Management of Thrombotic Microangiopathy overlap syndrome: A clinical trial

Thesis

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Contents

List of Abbreviations

ADAMTS13	A disintegrin and metalloproteinase with a thrombospondin type1 motif, member 13
AFLP	Acute fatty liver of pregnancy
aHUS	Atypical hemolytic uremic syndrome
APHge	Antepartum hemorrhage
APLS	Antiphospholipid syndrome (catastrophic) (CAPS)
APS	Antiphospholipid syndrome
ARDS	Adult respiratory distress syndrome
AST/ALT	Aspartate aminotransferase/Alanine aminotransferase
ATIII	Antithrombin III
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood cell
CMP	Complete metabolic panel
COCP	Combined oral contraceptive pill
CSA	Cyclosporine A
CT	Computerized tomography
DAT	Direct antiglobulin test
DIC	Disseminated intravascular coagulation
ESRD	End-stage renal disease
FBC	Full blood count
FDA	Food and drug administration
GVHD	Graft-versus-host disease

HAART	Highly active antiretroviral therapy
HBP	High blood pressure
HCT	Hematocrit
HEENT	Head, ears, eyes, nose and throat
HELLP	Hemolysis, elevated liver enzymes and low platelets
HGB	Hemoglobin
HIV	Human immunodeficiency virus
HRP	Horseradish peroxidase
HUS	Hemolytic uremic syndrome
ICHge	Intracranial hemorrhage
IgG	Immunoglobulin G
IQR	Interquartile range
IV	Intravenously
LCHAD	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
LDH	Lactate dehydrogenase
LFTs	Liver function tests
LMWH	Low molecular weight heparin
LSCS	Lower segment cesarean section
MAHA	Microangiopathic hemolytic anemia
MRI	Magnetic resonance imaging
OD	Once daily
PET	Pre-eclampsia
PEX	Plasma exchange
PG	Primigravida
PGF	Placental growth factor

PI	Plasma infusion
PPHge	Postpartum hemorrhage
PT	Prothrombin time
PV	Plasma volume
S/D FFP	Solvent/detergent-treated fresh frozen plasma
SIRS	Systemic Inflammatory Response Syndrome
SLE	Systemic lupus erythematosus
Stx-HUS	Shiga toxin–associated hemolytic-uremia syndrome
SVD	Spontaneous vaginal delivery.
sVEGFR-1	Soluble vascular endothelial growth factor receptor-1
TAM	Transplant-associated microangiopathy
TBV	Total blood volume
TLC	Total leucocytic count
TMAs	Thrombotic microangiopathies
TMB	Tetramethylbenzidine
TTP	Thrombotic thrombocytopenic purpura
U + E	Urea and Electrolytes test
ULVWF	Ultra large multimers of VWF
VEGF	Vascular endothelial growth factor
VWF	Von Willebrand factor

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Introduction

The thrombotic microangiopathies are microvascular occlusive disorders characterized by systemic or intrarenal aggregation of platelets, thrombocytopenia and mechanical injuries to the erythrocytes. The thrombotic microangiopathies include thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). The incidence of thrombotic microangiopathies is one in every 25000 births. These microangiopathies are often mistaken for preeclampsia and the HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome leading to a delay in the diagnosis and treatment thus contributing to the significant mortality and morbidity ***(Patnaik et al., 2003).***

In the last 15 years there has been a marked increase in the understanding of the pathogenesis of TTP. It is now recognized that congenital and acute acquired TTP are due to a deficiency of von Willebrand factor (VWF) cleaving protein ***(Fujikawa et al., 2001; Levy et al., 2001).***

Ultra large multimers of VWF (ULVWF) released from endothelium are not cleaved appropriately, and cause spontaneous platelet aggregates in conditions of high shear, such as in the microvasculature of the brain, heart and kidneys. Diagnosis can be difficult, as there is clinical overlap with haemolytic uraemic syndrome (HUS),

autoimmune disease and a spectrum of pregnancy-related problems ***(Furlan et al., 1998).***

Thrombotic thrombocytopenic purpura was originally characterized by a pentad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fluctuating neurological signs, renal impairment and fever, often with insidious onset. However, TTP can present without the full pentad; up to 35% of patients do not have neurological signs at presentation and renal abnormalities and fever are not prominent features. The revised diagnostic criteria state that TTP must be considered in the presence of thrombocytopenia and MAHA alone ***(Galbusera et al., 2006).*** This can result in an increased referral of other TMAs. TTP remains a diagnosis based on clinical history, examination of the patient and the blood film.

The Subgroups of TTP are congenital TTP, Acute idiopathic TTP, HIV-associated TTP, Drug-associated TTP, Transplant-associated microangiopathy, Malignancy-associated thrombotic microangiopathy, Pancreatitis-associated TTP and Pregnancy-associated TTP.

Pregnancy can be the initiating event for approximately 5– 25% of TTP cases ***(Vesely et al., 2004; Scully et al., 2008),*** which are late onset adult congenital TTP or acute idiopathic TTP. Differentiating TTP from the

more common pregnancy-related TMAs, such as pre-eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) and HUS is difficult, especially if TTP presents post-partum (Table 1). Thrombosis occurs in the placenta in untreated TTP pregnancies and results in fetal growth restriction, intrauterine fetal death and pre eclampsia. There is a continued risk of relapse during subsequent pregnancies ***(Ducloy-Bouthors et al., 2003; Scully et al., 2006).***

Table (1): Selective intensity of the main parameters in HELLP syndrome and its main imitators ***(Pourrat et al., 2015).***

	HELLP	AFLP	TTP	HUS
Hemolysis	+ to +++	0 to +	+++	++ to +++
Schistocytosis	+ to ++	0 to +	+++	++ to +++
Elevated LDH	++ to +++	+ to ++	+++	++ to +++
Elevated liver enzymes	++ to +++	++ to +++	0 to +	0 to +
Low platelet count	++ to +++	+ to ++	+++	++ to +++
Factor V	N or ↓	↓↓	N	N
Total bilirubin	+	++ to +++	+ to ++	+ to ++
Proteinuria	+++	+	+ to ++	+ to +++
Renal failure	0 to ++	+	0 to ++	++ to +++
DIC	+ to ++	+ to +++	0	0
Hypoglycemia	0 to +	+ to +++	0	0
ADAMTS 13 activity	Detectable	NA	Undetectable	Detectable
Fever	0	+	++	0

HELLP, hemolysis, elevated liver enzymes and low platelet count; AFLP, acute fatty liver of pregnancy; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic and uremic syndrome; LDH, lactate dehydrogenase; DIC, disseminated intravascular coagulation; ADAMTS 13, a disintegrin and metalloproteinase domain with thrombospondin type-1 motif A disintegrin and metalloproteinase with a thrombospondin type1 motif, member 1; NA, not assessed.

The Haemolytic uraemic syndrome is divided into diarrhea positive (D+) HUS, associated typically with verotoxin-induced bloody diarrhea, is treated with supportive care, which in some cases includes renal dialysis. Diarrhea negative (D-) HUS, not typically associated with bloody diarrhea, but may sometimes be associated with multisystem symptoms, similar to TTP, should be urgently treated with Plasma exchange (PEX) ***(Kim et al., 2011).***

The primary differentiating factor between HUS and TTP is the presence of oliguric/anuric renal impairment/failure in HUS. Increasingly, the role of complement defects in D-, atypical HUS is being defined ***(Kavanagh & Goodship, 2010)*** and use of the complement inhibitor, eculizumab, appears successful in these cases ***(Al- Akash et al., 2011; Riedl et al., 2011),*** but may also have a role in severe D+HUS ***(Lapeyraque et al., 2011).***

During the treatment of acute TTP we should start PEX with 1·5 PV exchanges, using plasma in all age groups and reassessed daily, the volume of exchange can be reduced to 1·0 PV when the clinical condition and laboratory test results are stabilizing but intensification in frequency and or volume of PEX procedures should be considered in life-threatening cases.