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POSTER ABSTRACTS

331.THROMBOTIC MICROANGIOPATHIES/THROMBOCYTOPENIAS AND COVID-19-RELATED THROMBOTIC/VASCULAR DISORDERS: CLINICAL AND EPIDEMIOLOGICAL

Clinical Outcomes of Congenital Thrombotic Thrombocytopenic Purpura: A Multinational Chart Review Study

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Background: Congenital thrombotic thrombocytopenic purpura (cTTP) is an ultra-rare, life-threatening genetic disorder. Severe deficiency of the von Willebrand factor-cleaving metalloprotease ADAMTS13 results in the formation of platelet-rich microthrombi, leading to platelet consumption and thrombocytopenia. Current treatment strategies primarily focus on replenishing ADAMTS13 through plasma-derived products. Research into the natural history of cTTP, clinical outcomes, disease burden, and treatment patterns is limited.
Aims: The primary objectives of this chart review were to describe the characteristics of cTTP patients, and the prevalence and incidence of clinical manifestations of cTTP and its complications. The secondary objectives were to describe the treatment patterns, treatment-related outcomes, and healthcare resource utilization in patients with cTTP.
Methods: This retrospective chart review, conducted across 9 sites in France, Germany, Italy, Spain, Switzerland, the United Kingdom, and the United States, collected patient-level data from medical records between January 1, 2009 and December 31, 2020. Patients with cTTP were included if they experienced any of the following index events between January 1, 2009 and December 31, 2017: diagnosis with cTTP, receipt of prophylactic treatment for cTTP, receipt of treatment on demand for an acute cTTP episode or isolatedthrombotic thrombocytopenic purpura (TTP) manifestation; or another cTTP-related major clinical event (Table 1). The date of the first qualifying index event was defined as the study index date. Patients were followed until loss to follow-up, enrollment in a clinical trial, the end of the study period, or death. All results were summarized using descriptive statistics. Ethics approval and informed consent were obtained where applicable.
Results: A total of 78 patients met the criteria for inclusion with a mean (SD) follow-up of 8.1 (3.1) years. The mean (SD) age at initial cTTP diagnosis and study index were 26.2 (17.3) years and 29.5 (15.7) years, respectively. Most patients were female (78.2%). The initial diagnosis was characterized clinically by systemic (n=44, 56.4%), neurological (n=26, 33.3%), gastrointestinal (n=23, 29.5%) and renal (n=22, 28.2%) manifestations (Table 2). A total of 92 acute cTTP episodes were reported by 55/78 (70.5%) patients during the study period, resulting in an event rate of 0.145 episodes per person-year (PPY). Most episodes (n=70/92, 76.1%) resolved without complications, 16/92 (17.4%) resolved but resulted in organ damage, and 2/92 (2.2%) resulted in death. The majority of acute cTTP episodes (n=85/92, 92.4%) required hospitalization, with 32/85 (37.6%) resulting in intensive care unit (ICU) admission. Four isolated TTP manifestations were reported at study index, all required hospitalization, with 1 patient admitted to ICU. A total of 64 isolated TTP manifestations were documented in 29 patients (37.2%) during the study period. The event rate of isolated TTP manifestations was 0.101 events PPY. Thrombocytopenia was the most commonly reported (n=49/64, 76.6%) symptom of isolated TTP manifestations recorded during the study period. Clinical resolution was achieved in most isolated TTP manifestations (n=58/64, 90.6%) and none resulted in death. Organ damage was reported in 22/78 (28.2%) patients during acute episodes during the study period or during isolated TTP manifestations at index, of which neurological (n=15), renal (n=11), and cardiac (n=8) damage were most common. Prophylaxis was initiated in 47/78 patients, with clinical symptoms (n=13/47, 27.7%) and pregnancy (n=13/47, 27.7%) as the most common reasons for initiation. Of the 65 prophylactic treatments administered, 41 (63.1%) were stopped or interrupted with the most common reasons being pregnancy (n=17; childbirth, stillbirth, prophylaxis during pregnancy), failure to achieve normalization of levels (n=6), and normalization of levels achieved (n=3).

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Conclusions: These findings demonstrate a substantial burden arising from disease-related manifestations in cTTP patients. Managing patients with cTTP is additionally burdensome to healthcare systems as many patients require multiple hospital and ICU stays. Novel, effective therapies with demonstrated efficacy and safety profiles may offer substantial benefits to patients and healthcare systems.

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Table 1. Index event definitions

Index event	Definition
cTTP diagnosis	• Confirmed by molecular genetic testing, documented in subject history or at screening • ADAMTS13 activity ≤10% of normal in the absence of an ADAMTS13 inhibitor* (patients currently receiving plasma-derived prophylactic therapy may exceed 10% ADAMTS13 activity at screening) *and/or* • Confirmed cTTP diagnosis based on other criteria specified by the healthcare professional (locally used criteria)
Acute cTTP episode	Defined as the presence of both of the following criteria: • Thrombocytopenia defined as a drop in platelet count ≥50% of baseline† OR a platelet count <100,000/μL • Microangiopathic hemolytic anemia defined as elevation of LDH >2×ULN

Isolated TTP manifestation	Based on the presence of any of the following criteria:
	• Thrombocytopenia defined as a drop in platelet count ≥25% of baseline at screening OR a platelet count <150,000/μL
	• Microangiopathic hemolytic anemia defined as elevation of LDH >1.5×ULN
	• Signs and symptoms including:
	  • Other neurological symptoms (eg, confusion, memory issues, irritability, dysarthria, focal or general motor symptoms including seizures, and headache) as per the opinion of the investigator/treating physician
	  • Lethargy
	  • Abdominal pain
	  • Increase in serum creatinine >1.5×baseline

cTTP-related clinical event	Cerebrovascular event, cardiovascular event, thrombosis, organ-related event, gastrointestinal event, bleeding, neurologic event, or any other acute clinical event related to cTTP. Events were reported based on the physician's assessment

cTTP, congenital thrombotic thrombocytopenic purpura; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura; ULN, upper limit of normal
*Documented in plasma samples withdrawn at 2 different time points with an interval of more than 14 days.
†Baseline defined as most recent measurement prior to episode

Table 2. Clinical symptoms at cTTP diagnosis

Signs and symptoms*	Patients, n (%) (N=78)
Systemic manifestations and prodromes	44 (56.4%)
Neurological manifestations	26 (33.3%)
GI/HPB	23 (29.5%)
Cardiovascular manifestations	12 (15.4%)
Renal manifestations	22 (28.2%)
Ophthalmic involvement	4 (5.1%)
Pulmonary involvement	1 (1.3%)
Bleeding	15 (19.2%)
Musculoskeletal involvement	3 (3.9%)
Skin	5 (6.4%)

GI/HPB, gastrointestinal/hepato-pancreato-biliary
*Patients could experience more than one symptom

Figure 1

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