A Retrospective Chart Review on the Toxicity of Pegylated Asparaginase in Adult Patients with Acute Lymphoblastic Leukemia

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A
cute lymphoblastic leukemia (ALL) is among the most common hematologic malignancies, with an annual incidence of 6020 patients in the United States, of which 2000 to 2500 cases occur in adults. Trends have shown an early peak between the ages of 4 and 5 years, with another increase after the age of 50 years. With the utilization of pediatric protocols, overall survival in adults has increased from less than 10% to between 30% and 45%. Possible reasons for this disparity include the use of lower doses of chemotherapy (ie, vincristine and corticosteroids) and the omission of highly active agents (eg, asparaginase).

Background: Historically, complete remission rates seen in adult patients with acute lymphoblastic leukemia (ALL) have been significantly lower than among pediatric patients. Recently, there has been a shift toward more aggressive treatment of adults with ALL, using protocols similar to those used for pediatric patients. This has translated into increased complete remission rates in adults, but the 5-year overall survival rate remains significantly lower in adults (45%) than in pediatric patients (85%). Possible reasons for this disparity include the use of lower doses of chemotherapy (ie, vincristine and corticosteroids) and the omission of highly active agents (eg, asparaginase).

Objective: To determine the tolerability level of asparaginase in adult patients with ALL.

Methods: We performed a retrospective chart review of 25 consecutive adult patients with ALL who received treatment at New York-Presbyterian/Weill Cornell Medical Center between April 2006 and October 2010 to investigate the toxicity profile of intravenous pegaspargase used in these patients (at doses of 2000-2500 IU/m²). All patients received standard prophylaxis.

Results: Among the 25 patients included in this study, hepatotoxicity was evident in many of the patients. Overall, 10 (40%) patients had hyperbilirubinemia; of these patients, 3 also had bilirubin levels of >25 mg/dL, which were associated with fatal outcomes in all 3 cases. Hypertriglyceridemia was observed in 1 patient, with levels reaching >8500 mg/dL, and coinciding with pancreatitis. Hypofibrinogenemia was observed in 36% of the patients in our review. A total of 17 patients in this study died: 3 deaths were related to sepsis, 2 occurred during bone marrow transplant, 2 from multi-organ failure, and the cause of the other 10 deaths, which occurred during follow-up, could not be verified.

Conclusion: The results from our study show that severe toxicities may occur from the administration of pegaspargase, especially in patients aged >50 years. Prognostic factors determining which patients will develop significant toxicities are lacking, although dose and age appear to affect the incidence and severity of hepatotoxicity.

Asparaginase catalyzes the hydrolysis of L-asparagine to aspartic acid and ammonia, causing serum depletion of asparagines in circulation. Unlike normal cells, lymphoid cells are unable to synthesize asparagine de novo as a result of their lack of asparagines synthetase, and normally rely on serum asparagine for protein synthesis. Asparagine depletion disrupts
protein synthesis, causing selective apoptosis of leukemic cells while leaving normal cells unaffected.\(^5\)

Maximal asparagine depletion is essential for asparaginase efficacy, with higher response rates seen with complete depletion. In 1 study, a total of 85 patients were evaluated to determine the correlation between successful depletion of asparagine and overall survival and disease-free survival (DFS).\(^6\) After receiving pegaspargase at a dose of 2000 IU/m\(^2\), 22 of the 85 patients did not achieve successful asparagine depletion, and they had significantly inferior overall survival rate (hazard ratio [HR], 2.37; \(P = .002\)) and DFS (HR, 2.21; \(P = .012\)) compared with the 63 patients who achieved asparagine depletion.\(^6\)

The results of this study showed a clear benefit of using pegaspargase in a multidrug regimen for patients with ALL when therapeutic asparagine depletion is successful. The reasons for not achieving depletion may be attributable to the formation of asparaginase-neutralizing antibodies or to decreased doses of the drug. It is important to note that in this study, the dose of pegaspargase was capped at 3750 U, which many of the current treatment protocols do not mandate.\(^6\)

Despite the effectiveness of asparaginase as an anticancer drug, its use has been associated with several toxicities.\(^5,7\) The toxicities of asparaginase fall under 2 main categories: toxicities related to immunologic sensitization to the foreign protein, and those resulting from the inhibition of protein synthesis. The toxicities related to the inhibition of protein synthesis include pancreatitis, hyperglycemia, hepatotoxicity, hypoalbuminemia, and coagulation changes. The coagulopathy results from the decreased synthesis of fibrinogen and plasminogen, as well as decreases in antithrombin III, protein C, and protein S.\(^5,7\) These coagulation defects result in either bleeding or, more frequently, thrombotic events. Thrombotic events can range from deep-vein thrombosis to pulmonary embolus and central venous thrombosis.\(^8\)

Results from a limited number of early studies and clinical practice suggest that adults are more susceptible to asparaginase-associated side effects than children.\(^7\) Subsequently, toxicity concerns led to the modification of the treatment regimens for adult patients with ALL to reduce the intensity of asparaginase or to exclude it.\(^7\) In contrast to previous studies using pediatric protocols for adult patients,\(^8\) the recent data suggest that adults tolerate native asparaginase and pegaspargase in a manner similar to the pediatric population,\(^10\) but information regarding pegaspargase toxicity in elderly patients with ALL remains limited and has not been investigated in randomized controlled trials.

The pegylation of native L-asparaginase (Elspar) leads to the diminished immunogenicity of the modified molecule, while retaining the antineoplastic effects of the native enzyme.\(^5\) The advantages of using the pegylated enzyme have led to the approval of pegaspargase by the US Food and Drug Administration (FDA) for the treatment of patients with ALL who are hypersensitive to native L-asparaginase, and, more recently, for its approval as a component of a multi-agent chemotherapy regimen for the first-line treatment of ALL.\(^11\) Pegaspargase has a longer half-life than native enzyme (5.73 days vs 1.28 days).\(^3\) Therefore, treatment with pegaspargase results in prolonged asparaginase activity and the subsequent sustained depletion of asparagine.\(^5\)

The longer half-life of pegaspargase allows for its less frequent administration. Pegaspargase can be administered every 2 weeks, whereas native L-asparaginase has to be administered 2 to 5 times weekly.\(^5\)

**Toxicity concerns led to the modification of the treatment regimens for adult patients with ALL to reduce the intensity of asparaginase or to exclude it. In contrast to previous studies using pediatric protocols for adult patients, the recent data suggest that adults tolerate native asparaginase and pegaspargase in a manner similar to the pediatric population.**

A handful of retrospective studies have investigated the toxicities associated with the administration of pegaspargase. According to the prescribing information for pegaspargase, among 112 patients with relapsed ALL, 10% of previously nonhypersensitive patients experienced allergic reactions, as well as 32% of patients with previously noted hypersensitivity to *Escherichia coli* L-asparaginase.\(^12\) Douer and colleagues investigated 51 adults with ALL between the ages of 18 and 57 years who were given 2000 IU/m\(^2\) of pegaspargase in a protocol with vincristine, daunorubicin, and prednisone.\(^11\)

The results showed a 6% incidence of grade 3/4 allergic reactions, a 31% chance of grade 3/4 hyperbilirubinemia, a 63% chance of transaminitis, and a 5% chance of pancreatitis.\(^13\) This study has shown that pegylated asparaginase is tolerable in adults.\(^7\) Hepatotoxicity is the primary toxicity associated with pegaspargase.\(^8,14,15\)

Until December 2012, 3 preparations of asparaginase were approved by the FDA and were commercially available: L-asparaginase, pegaspargase, and erwinia asparaginase. The manufacturer of L-asparaginase made a financial decision to discontinue production in late 2012.\(^16\) L-asparaginase and pegaspargase are derived from *E. coli* and erwinia asparaginase from *Erwinia chrysanthemi*. The
E coli preparations are associated with a higher incidence of hypersensitivity reactions, although the incidence with the pegylated formulation is approximately 3% in asparaginase-naïve patients.

The withdrawal of native L-asparaginase from the market, coupled with the convenience and reduced toxicity of pegaspargase, have made pegaspargase the upfront treatment for patients with newly diagnosed and relapsed ALL.

We performed a retrospective chart review to investigate the tolerability of pegaspargase in patients with ALL to compare the frequency and severity of toxicities, as seen in previous studies. The clinical protocol was approved by the Institutional Review Board, and informed consent was obtained from all patients according to the US Department of Health & Human Services guidelines.

Methods

Patient Characteristics

A total of 25 consecutive adult patients with ALL, ranging in age from 21 to 84 years (median, 49 years) were treated at New York-Presbyterian/Weill Cornell Medical Center between April 2006 and October 2010. Of these patients, 5 patients had Philadelphia chromosome-positive ALL, a subtype that has been shown to have worse outcomes compared with patients without Ph+ ALL, particularly before the discovery of tyrosine kinase inhibitors.17,18 Patient demographics are outlined in Table 1. Of the total patients, 20 had relapsed disease. None of these patients had received asparaginase as part of their initial induction. All patients received standard prophylaxis with valacyclovir 500 mg orally daily, fluconazole 400 mg orally daily, and sulfamethoxazole plus trimethoprim 3 times weekly.

Treatment Protocol

All patients received pegaspargase at a dose of 2500 units/m² (except for 2 patients who received 2000 units/m²), administered intravenously over 1 hour. No doses were capped. Pegaspargase was administered as part of the various protocols that are used for this patient population (Table 2). Of the 25 total patients, 24 received premedication with a corticosteroid as part of the treatment regimen (ie, dexamethasone, or prednisone plus methylprednisolone). The choice of a corticosteroid was based on the regimen used.

Patients were monitored for infusion-related side effects during infusion and for 60 minutes after its completion. Laboratory studies were performed at least 3 times weekly (Table 3) for up to 14 days after an infusion and consisted of a complete blood count, including measures for platelets, prothrombin time, international normalized ratio (INR), fibrinogen levels, direct and indirect bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood urea nitrogen, creatinine, and lactate dehydrogenase. The amylose, lipase, and cholesterol levels were only tested if the patient was symptomatic and pancreatitis
was suspected. During this period, cryoprecipitate was administered for patients with fibrinogen levels of <100 mg/dL.

Data collection included patient demographics, infusion-related events, and laboratory parameters before administration and up to 4 weeks after the last administration of pegaspargase or until the resolution of abnormal events. Disease response, progression-free survival, and overall survival were noted but are not commented on in this report, because of the small number of patients evaluated and the heterogeneity of the population.

**Results**

**Toxicity Analysis**

The treatment-related toxicities are summarized in Table 4. One patient (4%) experienced an infusion-related reaction, which consisted of wheezing and shortness of breath and required supplemental oxygen. This patient was receiving pegaspargase as part of a multidrug regimen, but treatment with dexamethasone had been completed and therefore the patient was not premedicated with the initial dose. Therapy with pegaspargase was discontinued, the patient was treated with 1 mg/kg of methylprednisolone and diphenhydramine, and the symptoms resolved within 60 minutes. The patient was premedicated for the subsequent dose of pegaspargase with methylprednisolone (0.5 mg/kg) and diphenhydramine, and was subsequently rechallenged, without any incident.

A total of 9 (36%) patients had significant decreases in their fibrinogen level (<100 mg/dL), which normalized after receiving 1 or 2 transfusions of cryoprecipitate. Of these patients, 3 had elevations in INR of >1.6, with 1 patient having an INR of >6, which normalized after the administration of cryoprecipitate. Thrombotic events were seen in 2 patients: 1 had pulmonary embolism 1 month after the administration of pegaspargase, and the other patient had deep-vein thrombosis within 1 month of receiving 2 doses of pegaspargase, which were given 2 weeks apart. Both patients received enoxaparin and had no further complications.

A total of 10 (40%) patients had hyperbilirubinemia that could be attributed to pegaspargase (Table 4). For most of the patients, the bilirubin levels normalized within 2 weeks of infusion with no further elevations. In 1 patient, the bilirubin level reached a peak of 25 mg/dL and slowly resolved over a 1-month period; the patient was discharged with a bilirubin level of 5.7 mg/dL. That patient died several months later because of disease progression. In 2 patients, the bilirubin levels reached 29.4 mg/dL and 25.7 mg/dL, and both patients clinically deteriorated and died from multiorgan failure within 1 month of the administration of pegaspargase.

Of the 10 patients with hepatotoxicity, 9 were treated for relapsed disease. The contribution of other agents to their condition is difficult to assess. A total of 4 patients were receiving a 5-drug regimen (ie, cyclophosphamide, vincristine, prednisone, asparaginase, and daunorubicin); 4 patients received methotrexate, vincristine, asparaginase, and dexamethasone; and 2 patients received single-agent pegaspargase. Although methotrexate and daunorubicin can cause hepatotoxicity, hepatotoxicity from methotrexate or daunorubicin usually manifests as transaminitis.

**Table 4 Adverse Reactions in Patients Receiving Pegylated Asparaginase**

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Patients, N (%) (N = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hypofibrinogenemia</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Elevated INR</td>
<td>3 (12)</td>
</tr>
</tbody>
</table>

INR indicates international normalized ratio.

**Table 5 Mortality Data in Patients Receiving Pegylated Asparaginase**

<table>
<thead>
<tr>
<th>Mortality data/cause</th>
<th>Patients, N (%) (N = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths</td>
<td>17 (68)</td>
</tr>
<tr>
<td>Bone marrow transplant</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

*Total number of patients in this study.

The contribution of other agents to their condition is difficult to assess.

A single patient presented with severe abdominal pain, and laboratory results revealed a total cholesterol level of 700 mg/dL, triglycerides of 8470 mg/dL, and amylase and lipase levels peaking at 630 mg/dL and 400 mg/dL, respectively. The patient started therapy with oral gemfibrozil 600 mg twice daily, and the patient underwent a single plasmapheresis, with subsequent resolution of the hypertriglyceridemia within 1 week. This patient was not rechallenged with pegaspargase.

**Of the 10 patients with hepatotoxicity, 9 were treated for relapsed disease. The contribution of other agents to their condition is difficult to assess.**
The majority of the patients in this study had relapsed or refractory ALL. Of the 25 patients in this study, 17 (68%) died after the study ended (Table 5). Of the 17 deaths, 2 occurred during bone marrow transplantation, 3 as a result of sepsis, and 2 resulted from multi-organ failure, possibly secondary to hyperbilirubinemia (Table 5).

### Discussion

The increased use of pegylated asparaginase in adults has generated great interest and several review articles, of which the most comprehensive to date is by Stock and colleagues.\(^8,15,19\) In 2009, Stock and colleagues assembled a panel of expert physicians to develop specific recommendations for the prevention and management of asparaginase-induced toxicity based on a review of the medical literature and the panel members’ experiences.\(^8\) Their review highlights the significant differences in toxicity between the adult and pediatric populations of patients with ALL; however, the mean age for the adults in their review was 30 years compared with 49 years in our study.

<table>
<thead>
<tr>
<th>Patient (sex)</th>
<th>Age, yrs</th>
<th>Total dose, U (dosage, U/m(^2))</th>
<th>Doses, N</th>
<th>Baseline total bilirubin, mg/dL (direct); AST, U/L; ALT, U/L</th>
<th>Peak total bilirubin, mg/dL (direct); AST, U/L; ALT, U/L</th>
<th>Patient status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (M)</td>
<td>26</td>
<td>4675 (2500)</td>
<td>3</td>
<td>0.9 (0.2); 98; 253</td>
<td>13.2 (7.8); 242; 395</td>
<td>Deceased</td>
</tr>
<tr>
<td>2 (M)</td>
<td>36</td>
<td>5125 (2500)</td>
<td>2</td>
<td>0.8 (0.2); 35; 20</td>
<td>4.5 (2.4); 127; 63</td>
<td>Deceased</td>
</tr>
<tr>
<td>3 (F)</td>
<td>43</td>
<td>4250 (2500)</td>
<td>2</td>
<td>1.9 (0.7); 101; 270</td>
<td>8.1 (4.3); 80; 80</td>
<td>Deceased</td>
</tr>
<tr>
<td>4 (M)</td>
<td>49</td>
<td>5800 (2500)</td>
<td>1</td>
<td>1.7 (0.7); 81; 57</td>
<td>8 (5); 103; 70</td>
<td>Deceased</td>
</tr>
<tr>
<td>5 (F)</td>
<td>52</td>
<td>4150 (2500)</td>
<td>2</td>
<td>1.1 (0.2); 18; 22</td>
<td>9.9 (6.3); 139; 146</td>
<td>Alive</td>
</tr>
<tr>
<td>6 (F)</td>
<td>52</td>
<td>4075 (2500)</td>
<td>3</td>
<td>0.7 (0.1); 36; 40</td>
<td>10.1 (6.1); 112; 306</td>
<td>Deceased</td>
</tr>
<tr>
<td>7 (F)</td>
<td>60</td>
<td>4000 (2500)</td>
<td>1</td>
<td>0.4 (0.1); 88; 165</td>
<td>27.8 (10.3); 858; 837</td>
<td>Alive</td>
</tr>
<tr>
<td>8 (M)</td>
<td>70</td>
<td>4900 (2500)</td>
<td>1</td>
<td>0.5 (0.1); 36; 33</td>
<td>25.7 (16.4); 220; 369</td>
<td>Deceased</td>
</tr>
<tr>
<td>9 (M)</td>
<td>75</td>
<td>4950 (2500)</td>
<td>1</td>
<td>0.6 (0.1); 31; 46</td>
<td>4.3 (2.8); 62; 249</td>
<td>Deceased</td>
</tr>
<tr>
<td>10 (M)</td>
<td>84</td>
<td>3960 (2000)</td>
<td>2</td>
<td>0.9 (0.3); 19; 15</td>
<td>29.4 (19.8); 130; 102</td>
<td>Deceased</td>
</tr>
</tbody>
</table>

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase.

Their review highlights the significant differences in toxicity between the adult and pediatric populations of patients with ALL; however, the mean age for the adults in their review was 30 years compared with 49 years in our study.

### Table 6

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yrs</th>
<th>Baseline total bilirubin, mg/dL (direct); AST, U/L; ALT, U/L</th>
<th>Peak total bilirubin, mg/dL (direct); AST, U/L; ALT, U/L</th>
<th>Patient status</th>
</tr>
</thead>
</table>

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase.

The 2 most common toxicities in the patients in our study were hypofibrinogenemia (36%) and hyperbilirubinemia (40%). In the review by Stock and colleagues, the incidence of hypofibrinogenemia (<60 mg/dL) was 16%.\(^8\) The lower incidence in their study may be explained by the differences in definition, because we used <100 mg/dL.

In a study by Beinart and Damon, 93 patients receiving native L-asparaginase at 6000 U/m\(^2\) for induction therapy were analyzed for thrombotic events.\(^21\) Hypofibrinogenemia was defined as <50 mg/dL, and patients were treated with cryoprecipitate when levels fell to <70 mg/dL. Although previous studies have used <100 mg/dL of fibrinogen as their cut-off, Beinart and Damon hypothesized that patients who had severely reduced fibrinogen levels (ie, <50 mg/dL) also had decreased levels of anticoagulant proteins, thereby being at increased risk for thrombotic events.\(^21\) Of the 93 patients in that study, 6 patients experienced a thrombotic event during treatment with L-asparaginase; 3 of them had hypofibrinogenemia. This led the authors to suggest that in patients with ALL receiving asparaginase, fibrinogen levels of <50 mg/dL may be used as a marker for a hypercoagulable state.\(^21\)

No bleeding episodes were seen in any of our patients, suggesting that hypofibrinogenemia is usually not a fatal adverse event and can be managed with swift res-
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The 81-year-old patient who had a peak bilirubin level we have since adopted the practice of not correcting the fibrinogen level unless the level is <60 mg/dL or the patient is bleeding.

In our study population, hyperbilirubinemia was the most severe toxicity seen with pegaspargase. Grade 4 hepatotoxicity associated with hyperbilirubinemia, as defined by the National Cancer Institute (ie, >3 times baseline of bilirubin level), was reported in 10 of our patients. Of these, 3 patients had bilirubin levels elevated to approximately 10 mg/dL, which resolved within 1 to 2 weeks. In all, 3 other patients reached bilirubin levels of ≥25 mg/dL: in 1 patient this was resolved gradually over 1 month, and the other 2 died within 1 week of reaching the peak bilirubin levels (Table 6).

The median age of the 10 patients with hepatotoxicity was 52 years (range, 26-84 years) compared with 43.5 years (range, 21-84 years) for patients who did not have hyperbilirubinemia. Of the 6 patients with a bilirubin level of ≥9.9 mg/dL, all but 1 was aged ≥52 years (range, 26-84 years). Both patients who died from multi-organ failure coinciding with hyperbilirubinemia were elderly (ie, aged 70 years and 84 years).

Two cases of severe and persistent hyperbilirubinemia after receiving pegylated asparaginase were reported in correspondence by Kim.22 The 81-year-old patient who received 1 dose of 2500 U/m² had a peak bilirubin level of 19.5 mg/dL.22 The incidence of hyperbilirubinemia we report is higher than the 24% rate reported by Rytting and colleagues in 92 adults; however, the age range in their population was 14 to 71 years.14 This significant difference may reflect the higher proportion of older patients in our study and/or the dose of pegaspargase that we used. Our findings suggest that patients aged >50 years are at an increased risk for severe hepatotoxicity with this medication, which may be fatal in some patients.

Hypertriglyceridemia, as was seen in our sample in 1 patient, occurs infrequently compared with other toxicities; however, when it is present, it may be severe. Our patient had triglyceride levels in the 8000s mg/dL.

Overall in our study, 17 (68%) patients died—3 deaths were attributed to sepsis, 2 occurred during bone marrow transplantation, 2 resulted from multi-organ failure, and 10 deaths occurred during follow-up from progressing disease. The causes of death could not be ascertained for the 10 patients who died during follow-up. Eligibility criteria, such as age, subtype of disease, time after diagnosis, or even type of treatment regimen, did not exclude any patients from the study. In fact, the treatment regimens in our study were varied, and the patient population was heterogeneous in regard to ALL karyotype, age, and performance status. It should also be noted that most of the patients in our study had relapsed or refractory ALL.

Conclusion

In regard to the safety of pegaspargase, the previous literature has shown mixed outcomes, and many authors conclude that pegaspargase toxicity is infrequently severe and is often manageable by supportive care. In our study, 2 deaths were likely attributable to treatment with pegaspargase. Both patients were elderly, had hyperbilirubinemia, and had subsequent sepsis and/or multi-organ failure. One patient had severe acute pancreatitis and hypertriglyceridemia that was managed and resolved with the use of a single plasmapheresis and gemfibrozil. Hypofibrinogenemia remains a frequent toxicity of pegaspargase that can be well managed with the administration of cryoprecipitate and rarely leads to hemorrhagic events. Hypersensitivity occurred in a single patient and was drastically less frequent than was
Our study findings suggest that patients treated with pegaspargase should be closely monitored for side effects and should be managed according to guidelines from the National Comprehensive Cancer Network and those recommended by Stock and colleagues.8

Our study findings suggest that patients treated with pegaspargase should be closely monitored for side effects and should be managed according to guidelines from the National Comprehensive Cancer Network8 and those recommended by Stock and colleagues.4 Dose reduction, especially in the elderly, may be warranted, although controlled trials are needed to confer equal efficacy with lower doses. An awareness of the potential for significant hepatotoxicity, especially in patients aged >50 years, should be noted.  

Author Disclosure Statement
Dr Ippoliti is on the Speaker’s Bureau of Merck and Sigma Tau Pharmaceuticals; Dr Patel has no conflicts of interest to report.

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