Background

Thrombotic microangiopathy comprises a heterogeneous group of disorders characterized by injured endothelial cells that are thickened, swollen, or detached, mainly from arterioles and capillaries.[1,2] Pathological findings include vascular damage manifesting as arteriolar and capillary thrombosis, and characteristic abnormalities in the endothelium and vessel wall. Histologic and clinical features include schistocytes, microangiopathic hemolytic anemia, thrombocytopenia, and organ injury.

Prescribing Information

Thrombotic Microangiopathy Associated with HEMLIBRA and aPCC

Cases of thrombotic microangiopathy (TMA) were reported from clinical trials when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis. In clinical trials, TMA was reported in 0.8% of patients (3/391) and in 8.1% of patients (3/37) who received at least one dose of aPCC. Patients presented with thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury, without severe deficiencies in ADAMTS13 activity.

Evidence of improvement was seen within one week following discontinuation of aPCC. One patient resumed HEMLIBRA following resolution of TMA.

Consider the benefits and risks if aPCC must be used in a patient receiving HEMLIBRA prophylaxis. Monitor for the development of TMA when administering aPCC. Immediately discontinue aPCC and interrupt HEMLIBRA prophylaxis if clinical symptoms and/or laboratory findings consistent with TMA occur, and manage as clinically indicated. Consider the benefits and risks of resuming HEMLIBRA prophylaxis following complete resolution of TMA on a case-by-case basis.

Thrombotic microangiopathy cases in emicizumab-kxwh clinical trials, expanded access, compassionate use, and the postmarketing setting[3,4]

Clinical Trials, Expanded Access, and Compassionate Use:

Following an assessment of thrombotic microangiopathy (TMA) and serious thrombotic adverse events in the clinical development program, guidance and instructions were developed as part of a detailed risk mitigation strategy, and investigators were informed about the risk of thrombotic complications in October 2016.[3] The guidance developed includes instructions on the use and dosing of bypassing agents (BPAs) in combination with emicizumab-kxwh, as well as recommended medical supervision and laboratory monitoring after the administration of BPAs. These guidelines were implemented in all protocols and informed consent forms across all emicizumab-kxwh studies.

Postmarketing (*Initial FDA approval November 2017*):

Refer to the emicizumab-kxwh Prescribing Information for FDA-approved information on TMA associated with emicizumab-kxwh and activated prothrombin complex concentrate (aPCC).

TMA Cases at Data Cutoff of October 22, 2018[3,4]

Cases from Clinical Trials, Expanded Access, and Compassionate Use			
Cases (n=3)	Proximity to BPA Dosing Guidance Introduction (October 2016)*	On average a cumulative amount of >100 U/kg/24h of aPCC for 24h or more†	Clinical Trial Where Event Occurred
TMA case 1	Before	Yes	HAVEN 1
TMA case 2	Before	Yes	HAVEN 1
TMA case 3	After	Yes	HAVEN 1

Cases from the Postmarketing Setting	
Cases (n=1)	On average a cumulative amount of >100 U/kg/24h of aPCC for 24h or more†
TMA case 1	Yes

- *Revised guidance on the use and dosing of BPA in combination with emicizumab-kxwh was implemented October 2016. Before/After=event occurred prior to/after implementation of BPA guidance to all protocols across all emicizumab-kxwh studies.
- †Per HEMLIBRA Prescribing Information, cases of TMA and serious thrombotic events were reported when on average a cumulative amount of >100 U/kg/24 hours of aPCC was administered for 24 hours or more to patients receiving emicizumab-kxwh. Among pooled clinical trials (Phase 1/2, HAVEN 1, HAVEN 2, HAVEN 3, HAVEN 4), 13/130 (10%) instances of aPCC treatment consisted of on average a cumulative amount of >100 U/kg/24 hours of aPCC for 24 hours or more; 2 of 13 were associated with serious thrombotic events, and 3 of 13 were associated with TMA. No TMA or serious thrombotic events were associated with the remaining instances of aPCC treatment.

- Among the 3 TMA cases that occurred in the HAVEN 1 clinical trial, 1 occurred in the US, and 2 occurred outside of the US (Ex-US).[3] The postmarketing TMA case occurred in the US.

References

1. Textor SC, Leung N. Vascular injury to the kidney. In: Harrison's Principles of Internal Medicine,19th ed. 2015;
2. George JN, Nester CM. N Engl J Med. 2014;371:6546-66; 3. Data on file. Genentech, Inc. October 2018;
4. Oldenburg J et al. N Engl J Med. 2017;377:809-818.

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