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Recombinant human C1 esterase inhibitor for hereditary angioedema attacks: A European registry

Anna Valerieva[a]*, Maria T. Staevska[a], Vesna Grivcheva-Panovska[b], Milos Jesenak[c], Kinga Viktória Kőhalmi[d,e,f], Katarina Hrubiskova[g], Andrea Zanichelli[h], Luca Bellizzi[i], Anurag Relan[j], Roman Hakl[k] and Henriette Farkas[d]

ABSTRACT

Background: Hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency (C1-INH-HAE) is characterized by recurrent swelling attacks. A European treatment registry was established to review the adverse event profile and efficacy of recombinant human C1 esterase inhibitor (rhC1-INH) for HAE attacks.

Methods: Individuals with C1-INH-HAE were enrolled following a decision to treat with rhC1-INH and provision of written informed consent. Medical history and baseline HAE information were collected at screening. Healthcare providers entered data on HAE attacks, response to treatment, and adverse events using a web-based questionnaire.

Results: From July 1, 2011, through December 1, 2019, 71 patients with C1-INH-HAE (30 male/41 female; mean age, 47.3 years; age range, 19–78 years) in 9 countries reported 2356 attacks and were treated with rhC1-INH. Before registry entry, patients, including 20 (28.2%) who were on maintenance therapy/prophylaxis at registry enrollment, experienced a mean of 25 HAE attacks per year (median, 16 [range, 0–185]). Most treated HAE attacks were abdominal (46.1%), followed by peripheral (38.3%), oro-facial-pharyngeal (14.8%), urogenital (3.2%), and laryngeal (2.6%). The mean rhC1-INH dose was 3307 U (43.3 U/kg). Patients reported symptom improvement within 4 h for 97.8% of attacks (2305/2356) with rhC1-INH; most attacks (99.8%; 2351/2356) required only 1 dose. Five attacks were treated with a second dose (total rhC1-INH dose administered for attack, 4200 U). No hypersensitivity, thrombotic/thromboembolic events, or drug-related serious adverse events were reported.

Conclusion: The rhC1-INH treatment registry provided real-world data on the treatment of 2356 HAE attacks that were consistent with clinical trial data of rhC1-INH in patients with C1-INH-HAE.

Keywords: Angioedema, Hereditary, Complement C1 inhibitor protein, Recombinant human C1 esterase inhibitor, Registry, Ruconest

[a]Department of Allergology, Medical University of Sofia, Sofia, Bulgaria
*Corresponding author. E-mail: anna.valerieva@gmail.com
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INTRODUCTION

Hereditary angioedema (HAE) due to C1 esterase inhibitor (C1-INH) deficiency (C1-INH-HAE) is a rare condition estimated to affect approximately 1 in 50,000–67,000 individuals and is characterized by episodes of disabling and painful swelling.[1,2] These attacks can vary in severity from mild to severe or life-threatening and affect a variety of tissues, including those of the extremities, face, abdomen, and upper respiratory airways.[2] Symptoms generally begin in childhood and persist unpredictably throughout a patient's lifetime.[2] Therefore, it is necessary for a patient with C1-INH-HAE to always be prepared to treat HAE attacks. Guidelines from the World Allergy Organization and European Academy of Allergy and Clinical Immunology recommend that on-demand therapy be available for patients with C1-INH-HAE.[3]

Ruconest® (Pharming Technologies BV, Leiden, the Netherlands) is a recombinant human C1 esterase inhibitor (rhC1-INH) approved as an intravenous injection in multiple locations, including countries in Europe and the United States, for the treatment of acute HAE attacks in adolescents and adults with C1-INH-HAE.[4,5] As well, the indication was updated in the European Union in 2020 to include treatment of acute HAE attacks in children aged ≥2 years.[5] Clinical trial data[6–11] and observational studies[12,13] have shown rhC1-INH to be efficacious and well tolerated. Prescribing information for treatment of HAE attacks recommends weight-based dosing of rhC1-INH (<84 kg, 50 U/kg; ≥84 kg, 4200 U).[4,5] In addition, rhC1-INH has been investigated in a phase 2 study as long-term prophylaxis[14] and in a case series[15] and a prospective study[16] as short-term prophylaxis in patients with HAE. Since first approval of rhC1-INH, >100,000 vials have been provided globally to patients with HAE, supporting its safety profile.

In rare diseases, registries can be powerful tools for measuring postmarketing safety and efficacy outcomes of products and potentially improving patient care.[17,18] To further understand real-world outcomes with rhC1-INH, a multinational, observational registry was established in Europe to evaluate single and repeated treatment of HAE attacks with rhC1-INH.

METHODS

A prospective, noninterventional treatment registry was established for patients with C1-INH-HAE. Enrollment was initially restricted to patients aged ≥18 years; in 2017, the protocol was amended to include patients aged ≥12 years. Patients with C1-INH-HAE were enrolled following a decision to treat with rhC1-INH and after provision of written informed consent; for adolescents, written informed consent was co-signed by a parent or legal guardian and/or a separate assent form was signed. Because of the process for manufacturing rhC1-INH, patients were questioned about any prior exposure to rabbits and signs and symptoms suggestive of an allergic reaction. Exclusion criteria were acquired C1-INH deficiency, hypersensitivity to rhC1-INH, and known or suspected allergy to rabbits. The study protocol was conducted according to local laws and regulations and in accordance with the Declaration of Helsinki. The protocol was approved by the European Medicines Agency Pharmacovigilance Risk Assessment Committee.

Demographic information, medical history, and baseline HAE information (eg, time since diagnosis, frequency of previously treated attacks, use of prophylactic medication) were collected at a screening visit. Treatment decisions were at the discretion of the healthcare provider (HCP) involved in the patient's care according to their standards for the management of C1-INH-HAE and in line with the approved rhC1-INH summary of product characteristics. Following treatment with rhC1-INH, the HCP used a web-based questionnaire to enter data about the HAE attack (date, time, anatomical location), treatment (date, time, dose, administration [HCP or patient/non-HCP caregiver], any medication errors [if non-HCP administration]), patient-reported response to therapy within 4 h (timeframe chosen based on rhC1-INH clinical trial efficacy data[6–11] and other acute treatment studies[19–21]), and any adverse events (AEs). If clinical symptoms following rhC1-INH treatment suggested a potential immune response (eg, type I or type III hypersensitivity reaction, suspected reduced efficacy caused by neutralizing antibodies), the HCP could request immunologic evaluation using a central laboratory.

The primary endpoint of the study was incidence of AEs and insufficient efficacy reported after single or repeated treatment with rhC1-INH. Secondary endpoints were incidence of positive immunologic test findings, and AEs and medication errors related to self-administration. Data were summarized using descriptive statistics and analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

From July 1, 2011, through December 1, 2019, 71 patients with C1-INH-HAE (Table 1) in 9 countries (Bulgaria [n = 22], Croatia [n = 1], Czechia [n = 8], Hungary [n = 5], Italy [n = 5], North Macedonia [n = 11], Norway [n = 1], Poland [n = 3], and Slovakia [n = 15]) reported 2356 HAE attacks (range, 1–272 attacks per patient) and were treated with rhC1-INH within the registry. A slightly larger percentage of females (57.7%) were enrolled. The mean age of the patients was 47.3 years (range, 19–78 years), and the mean age at HAE diagnosis was 27 years (range, 3–70 years). At enrollment, the 71 patients had experienced a mean of 25 HAE attacks in the previous year, and 20 patients (28.2%) were receiving prophylaxis/maintenance therapy. Reasons patients provided for choosing rhC1-INH treatment were: current treatment prior to registry enrollment (n = 23), medication efficacy (n = 11), new HAE treatment (n = 7), switch from plasma-derived product (n = 7), experienced an HAE attack (n = 5), medication availability (n = 4), physician recommendation (n = 4), safety concerns with plasma-derived products (n = 3), or other (n = 7).

Characteristic	rhC1-INH (N = 71)
Sex, n (%)	
Male	30 (42.2)
Female	41 (57.7)
Race, n (%)	
White	71 (100)
Age at HAE diagnosis, y mean (range)	27 (3–70)
Age, y, mean (range)	47.3 (19–78)
Number of yearly attacks before enrollment	
Mean	25
Median	16
Range	0–185
Receiving prophylaxis/ maintenance therapy at enrollment, n (%)	20 (28.2)
Body weight, kg, mean	78.3

Table 1. Patient characteristics. HAE: hereditary angioedema, rhC1-INH: recombinant human C1-esterase inhibitor.

For the 2356 attacks, the most common anatomical location was abdominal (46.1%), followed by peripheral, oro-facial-pharyngeal (OFP), urogenital, and laryngeal (Table 2). Patients (N = 71) had a mean of 33 HAE attacks (median, 24 [range, 1–272]) while participating in the registry and were treated with an rhC1-INH dose of 50 U/kg or with 1 or 2 vials of 2100 U rhC1-INH. The mean rhC1-INH dose for the 1842 attacks that occurred in 49 patients weighing <84 kg was 43.5 U/kg (range, 14–117 U/kg); of these attacks, 740 (40.2%) were treated with rhC1-INH 50 U/kg, and 1102 (59.8%) with 2100 U or 4200 U of rhC1-INH. For the 514 attacks in 22 patients weighing ≥84 kg, the mean dose was 4110.1 U (range, 2100–4200 U); and 22 (4.3%) and 492 (95.7%) of these attacks were treated with an rhC1-INH dose of 2100 U and 4200 U, respectively. There was a similar low frequency of second-dose use for HAE attacks occurring in multiple locations compared with single-location HAE attacks (Table 3). There were no reports of medication errors for HAE attacks with available data on self/caregiver rhC1-INH administration.

Patients reported symptom improvement within 4 h in 2305 (97.8%) of the 2356 attacks, and treatment response was similar across attack locations (abdominal, 97.3%; peripheral, 98.1%; OFP, 97.1%; urogenital, 97.4%; and laryngeal, 95.2%). In addition, response rates were high and generally similar for HAE attacks in patients with body weight <84 kg versus ≥84 kg (Fig. 1). Of the 51 HAE attacks that did not exhibit symptom improvement within 4 h, 25 (49.0%) were in patients weighing <84 kg who were treated with a fixed dose of 1 vial of 2100 U, resulting in an rhC1-INH dose of <50 U/kg (range, 26.6–33.9 U/kg). In addition, 1 of the 51

Attack location, n (%)	All attacks (N = 2356)[a]	First attack (n = 71)[b]	Single-location attacks (n = 2242)
Abdominal	1085 (46.1)	30 (42.3)	1002 (44.7)
Peripheral	903 (38.3)	23 (32.4)	815 (36.4)
OFP	349 (14.8)	16 (22.5)	323 (14.4)
Urogenital	76 (3.2)	3 (4.2)	60 (2.7)
Laryngeal	62 (2.6)	5 (7.0)	42 (1.9)

Table 2. Treated HAE attack locations. HAE: hereditary angioedema, OFP: oro-facial-pharyngeal. *a. Includes 2242 attacks in 1 location, 109 attacks in 2 locations, and 5 attacks in 3 locations. b. Includes 65 attacks in 1 location and 6 attacks in 2 locations.*

All patients (N = 71)	All attacks (N = 2356)	First attack (n = 71)	Single location (n = 2242)	Two locations (n = 109)	Three locations (n = 5)
Dose, mean					
Number of units (U)	3307	3107	3336	2749	2520
U/kg	43.3	40.7	43.6	38.0	35.1
Number of doses, n (%)					
One	2351 (99.7)	70 (98.6)	2239 (99.9)	107 (98.2)	5 (100)
Two	5 (0.2)	1 (1.4)	3 (0.1)	2 (1.8)	0 (0)
Patients <84 kg (n = 49)	**All attacks (n = 1842)**	**First attack (n = 49)**	**Single location (n = 1741)**	**Two locations (n = 96)**	**Three locations (n = 5)**
Dose, mean					
Number of units (U)	3083	2873	3113	2575	2520
U/kg	43.5	42.0	43.9	37.3	35.1
Number of doses, n (%)					
One	1838 (99.8)	48 (98.0)	1738 (99.8)	95 (99.0)	5 (100)
Two	4 (0.2)	1 (2.0)	3 (0.2)	1 (1.0)	0 (0)
Patients ≥84 kg (n = 22)	**All attacks (n = 514)**	**First attack (n = 22)**	**Single location (n = 501)**	**Two locations (n = 13)**	**Three locations (n = 0)**
Dose, mean					
Number of units (U)	4110	3627	4112	4038	–
U/kg	42.7	38.6	43.0	42.5	
Number of doses, n (%)					
One	513 (99.8)	22 (100)	501 (100)	12 (92.3)	–
Two	1 (0.2)	0 (0)	0 (0)	1 (7.7)	

Table 3. rhC1-INH dosing. *During 1 HAE attack, rhC1-INH dosing was limited to 14 U/kg (total dose, 1050 U) because the patient presented with poor venous access; this oro-facial-pharyngeal attack showed improvement within 4 h. Also, during 1 HAE attack, a patient received 3 consecutive vials, recorded as a single treatment, for a total rhC1-INH dose of 117 U/kg.* HAE: hereditary angioedema, rhC1-INH: recombinant human C1-esterase inhibitor

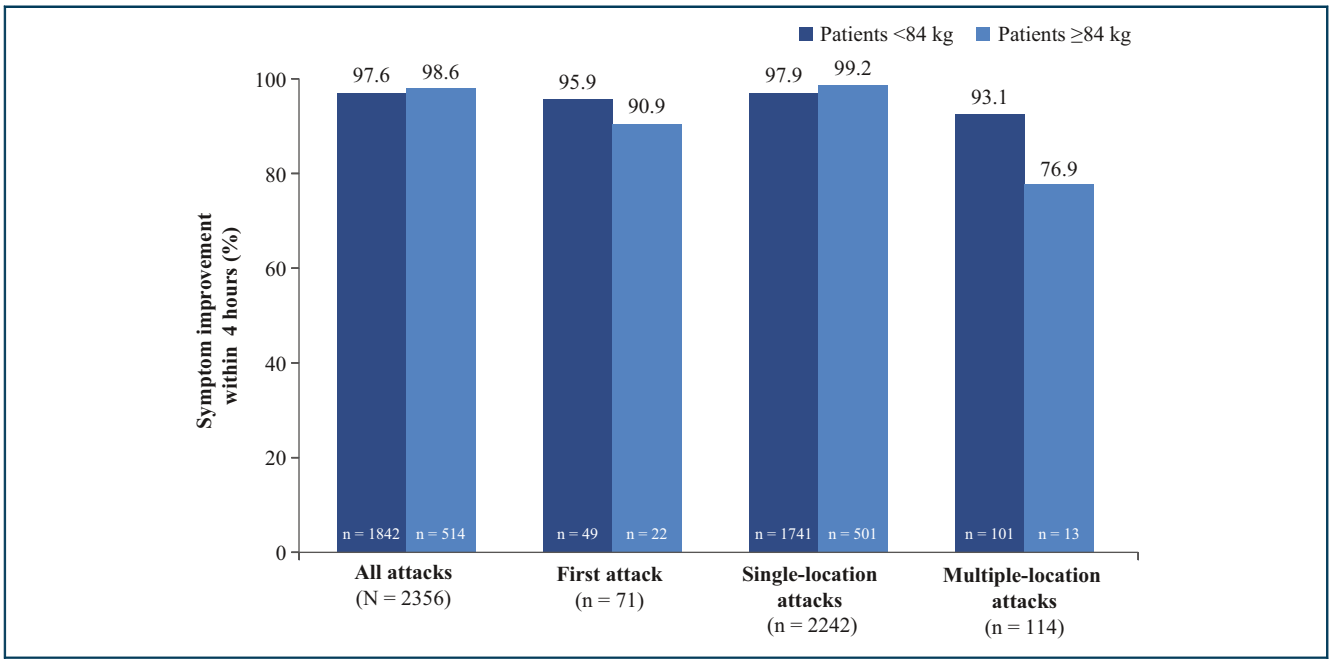

Fig. 1 Patient-reported symptom improvement within 4 h after administration of rhC1-INH. *rhC1-INH: recombinant human C1-esterase inhibitor.*

attacks was in a patient weighing 103 kg who received a fixed dose of 1 vial (2100 U), rather than the recommended dosing of 2 vials (4200 U). Most attacks (99.8%; 2351/2356) were treated with a single dose of rhC1-INH. Five attacks (4 in patients <84 kg and 1 in a patient ≥84 kg) were treated with two rhC1-INH doses (initial dose of 2100 U and second dose of 2100 U). Three of these were for an attack in 1 location, and 2 were for an attack in 2 locations. No hypersensitivity or thrombotic/thromboembolic events were reported. Serious AEs were reported for 5 patients (peripheral vestibular syndrome [n = 1], acute pyelonephritis [n = 1], breast cancer [n = 1], hospitalization due to multiple fractures from an accident [n = 1], laryngeal edema and death [n = 1]); none were considered by study investigators to be related to rhC1-INH treatment. In the case of laryngeal edema and death, a 44-year-old patient presented with an inability to speak and lost consciousness within 2 min of arrival at the hospital. The patient was noted to be cyanotic and not breathing; cardiopulmonary resuscitation was performed. rhC1-INH 4200 U was subsequently administered, and the patient was intubated after 3 attempts when severe laryngeal edema was observed. The patient remained unresponsive and died a few days later.

DISCUSSION

Given the rarity of HAE, patient registries have been established to provide additional clinical practice data on patient profiles and safety and efficacy outcomes of treatments for HAE, including icatibant, which still has an active registry,[22–30] and plasma-derived, nanofiltered C1-INH (pnfC1-INH).[31,32] While some registries have evaluated acute treatment for HAE attacks as well as prophylaxis, the rhC1-INH registry, which is ongoing, is focused on acute treatment of HAE attacks. The current rhC1-INH registry analysis indicates that most (97.8%) of the HAE attacks treated with rhC1-INH had symptom improvement within 4 h, including 94.4% of attacks for which patients received their first treatment with rhC1-INH. The response rate was high across anatomical locations (abdominal, peripheral, OFP, urogenital, laryngeal) and for multi-location as well as single-location attacks. The high percentage of attacks with improvement within 4 h and benefit of rhC1-INH for subsequent HAE attacks are consistent with published rhC1-INH clinical trial data.[6–9] Similarly, in a prospective, real-world study of 21 patients with 544 HAE attacks treated with rhC1-INH (50 U/kg in patients weighing <84 kg and 4200 U in patients weighing ≥84 kg), median time to start of symptom improvement was 60 min

(range, 0–1320 min), and most attacks (96.9%) were treated with a single dose.[16] The treatment response observed in the current analysis is reassuring, given that rhC1-INH was underdosed for some HAE attacks. For example, 38.6% of the HAE attacks in patients <84 kg were treated with an rhC1-INH dose <50 U/kg, which is lower than the recommended dose of 50 U/kg for this weight class.[4,5] In addition, 4.3% of HAE attacks in patients ≥84 kg were treated with only 1 vial (2100 U) of rhC1-INH, also lower than the recommended dose of 4200 U for this weight class.[4,5]

Direct comparisons among registries are difficult because of differences in patient populations and parameters measured. An analysis of the icatibant registry, which evaluated effectiveness based on symptom resolution rather than symptom improvement, found that time to resolution was ≤5 h for 48.1% of HAE attacks, with 9.6% of attacks requiring rescue treatment with C1-INH.[23] The pnfC1-INH registry reported information about safety and usage in patients with HAE, but not response to acute treatment.[31] In the current registry analysis, rhC1-INH was well tolerated, with no safety concerns identified, no medication administration errors reported, and no treatment-related serious AEs observed. Data from the pnfC1-INH registry noted that 1 patient discontinued treatment due to a thromboembolic event deemed to be treatment-related,[31] and data from the icatibant registry showed 3 treatment-related serious AEs (ie, lack of drug efficacy, gastritis, and reflux esophagitis).[30] The current study has several limitations, including lack of a control group, lack of racial diversity, lack of adolescents enrolled in the registry, lack of information related to HAE attack severity and time to complete resolution, a small patient population from which HAE attacks were assessed, and potential for patient selection bias. Furthermore, the reported AEs were dependent on patient recall of the event.

CONCLUSION

The rhC1-INH European registry provides real-world data on the treatment of HAE attacks in adults. These data are consistent with previous reports and support the safety and efficacy of rhC1-INH therapy across multiple attack locations in patients with C1-INH-HAE.

Abbreviations

AE: adverse event; C1-INH: C1 esterase inhibitor; C1-INH-HAE: hereditary angioedema due to C1 esterase inhibitor deficiency; HAE: hereditary angioedema; HCP: healthcare provider; OFP: oro-facial-pharyngeal; pnfC1-INH: plasma-derived, nanofiltered C1 esterase inhibitor concentrate; rhC1-INH: recombinant human C1 esterase inhibitor.

Author consent to publish

All authors agreed to the publication of this work.

Ethics, consent and permissions statement

The study was conducted in multiple sites in 9 countries. The study protocol was conducted according to local law and regulations and in accordance with the Declaration of Helsinki. The protocol was approved by the European Medicines Agency Pharmacovigilance Risk Assessment Committee. All patients provided written informed consent before the initiation of data collection. For patients <18 years of age, written informed consent was co-signed by a parent or legal guardian and/or a separate assent form was signed.

Author contributions

All authors were involved in data acquisition and interpretation, drafting the manuscript, and critical content revisions. Although the sponsor was involved in the design of the study, data collection, and fact-checking of information, the content of this manuscript, the interpretation of the data, and the decision to submit the manuscript for publication were made by the authors independently. All authors approved the final manuscript.

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Availability of data and materials

The registry dataset is not publicly available but may be provided by the sponsor upon a reasonable written request.

Declaration of competing interest

A Valerieva reports serving as a consultant for Pharming Group NV; and receiving symposium sponsorship from Takeda/Shire, Sobi, and CSL Behring. MT Staevska reports receiving consultancy/speaker honoraria from Pharming Group NV and Sobi. V Grivcheva-Panovska reports serving as principal investigator for clinical trials sponsored by Pharming Group NV. M Jesenak reports receiving consultancy/speaker honoraria from CSL Behring, Shire, Sobi, and Takeda Pharmaceutical Co. Ltd.; and serving as a principal

investigator for clinical trials sponsored by BioCryst Pharmaceuticals, Inc. and Pharming Group NV. K Viktória Kőhalmi reports receiving consultancy/speaker honoraria from CSL Behring and Shire. K Hrubiskova reports serving as co-investigator for clinical trial sponsored by Pharming Group NV and receiving consultancy honoraria from Takeda Pharmaceutical Co. Ltd. A Zanichelli reports serving as a consultant for CSL Behring and Shire HGT. L Bellizzi is an employee of Pharming Group NV. A Relan is an employee of Pharming Healthcare Inc. R Hakl reports receiving consultancy/speaker honoraria from CSL Behring, Shire, and Takeda Pharmaceutical Co. Ltd.; and serving as a principal investigator for clinical trials sponsored by BioCryst Pharmaceuticals, Pharming Group NV, and KalVista Pharmaceuticals. H Farkas reports receiving research grants from CSL Behring, Pharming Group NV, and Shire/Takeda; consultancy/speaker fees and honoraria from BioCryst Pharmaceuticals, Inc., CSL Behring, Pharming, and Shire HGT/Takeda; serving as an advisor for these companies, and as a principal investigator for clinical trials/registries for BioCryst, CSL Behring, KalVista, Pharming, and Shire/Takeda.

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Author details
[a]Department of Allergology, Medical University of Sofia, Sofia, Bulgaria. [b]PHI University Clinic of Dermatology, School of Medicine, University Saints Cyril and Methodius, Skopje, Macedonia. [c]University Hospital in Martin, Comenius University in Bratislava, Jessenius Faculty of Medicine, Martin, Slovakia. [d]Hungarian Angioedema Center of Excellence and Reference, Department of Internal Medicine and Haematology, Semmelweis University, Budapest, Hungary. [e]Hospital of Hospitaller Brothers of St. John of God, Budapest, Hungary. [f]Department of Rheumatology and Clinical Immunology, Semmelweis University, Budapest, Hungary. [g]Comenius University in Bratislava and University Hospital, Bratislava, Slovakia. [h]ASST Fatebenefratelli Sacco, Ospedale Luigi Sacco-University of Milan, Milan, Italy. [i]Pharming Technologies BV, Leiden, the Netherlands. [j]Pharming Healthcare Inc., Warren, NJ, USA. [k]St. Anne's University Hospital, Masaryk University, Brno, Czechia.

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