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APS ACTION - AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking

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Abstract

AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking (APS ACTION) is the first-ever international research network that has been created specifically to design and conduct well-designed, large-scale, multi-center clinical trials in persistently antiphospholipid antibody (aPL)-positive patients. The founding principal of the APS ACTION is that it is an internationally collaborative effort, open to qualified investigators across the globe who are committed to further our understanding of APS and its management. Due to the hard work and collaborative spirit of APS ACTION members, in early 2012, APS ACTION launched two important collaborative international projects: 1) a randomized controlled trial of hydroxychloroquine in the primary thrombosis prevention of persistently aPL-positive but thrombosis-free patients without other systemic autoimmune diseases; and 2) a web-based registry of aPL-positive patients with or without systemic autoimmune diseases, which will also include annual blood collection for aPL-testing and future basic science studies. In the end, we hope to find better treatments for APS, which is a leading cause of thrombosis, pregnancy morbidity, and other life-altering consequences, – and to heighten awareness about this life-threatening, autoimmune condition.

Introduction

AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking (APS ACTION) is the first-ever international research network that has been created specifically to design and conduct well-designed, large-scale, multi-center clinical trials in persistently antiphospholipid antibody (aPL)-positive patients. The network is composed of a multidisciplinary group of physicians and investigators from around the world interested in APS research. The founding principal of the APS ACTION is that it is an internationally collaborative effort, open to qualified investigators across the globe who are committed to

further our understanding of APS and its management. APS ACTION currently consists of 31 members from 20 international centers.

The purpose of this “Note to the Editor” is to review the organizational structure, acknowledgments, and directions of APS ACTION.

Background

The International Congress on aPL is held every three years to discuss the recent advances and future directions in APS. The “13th International Congress on aPL”, chaired by Dr Silvia Pierangeli, was hosted in Galveston, TX, USA on April 13–16, 2010. The three-and-half day event included state-of-the-art lectures, “meet the professor” sessions tailored to the interest of junior scientists and clinicians, selected abstract oral presentations, poster sessions, a laboratory wet workshop to evaluate the performance of various aPL tests, and pre-conference “consensus” workshops for the task forces to report and discuss their conclusions.

The Antiphospholipid Syndrome (APS) Clinical Research Task Force (CRTF) was one of six task forces developed by the “13th International Congress on aPL” organization committee with the purpose of: a) evaluating the limitations of APS clinical research and developing guidelines for researchers to help improve the quality of APS research; and b) prioritizing the ideas for a well-designed multicenter clinical trial and discussing the pragmatics of getting such a trial done. Given that other task forces were designated to review the published aPL/APS studies (task forces on “criteria” aPL tests, “non-criteria” aPL tests, obstetric APS, management of thrombosis, brain involvement in APS, and catastrophic APS and non-criteria aPL-manifestations), the focus of the APS CRTF was not to evaluate specific studies/trials; instead the task force chose to have a critical “bird’s eye view” approach to APS clinical research.

The APS CRTF working algorithm was: a) a questionnaire that was sent to the APS CRTF members before the congress; b) a summary report that was prepared based on the responses to facilitate discussions during the pre-meeting workshop; c) a pre-meeting workshop; d) two plenary sessions based on the conclusions of the task force discussions where input from all the meeting attendees was received; and e) a final report that was circulated among other task force chairs for final remarks. Following this systematic working algorithm, the APS CRTF identified five major issues that impede APS clinical research and the ability to develop evidence-based recommendations for the management of aPL-positive patients: 1) aPL detection has been based on partially or non-standardized tests, and clinical (and basic) APS research studies have included patients with heterogeneous aPL profiles with different clinical event risks; 2) clinical (and basic) APS research studies have included a heterogeneous group of patients with different aPL-related manifestations (some controversial); 3) thrombosis and/or pregnancy risk stratification and quantification are rarely incorporated in APS clinical research; 4) most APS clinical studies include patients with single positive aPL results and/or low-titer aPL ELISA results; furthermore, study designs are mostly retrospective and not-population based, with limited number of

prospective and/or controlled population studies; and 5) lack of the understanding particular mechanisms of aPL-mediated clinical events limits the optimal clinical study design¹.

The core recommendation of the APS CRTF was that there is an urgent need for a true international collaborative approach to design and conduct well-designed prospective large-scale multi-center clinical trials of patients with persistent and clinically significant aPL profiles. Thus, an international collaborative working Summit took place in Miami, FL, USA (Nov 2–4, 2010) that resulted in the formation of a clinical trial research alliance entitled: **AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiONal Networking (“APS ACTION”)**.

Organizational Structure

The Founding Steering Committee of APS ACTION is composed of 28 members from 20 international centers (Appendix). The Executive Committee is composed of eight democratically elected members (Table 1), each representing different regions of the world. The number of APS ACTION members/centers is expected to increase in the near future as new membership applications are being accepted since November 2011.

The primary mission of APS ACTION is to prevent, treat, and cure aPL- associated clinical manifestations through high-quality, multicenter, and multidisciplinary clinical research. The secondary mission is to refine and advance the definitions of aPL- associated clinical manifestations through international collaboration and data sharing. The approach is that all the members work together through this research alliance to design and conduct clinical trials, collect data via an international registry, and leverage funding opportunities.

The progress noted below, is the result of a much hard work and communication among the founding members. In addition to regular electronic communications, teleconferences, and skype conferences, the governance documents calls for an Annual APS ACTION Summit each year, and a working mid-year meeting which have been productive. Since the 2010 Miami Summit that resulted in the creation of APS ACTION: 1) a one-day workshop took place in London, UK (May 2011); and 2) a two-day meeting (2nd APS ACTION Annual Summit) took place in Chicago, IL, USA (November 2011). In addition, the APS ACTION website (www.apsaction.org) was launched this year along with its identifying logo (Figure 1) that have been used internationally.

To attract young talent to APS research, APS ACTION has created the annual APS ACTION Young Scholar Award, given to three young physician-scientists nominated by APS ACTION members annually. The award recipients are invited to attend the APS ACTION Annual Summit, where they participate in the discussions and decisions of the organization. The goal of the Young Scholar Program is not only to bring new perspectives to our efforts, but also to create incentives for young scholars to become involved in this area.

Accomplishments - A Journey of Success from the Miami 2010 Summit to the Present

Due to the hard work and collaborative spirit of APS ACTION members, there has been exciting progress in its first year. During the Miami 2010 Summit, APS ACTION established six subcommittees (Clinical Trials; Database Creation and Data Collection; Biospecimen Collection and Handling; Mechanistic Studies; Collaboration with Other Registries; Funding; and Advocacy and Awareness) that have been working independently to advance various aspects of the organization's mission and research efforts.

During the first year of APS ACTION, the 'Clinical Trials' Subcommittee primarily focused on the development of a well-designed controlled multi-center clinical trial. Based on a pre-Miami Summit survey as well as the Miami Summit discussions, following "FINER" [Feasible; Interesting; Novel; Ethical; and Relevant] criteria² and "PICOT" [Population; Intervention; Comparison; Outcomes; Time] technique², it was decided that a hydroxychloroquine (HCQ) trial should be one of the first clinical studies designed and conducted by APS ACTION. The primary objective of the first trial designed by APS ACTION is to determine the efficacy of HCQ in the primary thrombosis prevention of 1,000 persistently aPL-positive but thrombosis free patients (age 18–60 years) with no other systemic autoimmune diseases over the five year study period. The secondary objectives are to determine: a) the thrombosis incidence rate; b) the effect of HCQ on mortality rate; and c) the effect of HCQ on aPL profile.

Similarly, during the first year of the network, the "Database Creation and Data Collection" Subcommittee worked on the development of the web-based³ international registry of persistently aPL-positive patients (with/without systemic autoimmune diseases). The primary objective of the "APS ACTION International Clinical Database and Repository" is to establish an international secure, web-based clinical database and repository of aPL-positive patients so that the natural course of at least 2,000 patients can be followed over 10 years. Secondary objectives are to analyze the occurrence rate of (and the risk factors for): a) new clinically symptomatic thrombosis (arterial, venous, or small vessel thromboses) confirmed by objective testing; and b) new non-thrombotic aPL-related manifestations (obstetrical manifestations, non-criteria manifestations). Furthermore, the APS ACTION "Clinical Database and Repository" will function as: a) a database for better defining aPL-related clinical problems and treatment responses; b) a repository for standardizing aPL tests; and c) a resource for future basic science and clinical research projects.

Given that adequate biospecimen collection, storage, and handling are critical to ensure integrity and adequacy of samples, the "Biospecimen Handling and Storage" Subcommittee, in collaboration with the "Mechanistic Studies" Subcommittee prepared a detailed manual for the handling of the blood samples that will be collected annually. In addition, four APS ACTION centers from different regions (USA, Europe, South America, and Australia) have been selected as the "core laboratories".

Future Directions

Based on the efforts described above, in early 2012, APS ACTION launched two important collaborative international projects: 1) a randomized controlled trial of HCQ in the primary thrombosis prevention of persistently aPL-positive but thrombosis-free patients without other systemic autoimmune diseases; and 2) a web-based registry of aPL-positive patients with or without systemic autoimmune diseases, which will also include annual blood collection for aPL-testing and future basic science studies.

Since November 2011, APS ACTION has been accepting applications from new centers that can contribute to its mission. Membership has been decided based on well-defined eligibility criteria that include the APS research interest of centers and their commitment and ability to participate in APS ACTION research activities. Physicians interested in participating in APS ACTION network can contact Joann Vega CCRC, APS ACTION lead coordinator, at apsaction@info.org.

Our hope is that APS ACTION will support and promote aPL/APS research internationally by: 1) designing collaborative large-scale clinical research projects that will help generate evidence-based recommendations for prevention and management of aPL-related clinical events; 2) maintaining a repository that will help us standardize aPL tests and perform mechanistic studies; and 3) generating private and government funding all around the world.

In the end, we hope to find better treatments for APS, which is a leading cause of thrombosis, pregnancy morbidity, and other life-altering consequences, – and to heighten awareness about this life-threatening, autoimmune condition.

Appendix

APS ACTION Founding Steering Committee: Laura Andreoli (2010 Young Scholar, University of Brescia, Brescia, Italy), Ware Branch (University of Utah School of Medicine, Salt Lake City, UT, USA), Robin Brey (University of Texas Health Science Center, San Antonio, TX, USA), Ricard Cervera (Hospital Clinic, Barcelona, Catalonia, Spain), Ceceilia B. Chighizola (University of Milan, Milan Italy), Hannah Cohen (University College London Hospitals, London, UK), Maria Cuadrado (St. Thomas Hospital, London, UK), Philip deGroot (University Medical Centre, Utrecht, Netherlands), Ronald Derksen (University Medical Centre, Utrecht, Netherlands), Doruk Erkan (Hospital for Special Surgery, New York, NY, USA), Paul Fortin (Centre Hospitalier Universitaire de Quebec, Quebec, Canada), Bill Giannakopoulos (2010 Young Scholar, St. George Hospital, University of New South Wales, Sydney, Australia), Nigel Harris (University of West Indies, Jamaica), Munther Khamashta (St. Thomas Hospital, London, UK), Steve Krilis (St. George Hospital, University of New South Wales, Sydney, Australia), Steven R. Levine (SUNY Health Science Center, Downstate Stroke Center, Brooklyn, NY, USA), Roger Levy (Universidade do Estado do Rio de Janeiro, Brazil), Michael Lockshin (Hospital for Special Surgery, New York, NY, USA), Sam Machin (University College London Hospitals, London, UK), Pierluigi Meroni (University of Milan, Milan, Italy), Tom Ortel (Duke University Medical Center, Durham, NC, USA), Vittorio Pengo (University Hospital,

Padova, Italy), Silvia Pierangeli (University of Texas Medical Branch, Galveston, Texas, USA), Guillermo Pons-Estel (2010 Young Scholar, Hospital Clínic, Barcelona, Catalonia, Spain), Jacob Rand (Montefiore Medical Center, Bronx, NY, USA), Robert Roubey (University of North Carolina, Chapel Hill, NC, USA), Jane Salmon (Hospital for Special Surgery, New York, NY, USA), Angela Tincani (University of Brescia, Brescia, Italy), Denis Wahl (Nancy University, Nancy, France).

APS ACTION Regular Members (2011 Young Scholars): Alessandra Banzato (University Hospital, Padova, Italy), Ceceilia B. Chighizola (University of Milan, Milan Italy), Guilherme de Jesus (Universidade do Estado do Rio de Janeiro, Brazil).

References

1. Erkan D, Derksen R, Levy R, et al. Antiphospholipid Syndrome Clinical Research Task Force Report. *Lupus*. 2011; 20:219–224. [PubMed: 21303838]
2. Thabane L, Thomas T, Ye C, Paul J. Posing the research question: not so simple. *Can J Aneasth*. 2009; 56:71–79.
3. Paul A. Harris, Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, Jose G. Conde, Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009; 42:377–381. [PubMed: 18929686]

Figure 1.
APS ACTION Logo

Table 1

APS ACTION Executive Committee

Doruk Erkan (Chair)	United States
Ware Branch	United States
Paul Fortin	Canada
Munther Khamashta	Europe
Steve Krilis	Asia-Pacific
Roger Levy	Latin America
Michael D. Lockshin	United States
Pierluigi Meroni	Europe