SLE: New Treatments
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Background:
To date, Belimumab is the only FDA-approved biologic for the treatment of SLE. There has been a growing number of clinical trials in SLE over the last two decades, however for the most part late phase clinical trials have resulted in failure. Reasons for failure of SLE trials include heterogeneity of patients, wrong drug targets, and complicated outcome measures. The SLEDAI and BILAG are two outcome measures based on disease activity markers commonly used in SLE clinical trials, however each has its own limitations. Despite this, the following drugs have shown promising results in late phase trials.

Voclosporin in lupus nephritis:
- Phase II study compared high and low dose Voclosporin in combination with Mycophenolate vs. Mycophenolate in lupus nephritis: rate of complete renal remission was higher in Voclosporin plus Mycophenolate group vs. Mycophenolate alone group at 24 and 48 weeks, but no dose response was observed.
  - Concerns were raised when 12 deaths were noted in the Voclosporin plus Mycophenolate group vs. one in the Mycophenolate alone group over 48 weeks. Most of these deaths were due to infections.
- Preliminary results from phase III study (AURORA) show a complete renal response rate of 40.8% in Voclosporin plus Mycophenolate group vs. 22.5% in Mycophenolate alone group at 52 weeks (p<0.001). More importantly only one death occurred in the Voclosporin group vs. 5 in the Mycophenolate alone group.

Belimumab in lupus nephritis:
- BLISS-LN study randomized 448 patients with clinically active, biopsy-confirmed lupus nephritis to Belimumab plus standard of care (MMF or Cyclophosphamide followed by azathioprine) vs. standard of care.
  - 43% in Belimumab group vs. 32% in standard of care group achieved primary efficacy renal response at 104 weeks, but this endpoint was not as stringent as complete renal response.

Baricitinib in SLE:
- 314 SLE patients randomized to Baricitinib 2mg vs. Baricitinib 4mg vs. placebo: Baricitinib 4mg group showed statistically significant SRI response compared to the Baricitinib 2mg group and placebo, in particular the resolution of arthritis. Baricitinib 2mg group did not appear to be effective. Phase III trial is ongoing.
  - Only 1 episode of DVT occurred in the Baricitinib 4mg group.

Ustekinumab in SLE:
- 102 SLE patients randomized to Ustekinumab vs. placebo: 62% of patients in Ustekinumab group achieved SRI-4 response vs. 33% in placebo at 24 weeks (p=0.006) with main effect in skin. However, no difference in BICLA response. Phase III trial is ongoing.

Anifrolumab in SLE:
- TULIP 1: Anifrolumab was no better than placebo in achieving SRI-4 response, but secondary analysis showed a statistically significant difference in BICLA response (37% in Anifrolumab group vs. 27% in placebo).
  - Most likely explanation: SRI-4 fails to capture smaller changes in overall disease activity.
- TULIP 2: Anifrolumab showed statistically significant better BICLA response compared to placebo at 52 weeks.

Q&A Pearls:
- Difference between Voclosporin and Tacrolimus: Voclosporin is a newer and more specific calcineurin inhibitor with better side effect profile.
- IL23 inhibition in SLE: this is an important target to study in SLE and lupus nephritis.