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Safety and Immunogenicity of Recombinant Human Thrombin with Absorbable Gelatin Powder when Applied as a Flowable Topical Hemostat

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ABSTRACT

Purpose: Flowable topical hemostats composed of absorbable matrices with thrombin are commonly used to reduce bleeding during surgery. Recombinant human thrombin (rThrombin) is used as a topical aid to hemostasis and can be applied directly, or with absorbable gelatin sponge, USP. This exploratory subgroup analysis evaluated the safety and immunogenicity of rThrombin when applied with gelatin powder compared to gelatin sponge and/or direct application.

Methods: The safety and immunogenicity of rThrombin were assessed in a previously described open-label, non-comparative clinical trial of 209 patients (clinicaltrials.gov identifier: NCT00491608). Adults (18 years of age or older) received rThrombin 1,000 Units/mL applied topically during a spinal or vascular (peripheral arterial bypass or arteriovenous vascular access) surgical procedure (Day 1); rThrombin was applied with gelatin powder for 45 of 209 patients. Antibodies were assayed by ELISA in samples collected at baseline and approximately 1 month later (Day 29). Adverse events were recorded over the 28 days of the study.

Results: Forty-five patients with a mean (SD) age of 59.8 (12.3) years underwent spinal (78%) or vascular (22%) surgical procedures and received rThrombin applied with gelatin powder (Gelfoam® [n=33] or Surgifoam® [n=12] powder). The most common adverse events were procedural pain (64%), nausea (42%), and muscle spasms (33%). One patient with a history of postsurgical pulmonary embolism experienced a serious adverse event of pulmonary embolism on Day 3, which was considered by the investigator as possibly treatment-related. No patient (n=0/43) had anti-rThrombin product antibodies at baseline or Day 29. By comparison, for the 164 patients (33% spinal and 67% vascular) who received rThrombin with gelatin sponge and/or by direct application, the incidence of procedural pain, nausea, and muscle spasms were 32%, 23%, and 7%, respectively. Antibody assessments in this group revealed that 4 patients (n=4/157) had pre-existing antibodies to rThrombin product at baseline; no patients became antibody positive by Day 29 (seroconversion or ≥ 10-fold increase in titer).

Conclusions: The immunogenicity of rThrombin when applied with gelatin powder as a flowable topical hemostat was comparable to that observed after application with gelatin sponge and/or directly. Adverse events were consistent with the surgical procedures performed; numerical differences in incidences for the two methods of rThrombin application were likely due to the larger proportion of patients undergoing spinal surgery in the gelatin powder group.

INTRODUCTION

- Topical hemostats are used to reduce bleeding during surgical procedures and are broadly divided into four categories (Figure 1; Spotnitz and Burks, 2010).
- Thrombin is frequently applied topically with absorbable gelatin sponge, USP, which can be milled to form gelatin powder and is commercially available as Gelfoam® powder (Pfizer, Inc.) and Surgifoam® powder (Ethicon, Inc.).
- Two flowable topical hemostats containing absorbable gelatin matrices and thrombin from human-pooled plasma are commercially available (Floseal®, Baxter Healthcare Corporation and Surgiflo®, Ethicon, Inc.).
- This exploratory subgroup analysis evaluated the safety and immunogenicity of recombinant human thrombin (rThrombin, RECOTHROM®, ZymoGenetics, Inc.) when applied with gelatin powder as a flowable topical hemostat.

METHODS

- Data from an open-label, multicenter, single group, clinical trial in 209 patients was used for these exploratory analyses (Figure 2; Singla, 2009).
- Eligible patients were ≥18 years of age and underwent spinal operations, arterial reconstruction (including peripheral arterial bypass), or arteriovenous vascular access procedures.
- Topical rThrombin (RECOTHROM, 1000 Units/mL) was applied with gelatin powder (Gelfoam or Surgifoam), or gelatin sponge and/or by direct application for hemostasis during a single procedure on Day 1.
- The presence of anti-rThrombin product antibodies was evaluated by ELISA using blood samples collected at baseline and Day 29. Antibodies to rThrombin product were further tested for their ability to neutralize native human thrombin.
- Adverse events (AEs) and clinical laboratory values were monitored throughout the 28 days of the study.
- Safety and immunogenicity results were summarized using descriptive statistics.

Figure 1. Topical Hemostat Categories

Mechanical Hemostats
- Gelatin sponge (may be used with thrombin)
- Collagen
- Cellulose
- Polysaccharide spheres

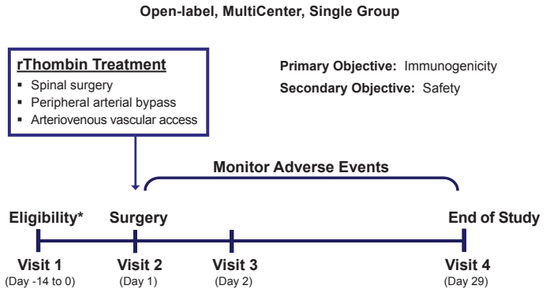
Active Hemostats
- Bovine thrombin
- Human pooled plasma thrombin
- Recombinant human thrombin

Flowable Hemostats
- Gelatin powder*
- Gelatin powder + thrombin

Fibrin Sealants
- Fibrinogen + thrombin

* Milled from absobable gelatin sponge, USP.

Figure 2. rThrombin Phase 3b Study



* Eligible patients had a definite or likely prior bovine thrombin exposure.

- Singla NK, et al. J Am Coll Surg 2009;209:68-74.
- Spotnitz and Burks. Clin Appl Thromb Hemost 2010;16:497-514.

- This study was funded by ZymoGenetics, Inc.
- ClinicalTrial.gov identifier: NCT00491608.

RESULTS

- rThrombin was applied with gelatin powder in 45 of 209 patients by 2 of 19 investigative sites enrolling patients in the study. These patients underwent spinal (78%) or vascular (22%) surgical procedures, and the source of the gelatin powder was Gelfoam powder (n=33) or Surgifoam powder (n=12).
- The median amount/volume (range, mL) of rThrombin used during the study surgical procedure was 27,000 Units/27.0 mL (4 to 40 mL) for patients receiving rThrombin with gelatin powder and 10,000 Units/10.0 mL (1 to 50 mL) for patients who had rThrombin applied with gelatin sponge and/or directly.
  - The volume of rThrombin applied with gelatin powder varied between the 2 clinical trial study sites, ranging from 5 mL to 40 mL at one site, and from 4 mL to 15 mL at the second site.
- Demographic and baseline characteristics were generally similar between the two groups, except that a greater proportion of patients receiving rThrombin with gelatin powder underwent spinal surgery (78% vs. 33%; Table 1).
- No patient (n=0/43) who received rThrombin applied with gelatin powder had anti-rThrombin product antibodies at baseline or Day 29. Of the patients who received rThrombin with gelatin sponge and/or by direct application, 2.5% (n=4/157) had pre-existing antibodies to rThrombin product at baseline; none became antibody positive by Day 29 (seroconversion or ≥ 10-fold increase in titer). None of the antibodies neutralized the activity of native human thrombin.
- Adverse events differed slightly by group, likely due to a larger proportion of patients undergoing spinal surgery in the gelatin powder group (Table 2).
- Serious adverse events were reported for comparable percentages of patients (22% vs. 23%), and the incidence of any specific serious adverse event was ≤ 2% in both groups, except for wound secretion, which was observed in 4% of patients receiving rThrombin with gelatin powder.
  - One patient with a history of postsurgical pulmonary embolism who received rThrombin applied with gelatin powder had a serious adverse event of pulmonary embolism on Day 3, which was considered by the investigator as possibly treatment-related.

Table 1. Patient Characteristics

Characteristic	rThrombin Applied with Gelatin Powder: Yes (N=45)	rThrombin Applied with Gelatin Powder: No (N=164)	Total (N=209)
Age (years)			
Mean (SD)	59.8 (12.3)	61.9 (13.4)	61.5 (13.2)
Median	62.0	64.5	64.0
Minimum, maximum	33, 80	30, 89	30, 89
Gender; n (%)			
Female	22 (49)	77 (47)	99 (47)
Male	23 (51)	87 (53)	110 (53)
Race; n (%)			
Asian	0	2 (1)	2 (1)
Black/African American	4 (9)	18 (11)	22 (11)
Hispanic	6 (13)	19 (12)	25 (12)
White	35 (78)	125 (76)	160 (77)
Type of study surgical procedure; n (%)			
Spine	35 (78)	54 (33)	89 (43)
Arterial reconstruction or PAB	2 (4)	73 (45)	75 (36)
Arteriovenous vascular access	8 (18)	37 (23)	45 (22)

SD = standard deviation; PAB = peripheral arterial bypass

Table 2. Adverse Events

Preferred Term[a]	rThrombin Applied with Gelatin Powder: Yes (N=45) n (%)	rThrombin Applied with Gelatin Powder: No (N=164) n (%)	Total (N=209) n (%)
Any advers event	45 (100)	152 (93)	197 (94)
Incision site pain	13 (29)	81 (49)	94 (45)
Procedural pain	29 (64)	53 (32)	82 (39)
Nausea	19 (42)	37 (23)	56 (27)
Constipation	10 (22)	32 (20)	42 (20)
Anemia	6 (13)	30 (18)	36 (17)
Muscle spasms	15 (33)	11 (7)	26 (12)
Hypotension	2 (4)	21 (13)	23 (11)
Pyrexia	10 (22)	10 (6)	20 (10)
Vomiting	5 (11)	14 (9)	19 (9)
Pain in extremity	7 (16)	10 (6)	17 (8)
Pruritus	6 (13)	9 (5)	15 (7)
Wound secretion	6 (13)	8 (5)	14 (7)
Arthralgia	5 (11)	5 (3)	10 (5)

Table includes adverse events reported for ≥ 10% of patients in any group and are reported by decreasing incidence for the total group.
[a] Adverse events were coded with Medical Dictionary for Regulatory Activities (MedDRA) Version 11.0.

CONCLUSIONS

- The immunogenicity of rThrombin when applied with gelatin powder as a flowable topical hemostat was comparable to that observed after application with gelatin sponge and/or by direct application.
- Adverse events were consistent with the surgical procedures performed; numerical differences in incidences for the two methods of rThrombin application were likely due to the larger proportion of patients undergoing spinal surgery in the gelatin powder group.
- There are several limitations to this exploratory analysis. Patients were not randomly assigned to receive rThrombin as a flowable topical hemostat, the median amounts and volumes of applied rThrombin differed between the groups, and patients receiving rThrombin with gelatin powder were not evenly distributed amongst the types of study surgical procedures.