111 CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME: WHAT IS NEW?

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Background Catastrophic antiphospholipid syndrome (CAPS) is a rare variant that accounts for 1% of patients with antiphospholipid syndrome.

Methods The current knowledge of this potential devastating entity comes from the International Registry of patients with CAPS, named 'CAPS Registry'. This presentation shows the results of the most recent analysis of the registry.

Results Small vessel thrombosis, laboratory features of microangiopathic haemolytic anemia, and development of multisystem involvement in a very short period of time are the main characteristics of this syndrome. Clinical manifestations are due to thrombosis but also, although the evidences are indirect, to excess of proinflammatory cytokines. Therefore, treatment strategy is based on the combination of anticoagulation, glucocorticoids, plasma exchange and/or intravenous immunoglobulins, the so-called triple therapy. In refractory cases or in those with initial life-threatening situation, rituximab may be an effective option. Recently, some cases of CAPS have been effectively treated with the addition of eculizumab to the triple therapy.

Conclusions Despite its low frequency, the mortality-related is still very high, ranging from 50% of patients in the first series to 37% in the most recent data.

112 RITUXIMAB FOR REFRACTORY MANIFESTATIONS OF THE ANTIPHOSPHOLIPID SYNDROME – THE ISRAELI EXPERIENCE

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Background Clinical manifestations of the antiphospholipid syndrome (APS) are heterogeneous and may be difficult to

treat. Evidence that B cells and particularly anti-phospholipid antibodies (aPL) are involved in APS-clinical events has been documented. Thus, the ability of rituximab (RTX) to deplete B cells and possibly reduce aPL titers makes it an appealing potential therapy for this autoimmune disease. Real world data on the usefulness of RTX treatment for APS is scarce. In this study we report outcomes of RTX administration in treating different manifestations of APS.

Methods In this retrospective case series, data from 3 medical centers in Israel was collected regarding the use of RTX to treat APS. Medical records were reviewed for clinical manifestations, indication for RTX treatment, concomitant medications, aPL status and the response to treatment. The latter was clinically defined as complete resolution of the indicated manifestation, partial improvement or no response.

Results We included 40 APS patients in this case series, 31 primary-APS and 9 with APS secondary to SLE. Our cohort consisted of 16 males and 24 females, mean age 39 ± 14 years, 29 were defined as triple-aPL positive. All patients presented with 1–2 difficult to treat manifestations including: diffuse alveolar hemorrhage (DAH-n=6), recurrent thrombosis despite anticoagulation (n=10), thrombocytopenia and/or hemolytic anemia (n=10), neurological manifestations (n=7), nephropathy (n=2) vasculitis/leg ulcers (Skin) (5p) and catastrophic-APS (n=2). Notably, 32 (80%) patients responded favorably (complete response - 22; partial improvement -10), 5 did not respond to RTX therapy and 3 patients died within 12 months (figure 1). Concomitant therapies (e.g. hydroxychloroquine, glucocorticoids, cyclophosphamide, plasmapheresis, azathioprine etc.) did not correlate with favorable responses, rather treatment with cyclophosphamide or plasmapheresis correlated with worse outcomes ($p < 0.01$). In this cohort, the rituximab protocol was linked with treatment success as 17 patients received 4 weekly doses of 375 mg/m^2 while 23 received 2 doses of 1000 mg 14 days apart. The former protocol resulted in 17/17(100%) responders, 12/17(70%) with a complete response, while following the latter protocol 15/23 (65%) responded, 10/23(45%) with a complete response ($p = 0.012$). A decrease in aPL titers within 2–6 months of RTX treatment correlated with a good response to rituximab therapy. Data regarding aPL titers within 2–6 months was available for 22 patients of whom 13 experienced a complete response correlating with a significant decrease in the RVVT-ratio, anti-cardiolipin-IgM and anti-beta2GPI-IgG titers ($p = 0.02$, 0.016 and 0.015 respectively).

Abstract 112 Figure 1 Response of APS manifestation to rituximab treatment

Conclusions Herein, consistent with previous small case series, we report a good therapeutic response to RTX in patients with difficult to treat manifestations of APS. The RTX treatment protocol may affect response to therapy and a decrease of aPL titers within 2–6 months following therapy may predict a better response. Larger studies are required to confirm these results.

113 NEUTROPHILS AND INNATE IMMUNITY IN THE PATHOGENESIS OF SLE

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Background Innate immunity cells, cytokines and inflammatory pathways have been recognised as inducers and amplifiers of autoimmune responses and tissue injury in SLE.

Methods Published experimental data during the last five years on the contribution of innate immunity, particularly neutrophils and type I interferon, are summarized and their clinical implications are discussed.

Results Recent genome-wide expression studies have implicated neutrophils in human SLE and lupus nephritis. Through a combined transcriptomic, epigenetic, and functional analysis, distinct subtypes of these cells have been identified in patients with SLE, with low-density granulocytes exhibiting excessive death by generation of extracellular chromatin traps (NETs) that are decorated with immunostimulatory/alarmin molecules such as interleukin-33 and promote the activation of other immune cells, type I interferon (IFN) production and endothelial injury. Intracellular protein citrullination mediated by neutrophil peptidylarginine deiminases (PADs) is critical for NETs formation and accordingly, targeting PADs ameliorates lupus disease by reducing autoantibodies, type I IFN, immune cell activation, vascular dysfunction, and NET immunogenicity. Notably, activation of Toll-like receptors (TLR)-7/8 in neutrophils causes proteolytic cleavage of the N-terminal part of Fc γ -receptors (Fc γ RIIA), thus abrogating their capacity to phagocytose immunocomplexes while promoting their death by NETosis.

Mechanistically, recruitment of syntenin-1 by UNC93B1 has been reported to facilitate the sorting of TLR-7 into multivesicular bodies, therefore offering dynamic regulation of TLR-7 activation/signaling. Besides NETs, a number of other pathways may enhance IFN production in SLE such as apoptosis-derived membrane vesicles through activation of cGAS–STING, and photosensitivity-induced IFN-kappa released by keratinocytes. The latter is in line with clinical observations that therapeutic blockade of IFN or downstream signaling may be particularly beneficial in cutaneous manifestations of SLE. Remarkably, IFN signature is present in multiple immune cell types in SLE such as in B-cells where it causes breach of tolerance, promoting autoreactive B cell development into the autoantibody-forming cell and germinal center pathways. In T-cells, SLE patients who carry the *STAT4* risk allele rs7574865[t] display augmented inflammatory responses to IL-12 and IFN- α , and vice versa, IFN- α may augment the IL-12-induced *STAT4* activation, therefore highlighting a subgroup of patients who may benefit from IFN α /JAK/STATs targeting.

Conclusions Culminating research further supports the critical role of neutrophils and innate immune pathways in SLE pathogenesis. Elucidation of intracellular pathways pertaining to production and regulation of important mediators such as IFN may provide novel insights towards development of targeted therapies.

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114 REPEAT RENAL BIOPSY IN THE MANAGEMENT OF LUPUS NEPHRITIS

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Background The therapy of lupus nephritis remains toxic and only partially effective but the benefits in terms of renal and patient survival are clear. However, there is considerable heterogeneity in the prognosis of individual patients and in their response to and tolerance of therapy. Accurate assessment of disease activity to guide therapy is limited by the complex relations between clinical biomarkers - serum creatinine, urine protein and sediment - with histologic activity. Renal biopsy is invasive with well characterised, if rare, risk of haemorrhage. While the initial biopsy confirms the diagnosis, nephritis class and other parameters, prediction of treatment response and long term outcome is limited. The extent to which the cost and risk of repeat biopsy can be justified in terms of improving long term prognosis is unclear resulting in wide variances in current practice and advice. As better targeted therapies become available in parallel with better pathway and target identification in the biopsy there is the potential role for sequential biopsy to influence the type and duration of treatment.

Methods A small number of prospective studies have examined protocol biopsies, with a larger number of observational studies limited by inconsistent indications for repeat biopsy. Outcomes have included descriptions of changes in histologic class, activity and chronicity, associations between histologic activity and clinical biomarkers, impact on treatment decisions, renal prognosis in terms of renal relapse or loss of renal function, and safety.

Results Activity on repeat protocol biopsy has been associated with increased risk of relapse and loss of function.¹⁻³ Trends in change in histologic class have been progression from II to IV-G, from IV to IV + V, and for the subtypes of IV-G and IV-S to remain the same. In a small number of cases a non-lupus renal diagnosis was discovered. When compared to changes in urine protein, one third of complete proteinuric responders had histologic activity, while almost one half of non-proteinuric responder had no histologic activity. The impact of repeat biopsy on therapeutic decision remains controversial with evidence for and against.

Conclusions Repeat renal biopsy studies have contributed to our understanding of the course of nephritis and provide information unavailable from other sources. While arguments in favour of protocol biopsy continue, no long term benefit on hard outcomes has been defined. Clinical utility of repeat biopsy is highest when there is uncertainty on treatment decisions, such as, with persisting proteinuria or falling GFR, in the absence of an apparent treatment response or when