APMAT, A Multi-Centre Observational Study of Patients with Microangiopathic Thrombocytopenia
Jim Y Tiao and Ross I Baker (Western Australia Centre for Thrombosis and Haemostasis, Murdoch University; Perth Blood Institute, Hollywood Specialist Centre, Western Australia)

Abstract:
Microangiopathic Thrombocytopenia (MAT) is a rare but often fatal collection of disorders. The disorder can be categorised by distinct disease states including thrombotic thrombocytopenia purpura (TTP) and atypical haemolytic uraemic syndrome. Clinical presentations of MAT, however, often represent different but related aetiologies from overlapping syndromes. TTP has an incidence rate of 2-15 cases per million people-years. When left untreated, it has a mortality rate of ~90%; with treatment the mortality rate remains relatively high (~20%). Moreover, TTP patients often suffer a high rate of recurrent relapses. Aetiology but related aetiologies from overlapping syndromes. TTP has an incidence rate of 2-15 cases per million people-years. When left untreated, it has a mortality rate of ~90%; with treatment the mortality rate remains relatively high (~20%). Moreover, TTP patients often suffer a high rate of recurrent relapses.

Aims of the study:

1. Develop the APMAT research network protocol
2. Formation of an AP medical advisory panel of APMAT experts for individual clinical advice
3. Establish a clinical adjudication committee for independent classification of MAT patients
4. Standardise laboratory testing for ADAMTS13 and any other novel assays in the AP region
5. Facilitate basic science and translational clinical research into MAT.

Background:
Microangiopathic Thrombocytopenia (MAT) is a rare but often fatal collection of disorders. The disorder can be categorised by distinct disease states including thrombotic thrombocytopenia purpura (TTP) and atypical haemolytic uraemic syndrome. Clinical presentations of MAT, however, often represent different but related aetiologies from overlapping syndromes. TTP has an incidence rate of 2-15 cases per million people-years. When left untreated, it has a mortality rate of ~90%; with treatment the mortality rate remains relatively high (~20%). Moreover, TTP patients often suffer a high rate of recurrent relapses. Aetiology

Thrombotic Thrombocytopenia Purpura (TTP): (thrombi is platelet and VWF rich)

Congenital TTP: Mutant ADAMTS13 with deficient activity

Acquired TTP: ADAMTS13 activity neutralised by auto-antibody

APMAT Network Research Focus

Disease progression independent of ADAMTS13 activity


differentiate between TTP and other thrombotic microangiopathies

1. Differential diagnosis between TTP and other thrombotic microangiopathies remains challenging

<table>
<thead>
<tr>
<th>Disease</th>
<th>Common symptoms</th>
<th>Differential symptoms</th>
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</thead>
<tbody>
<tr>
<td>Haemolytic uraemic syndrome</td>
<td>Thrombocytopenia, haemolytic anaemia with schistocytes</td>
<td>Haemostatic deficiencies, E. coli 0157:H7, Shigella dysenteria Hemorrhagic colitis High serum creatinine</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>Haemolytic anaemia, thrombocytopenia</td>
<td>Elevated liver enzymes</td>
</tr>
<tr>
<td>Pre-eclampsia, eclampsia</td>
<td>Thrombocytopenia, proteinuria</td>
<td>Hypertension Peripheral edema Proteinuria Increased D-dimer</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>Thrombocytopenia</td>
<td>Markedly decreased D-dimer Prolonged prothrombin time</td>
</tr>
<tr>
<td>Coagulopathic antiphospholipid syndrome</td>
<td>Thrombocytopenia</td>
<td>Antiphospholipid antibodies</td>
</tr>
<tr>
<td>Evans syndrome</td>
<td>Haemolytic anaemia, thrombocytopenia</td>
<td>Antiphospholipid antibodies</td>
</tr>
<tr>
<td>Haemolytic-urthrombocytopenia syndrome</td>
<td>Thrombocytopenia</td>
<td>Antiphospholipid antibodies</td>
</tr>
</tbody>
</table>

2. Two classes of ADAMTS13 auto-antibody exist:

- Neutralising
- Non-neutralising

APMAT Network TTP Patient Sample Collection For R&D:

1. The blood samples for genetic analysis and health information are given a unique patient identification number.
2. The link between the original number and the new number is only safely stored, and the sample may only be linked back to participants by very few designated people following strict procedures.

Patient Recruitment:

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Applications of recombinant ADAMTS13 expressed in KM71H P. pastoris yeast:

ADAMTS13: MP

1. ADAMTS13 auto-antibody ELISA signature
- Full length and variants

2. Proof of concept: can rADAMTS13 and variants act as a dominant negative?
- Mapping putative dominant negative domain(s)

3. Antigen for monoclonal antibody generation

tADAMTS3 variants

Belfenda assay: ADAMTS13 activity in Belfenda Units