IMATAS

(International Microangiopathic Thrombocytopenia ADAMTS-13 Standardization) Collaborative study

Von Willebrand Factor Subcommittee

Person responsible: Ross I Baker and Simon De Meyer (Co-chairs)

Description Abstract

ADAMTS-13 is a circulating enzyme, which specifically cleaves the ultra large multimeric von Willebrand factor (vWF) and regulates shear dependent platelet glycoprotein Ib mediated thrombus growth and blood vessel occlusion. Deficiency of ADAMTS13 is increasingly being recognized as a common cause of microangiopathic thrombocytopenia (MAT) and in particular at a level of <10% is diagnostic of thrombotic thrombocytopenic purpura (TTP). ADAMTS-13 testing is now the cornerstone in the diagnosis, prognosis and treatment of patients with life threatening thrombotic microangiopathy and thrombocytopenia. A large number of ADAMTS-13 activities, antigen and antibody tests are available using different methodologies and platforms. The result of an ADAMTS-13 activity and antibody test will define a diagnosis of TTP (<10% activity) or aHUS (>10% activity), decide whether the TTP is immune mediated (iTTP) or congenital (cTTP), guide therapeutic decisions of plasma exchange, immunomodulation, complement inhibition, VWF blocking, ADAMTS-13 replacement or splenectomy. ADAMTS-13 testing may be useful to monitoring the duration and success of therapy and TTP relapse risk. Molecular testing for ADAMTS-13 and complement pathway mutations can provide further diagnostic information but the widespread use and access is limited.

However precision and clinical interpretation of the ADAMTS-13 activity assay around the 10% cut off level is still problematic that will lead to variation in important clinical decisions and management. The approval and government funding of expensive drug therapy also depends on the performance and interpretation of the ADAMTS13 activity result. Interpreting anti ADAMTS-13 antibody assay is even more difficult because the definition between normal and abnormal titres is unclear leading to misdiagnoses of a pathological antibody affecting ADAMTS-13 function. The ADAMTS-13 antigen level at presentation also has prognostic significance that could form the basis to consider more intense initial TTP therapy. Further work is required to standardise ADAMTS-13 testing
for the different clinical situations of the new MAT diagnosis, whether it is iTTP or cTTP, TTP treatment, monitoring and prediction of relapse.

For these reasons, access to reliable, readily available ADAMTS-13 result and appropriate clinical interpretation is crucial.

In order to address this unmet need, the ISTH VWF subcommittee will coordinate a multicentre international study (IMATAS) to examine the standardisation, analytical performance and clinical interpretation of ADAMTS-13 testing.

**Design and methodology (Data expected to collect, sample size and statistical analysis):**

IMATAS Collaborative will conduct longitudinal studies in 2020 and 2021 with two surveys 6 months apart in up to 100 participating international ADAMTS-13 testing laboratories in Europe, North and South American and Asia Pacific regions. Participation will be open to all ISTH members with an interest and expertise in ADAMTS-13 assays and its clinical interpretation. The standard of care ADAMTS-13 testing methodology will be reviewed and similar methods will be grouped for aggregate analysis. A manual will be developed for processing the lyophilized samples and performing and reporting the results in each survey, 10 lyophilized plasma samples with different blinded predetermined ADAMTS-13 activity, antibody and antigen levels and control plasma reagents will be sent to participating laboratories and the results interpreted by the reporting clinician for TTP/aHUS or other diagnosis. Some cases will have a clinical scenario attached for likely diagnosis to the designated lyophilized sample. The source of the plasma for lyophilization will be discarded plasmapheresis collection (>1L) of newly diagnosed TTP patients. Alternate sources for laboratory testing strategies include ADAMTS-13 affinity purified stripped plasma with known amounts of recombinant ADAMTS13 added, anti ADAMTS-13 affinity purified antibody from plasma or ADAMTS-13 monoclonal antibody added to normal pooled plasma in known concentration. Specific results will beconfidentially sent to each laboratory for individual feedback and comment for quality performance improvement. Collective IMATAS results will analysed for mean value, coefficient of variation, and z scores for inter and intra laboratory measurement. In addition the specificity, sensitivity and positive and negative predictive value of ADAMTS-13 measures will be calculated from the clinical cases and result interpretation.
SSC Subcommittee Project/Collaborative Project

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):

Up to 100 participating international ADAMTS-13 testing laboratories in Europe, North and South American and Asia Pacific regions will report the results of 4 ADAMTS-13 surveys conducted 6 months apart in 2020-2021. A call for participation will be made from ISTH members through the ISTH with country/region leaders appointed to contact suitable institutions within their jurisdiction. A minimum requirement for the number of routine ADAMTS-13 testing performed each year for will be agreed prior to enrollment in IMATAS. Plasma from discarded plasmapheresis collections will be collected from TTP patients after local IRB approval.

Expected timeline:

- Project stage/set up
  - Initial International Steering Advisory Board meeting Melbourne July 2019
  - Launch April 2020
  - Duration 3 years
  - Finalization/analysis 2022
  - Reporting ISTH June 2021, final report ISTH 2022

Expected outcomes (i.e. publications):

- Original Article for publication of results
- ISTH International Quality Assurance validation and continuous improvement of ADAMTS-13 testing.
- ISTH SSC guidance document for performing and interpreting ADAMTS-13 testing

Description of project set/up and management, needed infrastructure and resources (summary):

- International Steering Committee formed July 2019. Twice yearly meetings (one at ISTH meeting and one teleconference).
  - Ross I Baker (Australia) and Simon De Meyer (Belgium) Co-chairs, Ian Mackie (UK), Adam Cuker (USA), Doyeun Oh (Korea) Johanna Kremer Hovinga (Switzerland), Jameela Sathar (Malaysia), Steve Kitchen (UK), Spiro Cataland
IMATAS Regional leaders identified

Seeding grant from ISTH awarded

Project partners established (ECAT Foundation, Industry, other grants)

Appointment of an IMATAS Project Officer

Sample preparation

Ethics and other regulatory submission

Distribution of lyophilized samples

Data analysis

Steering Committee writing workshop

References:


