHD, intubation for documented intrinsic lung disease, grade 4 neurotoxicity, previous or concomitant systemic t-PA therapy, concomitant use of heparin or other anticoagulants	Uncontrolled bleeding, hemodynamic instability
Patient characteristics		
Age median, yrs (range)	34 (0–63)	35 (8 months to 62 years)
Sex, female, %	43	47

[4] Based on jaundice (bilirubin ≥34.2 μM), hepatomegaly and/or right upper quadrant pain, and ≥5% weight gain from admission, with or without ascites. Patients who met at least two criteria and had a liver biopsy were also eligible. Patients not addressed by the Bearman model were eligible if VOD was considered their major clinical problem and organ failure was present in at least one other organ system. Patients with a concurrent, potential confounding cause of liver dysfunction such as GVHD or inconsistent findings evident on ultrasound imaging were required to have biopsy-proven VOD to be considered eligible. Patients who had failed prior treatment with t-PA and heparin were eligible.

Author, year, reference number	Richardson 2010 [37]	Richardson 2002 [36]
Risk factors, %		
Treatment with busulfan/ cyclophosphamide	42/80	53/75
TBI	46	33
Pre-existing liver disease	NA	100
Type of transplant, % (I vs. C)		
Allogeneic	87	68
Autologous	13	32
Duration of treatment, median, days	Arm A: 19 (range 2–82) Arm B: 20 (2–65)	15 (range 1–139)
VOD risk status, n	NA	High-risk population
Evaluation of VOD	Jaundice (total serum bilirubin ≥2 mg/dL) and at least two associated signs (ascites, weight gain >5 % from baseline, hepatomegaly or right upper quadrant pain, by day + 35 post HSCT + US to confirm diagnosis	Jaundice (bilirubin ≥34.2 μM), hepatomegaly and/or right upper quadrant pain, and ≥5% weight gain from admission, with or without ascites. Patients who met at least two criteria and had a liver biopsy, patients not addressed by the Bearman model were eligible if VOD was considered their major clinical problem and organ failure was present in at least one other organ system. Patients with a concurrent, potential confounding cause of liver dysfunction such as GVHD or inconsistent findings evident on ultrasound imaging were required to have biopsy-proven VOD to be considered eligible.
Follow-up, months	NA	NA
Loss to follow-up, n	4 vs.6	NA
Outcomes (I vs. C)		
Efficacy		
Overall mortality on day +100, n (%)	87 (58)	57 (65)
Disease-related mortality + 100 days, n (%)	NA (28–29)	NA
Resolution of VOD, n (%)	65 (46)[5]	32 (36), 95% CI: 26%, 47%[6]
Health-related quality of life, n (%)	NA	NA
Safety		
Overall AEs, n (%)	144 (97)	NA
AEs (grade 3–4), %	132 (89)	NA
Treatment-related mortality, %	0	NA
Treatment-related AEs, %	12 (8)	NA
Treatment-related AEs grade 3 or 4, n (%)	5 (3)	0

AE= adverse event; CI= confidence interval; CR= complete response; GVHD= graft-versus-host-disease; MOF= multi-organ failure; NA= data not available; t-PA= tissue-plasminogen activator; TBI=total body irradiation; VOD= veno-occlusive disease

[5] Defined as total serum bilirubin <2 mg/dL after initiation of defibrotide with resolution of VOD-related MOF

[6] Defined as evidence of improvement in VOD-related symptoms and concurrent MOF, and a concomitant or subsequent decrease in bilirubin to less than 34.2 μM

Risk of bias tables

The internal validity of the included studies was judged by two independent researchers. In case of disagreement, a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [30] and in the Guidelines of EUnetHTA [32].

Table A2-1: Risk of bias – study level (randomised studies)

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding			Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating physician	Outcome assessors			
Corbacioglu 2012 [15]	Yes	Yes	No	No	Yes	Yes	No[1]	Low
1 = Patients of both groups were treated with defibrotide when they developed VOD; thus for all outcomes besides the primary outcome, no formal conclusions on the effect can be drawn.								

Table A2-2: Risk of bias – study level (non-randomised studies)

Study reference/ID	How was the treatment group determined for each patient?	Were treatment groups comparable at baseline?	What steps were taken to minimise bias?	Were all relevant outcomes reported?	Whether intention-to-treat was appropriately implemented?	Any other problems that could put the study at a high risk of bias
Prophylaxis of VOD						
Qureshi 2008 [34]	Allocation determined according to date of treatment with consecutive inclusion for intervention group	Unclear[1]	None	Unclear[2]	Not applicable	Low number of patients, intervention group patients matched with historical controls
Chalandon 2004 [35]	Allocation determined according to date of treatment with consecutive inclusion	No	None	Unclear	Not applicable	Intervention group patients matched with historical controls
Treatment of VOD						
Richardson 2010 [37]	Unclear[4]	Not applicable	Unclear[5]	Yes	Not applicable	-
Richardson 2002 [36]	Unclear[6]	Not applicable	No	Unclear	Not applicable	-
1 = Only few baseline variables are listed and several risk factors for developing VOD are therefore not described. 2 = Methods, outcomes, planned statistical analyses were not described. 3 = Reported outcomes especially for adverse events are scarce. 4 = In this dose-finding trial, no details are provided on how the allocation sequence was generated and how the patients were allocated. 5 = Patients were stratified according to age and conditioning treatment, but the trial was open-label. 6 = Unclear whether all patients were enrolled consecutively.						

Table A2-3: Risk of bias – outcome level

Outcome Trial	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realised	Selective outcome reporting likely	Other aspects according to risk of bias	Risk of bias – outcome level
Prophylaxis of VOD						
Incidence of VOD						
Corbacioglu 2012 [15]	Low	Low	Low	Low	Low	Low
Qureshi 2008 [34]	High	High	NA	High	High[2]	High
Chalandon 2004 [35]	High	High	NA	Low	Low	High
Overall mortality						
Corbacioglu 2012 [15]	Low	Low	Low	Low	High[1]	High
Qureshi 2008 [34]	High	Low	NA	High	High[2]	High
Chalandon [35]	High	Low	NA	Low	Low	High
Disease-specific mortality						
Corbacioglu 2012 [15]	Low	Low	Low	Low	High[1]	High
Chalandon [35]	High	High	NA	Low	Low	High
Grade 3–4 adverse events						
Corbacioglu 2012 [15]	Low	Low	Low	Low	High[1]	High
Qureshi 2008 [34]	High	High	NA	High	High[2]	High
Chalandon [35]	High	High	NA	Low	Low	High
Treatment-related mortality						
Corbacioglu [15]	Low	Low	Low	Low	High[1]	High
Chalandon [35]	High	High	NA	Low	Low	High

Outcome Trial	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realised	Selective outcome reporting likely	Other aspects according to risk of bias	Risk of bias – outcome level
Treatment of VOD						
Overall mortality						
Richardson 2010 [37][3]	High	Low	NA	Low	Low	High
Richardson 2002 [36][4]	High	Low	NA	Unclear	Low	High
Disease-specific mortality						
Richardson 2010 [37][3]	High	High	NA	Low	Low	High
Resolution of VOD						
Richardson 2010 [37][3]	High	High	NA	Low	Low	High
Richardson 2002 [36][4]	High	Unclear	NA	Unclear	Low	High
Grade 3–4 adverse events						
Richardson 2010 [37][3]	High	High	NA	Low	Low	High
Treatment-related mortality						
Richardson 2010 [37][3]	High	High	NA	Low	Low	High

1 = Patients of both groups were treated with defibrotide when they developed VOD;
thus for all outcomes besides the primary outcome, no formal conclusions on the effect can be drawn.

2 = Unclear follow-up for both groups; unclear concomitant therapies; unclear distribution of risk factors for VOD between both groups

3 = Even though this was a randomised controlled trial, the primary objective of this study was to determine the optimal dosages and not to compare the intervention with other treatment options. Thus this study was treated like an uncontrolled trial.

4 = Uncontrolled study design

Abbreviations: NA = not applicable

Applicability table

Table A3-1: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Prophylaxis of VOD The age of patients in the three included studies showed a wide range from <1 year to 60 years, which is consistent with the target population. It is unresolved as to whether the results of the RCT (paediatric study patients only) are applicable to adults. Historic controls served as comparators in two studies. One control was enrolled from 1999–2002 and the other control group from 2001–2004. Since then, a better characterisation of risk factors for the development of VOD may limit the applicability with reduction of allogeneic HSCT in patients at high risk and use of dose-reduced conditioning regimens. Treatment of VOD The age of patients of both studies varied widely between eight months and 63 years, which is consistent to the target population.
Intervention	Prophylaxis of VOD In the included studies, different dosages of defibrotide were administered, ranging from 10–25 mg/kg/day. Patients of two studies received additional medication (concomitant UDCA, low-dose heparin), which might have influenced the results. Treatment of VOD Administered dosages were different in the two included studies (25–60 mg/kg/day). All patients additionally received transfusions.
Comparators	Prophylaxis of VOD In the RCT, patients who received defibrotide for the prophylaxis of VOD were compared to patients who received no prophylaxis. The other two studies compared the use of defibrotide to historical control group patients who did not receive defibrotide. Historical control groups often differ significantly concerning co-intervention and prognostic factors, therefore, comparability is limited [30]. Treatment of VOD In the dose-finding RCT, the comparator included was not relevant for the study question. No control group was implemented in the prospective case series. Therefore, both studies were not appropriate to evaluate the effectiveness of defibrotide treatment.
Outcomes	Prophylaxis of VOD Overall mortality, disease-related mortality and the incidence of VOD were the outcomes most frequently reported. In the RCT, patients in the control group were treated with defibrotide once VOD developed. Outcomes other than the primary (i.e. incidencve of VOD), may have been biased. Treatment of VOD Overall mortality on day + 100 and resolution of VOD were the most important outcomes reported from the two included studies, aiming to reflect the effectiveness of defibrotide for VOD treatment.
Setting	Included studies were conducted either in Europe or the United States. Clinical settings were not described in all of the studies, but it is likely that all patients received-standard care at university hospitals or transplant centres.

Search Strategies

Medline Search Strategy

Database: Ovid MEDLINE(R) <1946 to November Week 3 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 29, 2014>, Ovid MEDLINE(R) Daily Update <November 19, 2014>, Ovid OLDMEDLINE(R) <1946 to 1965>	
Search Strategy:	
1	exp Hepatic Veno-Occlusive Disease/ (1125)
2	veno-occlusive disease*.mp. (2785)
3	venoocclusive disease*.mp. (219)
4	VOD.mp. (1663)
5	venous occlusion*.mp. (3860)
6	1 or 2 or 3 or 4 or 5 (7859)
7	Defitelio*.mp. (1)
8	Defibrotide*.mp. (390)
9	Defibrinotide*.mp. (1)
10	proc#clide*.mp. (3)
11	7 or 8 or 9 or 10 (391)
12	6 and 11 (102)
13	exp Clinical Trial/ or double-blind method/ or (clinical trial* or randomized controlled trial or multicenter study).pt. or exp Clinical Trials as Topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab. (1247414)
14	((systematic adj3 literature) or systematic review* or meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*)).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or "cochrane database of systematic reviews".jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt. or review.pt. (2095639)
15	13 or 14 (3133683)
16	12 and 15 (37)
17	remove duplicates from 16 (36)

30.12.2014

Embase Search Strategy

No.	Query Results	Results	Date
#1	'clinical article'/de OR 'clinical trial'/de OR 'clinical trial (topic)'/de OR 'cohort analysis'/de OR 'control group'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'in vivo study'/de OR 'major clinical study'/de OR 'meta analysis'/de OR 'multicenter study'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'practice guideline'/de OR 'prospective study'/de OR 'randomized controlled trial (topic)'/de AND ('liver vein obstruction'/exp OR 'hepatic veno-occlusive disease' OR 'hepatic veno-occlusive diseases' OR 'veno-occlusive disease' OR 'veno-occlusive diseases' OR 'venoocclusive disease' OR 'venoocclusive diseases' OR 'vein occlusion'/mj OR 'venous occlusion' OR 'venous occlusions' OR vod) AND ('defibrotide'/exp OR defitelio* OR defibrinotide* OR prociclide* OR procyclide* OR dasovas OR noravid) AND 'human'/de OR ('liver vein obstruction'/exp OR 'hepatic veno-occlusive disease' OR 'hepatic veno-occlusive diseases' OR 'veno-occlusive disease' OR 'veno-occlusive diseases' OR 'venoocclusive disease' OR 'venoocclusive diseases' OR 'vein occlusion'/mj OR 'venous occlusion' OR 'venous occlusions' OR vod AND ('defibrotide'/exp OR defitelio* OR defibrinotide* OR prociclide* OR procyclide* OR dasovas OR noravid) AND ([cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim))	125	30 Dec 2014

CRD Search Strategy

#### Defibrotide (MEL 2015) ER/AN	
1	(Defitelio*)
2	(Defibrotide*)
3	(Defibrinotide*)
4	(prociclide*)
5	(procyclide*)
6	#1 OR #2
6 Hits	

30.12.2014

Search Strategy for the Cochrane Library

Search Name: Defibrotide (Defitelio) for VOD Last Saved: 30/12/2014 17:00:41.921	
ID	Search
#1	MeSH descriptor: [Hepatic Veno-Occlusive Disease] explode all trees
#2	veno-occlusive disease* (Word variations have been searched)
#3	venoocclusive disease* (Word variations have been searched)
#4	VOD (Word variations have been searched)
#5	"venous occlusion" (Word variations have been searched)
#6	#1 or #2 or #3 or #4 or #5
#7	Defitelio* (Word variations have been searched)
#8	Defibrotide* (Word variations have been searched)
#9	Defibrinotide* (Word variations have been searched)
#10	prociclide* (Word variations have been searched)
#11	procyclide* (Word variations have been searched)
#12	dasovas (Word variations have been searched)
#13	noravid (Word variations have been searched)
#14	#7 or #8 or #11
#15	#6 and #14
15 Hits	

Ongoing research

On 16 February 2015 a search in databases www.clinicaltrials.gov, clinicaltrialsregister.eu and www.who.int/ictrp was conducted; the following ongoing trials were identified:

Table A5–1: Ongoing research

Study identifier	Sponsor/ Collaboration	Time	Study type	Number of patients	Age group	Intervention	Comparator	Medical condition	Endpoints
NCT00628498	Gentium SpA, Jazz Pharmaceuticals	12/2007-12/2015	Phase III, single-arm, open-label	1000	Child, adult, senior	Defibrotide (treatment)	-	Hepatic VOD	Complete response of VOD, survival
JPRN-UMIN000013454	Fukushima Medical University Hospital, Atsushi Kikuta	Start date: 05/2014	Single-arm, non-randomised	20	Not applicable	Defibrotide (treatment)	NA	VOD	Survival at day 100 post SCT in patients with VOD after SCT
JPRN-UMIN000013455	Fukushima Medical University Hospital, Atsushi Kikuta	Start date: 05/2014	Parallel, randomised	75	Max. 50 years old	Defibrotide (prophylaxis)	Standard treatment	VOD	Incidence of VOD until day 30 post SCT

NA= data not available; DVT= deep vein thrombosis; SCT= stem cell transplantation; VOD= veno-occlusive disease