Clinical profile and treatment outcomes in patients with hereditary angioedema with normal C1 esterase inhibitor

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ABSTRACT

Background: Hereditary angioedema (HAE) is often caused by low serum levels or functional deficiency in C1 inhibitor (C1-INH); however, in some cases, C1-INH serum level and function are measured as normal (HAE-nl-C1INH). Management of HAE-nl-C1INH is similar to management of HAE with C1-INH deficiency, including on-demand therapy for angioedema attacks and, potentially, prophylaxis. Recombinant human C1 esterase inhibitor (rhC1-INH) is indicated for treatment of acute HAE attacks. This study assessed the clinical profile and treatment outcomes in an HAE-nl-C1INH population with a history of rhC1-INH treatment.

Methods: Medical records containing patient-reported outcomes from ten US treatment centers were analyzed retrospectively for medical history, angioedema attack characteristics, attack treatments, and clinical outcomes.

Results: Twenty-three patients were included, with wide US geographic representation. Most patients (87.0%) were female; median age was 36.0 years (range, 19–67 years). Of 20 patients with available data, 4 had their first angioedema attack during childhood (aged <12 years), 3 during adolescence (aged 12–17 years), and 13 during adulthood (aged 18–29 years, n = 7; aged ≥30 years, n = 6). Median age at HAE-nl-C1INH diagnosis was 31.5 years (range, 9–59 years). Previous failed treatments included high-dose antihistamines (n = 20) and corticosteroids (n = 20). Use of US Food and Drug Administration (FDA)-approved HAE therapy positively impacted patient-reported assessments of angioedema attacks. Most patients were taking rhC1-INH or lanadelumab as prophylaxis and icatibant or rhC1-INH for acute management. Most patients reported improved disease control with these therapies, including reductions in angioedema attack frequency and severity. Although most patients were receiving prophylactic therapy, availability of treatment for breakthrough attacks was important.

Conclusion: Findings from this retrospective study support use of FDA-approved HAE medications for prophylaxis and acute treatment of HAE attacks in patients with HAE-nl-C1INH. Individualized HAE treatment regimens were needed to optimize therapeutic outcomes.
INTRODUCTION

Hereditary angioedema (HAE) is a rare genetic disorder associated with unpredictable episodes of cutaneous and/or submucosal swelling at various anatomic locations including the abdomen, extremities, genitourinary tract, face, larynx, or oropharynx. In most cases, the pathophysiology of HAE has been linked to genetic mutations that affect C1 esterase inhibitor (C1-INH), a key regulator of several proteases involved in the complement and contact systems. There are 2 fundamental types of HAE: HAE due to a deficiency of C1-INH (HAE-C1INH) and HAE with normal C1-INH (HAE-nl-C1INH), with HAE-C1INH subclassified as type I (characterized by deficiency in C1-INH levels and function) and type II (characterized by normal C1-INH levels but diminished functional C1-INH activity). HAE-C1INH (type I and type II), which has an estimated prevalence of 1 in 50,000 individuals, is caused by mutations in the SERPING1 gene. In HAE-nl-C1INH, no mutation in the SERPING1 gene is observed, and protein levels and function of C1-INH are normal.

The prevalence, etiology, and pathophysiology of HAE-nl-C1INH are not well understood. Although some patients have a mutation in a gene that encodes coagulation FXII (F12), plasminogen (PLG), angiotropin 1 (ANGPT1), kininogen 1 (KNG1), myoferlin (MYOF), or heparan sulfate glucosamine 3-O-sulfotransferase 6 (HS3ST6), most HAE-nl-C1INH patients are classified as HAE-unknown (ie, no mutation identified). Dysregulation of the contact system (kallikrein-bradykinin formation) appears to play a role in the pathophysiology of HAE-nl-C1INH, with evidence of higher plasma kallikrein activity in patients with HAE-nl-C1INH versus controls without swelling or patients with idiopathic histaminergic angioedema. Bradykinin release, which is known to mediate angioedema in HAE with C1-INH deficiency, has been implicated in HAE-nl-C1INH associated with mutations in F12, PLG, KNG1, and HS3ST6. Patients with HAE-nl-C1INH tend to experience attacks that are similar to those experienced by patients with type I or type II HAE. However, facial and oropharyngeal involvement are relatively more common in HAE-nl-C1INH, and mortality related to asphyxiation has been reported. Patients with symptomatic HAE-nl-C1INH are predominantly women, and the typical onset of symptoms is during late adolescence or early adulthood. In many women with HAE-nl-C1INH, estrogen exposure is associated with HAE symptom onset.

Management of patients with HAE-nl-C1INH includes on-demand therapy for angioedema attacks (ie, C1-INH products, icatibant, ecallantide) and may include prophylaxis (eg, C1-INH products, lanadelumab). US Food and Drug Administration (FDA)-approved therapies, while not excluding HAE-nl-C1INH patients as part of the indication, were approved based on clinical trial data in patients with HAE type I or type II. Recombinant human C1 esterase inhibitor (rhC1-INH) is one HAE therapy indicated for the treatment of acute attacks in adults and adolescents with HAE in the United States and individuals with HAE aged ≥2 years in the European Union. rhC1-INH has been shown to be efficacious and well tolerated for treatment of attacks in patients with HAE with C1-INH deficiency and also has been investigated as prophylactic therapy in patients with HAE. To date, there have been no randomized, placebo-controlled clinical studies specifically evaluating HAE treatments in a population with HAE-nl-C1INH. As well, there is an unmet need to evaluate the clinical profile of FDA-approved HAE therapies in the clinical practice setting in patients with HAE-nl-C1INH. The aim of this study was to characterize the clinical profile and treatment outcomes of angioedema attacks in an HAE-nl-C1INH population who had a history of treatment with rhC1-INH.
METHODS

In this retrospective study, medical records from 10 US treatment centers were reviewed. These centers, located in Connecticut, Florida, Illinois, Minnesota, North Carolina, Ohio, Texas, Utah, and Washington, provided wide geographic representation across the United States. Any individuals diagnosed with HAE-nl-C1INH who received previous or current treatment with rhC1-INH and had documented patient-reported outcomes in the medical record were eligible for inclusion in the study. Information was extracted from medical records by the authors and/or designated medical staff at the treatment centers via use of a standardized form that included demographics, medical history, angioedema attack characteristics, treatments used to manage attacks, and clinical outcomes. This retrospective chart review used deidentified data from existing medical records; institutional review board approval was not required.

RESULTS

A total of 23 patients with HAE-nl-C1INH were included in the study. Most patients (87.0%) were female; median age was 36.0 years (range, 19-67 years). Surgical histories included hysterectomy (n = 10), appendectomy (n = 8), and cholecystectomy (n = 8). Four female patients reported a history of endometriosis. Of the 20 patients with available data, median age at onset of angioedema was 19.0 years (range, 8-56 years). Thirteen patients had their first attack in adulthood (aged 18-29 years, n = 7; aged ≥30 years, n = 6), 3 during adolescence (aged 12-17 years), and 4 during childhood (aged <12 years). Median age at diagnosis of HAE-nl-C1INH was 31.5 years (range, 9-59 years). Twenty patients had documentation in their medical records of previously failing treatment with high-dose antihistamines; 20 patients had failed corticosteroids to prevent/treat attacks; 3 patients had failed omalizumab, which supports a nonhistaminergic process for angioedema attacks in these patients; and 6 patients had failed tranexamic acid.

Overall, availability and use of an FDA-approved HAE therapy for these 23 patients with HAE-nl-C1INH positively impacted patient-reported assessments of angioedema attacks (Table 1). The majority of patients were receiving lanadelumab or rhC1-INH as prophylaxis and icatibant or rhC1-INH for acute management. Other medications included plasma-derived C1-INH (pdC1-INH) as prophylaxis or acute therapy and ecallantide as acute therapy. Most patients reported improved disease control with FDA-approved therapies, including reductions in attack frequency and severity. However, treatment regimens and outcomes varied widely. Although most patients were receiving prophylactic therapy (eg, lanadelumab), all patients had acute treatment for breakthrough attacks available.

DISCUSSION

Findings from this retrospective study support that management strategies used to treat patients with type I or type II HAE (ie, prophylactic and/or on-demand [acute] medications) may be beneficial in a population with HAE-nl-C1INH. However, the regimens and outcomes varied widely, reinforcing that individualized treatment regimens are needed to optimize therapeutic outcomes in patients with HAE-nl-C1INH. Furthermore, consistent with treatment guidelines for HAE,2 availability of acute therapies for angioedema attacks was necessary for these patients with HAE-nl-C1INH, regardless of whether or not prophylactic agents were administered.

To our knowledge, this is the first published study on the use of rhC1-INH as part of an overall management strategy in patients with HAE-nl-C1INH. Inclusion of therapies previously studied for the treatment of patients with HAE type I or type II resulted in improved clinical response, including reductions in the frequency and severity of HAE attacks in the current HAE-nl-C1INH population. Several patients obtained therapeutic benefit from FDA-approved HAE therapies after previous use of a different approved agent failed to provide adequate improvement or resulted in adverse events that limited tolerability. This finding emphasizes the need for an individualized treatment approach, as recommended in HAE treatment guidelines.2 Observational data have been published for several FDA-approved HAE therapies. Acute treatment with pdC1-INH reduced attack duration in a subgroup analysis comparing treated versus untreated attacks in 11 patients with...
| Patient | Patient Sex (Age) | C1-INH, mg/dL | C4, mg/dL | C1-INH Function, % | Surgical History and Comorbidities | Previous tx | Current Prophylaxis | Current tx for Acute Attacks | Patient-Reported Outcomes Prior to Current tx | Patient-Reported Outcomes After Current tx |
|---------|-------------------|---------------|------------|-------------------|-----------------------------------|-------------|-------------------|-----------------------------|---------------------------------------------|---------------------------------------------|
| 1       | Female (40 y)     | 26            | 17         | >100              | Cholecystectomy, several endoscopies, TAH | pdC1-INH and icatibant | Lanadelumab | rhC1-INH | Abdominal and throat attacks 1-2 times/wk | Better control; 1-2 attacks/mo |
| 2       | Female (63 y)     | 42            | NR         | >100              | Cholecystectomy, partial hysterectomy, rheumatoid arthritis, thyroidectomy | pdC1-INH or rhC1-INH q 3 d for prophylaxis; icatibant for acute therapy | Lanadelumab | Icatibant | – | Better control with lanadelumab; icatibant used 1 time/mo |
| 3       | Female (36 y)     | NR            | 24         | 121               | Cholecystectomy, several endoscopies, hysterectomy, Nissen fundoplication | Reaction to rhC1-INH; allergy test negative; SC pdC1-INH and ecallantide/ icatibant | pdC1-INH | Ecallantide/ icatibant | Mostly uncontrolled | Mostly controlled |
| 4       | Female (21 y)     | 20            | 39         | >100              | Appendectomy | NR | Lanadelumab weekly | Ecallantide/ icatibant | Effective prophylaxis during first 7-8 d; then, acute tx required daily until next lanadelumab dose | Lanadelumab dosing changed to weekly and acute therapy q 2-3 d |
| 5       | Female (33 y)     | 29            | 30         | 117               | Appendectomy, cholecystectomy, endometriosis, several exploratory laparoscopies, TAH, tonsillectomy | NR | Lanadelumab | Icatibant/ rhC1-INH | 1-2 attacks/wk | 1-2 attacks/mo |
| 6       | Female (26 y)     | 28            | 26         | 96                | Endometriosis, hysterectomy | pdC1-INH and ecallantide for acute therapy; icatibant not used due to severe abdominal pain | rhC1-INH | None | Attacks 3-4 times/mo | 1-2 attacks q 6-8 wk |
| Patient | Patient Sex (Age) | C1-INH, mg/dL | C4, mg/dL | C1-INH Function, % | Surgical History and Comorbidities | Previous tx | Current Prophylaxis | Current tx for Acute Attacks | Patient-Reported Outcomes |
|---------|------------------|---------------|-----------|-------------------|-----------------------------------|-------------|-------------------|---------------------------|--------------------------|
| 7       | Female (54 y)    | 32            | 49        | 110               | Diverticulitis, hypothyroid, hysterectomy | Icatibant/pdC1-INH | rhC1-INH | Icatibant         | Severe laryngeal/facial swelling requiring ICU admittance/ intubation; 13 severe attacks, 9 requiring hospitalization, 2 requiring intubation | Well controlled; no ED visits |
| 8       | Female (41 y)    | 18            | 22        | 100               | Appendectomy, endometriosis, hypothyroid, hysterectomy | Failed icatibant and lanadelumab | pdC1-INH/rhC1-INH | rhC1-INH | 12 hospitalizations during tx | Attacks once weekly |
| 9       | Male (62 y)      | 37            | 35        | >90               | NR                                 | NR | None | rhC1-INH | Facial/finger attacks >2 times/wk | Attacks twice weekly |
| 10      | Male (67 y)      | NL            | NL        | NR                | Hypogamma-globulinemia              | NR | None | rhC1-INH | Facial and laryngeal swelling; 1-2 times/mo | Swelling decreased in 2 h; resolution in 4-6 h |
| 11      | Female (31 y)    | 31            | 20        | >100              | Migraines, sinus surgery           | Icatibant provided minimal, temporary relief; lanadelumab stopped due to lack of efficacy | pdC1-INH | rhC1-INH/pdC1-INH | Attacks occurring once per wk; ED visits q 1-2 mo | C1-INH products provided more definite relief; attack frequency decreased on pdC1-INH prophylaxis |
| 12      | Female (53 y)    | 50            | 23        | >100              | Diverticulitis, GERD, hysterectomy, IBS, migraines | pdC1-INH/ecallantide/icatibant | rhC1-INH | Icatibant | Abdominal, tongue, peripheral attacks occurring q 4 d, with 50% of attacks requiring second ecallantide dose | Attacks controlled “more so than previous regimens” |

(continued)
| Patient | Patient Sex (Age) | C1-INH, mg/dL | C4, mg/dL | C1-INH Function, % | Surgical History and Comorbidities | Previous tx | Current Prophylaxis | Current tx for Acute Attacks | Patient-Reported Outcomes
|----------|------------------|--------------|----------|-------------------|-----------------------------------|-------------|---------------------|-----------------------------|-----------------------------
| 13       | Female (43 y)    | NR           | NR       | 91                | Appendectomy, cholecystectomy     | Icatibant 1–2 times/d and ecallantide 1 time/wk (in office) | rhC1-INH    | Icatibant            | Abdominal/throat attacks    | Well controlled; decreased attack frequency and severity |
| 14       | Female (40 y)    | NR           | NR       | NR                | Endometriosis, GERD, hysterectomy, IBS, migraines | Pt believed pdC1-INH tx caused attacks | rhC1-INH    | Icatibant            | –                           | Attacks less severe vs prior episodes |
| 15       | Male (19 y)      | 33           | 15       | 86                | Autism (mild)                      | NR          | Danazol             | rhC1-INH                     | Good clinical response, 1 attack q 1–2 mo |
| 16       | Female (21 y)    | 41           | 30       | >100              | Adenoidectomy, appendectomy, neurocardiogenic syncope, tonsillectomy | NR          | rhC1-INH twice weekly | rhC1-INH                     | Very good clinical response, 1 attack q 10–14 d |
| 17       | Female (24 y)    | 31           | 22       | >100              | Several abdominal exploratory surgeries, anxiety, appendectomy, cholecystectomy, CVID, depression, EDS, GERD, IBS, POTS | NR          | None (intolerant to tranexamic acid) | rhC1-INH                     | Good clinical response, occasional use of rhC1-INH |
| 18       | Female (22 y)    | 26           | 24       | >100              | Dizziness/syncope, migraines, urticaria | NR          | Lanadelumab         | rhC1-INH                     | Good clinical response; symptoms 1 time/wk |
| Patient | Patient Sex (Age) | C1-INH, mg/dL | C4, mg/dL | C1-INH Function, % | Surgical History and Comorbidities | Previous tx | Current Prophylaxis | Current tx for Acute Attacks | Patient-Reported Outcomes |
|---------|------------------|---------------|-----------|-------------------|------------------------------------|-------------|---------------------|-----------------------------|--------------------------|
| 19      | Female (22 y)    | 25            | 9         | 80                | EDS, May Thurner syndrome, nutcracker syndrome, POTS | NR          | Lanadelumab         | rhC1-INH                    | Attacks affecting face, extremities, abdomen; 2-3 attacks/wk | Good clinical response; 1-2 attacks/mo |
| 20      | Female (19 y)    | 40            | 25        | >100              | Appendectomy, diabetes mellitus type 1, EDS, hypogammaglobulinemia, hystectomy, ileostomy, oophorectomy, POTS | NR          | NR                  | rhC1-INH                    | Recurrent attacks (2/wk) affecting extremities | Good clinical response; lost to follow up |
| 21      | Female (39 y)    | 34            | 36        | 89                | Tonsillectomy                      | None        | Lanadelumab/rhC1-INH| Icatibant                   | Multiple attacks/wk affecting face and periphery | Variable attack rate (1-2/wk to 1-2/mo) |
| 22      | Female (61 y)    | 35            | 39        | NR                | Cholecystectomy, GERD, exploratory laparotomy | pdC1-INH and rhC1-INH | Lanadelumab         | Icatibant                   | Icatibant required 2-3 times/mo | Attacks 1-2 times/mo |
| 23      | Female (27 y)    | 36            | 29        | >92               | Appendectomy, cholecystectomy, EDS, hypogammaglobulinemia, May Thurner syndrome, nutcracker syndrome, POTS | NR          | NR                  | Icatibant                   | Recurrent attacks affecting extremities; treated at times for idiopathic anaphylaxis with some relief; attacks several times a week | Clinical response, attacks 1-2 times/mo |

Table 1. Clinical profile, treatment, and patient-reported outcomes. *Normal range in adults typically 10 or 14 mg/dL to 40 or 44 mg/dL. **Normal range, >67%. ***C1q = 1.6 μg Eq/mL (normal range, <3.9 μg Eq/mL). C1-INH, C1 esterase inhibitor; CVID, common variable immunodeficiency; ED, emergency department; EDS, Ehlers-Danlos syndrome; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; ICU, intensive care unit; NL, normal; NR, not reported; pdC1-INH, plasma-derived C1 esterase inhibitor; POTS, postural orthostatic tachycardia syndrome; pt, patient; rhC1-INH, recombinant human C1 esterase inhibitor; SC, subcutaneous; TAH, total abdominal hysterectomy; tx, treatment
HAE-nl-C1INH.\textsuperscript{37} In a pdC1-INH registry analysis of data for 38 attacks in 21 patients with HAE-nl-C1INH and mutations in the F12 gene (HAE-FXII), symptomatic improvement was seen within 60 min post-treatment in most attacks.\textsuperscript{38} In a retrospective study of 57 patients with HAE-FXII, similar efficacy was reported for pdC1-INH and icatibant in the acute treatment of HAE attacks.\textsuperscript{20} Findings from an icatibant registry (HAE-nl-C1INH, \(n = 22\); HAE type I, \(n = 153\)\textsuperscript{39} and a single-center, prospective, open-label study (HAE-nl-C1INH, \(n = 25\); HAE type I, \(n = 19\)\textsuperscript{40}) support the effectiveness of icatibant in the acute treatment of attacks in patients with HAE-nl-C1INH, although time to resolution of an attack was substantially longer in patients with HAE-nl-C1INH versus HAE type I and patients with HAE-nl-C1INH were more likely to require more than one dose of icatibant. A case report of an adolescent with HAE-nl-C1INH reported successful use of ecallantide for an attack.\textsuperscript{41} Although tranexamic acid has had limited benefit in patients with HAE type I or type II,\textsuperscript{6} it has appeared to provide benefit as prophylaxis in some patients with HAE-nl-C1INH.\textsuperscript{20,37,42,43}

The mechanisms of HAE in patients with normal C1-INH are not well characterized, but may involve inhibition of complement or contact pathways and/or specific genetic mutations.\textsuperscript{4} Regardless of the specific mutation, it has been shown that these patients have overactivity of the contact system; therefore, C1-INH replacement therapy is a reasonable treatment to inhibit the production of bradykinin.\textsuperscript{4,44,45} The use of medications proven effective for HAE with C1-INH deficiency is a logical therapeutic approach in HAE-nl-C1INH, as there appear to be common mediators in the contact system (ie, bradykinin release).\textsuperscript{4,6,46}

Consistent with previous research on HAE-nl-C1INH,\textsuperscript{15,18,20,38,39,43} the patient population in the present study was primarily female, and disease onset occurred by early adulthood in the majority of patients. There was a delay of >10 years, on average, between HAE symptom onset and diagnosis. A timely diagnosis of HAE-nl-C1INH is important, as the lack of an accurate diagnosis can leave patients struggling for years with unexplained and untreated symptoms, which may lead to secondary issues, such as depression and anxiety. However, accurate diagnosis of HAE-nl-C1INH is difficult due to the lack of specific diagnostic tests or biomarkers.\textsuperscript{4,47} In the absence of an identified genetic mutation, a family history of recurrent angioedema and failure to respond to high doses of antihistamines during an angioedema attack may be considered by an HAE specialist to aid in the diagnosis of HAE-nl-C1INH.\textsuperscript{2} In some patients with a partial response to high-dose antihistamines, additional mast cell targeted therapy (eg, omalizumab) may be warranted.\textsuperscript{2} In the current study, most patients had failed to respond to antihistamines and/or omalizumab prior to treatment with rhC1-INH.

Patients in the current study experienced HAE attacks involving a wide range of anatomic locations, including the abdomen, extremities, face, and tongue, as has been reported in patients with HAE with C1-INH deficiency.\textsuperscript{4,15,19} Historically, some patients with abdominal attacks of angioedema have experienced unnecessary abdominal surgeries related to painful and disabling symptoms of an attack.\textsuperscript{48,49} Of note, a substantial percentage of patients in the current study had a medical history of some form of abdominal surgery (eg, hysterectomy, oophorectomy, appendectomy, cholecystectomy). In some women with HAE-nl-C1INH, attacks may be triggered or exacerbated by high estrogen levels.\textsuperscript{18-20} Therefore, avoidance of exogenous estrogens (eg, oral contraceptives, hormone replacement therapy) is an important first step in the management of HAE-nl-C1INH.\textsuperscript{2,50}

Limitations of the current study include the diagnosis of HAE-n1-C1INH being determined previously by individual clinicians and not standardized as a part of the inclusion criteria, bias related to sampling, the small sample size, and the open-label and retrospective design. There are also inherent limitations in any retrospective study design, including lack of standardization in reporting of clinical features, timing and dosing of therapy administration, and outcome measures. In addition, clinical outcomes in this case series were subjective, with quantification of improvement limited.
CONCLUSION

This study affirms that FDA-approved HAE therapy may be beneficial in patients with HAE-nl-C1INH and should be considered as part of an individualized patient management strategy. This includes the availability of acute therapies for angioedema attacks, regardless of whether or not prophylactic agents are administered. Further refinements are needed in the definition of HAE-nl-C1INH, along with research on diagnostic indicators. In addition, further studies in patients with HAE-nl-C1INH are warranted to compare efficacy of therapies, and possible differential response by subtype.

Abbreviations
ANGPT1, angiopoietin 1; C1-INH, C1 inhibitor; FDA, US Food and Drug Administration; HAE, hereditary angioedema; HAE-FXII, HAE-nl-C1INH and mutations in the F12 gene; HAE-nl-C1INH, hereditary angioedema with normal C1 inhibitor serum levels and function; HS3ST6, heparan sulfate glucosamine 3-O-sulfotransferase 6; KNG1, kinogen 1; MYOF, myoferlin; pdC1-INH, plasma-derived C1 esterase inhibitor; PLG, plasminogen; rhC1-INH, recombinant human C1 esterase inhibitor.

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Availability of data and materials
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Ethics, consent, and permissions statement
This study was conducted at multiple sites in the United States. Because data were obtained by retrospective extraction of deidentified patient information contained in medical records, IRB approval and written informed consent were not obtained.

Author contributions
All authors were involved in data acquisition, analysis, and interpretation, drafting the manuscript, and critically revising the manuscript. All authors approved the final manuscript. The sponsor was involved in the study design and reviewed the manuscript for medical accuracy but had no decision in the submission of the final manuscript for publication.

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Declaration of competing interest
Douglas H. Jones reports being a consultant for and receiving consulting fees from BioCryst, Pharming Technologies BV, and Takeda Pharmaceutical Company Ltd.

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