MRL/lpr mice. Complications of human studies are the measurements of complement activation and the multiplicity of potential modes of action. There is also the diversity of immunogenetic backgrounds in lupus and evidence that contributions of different pathways may differ between patients or at different phases of disease.

Learning Objectives

- Explain the rationale for complement inhibition in ANCA associated vasculitis
- Discuss the clinical evidence of efficacy of complement inhibition in ANCA associated vasculitis
- Describe lessons can be learned from the ANCA associated vasculitis of relevance to the exploration of complement inhibition in SLE

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Hot topics: highlighting accomplishments in lupus research

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TRANSLATIONAL INSIGHTS INTO THE PATHOGENESIS TRANSFORMING SLE TREATMENT

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Systemic lupus erythematosus (SLE) is a heterogeneous disease characterized by abnormalities in cellular and humoral immunity. Key disturbances comprise abnormal cytokine production (increased type I IFN, IL-6, IL-17, IL-12 and IL-23, BAFF) and B lineage cell abnormalities. In the light of the recent SARS-Cov2 pandemic, the role of type I IFN and humoral immunity became of great interest and a number of similarities, but also subtle differences, to SLE became apparent and will be addressed based on recent data.

Inflammatory cytokines or their corresponding cytokine receptors have been identified as therapeutic targets. Since these cytokines activate various intracellular pathways, such as Jak/Stat signaling, activation of the NfκB or BCR signaling pathways (i.e. spleen tyrosine kinase [Syk]), Bruton's tyrosine kinase (BTK), small molecules inhibiting these pathways are being investigated in various clinical studies permitting a concept of multiple targeting therapy.¹ Recent study experiences blocking Jak1/Jak2 pathways with baricitinib showed clinical improvements over 24 weeks² and identified a number of molecules downstream of Stat1, Stat2, and Stat4 correlating

with SLE activity.³ A Phase Ib/IIa trial using tofacitinib as Jak1/Jak3 selective inhibitor in SLE has also been reported limited to safety but also mechanistic insights.⁴

The recent identification of hyporesponsive but not hyper-responsive B cell functions among SLE and other autoimmune diseases (RA, Sjögren's) require consideration of anergic post-activated (APA) B cells with increased phosphatase activity and responding to CD40 stimulation most pronounced in SLE.⁵ As a result, inhibitors of preferred B cell activation pathways (BTK4, Syk etc.) that generated hope based on experiences with anti-CD20 therapy failed in various SLE and rheumatoid arthritis trials, including a Phase 2 study with the BTK inhibitor fenebrutinib (GDC-0853)⁴ and evobrutinib (e-ACR 2020). Notably, evobrutinib was very efficacious in RRMS5 which also opens new avenues of the understanding of a differential pathogenesis⁶ of the two diseases. Thus, consideration of APA B cells in certain autoimmune diseases responding to CD40 activation may guide the development of successful new therapies in SLE and other diseases.

Learning Objectives

- Discuss the translational rationale and distinct mechanisms of action for novel therapeutic targets in SLE within the context of APA B cells
- Explain the significance of certain signaling pathways, especially Jak/Stat and BCR/TLR signaling as potential treatment targets in SLE

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CLINICAL SCIENCE HIGHLIGHTS THAT ARE TRANSFORMING TREATMENT

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The recent approvals of treatments that, when added to established background therapies, significantly increase response rates in systemic lupus erythematosus (SLE) is exciting. These approvals include belimumab and voclosporin for lupus nephritis (LN), and the anticipated approval of anifrolumab for cutaneous and musculoskeletal SLE, with several more treatments in the pipeline. And yet, 40–50% of patients in trials do not reach the desired improvement. Achieving lupus low disease activity score (LLDAS) maintained for one year occurs in only 50% of patients. The proportion of LN patients reaching end stage kidney disease (ESKD) has not declined in the last decade. Furthermore, the problems of serious adverse

events identified in every clinical trial pose hazard to quality and quantity of life.

The unmet needs evident in these trials are:

1. Earlier diagnosis and treatment
2. Strategies to identify responders early
3. Strategies to anticipate flares before they are clinically apparent
4. Optimization of background therapies
5. Even better new treatments or combination therapies
6. Reduction of risk for damage and death

In LN, delaying renal biopsy by 3 months increases risk of poor outcomes and delaying by 6 months increases risk of end-stage kidney disease by 9-fold.^{1, 2} In a California study of LN patients with government insurance (Medicaid), only 31% were treated with immunosuppressive approaches 1 year after diagnosis.³ Added to these disturbing delays are problems with patients' treatment compliance, which is well less than 60% in many populations. It is also important to identify responders early, with LN there is a strong association between good outcome and decline in proteinuria, with the goal of $\leq 0.7/24$ hours at one year associated with better outcomes.⁴ Several laboratories are reporting panels of cytokines/chemokines and other proteins in serum or urine that predict lupus flare; none are yet widely available for clinical use. Regarding background therapies, all SLE patients that can tolerate it should receive hydroxychloroquine, since it reduces mortality by 35% (over 12 years). Reducing prednisone to the lowest dose possible is also a major goal, whilst finding the balance between damage from active disease and that caused by prednisone and other treatments. Some of the interesting new treatments in clinical trials include inhibition of plasmacytoid dendritic cell activation (a major source of interferon type 1), antibodies to CD20 that are more depleting and less immunogenic than rituximab, and inhibitors of pathways activated by cytokines and receptors in and on B and T cells. Finally, close attention to preventing damage (in addition to reducing immunosuppression) will improve quality and quantity of life, including prevention of infections (COVID vaccination is recommended for SLE patients), accelerated atherosclerosis and osteoporosis with fractures.

In conclusion, the recent advances are transformative in that we can suppress disease activity to protect from organ damage in increasingly higher proportions of patients with SLE, but there is a long way to go and much hard thinking lies ahead.

Learning Objectives

- Describe the efficacy of novel treatment interventions and combinations in improving outcomes in patients with SLE/LN
- Discuss current unmet needs in the management of SLE/LN and how novel treatments may overcome these
- Explain the need for the improving fast access to treatment, whilst minimizing costs and adverse treatment effects, and the importance of educating patients and caregivers about these

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Plenary II: Treatment challenges

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TREATMENT OF CAPS: WHICH DRUGS AND IN WHICH ORDER?

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Antiphospholipid syndrome (APS) may be complicated by a 'thrombotic storm' called catastrophic antiphospholipid syndrome (CAPS), which can lead to multiple organ failure and admission of patients to the intensive care unit. An international consensus statement defined CAPS as the occurrence of: at least three organ/tissue/vessel involvement, occurring in less than a week, with biopsy-proven small vessel occlusion, in patients with defined APS.¹ The prognosis of CAPS is severe but has drastically improved in the last two decades from a 58% mortality in 1996 to a 23% in-hospital death in 2020.² The CAPS classification criteria do not encompass the full spectrum of severe thrombotic APS and patients with pre-CAPS or near-CAPS share the same prognosis as CAPS patients and should probably be treated identically.³ Several treatments have been tested, reported and recommended in the management of CAPS, but all these recommendations rely on a very low level of evidence and are mainly based on the publications from the a single group, the CAPS Registry.⁴ Anticoagulation is the cornerstone treatment of CAPS as it is the only one associated with better outcome in several cohorts.⁵ Heparin (unfractionated or low-molecular-weight) is the treatment of choice and its efficacy must be monitored with heparinemia. The combination of anticoagulation and corticosteroids (i.e. double-therapy) should be provided for every CAPS patient and triple-therapy (double-therapy plus plasma exchange or intravenous immunoglobulins) in patients with life-threatening involvement. In patients with CAPS associated with systemic lupus erythematosus, cyclophosphamide should probably be associated to triple-therapy. When triple-therapy has failed, antiplatelet agents can be added to the standard regimen. Successful use of rituximab and eculizumab have been reported in some refractory patients, however the level of evidence supporting their use is extremely low.

Learning Objectives

- Describe CAPS as a rare and severe complication of antiphospholipid syndrome
- Explain the importance of early treatment, even in pre-CAPS/near-CAPS patients
- Describe why combination of anticoagulation and corticosteroids is the cornerstone treatment of CAPS and that life-threatening CAPS episodes should be treated with a triple-therapy including anticoagulation, corticosteroids and intravenous immunoglobulins or plasma exchange
- Discuss the importance of continued anticoagulation in CAPS-related severe thrombocytopenia
- Explain why rituximab and eculizumab may be useful in refractory CAPS patients