The Journal of Emergency Medicine, Vol. 50, No. 4, pp. 567–580, 2016

0736-4679

http://dx.doi.org/10.1016/j.jemermed.2015.11.008

Original Contributions

EFFICACY OF DIFFERENT MEDICAL THERAPIES FOR THE TREATMENT OF ACUTE LARYNGEAL ATTACKS OF HEREDITARY ANGIOEDEMA DUE TO C1-ESTERASE INHIBITOR DEFICIENCY

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☐ **Abstract—Background: Hereditary angioedema (HAE) is a rare disease characterized by C1-esterase inhibitor (C1-INH) deficiency, resulting in periodic attacks of acute edema, which can be life-threatening if they occur in the upper airway. No head-to-head comparisons of different treatment options for acute HAE attacks are available. Because immediate symptom relief is critical for potentially life-threatening laryngeal attacks, it is important to determine the treatment option that provides optimal treatment response. Objective: Review and compare data from clinical studies that evaluated the efficacy and safety of treatments for laryngeal HAE attacks. Methods: We conducted an indirect comparison of clinical outcomes from prospective studies for treatment of 881 acute laryngeal attacks with plasma-derived C1-INH concentrate (pdC1-INH) at fixed doses (500 or 1000 U) or a body weight-adjusted dose (20 U/kg), recombinant C1-INH concentrate at a fixed dose (2100 U), or a body weight-adjusted dose (50 U/kg), icatibant (30 mg), or ecallantide (30 mg). Comparisons included time to onset of symptom relief and need for re-dosing or emergency procedures. Results: The median time to onset of symptom relief ranged between 15 min and approximately 2 h, and was shortest with body weight-adjusted doses of pdC1-INH. The proportion of laryngeal attacks with re-dosing ranged between 0% and 72%. No re-dosing was needed after treatment with a single body weight-adjusted dose of pdC1-INH (48 attacks). Conclusions: Available data suggest that among different HAE treatments, body weight-adjusted pdC1-INH (20 U/kg) provides the most reliable treatment response for treatment of laryngeal HAE attacks.** © 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

☐ **Keywords—C1-INH; efficacy; HAE; laryngeal; re-dosing**

INTRODUCTION

Hereditary angioedema (HAE) due to C1-esterase inhibitor (C1-INH) deficiency (HAE–C1-INH, hereafter called HAE) is a rare autosomal dominant disorder caused by reduced expression of normal C1-INH (type I HAE) or expression of less functional C1-INH (type II HAE) (1,2). Patients with HAE experience intermittent episodic swellings that may affect the skin or

Konrad Bork is a consultant of CSL Behring, Shire, and ViroPharma. He has not received compensation for his work on this manuscript. Jonathan A. Bernstein and Timothy J. Craig are speakers/consultants of CSL Behring, Dyax, Shire, and ViroPharma, and have received financial support for research from CSL Behring, ViroPharma, Pharming, Shire, and Dyax. They have not received compensation for their work on this manuscript. Thomas Machnig is an employee of CSL Behring.

No institutional review board approval was required for this study.

Received: 18 August 2015;
Accepted: 10 November 2015

gastrointestinal tract and are potentially life-threatening in case of laryngeal attacks. Clinical symptoms of laryngeal attacks include hoarseness, stridor, dyspnea, the feeling of having a lump in the larynx, dysphagia, and voice change (3). Although laryngeal attacks are rare (approximately 1% of HAE attacks), at least 50% of patients with HAE experience a laryngeal attack at least once in their lifetime (3). Mortality of 14% to 33% due to untreated and unrecognized laryngeal attacks has been reported, highlighting the importance of early diagnosis of HAE and providing patients with appropriate treatment for potentially life-threatening HAE attacks (4,5).

International consensus guidelines recommend plasma-derived C1-INH concentrate (pdC1-INH; Berinert® [CSL Behring, King of Prussia, PA] or Cinryze® [Shire, Lexington, MA], at fixed doses of 1000 U and body weight-adjusted doses of 20 U/kg) or recombinant C1-INH concentrate (rhC1-INH, Ruconest® [Salix Pharmaceuticals, Inc., Raleigh, NC]), bradykinin B2 receptor antagonist icatibant (Firazyr® [Shire]), or kallikrein inhibitor ecallantide (Kalbitor® [Dyax Corp., Burlington, MA]) for the treatment of acute HAE attacks (6–10).

To date, no head-to-head comparisons of the efficacy and safety of different treatment options for acute HAE attacks are available. Because fast response to treatment is especially important for potentially life-threatening laryngeal attacks, we reviewed and compared available data from clinical studies on treatment of laryngeal attacks that evaluated the efficacy and safety of different treatment options for the rare but potentially life-threatening cases of laryngeal attacks. Comparisons include efficacy in terms of treatment response and need for re-dosing.

METHODS

Search Methods and Data Collection

Reports on the treatment of laryngeal attacks with licensed HAE treatments (see Table 1) were identified by a systematic database search in PubMed and EMBASE in May 2015. The full search strategies are provided in Appendix 1 (available online). In addition, we searched the Internet, specifically, publications listed in clinicaltrials.gov for completed HAE studies (as of April 2015) and Web sites of regulatory agencies. Titles and abstracts from electronic databases and publications associated with completed HAE studies in clinicaltrials.gov were examined for eligibility. We obtained the full text of all relevant records. Data extracted on treatment of laryngeal attacks in patients with HAE type I or II with different treatments included efficacy endpoints, the need for re-dosing, and the need for emergency procedures (e.g., intubation).

Assessment of Risk of Bias

The risk of selective outcome reporting was assessed based on the process described by Dwan et al. for all relevant studies identified in the systematic literature search (11). For each study, we extracted results for the outcomes used in this comparison of treatment options for laryngeal attacks. Outcomes that were not fully reported but may have been assessed based on the reported methods were highlighted. The assessment of

Table 1. Treatment Options for Acute HAE Attacks

Trade Name (Manufactured for)	Active Substance	Licensed for	Recommended Dose & Route of Administration
Berinert® (CSL Behring)	Human pasteurized, nanofiltered pdC1-INH	Europe: acute treatment & short-term prophylaxis US: acute treatment only	20 U/kg, intravenous
Cinryze® (ViroPharma)	Human pasteurized, nanofiltered pdC1-INH	Europe: acute treatment & prophylaxis US: prophylaxis only	1000 U, intravenous
Ruconest® (Pharming)	rhC1-INH	Acute treatment (not for treatment of laryngeal attacks in the US)	50 U/kg,* intravenous (≥84 kg: 4200 U)
Firazyr® (Shire)	Icatibant, bradykinin 2 receptor antagonist	Acute treatment	30 mg,† subcutaneous
Kalbitor® (Dyax)	Ecallantide, kallikrein inhibitor	Acute treatment (US only)	3 × 10 mg,‡ subcutaneous

HAE = hereditary angioedema; pdC1-INH = plasma-derived C1-esterase inhibitor concentrate; rhC1-INH = recombinant C1-esterase inhibitor concentrate; US = United States.

* In case of insufficient clinical response, an additional dose can be administered. Not more than two doses should be administered within 24 h.

† In case of insufficient relief or recurrence of symptoms, additional injections may be administered at intervals of at least 6 h. No more than 3 injections should be administered within 24 h.

‡ If attack persists, an additional dose may be administered within 24 h.