Poster #35

Summary of thrombotic or thrombotic microangiopathy events in persons with hemophilia A taking emicizumab

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Summary

Emicizumab is approved for prophylaxis of hemophilia A (HA) and has been used by more than 6,100 persons across the globe as of December 31, 2019.

+ aPCC (>100 U/kg/24hrs for ≥24 hours)

Clinical trials of emicizumab prophylaxis for HA identified a risk of thrombosis (blood clots) and thrombotic microangiopathy (TMA) when used along with activated prothrombin complex concentrate (aPCC).

Available data were analyzed for thrombotic events and TMA. A total of 20 events were identified: 16 thrombotic events and four TMA events.

Thrombosis and TMA are known risks associated with use of emicizumab + aPCC together; six of these events occurred. All other thrombotic events (13) occurred in persons with pre-existing risk factors [one event was excluded].

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Introduction

Emicizumab

- Emicizumab is a drug with a unique mechanism of action, and is administered through subcutaneous injection in persons with HA.[1–5]
- Studies established emicizumab's efficacy and safety for routine prophylaxis,[6–9] leading to approval in persons with inherited HA with or without factor (F) VIII inhibitors.[3,4] Through 2019, more than 6,100 persons have received emicizumab across the globe.[5]

Thrombosis

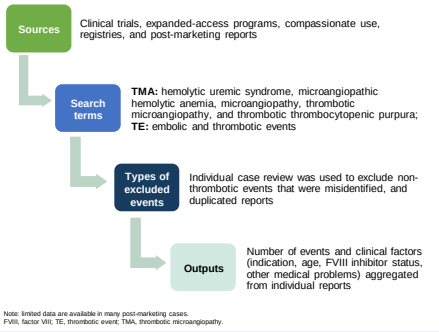
- Studies identified a risk of thrombosis (i.e. blood clotting) and thrombotic microangiopathy (TMA; a clinical syndrome due to damage caused by microscopic blood clots in small blood vessels) when emicizumab was used with aPCC dosed on average >100 U/kg/24 hours for ≥24 hours.[3,4]
- While thrombotic events (TEs) have been observed in persons with coagulation disorders,[10] further studies on their occurrence in HA are needed.
- Myocardial infarction (MI; heart attack) is a complication that can be caused by thrombosis. A previous study found its occurrence in persons with inherited HA is similar to that in an age-/sex-matched population without HA.[11] Cardiovascular risk factors (such as hypertension) are common in inherited HA, but reported incidence varies.[12]

Methods

All available sources of information (i.e. clinical trials, post-marketing reports) on thromboses and TMA events in persons treated with emicizumab were searched through December 31, 2019.

- Then individual cases were reviewed to ensure only relevant events were included (**Figure 1**).

Figure 1. Approach to identify thrombotic and TMA events in persons treated with emicizumab.



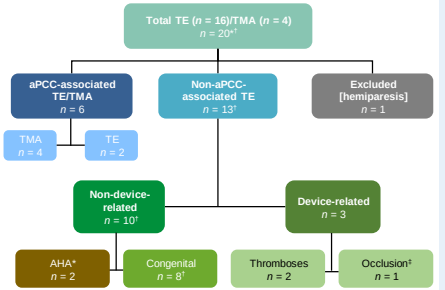
Note: limited data are available in many post-marketing cases.
FVIII, factor VIII; TE, thrombotic event; TMA, thrombotic microangiopathy.

Results

A total of 20 events were identified, including 16 thrombotic events and four TMAs (Figure 2).

- Following individual case review, only one event was excluded: a case of hemiparesis (i.e. weakness of one side of the body caused by a brain bleed rather than a clot) with no described thrombosis.

Figure 2. Summary of thrombotic and TMA events across all persons treated with emicizumab.*

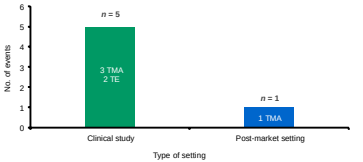


*Includes off-label use. †Two events occurred in one person. ‡Captured thrombotic event through described search terms; however, does not fit the clinical definition of thrombosis.
AHA, acquired hemophilia A; aPCC, activated prothrombin complex concentrate; TE, thrombotic event; TMA, thrombotic microangiopathy.

Guidance on use of emicizumab alongside aPCC was issued following five cases of thrombotic/TMA events in the HAVEN 1 clinical trial (Figure 3).

- Since guidance on use of emicizumab + aPCC together was issued, one TMA occurred in association with use above the product label warning.

Figure 3. Thrombotic and TMA events associated with emicizumab + aPCC >100 U/kg/24hrs for ≥24 hours.[3]



aPCC, activated prothrombin complex concentrate; TE, thrombotic event; TMA, thrombotic microangiopathy.

- Risk minimization measures regarding aPCC use with emicizumab include healthcare provider, patient, and caregiver education, and warnings and precautions (boxed warning in US; black triangle in EU).[3,4]
- Post-marketing monitoring of aPCC-related thrombotic and TMA events include ongoing safety monitoring in clinical studies, and studies specifically evaluating thrombotic/TMA events.[5]

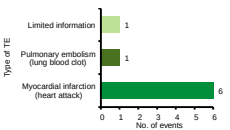
Device occlusion is a known risk of having a central venous access device (CVAD).[13]

- Of the two cases of CVAD-related (venous) thromboses and one case of CVAD occlusion, all are recovered/resolving, with no change to emicizumab prophylaxis.

Risk factors for thrombosis were present in all cases of non-device-related TEs.

- Both acquired hemophilia A (AHA) cases occurred in individuals with severe medical problems/complicated medical histories. [Emicizumab is not approved for use in AHA by the US Food and Drug Administration.]
- All non-aPCC-related TEs in congenital HA were associated with a history of cardiovascular disease or risk factors for thrombosis (**Figure 4**).

Figure 4. Thrombotic events in congenital HA (8 events in 7 persons).

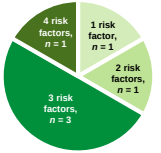


- Median age: 53 years
- One PwHA had two events: pulmonary embolism and heart attack[14]
  - History of venous thromboembolism; smoker
- One case of heart attack is unconfirmed: follow-up pending

HA, hemophilia A; PwHA, person with hemophilia A; TE, thrombotic event.

- All reported cases of myocardial infarction (heart attack) were associated with known cardiovascular risk factors (**Figure 5**).

Figure 5. Number of myocardial infarction (heart attack) events categorized by number of reported risk factors (*n* = 6).



No heart attacks occurred in those with no cardiovascular risk factors

Risk factors were present in all cases of heart attack in congenital HA

- Cardiovascular risk factors included hypertension, hyperlipidemia, ischemic heart disease, smoking, and advanced age
- Two events occurred in clinical trials; four in the post-market setting

HA, hemophilia A.

- The majority of TEs resolved, and few were reported as related to emicizumab. One fatal outcome occurred concurrent to other life-threatening events and critical illness.

Conclusions

Experience with emicizumab is growing. Thrombotic and TMA events when emicizumab is used with aPCC >100 U/kg/24hrs for ≥24 hours are known risks being managed with boxed warnings and risk minimization measures.

All other thrombotic events in persons treated with emicizumab were associated with other known medical problems or pre-existing risk factors.

Roche continues to carefully evaluate thrombotic and TMA events in post-marketing studies and registries.[5]

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Disclosures

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