The anti-IL-12/23 agents have generated much interest and discussion. Studies have shown that ustekinumab (Stelara, Janssen) is an efficacious agent whose results can be maintained for long periods of time. Coupled with enthusiasm for ustekinumab’s efficacy, however, are lingering concerns about safety. Although the adverse event profile for ustekinumab has been favorable thus far, an investigational agent in the same therapeutic class has been associated with cardiac risks. Given many psoriasis patients’ predisposition to a variety of health issues, recent conjecture regarding safety has taken on added weight. Ahead, I will examine the latest data on ustekinumab safety and discuss the clinical implications.

Recent Data Analysis
A recent study in JAMA evaluated the possible association between IL-12/23 agents and major adverse cardiovascular events (MACEs). Investigators reviewed controlled trials and found 10 out of a total 3,179 patients receiving anti-IL-12/23 therapies experienced MACEs compared with zero events in 1,474 patients receiving placebo. Only one of 3,858 patients receiving anti-TNF agents experienced a MACE. While the 10 events reported with IL agents do not constitute a statistically significant difference from TNF agents or placebo, the numbers nonetheless deserve attention.

Another study, looking at the broad long-term safety profile of ustekinumab through three years of treatment, evaluated all Phase II data as well as both PHOENIX trials. Rates of adverse events (AEs) were comparable among patients treated with placebo (50.4 percent), ustekinumab 45mg (57.6 percent), or ustekinumab 90mg (51.6 percent). Serious adverse events (SAEs) were comparable across all treatment groups. Rates of AEs per 100 patient-years of follow-up and SAEs were comparable between ustekinumab doses.

A follow-up to the study evaluated the impact of ustekinumab on infections and malignancies—both theoretical risks associated with the blocking of IL-12 and IL-23—in patients exposed for up to three years. Researchers observed that rates of overall infections per 100 patient-years were similar among placebo (121.0), ustekinumab 45mg (145.7), and ustekinumab 90mg (132.2) groups, with overlapping confidence intervals, and remained stable through three years in ustekinumab groups. Rates of serious infections during the placebo-controlled periods were similar between placebo (1.70) and 90mg (1.97) groups, yet lower in the 45mg group (0.49). Malignancies were also comparable among groups (placebo: 1.70; 45mg: 0.99; 90mg: 0.98) and remained stable over time in ustekinumab groups, while rates of malignancies, excluding non-melanoma skin cancer, were comparable with rates expected in the general population.

Smaller studies have looked at short-term safety. A British study assessed the efficacy and safety of ustekinumab in patients with severe psoriasis attending 10 dermatology centers in the UK and Ireland. Aside from strong efficacy results, the investigators noted that ustekinumab therapy was well tolerated, with SAEs occurring in 2.3 percent of patients. Meanwhile, results from a Japanese study showed SAEs occurring in 4.8 percent and 6.3 percent of patients taking ustekinumab 45mg and 90mg, respectively. Through week 72, similar rates and types of AEs and SAEs were reported in patients receiving 45 and 90mg. Rates of injection site reactions and antibodies to ustekinumab were low. Ustekinumab was efficacious and generally well-tolerated in Japanese patients with moderate-to-severe plaque-type psoriasis through 72 weeks.

Clinical Implications
These data are consistent with broader findings and
are helping to cement a reliable safety profile for the agent. While many of these studies note their limited nature, AEs still warrant consideration in our clinical judgments, particularly regarding cardiac events. Ustekinumab is a valuable and efficacious first-line therapy for patients with moderate to severe psoriasis, however, for patients with two or more risk factors for cardiac disease, clinicians should consider other agents at the outset. For example, some reports associate TNF inhibition with a decrease in incidence of cardiovascular events in psoriasis patients, however this has not been seen as of yet in the IL-12, IL-23-treated patients. Although MACE have been limited thus far in ustekinumab trials, I would find it too aggressive to use in patients with diabetes, obesity, hypertension, hyperlipodemia, and other cardiac risk factors. If a patient with two or more of these risk factors fails TNF therapy, then perhaps should consider ustekinumab because of its efficacy pedigree.

Until more is known about the specific nature of the association between ustekinumab and cardiac risk factors, I recommend a more conservative clinical approach for patients with multiple cardiac risk factors. Ustekinumab is an extremely valuable agent and its overall safety profile appears to be favorable. However, with only 12,000 people treated, we still have yet to learn of the true significance of the relative infrequency of cardiac events in studies thus far.

Dr. Bagel is on the speaker’s bureau for Abbott Laboratories, Amgen, Janssen, Galderma, and Leo Pharma.

Jerry Bagel, MD is Clinical Associate Professor of Dermatology, College of Physicians and Surgeons of Columbia University, New York. He is Director of Psoriasis Treatment Center of Central New Jersey.


Now Available: Rosacea Module
By Julie C. Harper, MD
Earn 4 hours of CME Category 1 Credit Hours

DermEdOnline provides medical dermatology CME Learning Modules. The first of 36 that make up a complete core curriculum — Tumors, Rosacea, and Acne — are coming soon!

DermEdOnline is available to Board Certified Dermatologists, Dermatology Resident’s, Dermatology Physician Assistants and Nurse Practitioners, and other qualified medical professionals interested or in need of a comprehensive medical dermatology reference and resource.