NAME OF PROJECT:

An international, multi-centre study to validate the Taipan snake venom time as a lupus anticoagulant screening test with ecarin time as confirmatory test

Subcommittee: Lupus anticoagulant/antiphospholipid antibodies

Person responsible (Chair / Principal Investigator): Dr Gary W. Moore

Description Abstract

State the application’s broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Suggested length is 2-3 paragraphs.

Taipan snake venom time (TSVT) and ecarin time (ET) for lupus anticoagulant (LAC) screening and confirmation respectively have analytical advantage over the conventional dRVVT and APTT assays of being unaffected by vitamin K antagonists (VKA) since the venoms, which directly activate prothrombin, can also activate the VKA-induced under-carboxylated form. However, the most recent ISTH SSC LAC guideline recommends against use of such assays in LAC detection repertoires, citing absence of standardised commercial reagents and requirement for further evaluation in VKA anticoagulated patients as the reasoning. Whilst the latter may be true, TSVT and ET venoms standardised for LA testing have been available from one UK manufacturer for over a decade.

The arrival of oral direct factor Xa inhibitors in the anticoagulant armoury has prompted a resurgence of interest in TSVT for LA detection since direct prothrombin activation bypasses their potential interference in clotting tests. Recent attempts by reagent manufacturers to improve specificity of dRVVT in anticoagulated patients have achieved mixed success in that there is a reduction in false-positives but an increase in false-negatives. Without a clear and immediately available alternative, TSVT/ET analysis has potential to improve LAC detection in a group of patients where standard treatment compromises conventional assays. A number of single centre publications on TSVT testing, usually with ET confirmatory testing, exist from before after the ISTH SSC guideline. A multi-centre evaluation of TSVT/ET testing for LAC in anticoagulated and non-anticoagulated patients is planned to validate the assays to promote recommendation and wider adoption.

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

Describe concisely the research design and methods for achieving these goals. Suggested length 2-3 paragraphs

Each centre will apply the manufacturer’s technique to the analytical platform in local use, ensuring that stated relative volumes of test plasma and reagents are maintained. Within- and between-run precision will be assessed with locally employed commercial LAC-negative and LAC-positive control plasmas. Each centre will generate their own reference interval/cut-off for TSVT ratio, ET ratio, percent correction and normalised screen/confirm ratio, from at least 120 normal donors.

Sensitivity and specificity will be assessed by assaying TSVT/ET in residual plasmas from patients with established APS, LAC-negative diseased controls, anticoagulated non-APS patients, and non-APS patients whose plasmas contain potential assay interfering factors. Additionally, sets of the NIBSC/WHO LAC reference plasmas (negative, moderate LAC-positive, strong LAC-positive) will be provided to each centre.
Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):

Suggested length 2-3 paragraphs

This is a retrospective study so analyses will be performed on residual plasma samples from routine diagnostic testing. All plasmas from patients with established APS must have evidence of persistent LAC, ideally with evidence from testing on other aliquots of the sample that will be used for TSVT/ET. Samples from initial diagnostic testing (i.e. without evidence of persistence) will not be used unless from triple-positive patients. For patients with established APS, centres will be asked to aim for 20 samples from non-anticoagulated patients, 20 anticoagulated with VKAs and 20 anticoagulated with direct FXa inhibitors.

Participants will be asked to aim to collect and test between 50-100 samples from non-anticoagulated patients with thrombosis or pregnancy morbidity with normal dRVVT & APTT testing, 20 from VKA anticoagulated non-APS patients and 20 from direct FXa inhibitor anticoagulated non-APS patients. To further assess specificity, centres will collect up to 20 plasmas from non-APS patients with non-LA causes of elevated clotting times with potential to interfere with TSVT and/or ET, such as UFH, LMWH or DTI anticoagulation, prothrombin deficiency, a/hypo/dys-fibrinogenemias, grossly elevated D-dimers, paraproteins, amyloidosis.

Institutions are already recruited: 2 in the UK, 3 in Europe, 1 in the USA. There are sufficient reagents to recruit one more centre, which is ongoing.

Expected timeline:

- Project stage/set up: July 2017 – January 2018
- Launch: February 2018
- Duration: approximately 18 months
- Finalization/analysis: Mid-late 2019
- Reporting: Late 2019 – early 202

Expected outcomes (ie. publications):

Publications

Publication type (SSC Communication, Guidance document or original article): SSC communication ± original article

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

Each centre will use their existing analytical equipment, control preparations and associated consumables. TSVT/ET reagents and NIBSC/WHO reference plasmas provided by manufacturers. Data will be handled centrally.

Possible references:

- Moore GW, Smith MP, Savidge GF. The ecarin time is an improved confirmatory test for the taipan snake venom time in warfarinised patients with lupus anticoagulants. Blood Coagul Fibrinolysis 2003;14:307-312


Pouplard C, Vayne C, Berthomet C, Guery EA, Delahousse B, Gruel Y. The Taipan snake venom time can be used to detect lupus anticoagulant in patients treated by rivaroxaban. *Int J Lab Hematol* 2017;39:e60-e63

CLSI. Laboratory testing for the lupus anticoagulant; approved guideline. CLSI document H60-A. Wayne, PA. Clinical and Laboratory Standards Institute; 2014


