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 type 1 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 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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09

NOVEL INTRACELLULAR PATHWAYS

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Systemic lupus erythematosus (SLE) is a heterogeneous disease characterised by abnormalities in cellular and humoral immunity. Here disturbances in cytokine production and B lineage cell disturbances became very evident in recent years. Identification of increased interleukin (IL)-6, IL-17, IL-12 and IL-23, BAFF, and especially type I interferon (IFN) production by different cell types, provided the rationale for targeting these cytokines or their corresponding cytokine receptors using biologics. Since these cytokines activate various intracellular pathways, such as Jak/Stat signaling, activation of the NfκB or using spleen tyrosine kinase (Syk), Bruton's tyrosine kinase (BTK), small molecules inhibiting these pathways are being investigated in various clinical studies.

It should be emphasised that most of the above-mentioned intracellular pathways may vary between different immune cells and tissues and can have interactions which have not been fully described. However, certain strategies target multiple key pathways along with inhibiting various cytokines (multiple targeting therapy),¹ which holds the promise to cover broadly heterogeneous SLE, a therapeutic principle that has already been introduced in other disciplines, such as antihypertensive and anti-infectious treatment algorithms.

As a first example in patients with SLE, treatment with the Jak1/Jak2 blocking agent (jakinib) baricitinib showed improvements of skin and joint manifestations among patients with a daily dose of 4 mg/d but less pronounced under 2 mg/d in a Phase II trial over 24 weeks.² Another Phase Ib/IIa trial using tofacitinib as Jak1/Jak3 selective inhibitor in SLE has been reported without substantial safety concerns and early signs of efficacy.³ In addition to jakinib in studies with SLE, there are also trials of inhibitors of other pathways (BTK⁴, Syk etc.) that hold promise for a new era of more efficacious and well-tolerated therapies, which may address the current and substantial need for the effective treatment of SLE. Of note, recent Phase 2 data of the BTK inhibitor fenebrutinib (GDC-0853) targeting B cells, monocytes and mast cells did not demonstrate differentiating efficacy in general SLE⁴. While this is an unexpected but interesting finding, targeting BTK in SLE needs to be further explored based on convincing efficacy of the BTK inhibitor evobrutinib in relapse-remitting multiple sclerosis.⁵

Learning Objectives

- Discuss the potential for novel therapeutic targets in SLE
- Explain the significance of certain signaling pathways with a particular focus on Jak/Stat system and current treatment developments in SLE

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10

MOLECULES IN EARLY DEVELOPMENT

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'Eclectic', what a great word to describe the approaches to the development of drugs in systemic lupus erythematosus (SLE)! 'Eclectic' comes from a Greek verb meaning 'to select' and was originally applied to ancient philosophers who were not committed to any single system of philosophy; instead, these philosophers selected whichever doctrines pleased them from every school of thought.¹ Much like the ancient Greek philosophers, drug target selection in SLE has spanned many pathways. Although belimumab has been the sole drug approved to date via the traditional route of a randomised controlled trial, it's just a matter of time before drugs targeting other molecules and pathways are granted approval for SLE and lupus nephritis.

The potential drug targets in SLE appear limitless, making decisions regarding resource allocation incredibly challenging. Should components of the innate or the adaptive immune system be targeted? Perhaps both? This presentation will review various strategies being pursued in order to inhibit key pathways in SLE. The emphasis will be on investigational agents in Phase I and Phase II programmes.^{2–7}

Learning Objectives

- Describe strategies for inhibiting the type I interferon pathway
- Discuss methods to target B and T cells
- Review approaches to down-regulate pro-inflammatory cytokines

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