

Immunosafety of Recombinant Human C1-Inhibitor in Hereditary Angioedema: Evaluation of IgE Antibodies

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Abstract

Background Recombinant human C1-inhibitor (rhC1INH) purified from milk of transgenic rabbits is used for the treatment of acute attacks in patients with hereditary angioedema (HAE) due to C1-inhibitor (C1INH) deficiency.

Objective The objective was to investigate the risk of rhC1INH inducing IgE antibodies or eliciting anaphylactic reactions.

Methods In subjects treated with rhC1INH, we retrospectively analysed the frequency and clinical relevance of pre-exposure and potentially newly induced IgE antibodies against rabbit and other animal allergens including cow's milk by the ImmunoCAP® Specific IgE blood test system.

Results 130 HAE patients and 14 healthy subjects received 300 administrations of rhC1INH, 65 subjects (47.4 %) on one occasion; 72 (52.6 %) on at least two occasions (range 2–12; median 2). Five subjects had pre-existing anti-rabbit epithelium IgE; the subject with the highest levels and a previously undisclosed rabbit allergy developed an anaphylactic reaction upon first exposure to rhC1INH, whereas the other four subjects with lower

pre-existing IgE levels (Class 1–3), did not. No other anaphylactic reactions were identified in any of the subjects exposed to rhC1INH. Analysis of post-exposure samples revealed that the risk of inducing new or boosting existing IgE responses to rabbit or cow's milk allergens was negligible.

Conclusion The propensity of rhC1INH to induce IgE antibodies following repeated administration of rhC1INH is low. Subjects with substantially elevated anti-rabbit epithelium IgE antibodies and/or clinical allergy to rabbits may have an increased risk for an allergic reaction. No other risk factors for allergic reactions to rhC1INH have been identified.

1 Introduction

Recombinant human C1-inhibitor (rhC1INH; conestat alfa, Ruconest®, Swedish Orphan Biovitrum AB, Stockholm, Sweden) has been developed for the treatment of acute angioedema attacks in patients with hereditary angioedema (HAE) due to C1-inhibitor (C1INH) deficiency. In two randomized, placebo-controlled studies, rhC1INH was efficacious and well tolerated in patients experiencing HAE attacks [1]. rhC1INH protein is expressed in the milk of transgenic rabbits and has an amino-acid sequence identical to that of endogenous C1INH [2, 3]. After purification, the final rhC1INH product contains <1 ppm rabbit C1INH and <20 ppm impurities that originate from the rabbit host (host-related impurities [HRIs]) [4].

Administration of any therapeutic protein product may lead to an unwanted immune response in the recipient [5, 6]. Among potential responses are reactions mediated by IgE antibodies, which may lead to symptoms ranging from erythema, urticaria, wheezing and bronchospasm to

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life-threatening laryngeal/pharyngeal oedema and anaphylactic shock [7]. IgE-mediated hypersensitivity reactions in principle can be directed against the therapeutic protein itself or against HRIs. Moreover, IgE antibodies can be pre-existing and mediate acute reactions upon first exposure to the product. For example, recombinant human serum albumin (rHSA) produced in the yeast *Pichia pastoris* has been reported to cause hypersensitivity reactions in healthy subjects with pre-existing IgE antibodies to *Pichia* proteins [8]. Administration of a recombinant product can also induce the formation of IgE antibodies and induce allergic reactions upon retreatment.

Here we report the results of a retrospective analysis performed to determine the frequency and clinical relevance of pre-exposure IgE antibodies to rabbit proteins and other potentially relevant animal allergens in subjects administered rhC1INH. The potential of the product to induce IgE antibodies against rabbit and other selected allergens was also investigated.

2 Methods

2.1 Study Designs and Subjects

Data were collected from healthy subjects and patients with HAE due to C1INH deficiency included in eight clinical studies of rhC1INH through September 2008. Participants were excluded from a study if they reported a medical history of allergy to rabbits. Notably, increased levels of IgE against rabbit dander was not an exclusion criterion. Criteria for inclusion and exclusion of patients with HAE have been described elsewhere [1, 9, 10]. rhC1INH was administered intravenously and doses were expressed in units (U) or U per kg body weight with one U defined as the C1INH activity in 1 mL of pooled normal human plasma.

Eight clinical studies were included in the analysis (Table 1). Study 1101 was an open-label dose-escalation study in 12 patients with HAE who were not having an angioedema attack at the time of rhC1INH administration [9]. Patients were exposed twice to rhC1INH at doses ranging from 6.25 to 100 U/kg. Study 1106 was an open-label trial in 14 healthy subjects who were administered up to five doses of 100 U/kg rhC1INH at 3-week intervals. The other six studies assessed rhC1INH as a treatment for acute angioedema attacks in symptomatic HAE patients. The first of these studies was an open-label trial comprising a single-centre phase (1202 [clinicaltrials.gov identifier: NCT00261053]) followed by a multicentre extension phase (1203 [NCT00262288]) [10]. Fourteen patients were included, seven of whom received a repeated

treatment. Treatment consisted of 100 U/kg of rhC1INH. Subsequently, two multicentre, double-blind, randomized, placebo-controlled studies were performed (1205 [NCT0022514] and 1304 [NCT00262301]) in 70 symptomatic HAE patients, 29 of whom received placebo, 12 rhC1INH at 50 U/kg and 29 patients rhC1INH at 100 U/kg [1]. Both randomized studies included an extension phase in which patients received open-label rhC1INH treatment for 155 HAE attacks.

HAE patients treated with saline placebo in the two randomized studies were not included in the analysis unless the patients later received open-label rhC1INH treatment in the study extension phases.

Studies were conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and national regulatory provisions. Study protocols were approved by the ethics committee or institutional review board at each study centre. All subjects provided written informed consent.

2.2 Sample Collection and Handling

Blood samples were collected from subjects at scheduled time-points before and after administration of rhC1INH. For the current analysis, pre-exposure samples taken at study screening visits and post-exposure samples collected 22 and 90 days after the last administration of rhC1INH were used. In some studies, subjects were administered rhC1INH on more than one occasion (Table 1). In the event of repeated administration, the sampling schedule was reset with the day of repeated administration becoming day 0. Samples were collected from subjects as citrated blood, processed and initially stored as aliquots of plasma until IgE testing.

2.3 IgE Antibody Assays

Pre-exposure plasma samples were tested for the presence of IgE antibodies against 14 animal-derived allergens using the ImmunoCAP® Specific IgE blood test system (Phadia AB, Uppsala, Sweden). The allergens tested for were preparations from rabbit dander, rabbit urine, rabbit meat, rabbit serum, cow milk, cow dander, cow meat, guinea pig epithelium, cat dander, dog epithelium, horse dander, hamster epithelium, rat mix and mouse mix, as prepared by the manufacturer and supplied as ImmunoCap® Phadiatop IgE tests. IgE antibodies against a tested allergen were considered present if the IgE level in a sample was >0.35 kU/L (Class 1 or greater). The following classes of IgE levels were distinguished: class 0: ≤0.35 kU/L; class 1: >0.35–0.7 kU/L; class 2: >0.7–3.5

Table 1 Overview of the clinical studies included in the analysis

Study no.	Study population	rhC1INH dose	Subjects administered rhC1INH	rhC1INH administrations performed per subject	Total no. of rhC1INH administrations
1101	Asymptomatic HAE patients	6.25–100 U/kg	12	2	24
1106	Healthy subjects	100 U/kg	14	1–5	59
1202 and 1203	Symptomatic HAE patients	100 U/kg	14 ^a	1–2	21
1205 RCT	Symptomatic HAE patients	50 U/kg or 100 U/kg	25 ^b	1	25
1205 OLE	Symptomatic HAE patients	50 U/kg or 2 × 50 U/kg ^c	38 ^{b,d}	1–7 ^d	79 ^d
1304 RCT	Symptomatic HAE patients	100 U/kg	16 ^b	1	16
1304 OLE	Symptomatic HAE patients	2,100 U or 2–3 × 2,100 U ^e	41 ^{b,d}	1–12 ^d	76 ^d

rhC1INH recombinant human C1-inhibitor, HAE hereditary angioedema, OLE open-label extension, RCT randomized controlled trial

^a One patient also participated in study 1101

^b Sixteen patients in the randomized controlled studies 1205 and 1304 also participated in the OLE studies

^c Patients were treated with 50 U/kg with the option of a second 50 U/kg dose

^d The OLE studies were ongoing at the time of the IgE analyses

^e Patients were treated with one vial of 2,100 U with the option of one or two additional vials of 2,100 U

kU/L; class 3: >3.5–17.5 kU/L; class 4: >17.5–50 kU/L; and class 5: >50 kU/L.

Pre-exposure samples were also assessed with a qualitative ImmunoCAP® Phadiatop assay, a test used to indicate the presence or absence of atopic constitution. Post-exposure plasma samples were tested for IgE antibodies against rabbit epithelium (dander), rabbit meat and cow's milk.

2.4 Correlation of IgE Antibody Status to Clinical Symptoms

Adverse events (AEs) were assessed in all studies. An AE was defined as any undesirable experience or sign (including an abnormal laboratory value). For the current analysis, AEs with a possible underlying allergic basis were identified from the safety database of each study. These were identified as AEs occurring within 7 days of administration of the rhC1INH product possibly indicative of a type I hypersensitivity reaction: mucosal manifestations (e.g., rhinitis, conjunctivitis), skin manifestations (e.g., erythema, itching, pruritus, urticaria), broncho-pulmonary manifestations (e.g., dyspnoea, asthma), or circulatory manifestations (e.g., hypotension, shock). A broad definition of allergic-type AEs, compared with the commonly applied one for anaphylaxis in clinical practice [7], was used to ensure all possible cases were reviewed.

2.5 Statistical Analyses

Results of the IgE antibody tests were reported using descriptive statistics.

3 Results

3.1 Subjects

By the cut-off date of this analysis, 144 subjects (130 HAE patients and 14 healthy subjects) had together received 300 administrations of the rhC1INH product (see Table 1 for subject numbers and administrations by study). Eight HAE patients were excluded from this retrospective analysis due to the non-availability of plasma samples ($n = 7$) or an insufficient sample volume ($n = 1$). One HAE patient participated in two studies (see Table 1) and was included in duplicate; therefore, the total number of subjects in the analysis was 137. Overall, 65 subjects (47.4 %) were exposed to rhC1INH once and 72 (52.6 %) were administered the product on two or more occasions (range 2–12; median 2). Demographic data and baseline clinical characteristics for the analysis population are shown in Table 2.

3.2 Anti-rabbit IgE Antibodies

Prior to rhC1INH exposure, five subjects had anti-rabbit epithelium IgE antibodies (Fig. 1). One of these was a 20-year-old female healthy subject who developed the only anaphylactic reaction observed in the study population. This anaphylactic reaction became manifest during her first exposure to the rhC1INH product. This AE presented as sneezing, conjunctivitis, facial erythema and oedema, dyspnoea and sinus tachycardia shortly after the start of infusion, and was judged to be probably related to the administration of study drug by the clinical investigator. Following symptomatic treatment with anti-histamines and

inhaled β -agonists, the subject's clinical condition normalized within 1 h. The subject subsequently revealed a medical history—not disclosed at screening—of similar symptoms upon exposure to rabbits. This subject had the highest levels of IgE (Class 4) against rabbit epithelium of any subject at screening (39.6 kU/L vs. <5.0 kU/L in all other subjects, see Fig. 1).

The other four subjects with positive but lower pre-existing IgE levels (Class 1–3) against rabbit epithelium did not develop anaphylaxis following exposure to rhC1INH. None of these subjects developed allergic-type symptoms following exposure to rhC1INH. There was no increase in IgE class during the study in any of these four subjects. One of these subjects had a flu-like syndrome that started 1 day after the second exposure to rhC1INH and resolved spontaneously after 3 days. This AE may have been an upper respiratory tract viral infection and was labeled by the investigator as unlikely to be related to study drug administration.

Three subjects had pre-exposure IgE against rabbit urine. One of these was the subject with anaphylaxis. Another was a subject with flu-like symptoms one day after

the second rhC1INH exposure. The third subject with anti-rabbit urine IgE at screening had no allergic symptoms following rhC1INH exposure.

None of the subjects had pre-exposure IgE against rabbit meat allergens, whereas one subject, a symptomatic HAE patient, had a positive test for IgE against rabbit serum (Class 1). This subject had no AE following administration of rhC1INH.

3.3 Anti-cow's Milk IgE Antibodies

Three subjects had positive pre-exposure IgE against cow's milk allergens (range Class 1–3, see Fig. 1). None of these three patients with pre-exposure IgE against cow's milk allergens experienced allergic-type AEs following rhC1INH administration. There was no increase in IgE class during the study in any of these subjects.

3.4 IgE Antibodies Against Other Animal Allergens

Twenty-three subjects (16 % of all subjects included in the study) had pre-existing antibodies against any of the other animal allergens tested. The most common pre-exposure IgE antibody found was against cat dander (Table 3). One of these 23 subjects reported a possible allergic-type AE; this subject was an asymptomatic HAE patient with pre-existing elevated IgE against cat dander (Class 1) but was negative for IgE against any rabbit or cow's milk allergens. This AE, conjunctivitis and rhinitis, occurred 3 days after exposure to rhC1INH but soon after exposure to a cat. This patient had a history of cat allergy and, hence, cat allergy was considered the likely cause of the reported symptoms. None of the other 22 subjects with pre-existing IgE to animal allergens reported any allergic-type symptoms following rhC1INH administration.

Table 2 Demographics and baseline clinical characteristics of the subjects included in the analysis (*n* = 137)

Parameter	Values
Age, y [mean $\pm$ SD (range)]	35.4 $\pm$ 13.8 (13–66)
Sex, male/female [n (%)]	50 (36.5)/87 (63.5)
Weight, kg [mean $\pm$ SD (range)]	76.9 $\pm$ 17.8 (45–128)
Body mass index, kg/m ² [mean $\pm$ SD (range)]	26.6 $\pm$ 5.4 (18.7–44.5)
Clinical history of allergy [n (%)]	27 (19.7)
Presence of atopic constitution at screening [n (%)]	60 (43.8)

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Allergen																								
Rabbit dander	2	4	3	1	1																			
Rabbiturine	1	3	1																					
Rabbitserum						1																		
Cow's milk						1	1	3																
Cow dander						2		2		2														
Cow's meat											1													
Guinea pig epithelium		2	2	2	1	2				1							2							
Cat dander	2	2	5		5	4			3		1	1	2	3		2		2	1	1	1	2	3	1
Dog epithelium			2		2	3					1													
Horse dander	1		3			3				1	1					1								

Fig. 1 Overview of positive IgE tests in 24 patients with any IgE against animal derived allergens before exposure to recombinant human C1-inhibitor. Not shown are allergens (rabbit meat, hamster epithelium, rat and mouse allergen mixes) for which none of the

patients tested positive. Filled cells indicate a positive IgE test for the allergen, the number refers to the IgE class. Note that patient 2 developed an anaphylactic reaction upon administration of recombinant C1-inhibitor

Table 3 IgE antibody status in subjects ($n = 137$) before administration of the recombinant human C1-inhibitor product

IgE antibody status	No. (%) of subjects
Any pre-exposure IgE ^a	24 (17.5)
Specific pre-exposure IgE ^a	
Rabbit epithelium (dander)	5 (3.6)
Rabbit urine	3 (2.2)
Rabbit meat	0 (0)
Rabbit serum	1 (0.7)
Cow's milk	3 (2.2)
Cow dander	3 (2.2)
Cow's meat	1 (0.7)
Guinea pig epithelium	7 (5.1)
Cat dander	18 (13.1)
Dog epithelium	4 (2.9)
Horse dander	6 (4.4)
Hamster epithelium	0 (0)
Rat mix	0 (0)
Mouse mix	0 (0)
No pre-exposure IgE	113 (82.5)

^a Level ≥ 0.35 kU/L (Class 1 or greater)

3.5 Assessment of IgE Antibody Induction

To determine whether administration of the rhC1INH product could induce the production of IgE antibodies that might cause an allergic reaction upon repeated exposure, post-exposure samples were tested for IgE against selected allergens. IgE against rabbit epithelium and rabbit meat were assessed in these samples because any IgE antibody induction was expected to be primarily directed against rabbit allergens. Post-exposure samples were also tested for IgE antibodies against cow's milk as the presence of such antibodies could be clinically relevant if they were to cross-react with HRIs in the product.

Levels of IgE to the three tested allergens did not increase after administration of the rhC1INH product in any of the 24 subjects with pre-exposure IgE antibodies. In addition, none of the subjects experiencing predefined symptoms of potential allergic origin had increased levels of IgE antibodies following exposure.

Of the subjects without pre-existing IgE antibodies, three had increased IgE levels at day 22 or day 90 after the last administration of rhC1INH. One of these subjects, a healthy subject, developed IgE against rabbit meat just above test cut-off levels (0.13 [class 0], 0.40 and 0.60 kU/L [both class 1] at screening and days 22 and 90 after the fifth administration of rhC1INH, respectively).

One HAE patient had negative IgE against rabbit epithelium at screening but positive results (up to 2.9 kU/L [class 2]) thereafter. This patient received saline in the

randomized controlled trial and levels in a sample taken at 45 minutes before open-label treatment had increased to 1.6 kU/L (class 2), indicating that the IgE response had occurred before first exposure to rhC1INH. This patient reported no AE upon exposure to rhC1INH.

Finally, one HAE patient developed IgE against cow's milk just above cut-off levels (0.18 [class 0], 0.79 [class 2] and 0.62 kU/L [class 1] at screening and days 22 and 90 after the sixth administration of rhC1INH, respectively). In this patient, IgE against rabbit epithelium or meat remained negative.

None of these three subjects developed allergic-type symptoms upon first or repeated exposure to rhC1INH.

4 Discussion

The primary aim of this retrospective analysis was to investigate the clinical relevance of pre-exposure IgE antibodies to rabbit and other animal allergens in subjects administered the rhC1INH product. The only severe drug-related anaphylactic reaction occurred in a healthy subject with a history of rabbit allergy and a high level of pre-exposure IgE against rabbit epithelium. It is likely, therefore, that a risk for type I hypersensitivity reactions to the product exists in individuals with a clinical allergy to rabbits and/or substantially elevated levels of anti-rabbit epithelium IgE antibodies. rhC1INH was approved in Europe in 2010 for the treatment of acute angioedema attacks in patients with HAE due to C1INH deficiency. In Europe, rhC1INH is contraindicated in patients with a clinical rabbit allergy and pre-exposure testing for the presence of IgE antibodies against rabbit epithelium is indicated. Notably, disclosure of the pre-existing rabbit allergy symptoms would have led to exclusion of this subject from exposure to rhC1INH. Hence it remains to be established whether a test for IgE against rabbit epithelium provides additional information regarding risk for anaphylactic reactions to rhC1INH, especially since four other subjects had no allergic symptoms despite positive tests for IgE against rabbit epithelium at screening.

Among all subjects exposed to rhC1INH, the subject who developed an anaphylactic reaction to rhC1INH turned out to have the highest IgE against rabbit epithelium. However, this subject also had the highest level of IgE against rabbit urine (4.17 U/kg). Only two other subjects had elevated pre-exposure IgE against rabbit urine, 0.53 and 0.37 U/kg, respectively. Both these subjects also had elevated IgE against rabbit epithelium (4.99 and 1.87 U/kg, respectively), whereas two other subjects with IgE against rabbit epithelium just above the cut-off level of the assay were negative for IgE against rabbit urine. These data suggest that the test with rabbit urine may detect the

same IgE as is detected in the assay with rabbit epithelium, but that the latter assay is more sensitive. Of the 137 subjects tested, we identified 24 subjects who just prior to exposure to rhC1INH had at least one positive IgE test for animal-derived allergens. The only subject of all subjects exposed to rhC1INH who developed an anaphylactic reaction upon exposure to rhC1INH was among these 24 subjects and had by far the highest levels of IgE against rabbit dander-derived allergens. None of the other 23 subjects, including 11 who had IgE against multiple animal-derived allergens, developed an anaphylactic reaction upon exposure to rhC1INH. Subjects with strongly elevated IgE against epithelium-derived allergens from animals other than rabbits had no drug-related allergy type AEs upon exposure to rhC1INH. Of note, none of the three subjects with pre-exposure IgE antibodies to cow's milk experienced an allergic type AE following administration of the product, consistent with the notion that cow's milk allergens display only little homology with rabbit milk-derived allergens [11]. Thus, the current analysis based on a few subjects revealed no evidence that the presence of IgE antibodies against allergens other than rabbit epithelium constitutes an increased risk for allergic reactions.

In the vast majority of subjects exposed to rhC1INH there was no evidence for the induction of new IgE antibodies. The IgE response to cow's milk allergens in one subject was probably unrelated to rhC1INH exposure since there was no induction of detectable IgE against rabbit meat or epithelium. In the subject who developed just above cut-off levels of IgE against rabbit meat, it cannot be excluded that this minimal response was triggered by repeated exposure to rhC1INH. Nevertheless, this minimal response was clinically not relevant as this patient did not develop AEs during five treatments with rhC1INH nor was there an effect on clinical efficacy. Whether or not this new IgE response was indeed caused by exposure to rhC1INH is difficult to establish. The fact is that a similar *de novo* IgE response also occurred in a placebo-treated subject.

Single and repeated exposure to rhC1INH did not induce the production of IgE antibodies to selected rabbit allergens (epithelium and meat) or to cow's milk. Notably the maximum number of administrations in the patients was 12. Therefore, these data suggest that rhC1INH has a low, if any, sensitizing potential. This is a relevant observation as HAE patients tend to experience numerous acute attacks of angioedema and therefore require treatment on repeated occasions [12]. An overall low immunogenic potential of the rhC1INH product was also apparent in a separate analysis of IgM, IgG and IgA antibodies in symptomatic HAE patients [13]. In that analysis, no persistent or clinically significant antibody responses against HRIs or against rhC1INH itself were observed following treatment with the product.

IgE antibodies can be directed against the therapeutic protein itself. In another publication [13] we report that only one of 155 HAE patients who received rhC1INH had a treatment-emergent antibody response against rhC1INH itself. These anti-rhC1INH antibodies did not affect the efficacy or the functional activity of rhC1INH, and were not associated with the occurrence of an AE. This lack of clinically significant IgM or IgG antibody response against rhC1INH was one of the main reasons for us not measuring IgE against rhC1INH. Moreover, the only severe allergy-type AE related to administration of rhC1INH observed in all subjects exposed to rhC1INH occurred in the subject with the highest IgE level against rabbit epithelium during the first administration of rhC1INH, which provides a plausible explanation for the AE in this subject.

Analysis of IgG, IgM and IgA antibody responses against rhC1INH or against host-related impurities in 155 HAE patients exposed once or repeatedly to rhC1INH revealed that in one patient a treatment-emergent anti-rhC1INH antibody response occurred whereas in three patients (1.9 %) a treatment-emergent antibody response against host-related impurities was observed. None of these responses were associated with AEs [13].

The current data suggest that a small risk for type I hypersensitivity reactions upon exposure to rhC1INH exists in individuals with a pre-existing clinical allergy to rabbits. In patients without clinical allergy to rabbits or anti-rabbit epithelium IgE antibodies, the risk of type I hypersensitivity appears to be minimal. The rhC1INH product also has an apparently low propensity to induce production of IgE antibodies. Though these data do not rule out induction of an IgE response in an occasional patient, taken together they indicate a reassuring immunosafety profile of rhC1INH as a treatment for acute HAE attacks.

5 Conclusion

The risk for anaphylaxis on administration of rhC1INH product can be minimized by evaluating the patient for rabbit allergy. Furthermore, anti-rabbit IgE was not induced upon (repeat) administration of rhC1INH. Thus this study supports a reassuring immunosafety profile of rhC1INH as a treatment for acute HAE attacks.

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