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SPECIAL ARTICLE

Rivaroxaban in antiphospholipid syndrome (RAPS) protocol: a prospective, randomized controlled phase II/III clinical trial of rivaroxaban versus warfarin in patients with thrombotic antiphospholipid syndrome, with or without SLE

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on behalf of the RAPS Trial Protocol Collaborators

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Introduction: The current mainstay of the treatment of thrombotic antiphospholipid syndrome (APS) is long-term anticoagulation with vitamin K antagonists (VKAs) such as warfarin. Non-VKA oral anticoagulants (NOACs), which include rivaroxaban, have been shown to be effective and safe compared with warfarin for the treatment of venous thromboembolism (VTE) in major phase III prospective, randomized controlled trials (RCTs), but the results may not be directly generalizable to patients with APS. **Aims:** The primary aim is to demonstrate, in patients with APS and previous VTE, with or without systemic lupus erythematosus (SLE), that the intensity of anticoagulation achieved with rivaroxaban is not inferior to that of warfarin. Secondary aims are to compare rates of recurrent thrombosis, bleeding and the quality of life in patients on rivaroxaban with those on warfarin. **Methods:** Rivaroxaban in antiphospholipid syndrome (RAPS) is a phase II/III prospective non-inferiority RCT in which eligible patients with APS, with or without SLE, who are on warfarin, target international normalized ratio (INR) 2.5 for previous VTE, will be randomized either to continue warfarin (standard of care) or to switch to rivaroxaban. Intensity of anticoagulation will be assessed using thrombin generation (TG) testing, with the primary outcome the percentage change in endogenous thrombin potential (ETP) from randomization to day 42. Other TG parameters, markers of *in vivo* coagulation activation, prothrombin fragment 1.2, thrombin antithrombin complex and D-dimer, will also be assessed. **Discussion:** If RAPS demonstrates i) that the anticoagulant effect of rivaroxaban is not inferior to that of warfarin and ii) the absence of any adverse effects that cause concern with regard to the use of rivaroxaban, this would provide sufficient supporting evidence to make rivaroxaban a standard of care for the treatment of APS patients with previous VTE, requiring a target INR of 2.5. *Lupus* (2015) **24,** 1087–1094.

Key words: Antiphospholipid syndrome; systemic lupus erythematosus; venous thromboembolism; rivaroxaban; warfarin; thrombin generation

Introduction

Thrombotic antiphospholipid syndrome (APS) is an acquired autoimmune disorder characterized by venous and/or arterial thromboembolism associated with persistent antiphospholipid antibodies (aPL).[1–3] The current mainstay of the treatment of thrombotic APS is long-term anticoagulation

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with oral vitamin K antagonists (VKAs) such as warfarin. APS may occur alone, or with another autoimmune disease. Approximately 30%–40% of patients with systemic lupus erythematosus (SLE) have aPL[4] and 30%–40% of this group will develop thrombotic APS,[5,6] which is considered to be a major adverse prognostic factor in patients with SLE.[5] Appropriate management of thrombotic APS is of key importance to minimize its deleterious clinical impact.

Prospective, randomized controlled trials (RCTs) support the current recommendation of anticoagulation at a target international normalized ratio (INR) of 2.5 (range 2.0–3.0) for patients with APS, with or without SLE, presenting with a first venous thromboembolism (VTE) event, or a recurrent VTE event which occurred whilst off anticoagulation.[7–10] However, warfarin, the most widely used VKA in the United Kingdom (UK), has a slow onset of action (three to five days), a narrow therapeutic window, numerous drug and dietary interactions, and potential for variation of action with alcohol, intercurrent illness, exercise and smoking, and regular INR monitoring is required. VKAs present particular problems in patients with APS. First, VKA monitoring in patients with aPL can be complicated by the variable responsiveness of thromboplastin reagents to lupus anticoagulant (LA), which may in turn potentially influence the validity of the INR in patients with APS. Secondly, LA detection in patients on warfarin may be problematic because of the prolonged basal clotting time.[11] This potentially limits the ability to diagnose APS in patients on VKAs and also to monitor aPL status in those with an established diagnosis. The limitations of warfarin and other conventional anticoagulants have driven a search for new alternative anticoagulants.

The new generation non-VKA oral anticoagulants (NOACs) represent a major advance as, unlike warfarin, they are fixed dose with predictable effect and therefore do not require regular anticoagulant monitoring. In addition, they are not affected by changes in diet and alcohol intake and have fewer drug interactions that affect anticoagulant intensity, which would be expected to result in improved quality of life (QoL) for patients. Major phase III RCTs have established that rivaroxaban (Xarelto®; Bayer HealthCare) and dabigatran (Pradaxa®; Boehringer Ingelheim Ltd), and more recently apixaban (Eliquis®; Bristol-Myers Squibb-Pfizer) and edoxaban (Lixiana®), have comparable efficacy and safety to warfarin in the treatment of patients with VTE.[12–18] In 2011, rivaroxaban was licenced by the European Medicines Agency (EMA) for the treatment of deep vein thrombosis (DVT), prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults. In December 2012, rivaroxaban was also licensed by the EMA for the treatment of acute symptomatic PE with or without symptomatic DVT.[19] More recently, dabigatran and apixaban have been licensed by the EMA for the treatment of patients with VTE.[20,21] Rivaroxaban and dabigatran are endorsed for use in patients with VTE by the National Institute for Health and Care Excellence (NICE) in England.[22–25] All three agents are approved for use in the treatment of VTE by the United States Food and Drug Administration (FDA).[26–28] Among patients with acute VTE, approximately 10% have APS,[29] and it is therefore likely that some patients with APS were included in the phase III RCTs of NOACs versus VKAs in patients with VTE. However, aPL status was not systematically documented in these trials,[12–18] and their results may therefore not be directly generalizable to patients with APS where there remains an unmet need.

Thrombin is a pivotal component of the haemostatic mechanism, with increased *ex vivo* thrombin generation (TG) a key marker of thrombogenic potential with predictive value for the development of recurrent VTE.[30,31] Generation of thrombin via the tissue factor (TF) pathway is integral to the blood coagulation process, and thus, assessment of TF-triggered TG provides a useful means of studying the inhibitory actions of antithrombotic agents.[32] TG testing provides information about the dynamics of *ex vivo* thrombin generation, with the TG curve described in terms of: the lag-time, the time to peak, peak thrombin concentration, and endogenous thrombin potential (ETP), the area under the TG curve. Markers of *in vivo* coagulation activation, prothrombin fragment 1.2 (F1.2), thrombin-antithrombin complex (TAT) and D-dimer (a marker of activation of fibrinolysis secondary to coagulation activation), also provide information about an individual's thrombogenic potential,[30,31,33–38] and anticoagulation reduces the levels of these markers.[39–41] Warfarin (in non-APS patients) at a target INR of 2.5 (range 2.0–3.0) has been shown to reduce the ETP by 30%–50% compared with the pre-warfarin result[42] or normal controls.[43] It has been indicated in *in vitro* studies that rivaroxaban can downregulate and completely suppress the process of thrombin generation in whole blood and platelet-rich plasma using TG testing,[44] and that the ETP is an appropriate measure of the intensity of the anticoagulant effect in individuals on rivaroxaban.[45,46] Rivaroxaban was selected for

RAPS as its use was better established for VTE treatment at the time of setting up the trial.

The primary aim is to demonstrate, in patients with thrombotic APS with or without SLE, that the intensity of anticoagulation achieved with rivaroxaban is not inferior to that of warfarin. Secondary aims are to compare rates of recurrent thrombosis and bleeding, and the QoL in patients on rivaroxaban with those on warfarin.

Methods

Study design

RAPS is a phase II/III prospective, randomized controlled non-inferiority open-label clinical trial in patients with thrombotic APS, with or without SLE, currently receiving warfarin therapy. Eligible patients, who have provided their fully informed signed consent, will be randomized 1:1 to warfarin (continuation with standard of care) or rivaroxaban 20 mg daily. The RAPS clinical trial schema is shown in Figure 1 (Appendix A). The Appendix (A-I) is available on the *Lupus* website (http://lup.sagepub.com), with all references included in the manuscript. Potential participants will be identified by their physician during routine outpatient visits to the trial sites. Appendix B shows the regimen for (and includes detailed explanatory notes on) patients converting from warfarin to rivaroxaban.

Inclusion criteria

1. Patients with thrombotic APS,[47] with or without SLE, who have had either a single episode of VTE whilst not on anticoagulation or recurrent episode(s) which occurred whilst off anticoagulation or on sub-therapeutic anticoagulant therapy (definitions are in the Glossary in Appendix C).
2. Patients with a target INR of 2.5 (range 2.0–3.0).
3. Treated with warfarin for a minimum period of three months since last VTE.
4. Female patients must be using adequate contraception (defined in Appendix C) with the exception of postmenopausal or sterilized women.

Exclusion criteria (the majority of which are based on the guidance in the summary of product characteristics (SPC)[19]) are listed in Appendix D. Creatinine clearance is calculated using the Cockcroft and Gault formula.[48,49]

Laboratory criteria for aPL diagnosis are detailed in Appendix E. aPL are reassessed at baseline using established methods[50–54] to define aPL status at trial entry.

Duration of treatment and follow-up: Trial treatment will stop at day 180, at which point the patient will be offered appropriate anticoagulant care. The trial assessment schedule is summarized in Table 1 (Appendix F).

Primary outcome measure: Intensity of anticoagulation will be assessed using TG testing, with the primary outcome the percentage change in ETP from randomization to day 42. TG testing will be performed using the calibrated automated thrombogram (CAT) system (Thrombinoscope BV, Maastricht, The Netherlands) as described by Hemker *et al.*[55] In order to reduce intra-assay variation, paired samples for each patient will be tested at the same time. We and others have previously assessed thrombin generation in warfarinized patients using a trigger reagent that gives a reaction concentration of 5 pmol/l tissue factor and 4 μmol/l phospholipids.[56,57]

The time point of day 42 (first trial visit post-randomization) was chosen as the therapeutic effect of rivaroxaban would be expected to be stable after a minimum of 30 days of rivaroxaban therapy and would not be influenced by any residual warfarin, based on the biological half-lives of the vitamin K-dependent coagulation factors, which range from two to five hours (factor VII) up to 72 hours (factor II).[58]

Secondary outcome measures

a. Efficacy: i) recurrent VTE alone; ii) a composite of recurrent VTE and other thrombotic events (defined in the Appendix: C); iii) the thrombin generation curve will also be quantified in terms of: the lag-time, the time to peak, and peak thrombin concentration;[55] iv) markers of *in vivo* coagulation activation: F1.2, TAT and D-dimer;[31,33–41]
b. Safety i) serious adverse events (SAE); ii) all bleeding events (defined in Appendix C);
c. QoL; EQ-5D-5 L;[59]
d. Laboratory assessment of compliance: i) anti-Xa assay in patients on rivaroxaban;[60] ii) factor X amidolytic assay as an aPL-independent assessment of anticoagulation, in addition to an INR in patients on warfarin;[61] iii) percentage time in therapeutic range (TTR) between baseline and day 180 in patients on warfarin using the method described by Rosendaal *et al.*[62]

SAEs: Suspected unexpected serious adverse reactions (SUSARs) and other serious adverse

Table 1 RAPS trial assessment schedule

Assessment (Procedure/activity)	*Screening*	*Baseline*	*Visit 1 Day 42 (ideally -12days+14 days)*	*Visit 2 Day 90 (ideally±14days)*	*Visit 3 Day 180 (ideally±14days)*	*Visit 4 Day 210 (ideally±14days)*
Consent	X					
Medical History	X					
Demographics	X					
Patient review	X	X	X	X	X	X
Height	X					
Weight	X				X	
BMI	X				X	
Blood pressure	X				X	
FBC	X			X		
U&E, CrCl	X			X		
LFTs	X			X		
Anti-DNA	X					
aPL	X					
20 mL citrated blood sample for trial assessments (all patients)		X	X			
20 mL blood sample for the translational research (optional)		X	X			
Pregnancy tests		X		X	X	
Current medication	X	X	X	X	X	X
Document INRs		X	X	X	X	
Dispensation rivaroxaban		X		X		
Drug accountability of rivaroxaban			X	X	X	
Enquiry for bleeding symptoms	X	X	X	X	X	X
Enquiry for recurrent thrombosis	X	X	X	X	X	X
QoL questionnaire		X			X	

Timing of screening tests:
The following tests are repeated if screening was more than 14 days prior to randomization:
Full blood count (FBC)
Urea and electrolytes (U&E) and creatinine clearance (CrCl) (to be calculated using the Cockcroft & Gault formula)
Liver function tests (LFTs) to include ALT
*Anti-DNA tests no more than three months prior to randomization, i.e. testing for anti-DNA is not required within 30 days prior to randomisation
**Patients are diagnosed with thrombotic APS (defined in Appendix C) prior to trial entry. Results and dates of routine aPL tests establishing a diagnosis of thrombotic APS are documented in the CRF (i.e. testing for aPL is not required within 30 days prior to randomisation). aPL are reassessed at baseline using established methods,[50–54] to define aPL status at trial entry (Appendix E).
+INR to be performed only in patients randomised to remain on warfarin

events (SAEs) will be reported to the regulatory authorities and the research ethics committees, as appropriate. All SAE reports received from the study sites will be reviewed by independent medically qualified staff. If pregnancies do occur they should be reported within 24 hours of the investigator becoming aware.

Procedures for assessing QoL: QoL will be evaluated via the EQ-5D-5 L.[59] We believe this might pick up differences, particularly in the question on 'usual activities' and the visual analogue score.

Sample size: Rivaroxaban would be regarded as non-inferior to warfarin if the percentage change in ETP is not more than 20% higher (i.e. less anticoagulant effect) than that for warfarin. This non-inferiority limit of 20% is based on the inter-centre assay variability of test performance[63] and on clinical relevance. In patients on warfarin, at a comparable INR range, six weeks after starting warfarin treatment the standard deviation of percentage change in ETP was 36%.[42] Using a one-sided 2.5% significance level and 80% power, 51 participants per group are required. Allowing for 12% non-evaluable patients, a total of 116 patients need to be randomized. The sample size has not been adjusted for non-compliance since, unlike in a superiority trial, this would not necessarily reduce the power of a non-inferiority design.[64]

Randomization: Randomization will be stratified by centre and patient type (SLE/non-SLE) to ensure balance in treatment arms. Permuted blocks with a random block length will be used to allocate patients to treatments within each stratum.

Statistical analysis

Summary statistics will be calculated for baseline patient characteristics and study outcomes in each arm. Numbers and percentages will be used to summarize categorical variables, whilst means/standard deviations or medians/interquartile ranges will be used for continuous variables, as appropriate. All analyses will be performed on an intention-to-treat basis. No subgroup analyses are planned.

For the primary outcome, a regression model will estimate the difference in log-transformed ETP between the rivaroxaban and warfarin at day 42 with a two-sided 95% confidence interval (CI), adjusting for stratification variables and baseline ETP. Estimates and 95% CI on the log scale will be back-transformed to percentage changes for presentation. Sensitivity analyses for the primary outcome will consist of: a tobit regression model,[65] which can deal with censored values below the limit of detection of the assay, a per-protocol analysis excluding patients who did not comply with the trial protocol. Interpretation of the 95% CI for the effect of treatment in a non-inferiority trial is shown in Figure 2 in Appendix G.[66] Differences between the two arms for efficacy and safety secondary outcomes will be presented as estimates and 95% CIs. Differences in EQ-5D-5 L QoL scores will be presented as estimates and 95% CI, adjusting for baseline values and stratifying variables.

Anti-factor Xa assays in the patients on rivaroxaban (at day 42) and the INRs and factor X amidolytic assays in patients on warfarin (at baseline and day 42) will be correlated with log-transformed ETP to assess relationships with laboratory measures of compliance.

Changes to the protocol since first approval are detailed in Appendix H.

Discussion

Clinically, our hypothesis is that in patients with thrombotic APS with previous VTE, rivaroxaban could induce more predictable anticoagulation, with additional benefits to patients because there is no requirement for regular laboratory monitoring of anticoagulation. TG provides a global measure of anticoagulation, and can therefore assess the anticoagulant effects of both rivaroxaban and warfarin (drugs with very different modes of action on the coagulation mechanisms). It has been indicated that the ETP is an appropriate measure of the intensity of the anticoagulant effect in individuals on rivaroxaban.[45,46] If we can demonstrate i) that the anticoagulant effect of rivaroxaban is not inferior to that of warfarin; and ii) the absence of any adverse effects of rivaroxaban, we believe that this would provide sufficient supporting information to change practice for APS patients, i.e. to make rivaroxaban the standard of care for the treatment of patients with APS, with or without SLE, who have VTE requiring a target INR of 2.5, i.e. APS patients who have had a single VTE episode whilst not on anticoagulation or recurrent episode(s) which occurred whilst off anticoagulation or on sub-therapeutic anticoagulant therapy.

Secondary laboratory outcome measures of efficacy are also being determined to provide a comprehensive assessment of *ex vivo* thrombin generation and *in vivo* coagulation activation. The thrombin generation curve will therefore also be quantified in terms of: the lag-time, the time to peak, and peak thrombin concentration.[55] In addition, markers of *in vivo* coagulation activation, F1.2, TAT and D-dimer will provide supplementary information about thrombogenic potential.[31,33–41]

The question arises as to whether specific clinical trials are required in patients with thrombotic APS. Patients with APS are inherently different from other patients with a history of VTE by virtue of their aPL, particularly LA, which are known to interfere with a number of haemostatic mechanisms, and which could therefore potentially modulate the actions of anticoagulants. VKAs exert their anticoagulant action by inhibition of the vitamin K-dependent post-translational gamma-carboxylation of procoagulant factors II, VII, IX and X. However, VKAs also reduce the activity of the major naturally occurring anticoagulant protein C/S system (both protein C and S are vitamin K dependent), which potentially counterbalances the anticoagulant effects of VKAs. aPL have been demonstrated to induce reduced protein C and S activity *ex vivo*.[67–69] Whilst this may not entirely reflect the *in vivo* situation, it is plausible that aPL may increase the VKA-induced counterbalancing effect, and thus potentially shift the equilibrium further away from anticoagulation. Rivaroxaban and the other NOACs have very specific targets (factor Xa for rivaroxaban, apixaban and edoxaban and the active site of thrombin for dabigatran)[18–21] and would not be expected to directly influence protein C and S activity. As a result, these agents may have greater anticoagulant efficacy than warfarin in patients with APS. It is possible that aPL could directly interfere with the anticoagulant action of rivaroxaban, although this is unlikely as

rivaroxaban is a small molecule with high affinity for its specific target. The available phase III RCT of rivaroxaban, or other NOACs, compared with VKAs in the treatment of VTE may therefore not be generalizable to patients with thrombotic APS where there remains an unmet need.[12–18]

The RAPS trial will include patients who have APS, with or without SLE, currently on warfarin, target INR 2.5 for previous VTE. Patients will be randomized to either continue on warfarin or switch to rivaroxaban. Inclusion of patients with and without SLE is appropriate for the following reasons: first, many patients with 'primary' thrombotic APS have clinical features such as joint pain which in effect makes some of these patients 'lupus like'. Secondly, our findings in 'primary' thrombotic APS will be applicable to all APS patients, i.e. with or without SLE. Of note here, we have previously established that there is no difference in the risk of recurrent thrombosis between patients with SLE- and non-SLE-associated thrombotic APS.[70] Thirdly, no difference in the effect of rivaroxaban would be expected between patients with SLE-associated thrombotic APS or thrombotic APS alone. The randomization will be stratified by centre and also by patient type (SLE/non-SLE), to ensure a balance of patients in each arm for each centre and patient type.

At the end of the trial treatment period of six months, patients will be offered appropriate anticoagulant care determined on an individualized basis based on a number of factors, including feedback from the patients on their experience with rivaroxaban during the trial.

Monitoring, trial approvals and registrations are summarized in Appendix I.

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Conflict of interest statement

H Cohen has received grant/research support from Bayer, with honoraria for participation in meetings diverted to a local charity. The other investigators have nothing to declare.

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Hannah Cohen, Beverley Hunt, David Isenberg and Munther Khamashta designed the trial. All authors reviewed and edited the draft version of the manuscript and approved the final version. All authors have approved the final manuscript submitted.

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