Safety and Immunogenicity of Recombinant Human Thrombin: A Pooled Analysis of Results from 10 Clinical Trials

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Study Objective. To evaluate the safety and immunogenicity of recombinant human thrombin (rThrombin), an active topical stand-alone hemostatic agent.

Design. Analysis of pooled data from 10 rThrombin clinical trials.

Patients. A total of 644 adult and pediatric patients treated with rThrombin; 609 patients were included in the immunogenicity analysis.

Measurements and Main Results. In all studies, rThrombin was applied during a single surgical procedure (day 1); the procedures consisted of spinal procedures, major hepatic resection, peripheral arterial bypass, arteriovenous graft formation for hemodialysis access, and synchronous burn wound excision and skin grafting. A dosage of 1000 IU/ml of rThrombin was administered for more than 99% of patients. Adverse events and clinical laboratory values were monitored through day 29. Blood samples were obtained for immunogenicity analyses before the procedure and on day 29. Adverse events were mild or moderate in severity for the majority of patients; no patients discontinued from an rThrombin study due to adverse events. The most commonly reported adverse events in the 644 patients were incision site pain (305 patients [47.4%]), procedural pain (215 patients [33.4%]), and nausea (170 patients [26.4%]). Five patients (0.8%) died during the studies; all deaths were considered unrelated to rThrombin treatment. Antibodies to the rThrombin product developed in 5 (0.8%, 95% confidence interval 0.4–2.8%) of 609 patients by day 29, approximately 1 month after treatment; these antibodies did not neutralize the activity of native human thrombin. The development of antibodies did not appear to differ substantively by type of surgical procedure, amount of rThrombin administered, or patient age.

Conclusion. Recombinant human thrombin was well tolerated, and adverse events were consistent with those reported in the postoperative setting in the surgical populations studied. Approximately 1 month after treatment, less than 1% of the patients had developed antibodies to the rThrombin product, and these antibodies did not neutralize the activity of native human thrombin. These results support the safety of rThrombin when used as a topical aid to hemostasis in numerous surgical settings and for patients of differing ages.

Key Words: hemostatics, antibody formation, recombinant protein, surgery, rThrombin.

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Thrombin is a topical hemostat that is routinely used during surgical procedures. Before 2007, thrombin purified from bovine plasma sources was the only commercially available stand-alone thrombin product. In 2008, recombinant human thrombin (rThrombin) was licensed as a stand-alone thrombin product (Recothrom Thrombin, topical [recombinant]; ZymoGenetics, Seattle, WA) by the United States Food and Drug Administration (FDA).[1] It is indicated as an aid to hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible and control of bleeding by standard surgical techniques (e.g., suture, ligature, or cautery) is ineffective or impractical. Recombinant human thrombin is produced using a modified Chinese hamster ovary cell line and was developed as an alternative to the two other stand-alone topical thrombin products currently available in the United States: thrombin purified from bovine plasma (Thrombin-JMI; King Pharmaceuticals, Bristol, TN) and thrombin purified from human pooled plasma (Evithrom; Ethicon, Inc., Somerville, NJ), which was licensed in 2007.[2, 3]

The potential for transmission of blood-borne pathogens is a safety concern for therapeutic proteins purified from human plasma sources, whereas the development of antibodies after treatment is an important safety concern for any therapeutic protein.[4, 5] The potential risk for blood-borne pathogen transmission with products derived from human plasma is mitigated by donor selection, testing, and methods employed to remove or inactivate viruses that may be present. The clinical consequences of antibody formation may vary with the type of antibody present. For all stand-alone thrombin products, a specific concern is that antibodies to the therapeutic protein may also recognize native human thrombin, neutralizing its activity and potentially leading to increased clotting times, or rarely, resulting in severe bleeding. Adverse events resulting from immune-mediated inhibition of thrombin or other clotting factors are generally described as immune-mediated coagulopathies. Consistent with basic principles of immunology, antibody responses to any therapeutic protein may also be stronger and more rapid after application of an antigen to patients with preexisting antibodies (e.g., immunologic responses after vaccinations). Additional potential concerns for the bovine thrombin product are that it is xenogeneic and inherently immunogenic when administered to humans and that small amounts of other proteins (e.g., bovine factor V) are present as impurities in the product. Further, antibodies recognizing human clotting factors have been observed after exposure to the bovine thrombin product, including a recent study that was conducted after implementation of enhanced purification processes for the manufacture of the bovine thrombin product.[2, 6–8]

Thus, the objectives of this study were to analyze the safety and the immunogenicity of rThrombin using pooled data from clinical trials.

Methods

Study Design

Ten clinical trials of rThrombin were conducted in adult and pediatric patients in the United States between December 30, 2003, and July 10, 2010 (Table 1).[9–15] Details regarding each of these studies have been reported previously.[9–15] Recombinant human thrombin was administered in a range of surgical settings to patients of differing ages (including pediatric patients). Safety and immunogenicity responses after reexposure to rThrombin were examined in one of the 10 trials. Efficacy was prespecified as an end point in five phase II studies and one phase III study; the phase III study included bovine thrombin as a comparator.

Each clinical trial was conducted in accordance with their respective protocols and the ethical principles stated in the Declaration of Helsinki or the applicable good clinical practice guidelines as well as all applicable federal, state, and local laws, rules, and regulations. Institutional review boards or independent ethics committees approved the study protocol for each site. Written, informed consent or pediatric assent, if applicable, was obtained from each patient and/or patient's legal representative (guardian) before study-specific procedures or assessments were performed.

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Table 1. Summary of the 10 Clinical Trials of Recombinant Human Thrombin Included in the Analysis

Phase	Clinical Trial Protocol Number, Identifier[a]	Eligible Patient Population (surgical procedure; age)	Study Treatments	No. of Patients Treated with rThrombin[b]	No. of Patients Total
I[9]	499C05, part I	Spinal surgical procedure; age ≥ 18 yrs	rThrombin	9	9
II[10]	499C05, part II	Spinal surgical procedure; age ≥ 18 yrs	rThrombin or placebo	33	42
II[10]	499C06	Hepatic resection; age 18–75 yrs	rThrombin or placebo	17	28
II[10]	499C07	Peripheral arterial bypass procedure; age ≥ 18 yrs	rThrombin or placebo	17	27
II[10]	499C08	Arteriovenous graft formation for hemodialysis access; age ≥ 18 yrs	rThrombin or placebo	21	33
II[11]	499E02, NCT00371215	Skin graft after burn wound excision; age 2–75 yrs	rThrombin	72	72
III[12]	499E01, NCT00245336	Spinal procedure, hepatic resection, peripheral arterial bypass, or arteriovenous graft formation for hemodialysis access; age ≥ 18 yrs	rThrombin or bovine thrombin	205	411
IIIb[13]	499F04, NCT00491608	Spinal procedure, peripheral arterial bypass, or arteriovenous graft formation for hemodialysis access; age ≥ 18 yrs	rThrombin	209	209
IV[14]	499H01, NCT00859547	Synchronous burn wound excision and skin grafting; age ≤ 17 yrs	rThrombin	30	30
IV[15]	499G02, NCT00813904	Spinal procedure, peripheral arterial bypass, or arteriovenous graft formation for hemodialysis access; age ≥ 18 yrs	rThrombin	31[c, d]	31
Totals				644	892

rThrombin = recombinant human thrombin.
[a]Protocol numbers begin with "499" and ClinicalTrials.gov identifiers begin with "NCT."
[b]Includes patients assigned to rThrombin as well as patients assigned to placebo if they received rThrombin as rescue therapy after treatment with placebo.
[c]All patients had received one or more documented previous exposures to rThrombin before this study commenced.
[d]17 patients had also been treated in a previous rThrombin clinical trial: one patient had been treated in the phase III study[12] and 16 patients had been treated in the phase IIIb study[13] (patients were counted separately for each study in which they participated).

Descriptions of the 10 Clinical Trials Included in the Analysis

Surgical Procedures

In each study, rThrombin was applied topically as an aid to hemostasis during a surgical procedure on day 1. The types of surgical procedures were prespecified for each study and consisted of spinal procedures, major hepatic resection, peripheral arterial bypass, arteriovenous graft formation for hemodialysis access, and synchronous burn wound excision and skin grafting (Table 1).

Study Populations

Age ranges included in the rThrombin clinical trials varied; for example, patients younger than 18 years were included in two of the 10 studies (Table 1). In all studies, eligible patients had no known hypersensitivity to thrombin. Additional inclusion and exclusion criteria differed by study and have been previously reported.[9–15] Four studies included a placebo group, and one study included a bovine thrombin treatment group. Results for the patients receiving placebo or bovine thrombin were not included in this analysis, except for results for those patients given placebo, who also received rThrombin after randomization as rescue therapy during the study surgical procedure.

Safety Measures

Adverse events included those reported by the patient and those determined by the investigator

during questioning or evaluation of physical examination and laboratory data. Adverse-event reports were collected from the time the patient provided written informed consent or assent, through day 29, and were graded for severity with the National Cancer Institute's Common Terminology for Adverse Events, version 3.0 (grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening, grade 5 = fatal).[16] The relationship between adverse events and treatment with rThrombin was assessed by site investigators for each adverse event.

In the rThrombin clinical trials, two different methods were used to estimate exposure to rThrombin. In four studies, the volume of rThrombin used during the surgical procedure was estimated by subtracting the volume of rThrombin remaining in the basins, syringes, and spray pumps after the surgical procedure from the original volume of rThrombin prepared for the surgical procedure. In the other six studies, the volume of rThrombin used during the surgical procedure was estimated by counting the number of 5-ml vials prepared for the surgical procedure, which would thus represent the maximum possible exposure to rThrombin.

Laboratory parameters monitored during each study included hematology parameters (hemoglobin, hematocrit, total white blood cell count with differential, and platelet count), coagulation parameters (activated partial thromboplastin time, international normalized ratio, and prothrombin time), and serum chemistry (blood urea nitrogen and creatinine). Abnormal laboratory findings considered clinically significant by the site investigators were recorded as adverse events. Laboratory results have been presented previously for individual studies, and separate analyses of pooled laboratory data were not conducted.

Immunogenicity Measures

In each study, the presence of antibodies to rThrombin product was assessed by using samples collected at screening and/or on day 1, before the surgical procedure, and on day 29 (study end).

The immunogenicity of the rThrombin product was evaluated by using an enzyme-linked immunosorbent assay (ELISA) for detection of anti–rThrombin product antibodies and a neutralizing antibody assay to characterize the potential of antibodies to rThrombin product to neutralize human plasma–derived thrombin. The immunogenicity testing strategy followed a tiered approach designed to screen for binding antibodies, determine antibody titer, characterize antibody specificity, and assess the neutralizing potential of anti–rThrombin product antibodies.[10, 11] The same ELISA-based immunogenicity testing method was utilized throughout the rThrombin clinical trials.

Patients were considered to have developed anti–rThrombin product antibodies after treatment if they had undergone seroconversion or had a 1-titer unit increase or greater ($\geq$ 10-fold) in anti–rThrombin product antibody titer from screening or baseline to day 29.

Statistical Analysis

Statistical analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC).

The number and percentage of antibody-positive patients on day 29 were provided, and a 95% exact binomial confidence interval (CI) was calculated using the Clopper-Pearson method.[17]

Patients who were treated in two different rThrombin clinical studies were each counted twice in the safety and immunogenicity analysis sets. A sensitivity analysis was conducted without any data from the duplicate patients.

Results

The 10 rThrombin clinical trials included 892 patients; 644 of these patients were treated with rThrombin and were included in this analysis (Table 1). All 644 patients were treated with a topically applied rThrombin solution of 1000 IU/ml, except in the phase I study,[9] in which three patients received rThrombin 250 IU/ml and three received rThrombin 500 IU/ml. For most patients, rThrombin was applied directly or by spray, or with absorbable gelatin sponge. For some patients, rThrombin was applied with absorbable gelatin powder made from absorbable gelatin sponge, USP (e.g., for 45 of 209 patients in the phase IIIb study[13] [Table 1]).

For the 644 rThrombin-treated patients, the median age was 58.0 years (range 0.9–89 yrs), and slightly more than half of the patients were male (353 patients [54.8%]; Table 2). Some of the demographic characteristics reflected specific study entry criteria; for example, all pediatric patients ($\leq$ 16 yrs old) were undergoing burn wound excision and skin grafting (Table 1).

Table 2. Demographic Characteristics of the Study Patients

Characteristic	Type of Surgical Procedure					
	Spinal Procedure (n=216)	Hepatic Resection (n=79)	Peripheral Arterial Bypass (n=140)	Arteriovenous Access (n=107)	Burn Wound Excision and Skin Grafting (n=102)	All Patients (n=644)
Age (yrs), mean ± SD	57.11 ± 14.07	54.97 ± 15.55	66.38 ± 10.88	61.23 ± 13.89	30.44 ± 20.20	55.32 ± 18.68
Age (yrs), median (range)	57.5 (24–86)	56.0 (21–81)	66.0 (22–89)	60.0 (28–89)	31.5 (0.9–70)	58.0 (0.9–89)
Age group (yrs)						
≤ 16	0 (0)	0 (0)	0 (0)	0 (0)	30 (29.4)	30 (4.7)
17–64	140 (64.8)	57 (72.2)	53 (37.9)	63 (58.9)	69 (67.6)	382 (59.3)
≥ 65	76 (35.2)	22 (27.8)	87 (62.1)	44 (41.1)	3 (2.9)	232 (36.0)
65–74	49 (22.7)	12 (15.2)	51 (36.4)	22 (20.6)	3 (2.9)	137 (21.3)
≥ 75	27 (12.5)	10 (12.7)	36 (25.7)	22 (20.6)	0 (0)	95 (14.8)
Sex						
Male	100 (46.3)	43 (54.4)	81 (57.9)	62 (57.9)	67 (65.7)	353 (54.8)
Female	116 (53.7)	36 (45.6)	59 (42.1)	45 (42.1)	35 (34.3)	291 (45.2)
Race-ethnicity						
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.0)	1 (0.2)
Asian	3 (1.4)	6 (7.6)	0 (0)	3 (2.8)	0 (0)	12 (1.9)
Black or African-American	9 (4.2)	5 (6.3)	15 (10.7)	37 (34.6)	22 (21.6)	88 (13.7)
Hispanic	18 (8.3)	6 (7.6)	7 (5.0)	20 (18.7)	18 (17.6)	69 (10.7)
Native Hawaiian or Pacific Islander	0 (0)	1 (1.3)	0 (0)	0 (0)	0 (0)	1 (0.2)
Caucasian	185 (85.6)	59 (74.7)	115 (82.1)	38 (35.5)	56 (54.9)	453 (70.3)
Other	1 (0.5)	2 (2.5)	3 (2.1)	9 (8.4)	5 (4.9)	20 (3.1)

Data are no. (%) of patients unless otherwise specified.

Adverse events were reported for 618 (96.0%) of 644 patients, and for the majority of patients (437 [67.9%]), the maximal severity of adverse events was mild or moderate (411 patients) or no adverse events were reported (26 patients). No patients discontinued from the studies due to adverse events. Overall, the most commonly reported adverse events (≥ 10% of patients) were incision site pain (47.4%), procedural pain (33.4%), and nausea (26.4%; Table 3). Adverse-event incidences differed by surgical setting and age, although analysis of adverse-event data by patient age was confounded by differences in the types of surgical procedures represented among the patients in the different age groups.

Adverse events of at least grade 3 severity reported for 1% or more of the 644 patients included anemia (5.7% [37 patients]), incision site pain (3.7% [24 patients]), procedural pain (2.5% [16 patients]), hypertension or hypotension (1.7% [11 patients] each), and hypophosphatemia or nausea (1.2% [8 patients] each). Four adverse events of at least grade 3 severity were considered treatment related, including pulmonary embolism (two patients), deep vein thrombosis (one patient), and vascular graft thrombosis (one patient). The four patients with these events were aged 50–76 years and underwent four different types of surgical procedures. Five (0.8%) of the 644 patients died during the clinical studies; causes of death were hepatic insufficiency (failure) and sudden cardiac arrest, severe sepsis, sepsis, cardiac arrest, and respiratory failure. The deaths were considered by the investigators as not related to treatment with rThrombin.

A total of 609 patients had antibody data available at screening or baseline and on day 29, and were included in the immunogenicity analysis. Of these patients, five (0.8% [95% CI 0.4–2.8%]) developed anti–rThrombin product antibodies after treatment. A range of ages and types of surgical procedures was represented among the five patients who developed anti–rThrombin product antibodies (Table 4). The estimated volume (and amount) of rThrombin applied during the study surgical procedure ranged from 1–20 ml (1000–20,000 IU) for these five patients; for comparison, the estimated median applied volume for all 644 patients was 10.0 ml (range 1–60 ml [1000–60,000 IU]). Adverse events reported for these patients were all considered

Table 3. Adverse Events Reported in 10% of All Patients by Type of Surgical Procedure or by Age Group

	No. (%) of Patients by Type of Surgical Procedure					
Preferred Term[a]	Spinal Procedure (n=216)	Hepatic Resection (n=79)	Peripheral Arterial Bypass (n=140)	Arteriovenous Access (n=107)	Burn Wound Excision and Skin Grafting (n=102)	All Patients (n=644)
Incision site pain	123 (56.9)	55 (69.6)	79 (56.4)	48 (44.9)	0 (0.0)	305 (47.4)
Procedural pain	76 (35.2)	20 (25.3)	47 (33.6)	33 (30.8)	39 (38.2)	215 (33.4)
Nausea	84 (38.9)	27 (34.2)	34 (24.3)	16 (15.0)	9 (8.8)	170 (26.4)
Constipation	59 (27.3)	29 (36.7)	29 (20.7)	4 (3.7)	16 (15.7)	137 (21.3)
Pyrexia	42 (19.4)	25 (31.6)	18 (12.9)	5 (4.7)	8 (7.8)	98 (15.2)
Anemia	28 (13.0)	17 (21.5)	20 (14.3)	11 (10.3)	17 (16.7)	93 (14.4)
Pruritus	26 (12.0)	10 (12.7)	8 (5.7)	1 (0.9)	31 (30.4)	76 (11.8)
Insomnia	31 (14.4)	11 (13.9)	11 (7.9)	6 (5.6)	10 (9.8)	69 (10.7)
Vomiting	20 (9.3)	13 (16.5)	19 (13.6)	7 (6.5)	6 (5.9)	65 (10.1)

	No. (%) of Patients by Age Group					
	16 Years or Younger (n=30)	17–64 Years (n=382)	65 Years or Older (n=232)	65–74 Years (n=137)	75 Years or Older (n=95)	All Patients (n=644)
Incision site pain	0 (0.0)	165 (43.2)	140 (60.3)	80 (58.4)	60 (63.2)	305 (47.4)
Procedural pain	12 (40.0)	132 (34.6)	71 (30.6)	43 (31.4)	28 (29.5)	215 (33.4)
Nausea	1 (3.3)	96 (25.1)	73 (31.5)	42 (30.7)	31 (32.6)	170 (26.4)
Constipation	3 (10.0)	72 (18.8)	62 (26.7)	34 (24.8)	28 (29.5)	137 (21.3)
Pyrexia	4 (13.3)	66 (17.3)	28 (12.1)	18 (13.1)	10 (10.5)	98 (15.2)
Anemia	9 (30.0)	39 (10.2)	45 (19.4)	27 (19.7)	18 (18.9)	93 (14.4)
Pruritus	13 (43.3)	44 (11.5)	19 (8.2)	10 (7.3)	9 (9.5)	76 (11.8)
Insomnia	1 (3.3)	45 (11.8)	23 (9.9)	9 (6.6)	14 (14.7)	69 (10.7)
Vomiting	2 (6.7)	30 (7.9)	33 (14.2)	21 (15.3)	12 (12.6)	65 (10.1)

[a]Medical Dictionary for Regulatory Activities (MedDRA), version 13.1 (MedDRA Maintenance and Support Services Organization [MSSO], Chantilly, VA) preferred terms.

Adverse events are listed in order of decreasing incidence for all patients. If these conditions occurred before administration of the study drug, they were considered baseline conditions (unless they worsened after study drug administration); multiple occurrences of the same event for a patient were counted only once.

by the investigators as not related to treatment and were not consistent with adverse events caused by coagulopathies. Day 29 laboratory test results were available for three of the five patients, and day 15 results were available for a fourth patient; activated partial thromboplastin time, prothrombin time, and international normalized ratio values (assessed for three patients) were all within their normal ranges. Further, for all five patients, the antibodies did not neutralize the activity of native human thrombin.

Preexisting antibodies to rThrombin product were observed at screening or baseline in 13 (2.1% [95% CI 0.4–2.8%]) of the 609 patients in the immunogenicity analysis set. The titer of these antibodies did not increase by at least 1 titer unit ($\geq$ 10-fold) at day 29. These patients had not been previously exposed to rThrombin because they had not participated in prior rThrombin clinical studies, and Recothrom was not commercially available at the time their antibody status was assessed. Additional testing results were available for 11 of the 13 antibody samples, and none neutralized native human thrombin.

The immunogenicity of rThrombin was examined separately for 30 patients who had received a second exposure to rThrombin in one of the studies[15] (499G02; Table 1). None of these patients had antibodies to rThrombin product at study entry, and none (0% [95% CI 0.0–11.6%] of them developed anti–rThrombin product antibodies after the second exposure. The incidence of antibody development for the remaining 579 patients was less than 1% (5 patients [0.9% (95% CI 0.4–3.1%)]).

Seventeen patients treated with rThrombin in the 10 rThrombin clinical studies participated in two different studies, and data from both studies were included in this analysis. A sensitivity analysis performed after removing all data for these patients demonstrated that the inclusion of the duplicate patient data had little effect on the demographic, safety, or immunogenicity results.

Table 4. Characteristics of the Five Patients Who Developed Anti–rThrombin Product Antibodies After Treatment

Clinical Trial Protocol Number	Age (yrs)	Sex	Race-Ethnicity	Height (cm)	Weight (kg)	Surgical Procedure	Estimated Volume of rThrombin Applied (ml)[a]
499C07[10]	57	Female	Caucasian	158	79	Peripheral arterial bypass	10
499E01[12]	66	Male	Caucasian	178	80	Spinal procedure	1
499E01[12]	52	Female	Black or African-American	168	137	Spinal procedure	2
499E01[12]	37	Female	Black or African-American	158	111	Hepatic resection	20
499E02[11]	43	Female	Hispanic	158	73	Burn wound excision	5

[a]rThrombin concentration of 1000 IU/ml.

Discussion

In the 10 clinical trials included in the analysis, the safety and immunogenicity of topically applied rThrombin were assessed in a wide range of surgical settings for patients of different ages. Our analysis included data from 644 patients treated with rThrombin, representing the largest safety and immunogenicity sample reported for any stand-alone topical thrombin product. Recombinant human thrombin was generally well tolerated, and adverse events were consistent with those commonly observed postoperatively or in the surgical populations studied. Overall, the most common adverse events were incision site pain, procedural pain, and nausea.

Treatment with rThrombin resulted in a low incidence of anti–rThrombin antibody formation, with five (0.8% [95% CI 0.4–2.8%]) of 609 patients developing anti–rThrombin product antibodies after treatment. These five patients varied by age, sex, race-ethnicity, type of surgical procedures, and volume or amount of rThrombin applied. Common factors that might have led to antibody formation were not identified. None of the antibodies neutralized the activity of native human thrombin. The incidence of anti–rThrombin product antibody formation did not differ substantively in pediatric or adult patients and did not differ substantively after an initial or a second exposure in adults; in addition, the incidence was consistently low across all studies. Preexisting antibodies to the rThrombin product were observed at screening or baseline in 13 (2.1% [95% CI 0.4–2.8%]) of 609 patients. These 13 patients had no known previous exposure to rThrombin; thus, the antibodies may represent naturally occurring autoantibodies.[18, 19]

The safety and immunogenicity of topically applied, stand-alone thrombins have been directly compared in two clinical studies.[8, 12] A higher incidence of immunogenicity was reported for the bovine thrombin product in a study comparing it with the plasma-derived human thrombin product; safety profiles were reported as comparable for the two treatment groups.[8] The immunogenicity of rThrombin and bovine thrombin products was also directly compared in a phase III study: 3 (1.5%) of 198 patients developed anti–rThrombin product antibodies and 43 (21.5%) of 200 patients developed anti-bovine thrombin product antibodies ($p<0.001$) by 4 weeks after treatment with rThrombin or bovine thrombin product.[12] The overall incidence of adverse events was similar between treatment groups during the 4-week assessment period. In these comparative studies, no increased risk of coagulopathy was reported for the bovine thrombin group; although the studies were not designed or sufficiently power to detect a potential association between antibody formation and adverse clinical outcomes.

Conclusion

This pooled analysis examined safety and immunogenicity results from 644 patients treated with rThrombin in 10 different clinical trials. Recombinant human thrombin was well tolerated. Adverse events were consistent with those commonly observed postoperatively or in the surgical populations studied. Less than 1% of the patients developed anti–rThrombin product antibodies after treatment, and patients developing antibodies varied by age, sex, and race-ethnicity, were undergoing different types of surgical procedures, and received different volumes or amounts of applied rThrombin. The incidence of anti–rThrombin product antibody development did not differ substantively after a first or second exposure to rThrombin, and the

anti–rThrombin product antibodies did not neutralize native human thrombin. These results support the safety of rThrombin when used as a topical aid to hemostasis in numerous surgical settings and for patients of differing ages.

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