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Immunosuppression use in primary antiphospholipid antibody-positive patients: Descriptive analysis of the AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) Clinical Database and Repository ("Registry")

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Abstract

Background/Purpose: APS ACTION Registry was created to study the outcomes of patients with persistently positive antiphospholipid antibodies (aPL) with or without other systemic autoimmune disease (SAIDx). Given that immunosuppression (IS) is used for certain aPL manifestations, for example, thrombocytopenia (TP), our primary objective was to describe the indications for IS in aPL-positive patients without other SAIDx. Secondly, we report the type of IS used in patients with selected microvascular or non-thrombotic aPL manifestations.

Methods: An online database is used to collect clinical data. The inclusion criteria are positive aPL based on the laboratory section of the APS Classification Criteria, tested at least twice within one year prior to enrollment. Patients are followed every 12 ± 3 months. For this descriptive retrospective and prospective analysis, we included aPL-positive patients without other SAIDx and excluded those with new SAIDx classification during follow-up. For each patient, we retrieved clinical data at baseline and follow-up including selected aPL manifestations (diffuse alveolar hemorrhage [DAH], antiphospholipid-nephropathy [aPL-N], livedoid vasculopathy [LV]-related skin ulcers, TP, autoimmune hemolytic anemia [AIHA], cardiac valve disease [VD]), and IS medications.

Results: Of 899 patients enrolled, 537 were included in this analysis (mean age 45 ± 13 years, female 377 [70%], APS Classification in 438 [82%], and at least one selected microvascular or non-thrombotic aPL manifestation in 141 (26%)). Of 537 patients, 76 (14%) were reported to use IS (ever), and 41/76 (54%) received IS primarily for selected aPL manifestation. In six of 8 (75%) DAH patients, 6/19 (32%) aPL-N, 4/28 (14%) LV, 25/88 (28%) TP, 6/11 (55%) AIHA, and 1/43 (2%) VD, the IS (excluding corticosteroids/hydroxychloroquine) indication was specific for selected aPL manifestation.

Conclusion: In our international cohort, 14% of aPL-positive patients without other SAIDx were reported to receive IS; the indication was at least one of the selected microvascular and/or non-thrombotic aPL-related manifestations in half. Thrombocytopenia was the most frequent among those selected aPL-related manifestations; however, approximately one-third received IS specifically for that indication. Diffuse alveolar hemorrhage was frequently treated with IS followed by AIHA and aPL-N. Systematic controlled studies are urgently needed to better define the role of IS in APS.

Keywords

antiphospholipid syndrome, antiphospholipid antibodies, immunosuppression, non-criteria manifestations

Background

Antiphospholipid syndrome (APS) is characterized by thrombosis and/or pregnancy morbidity in association with antiphospholipid antibodies (aPL), lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti-β_2 glycoprotein-I antibodies (aβ_2GPI).[1] APS may exist in its primary form when it occurs in patients without systemic autoimmune disease (SAIDx), or in association with other autoinflammatory disorders, particularly systemic lupus erythematosus (SLE).[2]

The Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) was created in 2010 specifically to conduct large-scale multicenter clinical studies and trials in persistently aPL-positive patients. The goal of the APS ACTION Clinical Database and Repository ("Registry") is to study the natural course of persistently aPL-positive patients with or without other SAIDx over at least 10 years.[3]

Immunosuppression (IS) has been increasingly used in primary APS, specifically for microvascular disease, for example, diffuse alveolar hemorrhage (DAH), aPL-nephropathy (aPL-N), and hematologic non-thrombotic manifestations such as thrombocytopenia (TP).[4] However, there are no randomized control studies, and very limited number of systematic studies, to support the use of IS in aPL-positive patients without other SAIDx. Thus, our primary objective was to describe the general indications for IS medications in aPL-positive patients without other SAIDx. Secondly, we report the type of IS used in patients with selected microvascular or non-thrombotic aPL-related manifestations.

Methods

The inclusion criteria for the APS ACTION registry are positive aPL based on the updated Sapporo classification criteria at least twice within 1 year prior to enrollment. Patients are followed every 12 ± 3 months with clinical data and blood collection. Antiphospholipid antibody-specific medical history (including microvascular or non-thrombotic aPL-related manifestations), aPL/APS-related medications (anticoagulant/antiplatelet medications, hydroxychloroquine (HCQ), intravenous immunoglobulin (IVIG), plasma exchange, rituximab (RTX), azathioprine (AZT), corticosteroids (CS), cyclophosphamide, cyclosporine, methotrexate (MTX), mycophenolate mofetil (MMF), and "other" IS medications), and blood samples (for aPL-positivity confirmation) are collected at registry entry. At each annual follow-up visit, clinical data for the new aPL-related events and new SAIDx, blood

samples, and medication changes are collected. The registry data are managed using REDCap electronic data capture tool, a secure, web-based system designed to support research studies.[5]

In this descriptive retrospective and prospective analysis of the registry, we only included aPL-positive patients without other SAIDx and excluded those with catastrophic APS (CAPS) (given IS is part of the acute CAPS management) or with new SAIDx classification during follow-up (given the possibility of IS use part of the SAIDx management). We identified all patients who have ever received IS at baseline and/or during prospective follow-up, as well as investigator-reported indications for IS use and attribution of IS to selected microvascular or non-thrombotic aPL-related manifestations. For the purposes of this study, CS and HCQ use were not counted as IS medications, and only selected microvascular or non-thrombotic aPL-related manifestations were analyzed: DAH based on bronchoscopy/bronchoalveolar lavage and/or biopsy, aPL-N (biopsy-proven) and cardiac valve disease (VD) based on the definitions included in the 2006 revised Sapporo APS classification criteria report,[6] livedoid vasculopathy (LV)-related skin ulcers, TP defined as a platelet count of <100,000 per microliter tested twice at least 12 weeks apart, and autoimmune hemolytic anemia (AIHA) defined as anemia with the presence of hemolysis and with a positive direct antiglobulin test (DAT).

Data were summarized in a descriptive fashion; mean ± SD (SD) was used for continuous variables.

Results

As of July 2021, 899 patients were included in the registry; five were excluded due to CAPS and 357 (40%) were excluded due to another SAIDx at baseline (344) or during follow-up (13 [11 SLE and two rheumatoid arthritis). Of the remaining 537 patients (mean age at entry: 45 ± 13 years; 70% female; 70% white; 438 [82%] met the APS Classification Criteria; and 141 (26%) had at least one of the selected microvascular and/or non-thrombotic aPL-related manifestation), 76 (14%) used IS (ever) (excluding CS and HCQ) (Table 1).

Based on investigator-reported indications, of 76 IS users, 41 (54%) were treated primarily because of their selected aPL-related manifestation (16 patients had more than one selected aPL-related manifestations simultaneously or at different time points), whereas 35/76 (46%) received IS for other potential indications (Table 1 Footnote). Of note, 16 [46%] of the latter group also had one or more of the selected aPL-related manifestations (1 aPL-N, 7 LV, 7 TP, 1 AIHA, and 2 VD), although IS use was not reported for that indication. The number of patients fulfilling three of 11 American College of Rheumatology SLE Classification Criteria, that is, "lupus-like disease" was 16/41 in the former group and 6/35 in the latter group.

In a subgroup analysis of 141 (26%) patients with at least one selected microvascular and/or non-thrombotic manifestations reported at baseline and during the follow-up, (a) eight patients had DAH and 6 (75%) of these received IS for this indication (most commonly used medications were IVIG and/or RTX); (b) 19 (13%) had aPL-N and 6 (32%) received IS for this indication (MMF and/or RTX); (c) 28 (20%) had LV and 4 (14%) received IS for this indication (RTX); (d) 88 (62%) had TP and 25 (28%) received IS for this indication (IVIG and/or RTX); (e) 11 (8%) had AIHA and 6 (55%) received IS for this indication (IVIG and/or AZT); and (f) 43 (30%) had VD and 1 (2%) received IS for this indication (IVIG) (Table 1).

Discussion

In this descriptive retrospective and prospective analysis of our international cohort of aPL-positive patients without other SAIDx and CAPS, 76 (14%) of the cohort received IS medications other than CS and HCQ. The indication was at least one of the selected microvascular and/or non-thrombotic aPL-related manifestations (DAH, aPL-N, LV, TP, AIHA, and/or VD) in half of these patients. Although TP was the most common, DAH, aPL-N, and AIHA were frequently treated with IS.

There is no uniform approach to the management of microvascular or non-thrombotic APS, most probably due to heterogeneous organ involvement with different severity, lack of controlled studies, or compelling evidence supporting any treatment strategy. The only published systematic assessment of IS in APS has been a pilot prospective uncontrolled small (n: 19) study of RTX (the RITAPS study) for aPL-positive patients with microvascular disease or hematologic involvement.[7] This study suggested that despite causing no substantial change in aPL profiles, RTX is effective in some aPL-positive patients with TP, aPL-related skin ulcers, kidney disease, and cognitive dysfunction. The use of other traditional (e.g., MMF, AZT, or cyclophosphamide) and non-traditional (e.g., sirolimus and eculizumab) IS agents in APS is mostly based on case reports[8–11] and expert/consensus opinion.[4,12,13] In our analysis, the most commonly used IS medications were IVIG followed by RTX and MMF; the relatively higher proportion of patients treated with IS for specific aPL-related manifestations were those with DAH (75%) and AIHA (55%).

DAH is a rare manifestation of APS, which generally responds to CS. However, flares during CS tapering is common, and many patients require a steroid-sparing IS agent to achieve full remission. Based on a literature review of 66 patients with primary APS (excluding CAPS), cyclophosphamide- or RTX-based regimens achieve the

Table 1. Patients with Selected Microvascular and/or Non-thrombotic Manifestations (MV-NTM) (immunosuppressive [IS] medications were recorded in 76 patients; indication was for MV-NTM in 41 and "other"[a] in 35).

# of patients	DAH	aPL-N	LV	TP	AIHA	VD
Baseline	5	15	25	84	11	37
Follow-up	3	4	3	4	0	6
Total						
Alone or together with another MV-NTM	8[b]	19[b]	28[b]	88[b]	11[b]	43[b]
Alone as the only MV-NTM	4	4	16	70	6	25
Immunosuppression use (ever)	6	9	13	34	7	9
Immunosuppression use for MV-NTM[c]	6 (75%)	6 (32%)	4 (14%)	25 (28%)	6 (55%)	1 (2%)
IVIG	4	1	1	18	4	1
Rituximab (RTX)	5	4	3	14	2	0
Mycophenolate mofetil (MMF)	3	5	1	5	0	0
Azathioprine (AZT)	0	2	1	5	3	0
Plasma exchange (PE)	1	0	0	2	0	0
Cyclophosphamide (CYC)	1	1	0	3	0	0
Belimumab (BEL)	0	1	1	1	0	0
Eculizumab (ECU)	0	0	0	2	0	0
Sirolimus (SIR)	0	0	0	2	0	0
Other[d]	1	0	2	1	0	0
Hydroxychloroquine use (total)	5	10	19	41	6	16

Abbreviation: DAH: diffuse alveolar hemorrhage; aPL-N: aPL-nephropathy; LV: livedoid vasculopathy; TP: persistent thrombocytopenia < 100 × 10^9/l; HA: hemolytic anemia; and VD: cardiac valve disease.

[a]Immunosuppressive indications reported other than selected microvascular and non-thrombotic manifestations were (35/76): Lupus-like clinical features with musculoskeletal and/or hematologic involvement without SLE classification (n: 6, methotrexate [MTX], AZT); heparin-induced TP (n:1, IVIG); peripheral artery ischemia (n:1, IVIG, RTX); cognitive dysfunction (n:1, RTX, MMF); HELLP (hemolysis, elevated liver enzyme, and low platelet) syndrome (n:2, PE, IVIG); vasculitis (n:3, AZT, CYC, MMF, MTX); hidradenitis suppurativa (n:1, adalimumab); post-CVA acute renal failure(n:1, PE); interstitial lung disease (n:2, IVIG, RTX, MMF, CYC); pregnancy morbidity resistant to traditional management (n:2, IVIG); peripheral artery bypass surgery (n:1, eculizumab); primary biliary cirrhosis/autoimmune hepatitis/Crohn's disease (n:3, AZT); myasthenia gravis (n:1, AZT); renal transplant thrombotic microangiopathy/hepatopulmonary syndrome (n:2, CYC, MMF, tacrolimus); idiopathic pachymeningitis encephalopathy (n:2, AZT, RTX, CYC); dystonia/neuropathy (n:3, IVIG, PE, RTX, AZT, MMF, MTX); in vitro fertilization co-adjuvant treatment (n;1, IVIG); anticoagulation refractory TIA (n:1, RTX); and atopic dermatitis/alopecia (n:1, MMF).

[b]Corticosteroid use was reported in 3 DAH patients, 4 aPL-N, 4 LV, 19 TP, 3 AIHA, and 1 VD.

[c]16 patients had more than one MV-NTM simultaneously or at different time points.

[d]Abatacept, MTX, danazol, and tacrolimus.

highest remission rates (50%); other strategies include IVIG, plasmapheresis, MMF, and/or AZT.[14] Based on our small numbers, the most commonly used IS for DAH was RTX followed by IVIG and MMF.

Antiphospholipid antibody-associated nephropathy, which develops in less than 5% of aPL-positive patients, can present as acute or chronic disease.[15,16] Chronic aPL-N is usually slowly progressive, with no proven treatment. The use of anticoagulation in this scenario is controversial;[4] and there have been anecdotal reports of successful CS, cyclophosphamide, MMF, or RTX use.[7,9] Strong conclusions regarding the effectiveness of any of these regimens are difficult given the lack of systematic studies. One-third of our registry patients with aPL-N received IS, most commonly MMF and RTX, which supports the fact that international centers experienced in APS have different strategies while managing these patients.

Skin manifestations of aPL vary from livedo reticularis/racemosa to LV-related skin ulcerations.[17] For LV, CS are less preferable due to the risk of infection. For patients failing conservative management, RTX is an option;[4,7] in addition to the complete response of five RTX-treated patients with aPL-related skin ulcers in the RITAPS trial,[7] another primary APS patient with recurrent skin ulcers was reported to receive belimumab with partial improvement.[18] In our cohort, the most commonly used IS for LV was RTX; however, the majority of our cohort did not receive IS, which may be due to different management strategies of the centers or the severity of the LV presentation.

Twenty percent of aPL-positive patients develop mild-to-moderate TP;[19] however, TP usually does not require any treatment because the degree of TP is generally above 30–50 × 10^9 L.[20] For severe TP, CS and/or IVIG are first line treatments.[19] Azathioprine, MMF, or RTX are considered in CS-resistant cases.[20–23] In our registry, TP was the most frequent among those selected microvascular or non-thrombotic aPL manifestations; for patients

requiring treatment, the most common strategy was IVIG followed by RTX.

APL may be associated with the formation of autoantibodies directed against erythrocyte antigens, leading to premature destruction of red blood cells.[21] Almost 5% of aPL-positive patients develop DAT-positive AIHA,[19] which is usually treated with CS, AZT, MMF, RTX, or splenectomy.[20,24] In our study, almost half of the AIHA patients required treatment and the most commonly used IS was IVIG followed by AZT.

Valvular heart disease (vegetations and/or valve thickening) is the most common aPL-related cardiac manifestation. Depending on the definitions and the echocardiography method, that is, transthoracic versus transesophageal, 10%–50% of aPL-positive patients may develop VD.[25] Both aortic and mitral insufficiencies are common and require valve replacement in severe cases.[20] Cardiac valve thickening increases the risk for arterial/embolic events. Corticosteroids and anticoagulation generally do not lead to regression of cardiac valve lesions, but antithrombotic treatment is usually administered to decrease risk of embolic events, despite low evidence associated with outcome.[20] We found only one patient who received IS specifically for VD.

Based on a recent descriptive analysis of the APS ACTION Registry, TP, AIHA but not aPL-N, LV, or VD is observed more commonly in aPL-positive SLE patients, compared to those without SLE.[15] Similarly, CS, HCQ, AZT, cyclophosphamide, MTX, and MMF, but not IVIG, RTX, or plasma exchange use was more common in aPL-positive SLE patients. Thus, our previous and current registry analyses demonstrate that IS is part of the APS management strategy, independent of SLE Classification or SLE clinical features. We believe that IS has a role in the management of aPL-positive patients with selected clinical phenotypes, mainly microvascular APS and non-thrombotic APS; however, we are also aware that despite theoretical and preclinical evidence, clinical studies supporting the role of IS in APS is limited.[4]

Our study has several limitations including the retrospective baseline data collection, which may not provide the most accurate information about each IS medication. The number of patients with some of the selected aPL-related manifestations is relatively small. Furthermore, we cannot comment on the use of CS and HCQ for selected microvascular or non-thrombotic aPL-related manifestations included in our study given that these medications are commonly used for other indications (similarly we cannot comment how CS and/or HCQ use affected the decision-making regarding the IS use). Another limitation is an inability to indicate IS effect on aPL titers recognizing contradictory reports appear in the literature.[7] Lastly, our retrospective/prospective study design did not allow investigation of the effectiveness of IS medications; however, further studies are planned based on the prospective registry data. Despite these limitations, APS ACTION Registry has a heterogeneous group of aPL-positive patients from tertiary referral centers, representing a real-world experience; and this study will serve as a model for future analysis of the data and hopefully help build a future research agenda.

In conclusion, in our multi-center international cohort, 14% of aPL-positive patients without other systemic autoimmune diseases were reported to receive IS for selected aPL-related manifestations or other indications. Systematic studies and randomized controlled trials are urgently needed to better define the role of IS in APS.

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Statement for ethics approval

This study obtained approval from HSS APS ACTION IRB # 2014-252. All participants gave informed consent.

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