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Review

14th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends

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ABSTRACT

Antiphospholipid Syndrome (APS) is characterized by vascular thrombosis and/or pregnancy morbidity occurring in patients with persistent antiphospholipid antibodies (aPL). The primary objective of the APS Treatment Trends Task Force, created as part of the 14th International Congress on aPL, was to systematically review the potential future treatment strategies for aPL-positive patients. The task force chose as future clinical research directions: a) determining the necessity for controlled clinical trials in venous thromboembolism with the new *oral direct thrombin or anti-factor Xa inhibitors* pending the results of the ongoing rivaroxaban in APS (RAPS) trial, and designing controlled clinical trials in other forms of thrombotic APS; b) systematically analyzing the literature as well as aPL/APS registries, and creating specific registries for *non-warfarin/heparin anticoagulants*; c) increasing recruitment for an ongoing primary thrombosis prevention trial, and designing secondary thrombosis and pregnancy morbidity prevention trials with *hydroxychloroquine*; d) determining surrogate markers to select patients for *statin* trials; e) designing controlled studies with *rituximab* and other *anti-B-cell* agents; f) designing mechanistic and clinical studies with *eculizumab* and other *complement inhibitors*; and g) chemically modifying *peptide therapy* to improve the half-life and minimize immunogenicity. The report also includes recommendations for clinicians who consider using these agents in difficult-to-manage aPL-positive patients.

Contents

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1. Introduction

Antiphospholipid Syndrome (APS) is characterized by thrombosis and/or pregnancy morbidity occurring in patients with persistent antiphospholipid antibodies (aPL) [1]. Clinical manifestations of aPL represent a broad spectrum: a) asymptomatic aPL positivity (no history of thrombosis or pregnancy morbidity); b) non-criteria manifestations of aPL, e.g., livedo retucularis, thrombocytopenia, hemolytic anemia, cardiac valve disease, aPL-associated nephropathy, skin ulcers, or cognitive dysfunction; c) pregnancy morbidity (recurrent embryonic or fetal loss, preeclampsia, and growth restriction); d) venous, arterial, or small vessel thrombosis; and e) catastrophic APS (multiple organ thromboses commonly associated with microangiopathy).

The current mainstay of treatment for thrombotic APS is heparin followed by long-term anticoagulation with vitamin K antagonists (VKA) such as warfarin. Treatment with VKA in general is problematic because of numerous drug and food interactions, which necessitate frequent monitoring and potential under- or over-anticoagulation. Furthermore, monitoring of anticoagulation may be complicated by variable responsiveness of thromboplastin reagents to aPL, which may may potentially influence the validity of the prothrombin time (PT)/International Normalized Ratio (INR) [2].

The 14th International Congress on aPL was held in Rio de Janeiro, Brazil in September 2013. The APS Treatment Trends Task Force was one of five task forces developed by the meeting organization committee. The goal of the task force was to review potential new treatment strategies for aPL-positive patients rather than traditional anticoagulants or antiplatelet agents. Six subgroups of task force members systematically reviewed in vitro, animal, and completed and ongoing clinical studies in aPL-positive patients; following open discussions before and presentations during the 14th International Congress on aPL, the task force report was finalized.

2. Oral direct thrombin or anti-factor Xa inhibitors (new generation oral anticoagulants)

The oral direct inhibitors (ODI) of coagulation, also known as new generation oral anticoagulants (NOAC), include the direct thrombin inhibitor (DTI) dabigatran etexilate (Pradaxa®) [3], and the direct anti-factor Xa inhibitors rivaroxaban (Xarelto®) [4], apixaban (Eliquis®) [5], and edoxaban (Lixiana®) [6] (www.emc.medicines.org.uk) (Table 1). These agents, unlike warfarin, are fixed dose with predictable anticoagulant effect, do not interact with dietary constituents or alcohol, and have few reported drug interactions that affect anticoagulant intensity. Furthermore, monitoring of anticoagulant intensity of ODI is not routinely required due to their predictable anticoagulant effects.