immunity. There is evidence that abnormalities of B lineage cells (B and plasma cells) and imprints of type I interferon are key drivers in this disease. However, these findings are not found uniquely in each SLE patient which has implications for translational research: Delineation of molecular SLE endotypes have been identified that may allow better prediction of treatment response. Recent discoveries of gain-of-function mutations in toll-like TLR7 signalling in certain patients suffering from monogenetic SLE indicate the role of this pathway as potential treatment target.[1] Targeting enhanced cytokine signalling, in particular Jak/STAT continuous to be of interest as recent data of upadacitinib[2] and deucravacitinib.[3] were promising, although development of baricitinib[4 5] has not been continued.

Clinical experiences with belimumab provide evidence that indirectly blocking B cell survival can change the clinical course of the disease, including prevention of damage accrual. Advanced B cell targeting following the concepts of deeper tissue depletion overcoming the status of anergic B cells[6] and co-targeting plasma cells has been studied recently. These include more profound targeting by second generation anti-CD20 modalities (obinutuzumab),[7] CD19-CART[8] or employing other immune targets, such as CD38 (daratumumab),[9] BAFFR (ianalumab)[10] or the use of immune proteasome inhibition (zetomipzomib).[11] As more defined immune abnormalities in SLE may be identified as targets for treatment, use of bispecific antibodies[12] may hold promise to improve selective immune therapy with at least similar or even better efficacy/safety compared to current strategies.

REFERENCES

1. Brown GJ, *et al*. TLR7 gain-of-function genetic variation causes human lupus. *Nature*. 2022 May;**605**(7909):349–356. doi: 10.1038/s41586-022-04642-z. Epub 2022 Apr 27.
2. Merrill JT, *et al*. Efficacy and safety of ABBV-599 high dose (elsubrutinib 60 mg and upadacitinib 30 mg) and upadacitinib monotherapy for the treatment of systemic lupus erythematosus: a phase 2, double-blind, placebo-controlled trial. *Ann Rheum Dis*. 2023;**82**:91–92. OP0139.
3. Morand E, *et al*. Deucravacitinib, a tyrosine kinase 2 inhibitor, in systemic lupus erythematosus: a phase II, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol*. 2023 Feb;**75**(2):242–252. doi: 10.1002/art.42391. Epub 2022 Nov 11.
4. Petri M, *et al*. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-II). *Lancet*. 2023 Mar 25;**401**(10381):1011–1019. doi: 10.1016/S0140-6736(22)02546-6. Epub 2023 Feb 24
5. Morand EF, *et al*. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-I). *Lancet*. 2023 Mar 25;**401**(10381):1001–1010. doi: 10.1016/S0140-6736(22)02607-1. Epub 2023 Feb 24.
6. Weißenberg SY, *et al*. Identification and characterization of post-activated B cells in systemic autoimmune diseases. *Front Immunol*. 2019 Sep 24;**10**:2136. doi: 10.3389/fimmu.2019.02136.
7. Furie RA, *et al*. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis*. 2022 Jan;**81**(1):100–107. doi: 10.1136/annrheumdis-2021-220920. Epub 2021 Oct 6.
8. Mackensen A, *et al*. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. *Nat Med*. 2022 Oct;**28**(10):2124–2132. doi: 10.1038/s41591-022-02017-5. Epub 2022 Sep 15. Erratum in: *Nat Med*. 2022 Nov 3.
9. Ostendorf L, *et al*. Targeting CD38 with daratumumab in refractory systemic lupus erythematosus. *N Engl J Med*. 2020 Sep 17;**383**(12):1149–1155. doi: 10.1056/NEJMoa2023325.
10. Cortés-Hernández J, *et al*. Safety and efficacy of subcutaneous (S.C.) dose ianalumab (VAY736; anti-BAFFR mAb) administered monthly over 28 weeks in patients with systemic lupus erythematosus (SLE). *Ann Rheum Dis*. 2023;**82**:275–276. POS0120.
11. Saxena A, *et al*. Zetomipzomib (KZR-616) treatment results in clinically meaningful renal responses in patients with lupus nephritis. *Ann Rheum Dis*; 2023;**82**:891–892. POS1128.
12. Dang VD, *et al*. B- and plasma cell subsets in autoimmune diseases: translational perspectives. *J Invest Dermatol*. 2022 Mar;**142**(3 Pt B):811–822. doi: 10.1016/j.jid.2021.05.038. Epub 2021 Dec 24.

Learning Objectives

- Discuss the translational concepts of the SLE key signatures: type I IFN (convergence of various activated pathways) and B lineage abnormalities (plasmablasts including CD19-CXCR5- pre-plasmablasts, anergic B cells)
- Explain the impact of targeting type IFN abnormalities by blocking Jak/STAT and TL/signaling
- Discuss new concepts with deeper depletion of tissue-resident B cells and partial targeting of bone marrow plasma cells
- Develop the concept that bispecific antibodies may have value in treating SLE

32 OPTIMISING LUPUS DRUG TRIAL DESIGNS

Eric Morand. *Monash University, Melbourne, Australia*

10.1136/lupus-2023-la.32

Clinical trials for lupus have a high failure rate with only two drugs approved for the treatment of general systemic lupus erythematosus (SLE) in the last 60 years, despite at least twenty late-stage clinical trial programmes being pursued. Reasons for the high failure rate, especially in phase 3 trials, potentially include issues with the product being tested, but also issues intrinsic to the disease area. One domain is biological heterogeneity, which will never be directly under our control, although it might one day be addressed in a personalised medicine approach. The other, while also complex, is directly under our control: how trials are designed.

Analysis of recent trial success rates suggests some common factors among successful trials, including the use of glucocorticoid tapering. However, other data point to issues relating to the outcome measures used;[1] the SLE responder index (SRI) and BILAG-based composite lupus assessment (BICLA) endpoints are each based on 30-year-old disease activity measures that were never designed for use in clinical trials. A global academia-industry-patient collaboration has now commenced a project to reinvent clinical outcome assessment for use as a treatment response measure in SLE clinical trials: treatment response measure for SLE (TRM-SLE).[2] A five-stage scientific protocol using Delphi and nominal consensus methods has been developed to lead to this novel outcome measure, which will subsequently be validated in clinical trial data both retrospectively and prospectively.

REFERENCES

1. Connelly K, et al. Clinician-reported outcome measures in lupus trials: a problem worth solving. *Lancet Rheumatol*. 2021. doi:10.1016/s2665-9913(21)00119-3.
2. Connelly K, *et al.* Towards a novel clinical outcome assessment for systemic lupus erythematosus: first outcomes of an international taskforce. *Nat Rev Rheumatol*. 2023 Jul 11. doi: 10.1038/s41584-023-00993-7. Epub ahead of print.

Learning Objectives

- Increased understanding of the reasons for the lack of success of late-stage clinical trials in SLE
- Increased understanding of the limitations of current trial measures
- Awareness of a global project to develop and validate a new SLE clinical trial measure, TRM-SLE