MICROANGIOPATHY IN SLE: A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

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Thrombotic microangiopathy is a syndrome that comprises several disorders characterised by localised or diffuse microvascular thrombosis.^{1 2} These include the catastrophic antiphospholipid syndrome (CAPS),³ thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC) in the context of systemic infections or malignancies, hypertension-related, pregnancy-related and drug-related microangiopathic syndromes, and heparin-induced thrombocytopenia.⁴ Some of these clinical scenarios such as severe preeclampsia and HELLP syndrome may be suspected given the appropriate clinical context such as pregnancy. In other cases, the most important point is to perform a systematic and complete clinical history and physical examination looking for previous thrombosis or pregnancy morbidity, uncontrolled hypertension, bloody diarrhoea, and exposure to heparin or some concrete drugs such as ticlopidine, clopidogrel, chemotherapy agents, and alendronate that have been identified as probable cause of thrombotic microangiopathy. In addition, unexplained weight loss, gradual onset of symptoms, hepatomegaly or splenomegaly, or palpable lymphadenopathies may indicate the existence of malignancy triggering the thrombotic microangiopathy. High-grade fever accompanying chills may be the signs of systemic infection in the form of severe sepsis. A history of acute gastroenteritis with bloody diarrhea caused by verocytotoxin (Shiga-like toxin)-producing *Escherichia coli* but also *Shigella dysenteriae* type I and *Citrobacter freundii* might indicate HUS. In cases of severe hypertension, funduscopic exam is mandatory to rule out the evidence of exudates and papilla oedema pointing to a malignant hypertension.

However, differential diagnosis is not so easy in the real-world setting. On the one hand, the clinical picture may be very similar between different diseases.⁴ Kidney and neurologic involvement may be present in CAPS but also in malignant hypertension, severe sepsis, and TTP/HUS. Conversely, physicians should remember that in most causes of thrombotic microangiopathy, other than CAPS, antiphospholipid antibodies (aPL) may also be present. The aPL have been reported in some patients with TTP/HUS, but usually at low titers. In this context, a decrease in ADAMTS13 activity of fewer than 5% points to TTP as the most probable diagnosis. Infections are capable of inducing aPL but normally at low titer and they are not persistent over time. With all these data, in front of a patient with thrombotic microangiopathy, a comprehensive diagnostic workup should be carried out.

Learning Objectives

- Explain the main challenges in the differential diagnosis of microangiopathy in SLE
- Describe the treatment options for microangiopathy in SLE
- Discuss new trends in research on new markers for microangiopathy in SLE

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Plenary II: Novel Therapeutic Developments in 2020

PLASMA-CELL DIRECTED THERAPIES

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Autoantibodies of various specificities play key roles in the pathogenesis of systemic lupus erythematosus (SLE). They are directly responsible for manifestations such as autoimmune thrombocytopenia, autoimmune haemolytic anaemia, antiphospholipid syndrome, neonatal lupus/congenital heart block and most cases of transversal myelitis. In addition, autoantibodies to dsDNA and nucleosomes may essentially contribute to lupus nephritis.

Antibodies are produced by plasma cells. Short-lived plasma cells die within a few days after their differentiation, whereas long-lived plasma cells can live as long as the organism does. Most importantly, long-lived plasma cells are resistant to most conventional treatments including high-dose prednisolone, cyclophosphamide and anti-CD20 antibodies, because plasma cells are mostly devoid of CD20. Hence, refractory SLE may often be caused by long-lived plasma cells secreting pathogenic antibodies. For these reasons plasma cells represent an attractive target for the treatment of SLE and other antibody-mediated diseases.

Meanwhile, there are several treatments available, at least in clinical trials, which eliminate plasma cells including the long-lived ones:

- a. High-dose cyclophosphamide combined with anti-thymocyte globulin (also containing antibodies against plasma cells) and subsequent autologous stem cell transplantation. This vigorous procedure has substantial treatment-related morbidity and lethality, but, it can also cause an ‘immunological reset’ leading to long-term drug-free remissions of SLE. Of course, stem-cell transplantation affects most cells of the immune system, not only plasma cells.¹
- b. Proteasome inhibitors: Due to their extremely high production of antibodies within the endoplasmic reticulum, plasma cells are highly sensitive towards proteasome inhibition, which blocks the degradation of misfolded proteins, thereby inducing endoplasmic reticulum stress and the terminal unfolded proteins’ response leading to apoptotic cell death.² Proteasome inhibitors affect predominantly plasma cells, however, they may target also other cells with a very high synthesis of secretory proteins. We demonstrated that the proteasome inhibitor bortezomib, which is approved for treatment of multiple myeloma, can efficiently deplete short- as well as long-lived plasma cells in mice and thereby ameliorates murine lupus nephritis.³ Moreover, in a case series the outcomes of 15 SLE patients were analysed, who

had not sufficiently responded to standard treatment and hence, were offered treatment with bortezomib.⁴ The disease activity score SLEDAI and anti-dsDNA antibody titers decreased upon treatment. In all patients with active lupus nephritis proteinuria declined within 6 weeks after start of bortezomib. Total IgG concentrations decreased in most patients by approximately 25%, however, they usually remained within normal limits. All adverse events were mild or moderate. A proteasome inhibitor that targets preferentially immunoproteasomes is currently under investigation in clinical trials for the treatment of autoimmune diseases.

- c. TACI-Ig (atacept) is a soluble fusion protein of the extracellular domain of TACI and the Fc part of human IgG. Atacept binds and neutralises the TACI ligands BAFF and, even more importantly, APRIL, which is a key survival factor for plasma cells. Atacept eliminates quite specifically plasma cells and – as a consequence – causes often hypogammaglobulinemia with increased risk of infections. There is some evidence from placebo-controlled multi-centre clinical trials that atacept may ameliorate SLE disease activity.
- d. Anti-CD38 antibodies: CD38 is an ectoenzyme on the plasma membrane of different cell types such as many B and T cell subsets including plasma blasts and plasma cells. The anti-CD38 antibody daratumumab is approved for the treatment of multiple myeloma. Case reports indicate that daratumumab may be also beneficial in antibody-mediated autoimmune diseases such as severe autoimmune thrombocytopenia, autoimmune haemolytic anaemia and SLE.

In summary, plasma cell-targeted treatments may represent a new and highly effective treatment approach in SLE as well as other antibody-mediated diseases. Placebo controlled clinical trials are required to prove the efficacy and safety of plasma-cell depleting treatments in refractory SLE.

Learning Objectives

- Explain why plasma cells represent an attractive target for the treatment of SLE and other antibody-mediated diseases
- Discuss existing treatments, in clinical trials, which eliminate plasma cells and describe their potential for treating patients with SLE

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08

IL-12/23 DIRECTED THERAPIES IN SLE

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T-cell subsets that promote autoantibody formation and tissue damage play major roles in systemic lupus erythematosus

(SLE). Naïve T cells can be driven by interleukin (IL)-12 to Th1 subsets (which secrete interferon gamma [IFN γ] and activate macrophages), and by IL-23 to expand and maintain Th17 subsets (which secrete IL-17A and F and induce chemotaxis). IFN γ -secreting cells and IL-17-secreting cells are found in skin and kidney tissue in patients with active SLE, although not as prominently as cells secreting type 1 IFNs. IL-12 and IL-23 are heterodimers and share a common unit, p40, that binds to the receptor for each cytokine. Ustekinumab is a humanised monoclonal antibody, administered subcutaneously, that binds p40 and thus reduces cell activation by IL-12 and IL-23. It is FDA-approved for use in Crohn's disease, ulcerative colitis, plaque psoriasis and psoriatic arthritis – diseases in which inflammation clearly is driven in part by IL-17.

Results were published of an international, multicenter, double-blind, randomised Phase 2 trial in 102 patients with active SLE (excluding active nephritis or CNS or vasculitis) treated with standard care plus ustekinumab or placebo.¹ At 24 weeks of treatment, the primary outcome for ustekinumab was met: SRI-4 response occurred in 62% of the treatment group compared to 33% of the placebo. This 29% difference was highly significant, $p=0.006$. The BICLA measurement (based on BILAG rather than SLEDAI-2K measures of disease activity) did not show a significant difference between the groups, raising the debate as to which measures are more appropriate for various studies. However, ustekinumab was better than placebo in preventing worsening, as measured by BILAG, and in producing $\geq 50\%$ improvement in joint counts and CLASI measures of dermatitis. Follow-up studies have shown that the improvement induced by ustekinumab is sustained for 1 to 2 years.

Interestingly, clinical improvement was accompanied by a significant drop in gene signature and protein for type 2 IFN (IFN γ), but not type1 IFN. Response rates were similar in patients with high or normal type 1 IFN signatures. These IFN γ data suggest the interference with IL-12 may be more important in SLE than interference with IL-23, and that Th1 cells may be a good therapeutic target. Phase III studies are in progress.

Other potential treatments for SLE along this pathway include (1) targeting IL-23p19 (instead of p40) such as guselkumab and tildrakizumab (both FDA-approved for plaque psoriasis), (2) targeting IL17A such as secukinumab and ixekizumab (approved for ankylosing spondylitis, plaque psoriasis and psoriatic arthritis), and 3) anti-IL17R, brodalumab, approved for plaque psoriasis.^{2–3} Binding of IL-12 and IL-23 activates JAK/Stat pathways; it is likely that inhibitors such as baricitinib (a Phase II study showed efficacy in SLE), will be effective.

In summary, the ustekinumab trial identified a potential new therapy for SLE and suggests that focus on inhibition of IFN γ might be effective in some SLE patients.

Learning Objectives

- Describe the roles of T-cell subsets in SLE pathogenesis
- Explain why IL-12 and IL-23 directed therapies are interesting therapeutic targets in SLE
- Discuss some potential treatments being developed in this area for SLE

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