SKIN

EDITORIAL

Three Year Anniversary of the Introduction of Deucravacitinib to the US Market

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In September 2022, deucravacitinib, the first oral, highly targeted, allosteric TYK2 inhibitor was approved in the United States and other countries for the treatment of moderate to severe psoriasis. Unlike other janus kinase (JAK) inhibitors which bind to the catalytic domain of tyrosine kinase, deucravacitinib binds to the regulatory domain, having little impact on JAK1, 2, or 3. At the time of its introduction, it was the most highly targeted oral agent to block the IL-17/ IL-23 axis of cytokines which we know cause psoriasis.[1] It is that selectivity of deucravacitinib that contributes to its impressive safety.

Deucravacitinib does not exhibit any of the adverse events associated with other JAK inhibitors and, as a result, it was approved without any boxed warnings, unlike the other JAK inhibitors which carry boxed warnings for cancer, infection, heart attacks, clotting, and death. The safety of deucravacitinib was reinforced by 4-year data with more than 4,300 patient-years in a long-term extension trial known as POETYK LTE. In that trial, incidence rates of adverse events decreased from year 1 to year 4. The only exception was the onset of the COVID-19 pandemic, and COVID-19 rates did not differ from the general population. Excluding COVID-19 infection, the rate of serious infections was lower at 4 years than during the 1st year. Incidence rates for major adverse cardiovascular events and malignancies were low and comparable between years 1 and 4, and there were no venous thrombotic events in year 4. Acne, a well-known side effect of JAK inhibition, also dropped in frequency from year 1 (2.88/100 PY) to year 4 (0.95/100 PY).[2] Unlike abnormalities in hematologic parameters seen with other JAK inhibitors, there were no changes in hemoglobin, lymphocyte count, neutrophil count, or platelet count. Indeed, a psoriasis patient with myelodysplastic syndrome was successfully treated with deucravacitinib without exacerbation of the patient's hematologic disorder.[3] Serum chemistries were likewise unchanged, showing no increase in hepatic enzymes or kidney function. And, unlike other JAK inhibitors, there were no changes in serum lipids.[2] An expert review on laboratory changes seen in phase 3 double-blinded trials comparing deucravacitinib to placebo or apremilast concluded that deucravacitinib did not result in clinically meaningful laboratory changes, and the changes seen with JAK 1, 2, and 3 inhibitors were not seen.[4] Five-year data have been presented and show no change in safety issues in over 5000 patient years.

While the package insert for deucravacitinib refers to triglyceride elevations and liver

enzyme elevations, these are not borne out by review of pivotal trial data or by real world experience.[5] It should be noted that asymptomatic CPK elevations were noted in deucravacitinib treated patients as well as in patients who were treated with placebo in the clinical trials. Since exercise can cause CPK elevation, the clinical significance of this is questionable.

In terms of efficacy, deucravacitinib has emerged as one of the most effective oral agents we have for psoriasis.[6] In the POETYK PSO-1 trial, patients received either deucravacitinib 6 mg daily or apremilast 30 mg twice daily or placebo. At week 16, 58.4% of subjects achieved PASI 75 in the deucravacitinib arm compared to 35.1% in the apremilast arm and 12.7% in the placebo arm. The placebo arm ended at week 16. By week 24, the number of subjects achieving PASI 75 was 69.3% in the deucravacitinib arm compared to 38.1% in the apremilast arm.[6]

There are unique, often difficult to treat areas where deucravacitinib should be considered. In a study that specifically looked at scalp outcomes in patients with plaque psoriasis, the scalp severity Physician's Global Assessment (ss-PGA) of clear or almost clear scalp was achieved by 91.2% of subjects by week 16 with the majority achieving clear or almost clear scalp by week 8.[4] While the number of subjects with fingernail or palmoplantar involvement in that study were small (10 and 4 respectively), both are difficult to treat. The mean percent change in palmoplantar PASI score (pp-PASI) was 85.1% at week 16 with further improvement (100%) by week 24. Being a small molecule, deucravacitinib is a logical treatment for palmoplantar disease. Larger biologics are less effective and significantly slower, as it is difficult to achieve adequate levels in the skin of the palms and soles because of the small caliber of blood vessels in the distal exptremities.[7] Fingernails are also much more difficult to treat, and of course, lag behind improvement in skin, as the nailbed and nail matrix have to be cleared before nails can grow in normally. Nevertheless, there was a 15.9% improvement in modified Nail Psoriasis Severity Index (mNAPSI) in the study by Okubo, et al. That percent improvement increased to 20.3% by week 24 and 44.2% by week 52. Deucravacitinib has also proven highly effective for the treatment of genital psoriasis.[8]

Despite all the highly effective therapies we have for psoriasis, including biologics and small molecules, a proportion of patients are left with significant disease. A very successful use of deucravacitinib has been in conjunction with biology therapies for psoriasis. In a study by Guenin, et al, 20 patients with refractory psoriasis or psoriatic arthritis who were already being treated with an IL-17 inhibitor or an IL-23 inhibitor were started on deucravacitinib 6 mg a day in addition to their biologic therapy. All patients saw an additive effect for skin psoriasis. Psoriatic arthritis did not fare quite as well with 5 patients seeing more than a 1-point improvement in the Psoriatic Arthritis Impact of Disease (PsAID score). Five of 12 patients with psoriatic arthritis saw less than a 1-point improvement in that score, and 2 patients actually got worse.[9] Nonetheless, the uniform improvements in skin scores and slight improvements in joint scores justify the combination of deucravacitinib with biologics. Importantly, there were no changes in laboratory parameters, no increase in infections, and no malignancies or other serious adverse events reported.

Deucravacitinib is being studied for additional indications in the future. We already have very promising data regarding its use for

psoriatic arthritis.[10] Data suggests that higher dosing may be even more effective in psoriatic arthritis, and considering the safety of the 6 mg dose, it would be ideal to have higher doses.[10]

Another exciting use of deucravacitinib has been in the treatment of lupus. In a phase 2 trial of active systemic lupus erythematosus, deucravacitinib achieved more improvement in every parameter in disease assessment than placebo.[11] There have also been numerous case reports of the efficacy of deucravacitinib in cutaneous lupus and subacute cutaneous lupus.[12-18]

In summary, deucravacitinib is one of the most effective oral agents we have for psoriasis. Its efficacy is comparable to some of our biologic therapies. While direct comparisons have not been made to conventional oral therapies like methotrexate, cyclosporine, and acitretin, its efficacy in published trials compares well to those, and its safety profile is much better. Among oral therapies, its efficacy to risk ratio makes it one of our leading options for the treatment of moderate to severe psoriasis.

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