Deucravacitinib: An Oral, Selective, Allosteric Tyrosine kinase 2 Inhibitor for Active Systemic Lupus Erythematosus

An Expert Interview with Ronald van Vollenhoven

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Systemic lupus erythematosus (SLE) is a chronic, relapsing and remitting autoimmune disease,[1] affecting 13–7,714 per 100,000 individuals.[2] Inflammation in SLE can lead to tissue damage in any organ system, frequently due to acute flares,[1] with commonly affected organ systems including the cardiopulmonary, central nervous system, haematological, mucocutaneous, musculoskeletal and renal systems.[3] Consequently, patients with SLE can display a diverse array of symptoms and clinical presentations ranging from debilitating disease to potentially fatal organ dysfunction.[1,3,4]

Existing treatments for SLE, including corticosteroids, nonsteroidal anti-inflammatory drugs, immunosuppressants and anti-malarial drugs, can be limited in efficacy and tolerability.[5,6] Consequently, research continues into novel treatments including, deucravacitinib, which has been investigated in a phase II trial (NCT03252587) of patients with SLE.[7] In this expert interview, Professor van Vollenhoven discusses unmet needs in SLE and clinical results for deucravacitinib.

Q. What are the unmet needs in the treatment of systemic lupus erythematosus?

Despite the treatment of SLE progressing over the past few decades, there are still unmet needs. One need is for new treatment options for patients with very severe disease that cannot be controlled with the currently available drugs, to prevent irreversible organ damage and death. Another limitation is the morbidity associated with current treatments including side effects and disease relapse when tapering the medication dosage, particularly with oral corticosteroids. Additionally, even patients with well-controlled disease can experience unpredictable flares and the risk of flares can be taxing on the patient. A fourth unmet need is that many patients with SLE, even patients whose disease appears to be well controlled, can experience more general symptoms, which are not always easy to treat. These include general malaise, and sometimes mild cognitive disturbances, which are hard to measure and difficult for the patient to live with. In summary, the unmet needs are: 1) treatments for refractory disease; 2) treatments to maintain control without medication side effects; 3) treatments that diminish the risk of flares; 4) options to manage more general symptoms.

Q. What is deucravacitinib and what is the rationale for its use in the treatment of systemic lupus erythematosus?

Deucravacitinib is a small molecule that inhibits the enzyme tyrosine kinase (TYK) 2, part of the Janus kinase system, a group of enzymes important for inflammatory reactions. Blocking these enzymes could be used to reduce inflammation, although you do not want to block them

completely. Instead, it is possible to dampen this pathway by targeting specific enzymes; one of these is TYK-2. Deucravacitinib binds to TYK-2, diminishing its activity, which decreases interferon-related inflammation, in addition to the inflammation brought about by other cytokines including interleukin (IL)-12 and IL-23. So deucravacitinib may be beneficial for patients with SLE, a disease in which interferon is thought to play a role.[3]

Q. What were the aims, design and eligibility criteria of the PAISLEY study?

The PAISLEY study (NCT03252587) was a phase II clinical trial of 363 patients with SLE.[7] The objective was to determine the efficacy, safety, tolerability and dosage of deucravacitinib. Patients were randomly assigned, in addition to their regular medication, to receive placebo or deucravacitinib, at one of three different doses (3 or 6 mg twice daily, or 12 mg once daily). Eligible patients needed to have active SLE despite being on existing SLE treatments, and have skin disease and/or joint involvement.

Q. What were the primary and secondary endpoints and how well were they achieved?

The primary endpoint was the proportion of patients achieving a Systemic Lupus Responder Index (SRI)-4 response at Week 32. To be an SRI-4 responder, a patient had to have a ≥4-point improvement in Systemic Lupus Erythematosus Disease Activity Index 2000 score, and fulfil other criteria such as no worsening in British Isles Lupus Assessment Group (BILAG) index or Physician's Global Assessment of Disease Activity Scale.

In terms of results, more patients in the deucravacitinib groups achieved an SRI-4 response compared with patients receiving placebo, with this difference being statistically significant in the 3 mg group. The deucravacitinib 6 mg group also showed statistically significant improvements, although numerically lower than in the 3 mg group. Despite the deucravacitinib 12 mg once-daily group having the same total daily dose as the 6 mg twice-daily group, SRI-4 results were not significant, possibly due to side effects leading to patients stopping treatment. Key secondary endpoints were the BILAG-Based Composite Lupus Assessment score, specific inflammation in the joints and skin, and flares. In all instances patients receiving deucravacitinib 3 mg achieved statistically significant improvements in secondary endpoints with the exception of joint inflammation. Patients receiving the other two doses achieved clinically meaningful improvements in some secondary endpoints.

Safety is an important outcome for ensuring that benefits are balanced by acceptable risk. Safety was very good for the deucravacitinib groups, although more patients stopped treatment because of side effects with deucravacitinib 12 mg. However, some patients developed skin side effects, especially acne. Other positive results included no increases in major infections, opportunistic infections or tuberculosis. Some patients did develop infections, especially with the higher deucravacitinib dose, although the type of infection that stood out was herpes simplex, with lip soars more frequent with deucravacitinib than with placebo. This contrasts with other treatments where an increase in herpes zoster is a concern; no increase in these infections was seen in this study. Finally, no increase in the rates of COVID infections was seen during the pandemic.

Q. What will be the next steps in the clinical development of deucravacitinib?

As this was a phase II trial, it would not be sufficient to get the drug approved so a phase III study with a larger number of patients over a longer period of time is being designed. Hopefully this will confirm these positive results and lead to a new treatment for SLE. Deucravacitinib is also being developed for other indications and the US Food and Drug Administration has approved its use for psoriasis. ❑

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