Each evening as Americans finish cleaning up the kitchen from dinner and settle in front of their televisions (and laptops, tablets, phones, etc.), a commercial for a biologic therapy for psoriasis airs on the networks, and it goes a little something like this:

“I have moderate to severe psoriasis. I was sad. I lacked self-confidence, I hid and then I went on a biologic agent. My psoriasis has improved and I am a rock star.”

But then the commercial takes a different tone as an omniscient narrator lists the risks associated with these medications: serious infections, hospitalization, tuberculosis, cancer, and death. If you missed the beginning of the ad, you missed the whole point and would likely be terrified of these life-altering psoriasis medications.

Biologics, at least the tumor necrosis factor-alpha (TNF-a) blockers, are no longer new. Millions of people have used these drugs to treat a wide spectrum of inflammatory disorders. More than 100,000 people have used ustekinumab (Stelara), an anti–IL-12/23p40 monoclonal antibody, for psoriasis, psoriatic arthritis, and Crohn’s disease, and there are more than 10,000 subjects in clinical trials for the newer IL-17 monoclonal antibody drugs as well. Taken together, we have a great deal of data to evaluate the safety of these agents and weigh their benefits versus their risks.

Presented at the American Academy of Dermatology’s (AAD) 2017 meeting in Orlando, FL, OBSERVE-5, the Observational post marketing safety surveillance registry of etanercept (Enbrel) for the treatment of psoriasis, found that the risk of malignancy for biologic agents was 0.6/100 patient years.

What does this mean? Let’s break it down:

0.6/100 patient years = 6/1,000 patient years = 1/160 = 1/32 x5.

The average person in clinical trials is 47. Now, let’s imagine 32 people with psoriasis who are aged 47, not on a biologic agent, and follow them for five years. How many will develop cancer (i.e. prostate, breast, lung, melanoma, pancreas, brain), but not necessarily die by the time they are 52?

According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, just one.

The SEER database is not evaluating psoriasis patients who do have a higher baseline risk of lymphoma and/or bladder cancers. If 32 subjects are treated with a biologic agent, one individual will develop cancer within five years, a frequency equal to what is seen with the SEER registry.

The Psoriasis Longitudinal Assessment and Registry (PSOLAR), also presented at the 2017 AAD meeting, looked at risk of malignancy associated with biologics and methotrexate, excluding non-melanoma skin cancer. Researchers found that exposure to TNF inhibitors ≥12 months was associated with increased risk of overall malignancy, namely breast (0.09), prostate (0.08), lung (0.06), melanoma (0.06), and lymphoma (0.03)

So why are the direct-to-consumer (DTC) commercials so scary? Most psoriasis patients are treated with biologics as monotherapy. In other disease states, namely psoriatic arthritis, rheumatoid arthritis, and Crohn’s disease, combination therapy, i.e systemic steroids, methotrexate, 6-mercaptopurine, tends to be more common. When biologic agents are used in combination, the frequency of serious infections and malignancies increases. The FDA mandates that the DTC advertisements spell out the worst case scenarios.

Cancer aside, many other posters presented at the 2017 AAD annual meeting focused on potential risks associated with biologics, and this new data will help us

“Today we have biologics that result in 40 percent of patients being clear, 70 percent of patients being 90 percent improved, and 90 percent of patients being 75 percent improved within 12 weeks. This is incredible, but like previous therapies, biologics are not without risks.”

Are We All Clear?

Understanding the safety of biologics for psoriasis in real-world settings.

BY JERRY BAGEL, MD
better counsel our patients about the judicious use of these medications.

**RISK OF HEART DISEASE, STROKE**

In an analysis of major adverse cardiovascular events (MACE) among patients treated with biologics in PSOLAR, neither TNF inhibitors nor ustekinumab showed an increase in major adverse cardiovascular events risk, compared with topical/phototherapy in patients followed for 2.8 years.

The ESPRIT 10-Year Postmarketing Surveillance Registry of adalimumab (Humira) for moderate to severe psoriasis analyzed emergent cardiovascular events, serious infections, and cancer. The seven-year interim data show that the risks of heart disease, infection, and cancer were consistent with rates observed in adalimumab clinical trials and remained stable with up to seven years of overall exposure to adalimumab. The majority of patients remained free of cerebrovascular accident, congestive heart failure, myocardial infarction, infection, and malignancy as of November 2015.

**SUICIDE RISK**

Risk of suicide was not more frequent in psoriasis patients using biologics versus other psoriasis therapies, however suicide was about 1.5 times more frequent in psoriasis patients using biologics versus all other conditions where biologics were used. It may be that since there is an increase in suicide and suicidal ideation in psoriasis, more is seen in clinical trials; however we must keep evaluating this serious AE to determine if it is related to the drug and not the disease.

**COSENTYX SAFETY**

Another study looked at the safety of secukinumab (Cosentyx). In this study, common adverse events included upper respiratory infection (4.2 percent), superficial bacterial infections (4.2 percent), and diarrhea (4.2 percent).

Secukinumab showed no significant difference in rate of infection compared to other biologic agents and likewise provides an acceptable benefit to risk ratio for its intended use in psoriasis, according to a retrospective cohort analysis from a large US patient population. However, further post-marketing studies with large sample sizes are warranted.

**STELARA SAFETY**

The RADAR (Research on Adverse Drug Events and Reports) project analyzed the rate of all infections for ustekinumab versus standard oral systemic therapeutic agents (acitretin, cyclosporine, or methotrexate) in the management of psoriasis. It found that ustekinumab has a significantly lower rate of all infection compared to cyclosporine and no significantly different rate compared to acitretin or methotrexate. Targeting IL-12/23 by ustekinumab exposure poses no undue risk for infection compared to standard oral pharmacotherapeutic agents used in the management of psoriasis, the researchers concluded.

**TALTZ SAFETY**

UNCOVER-3 looked at the efficacy and safety of ixekizumab (Taltz) for moderate to severe plaque psoriasis. Blauvelt, et al. followed 1,346 subjects for two years. During this time, 23.5 percent developed nasopharyngitis, 7.5 percent developed an upper respiratory infection, 7.5 percent had injection site reactions, and 3.8 percent developed candida infection. Patients achieved similar response rates that remained consistently high through 108 weeks of ixekizumab treatment across all arms. The 108-week safety profile of ixekizumab was comparable to shorter treatment periods, the study showed.

When researchers looked at the safety of ixekizumab in pregnancy, 18/1359 (1.3 percent) females exposed to the medication became pregnant, resulting in 8/18 (44.4 percent) live births, and spontaneous and induced abortions in 5/18 (27.8 percent). Among live births, 7/8 (87.5 percent) were full-term and 1/8 (12.5 percent) were born prematurely. Pregnancy outcomes generally appear to be consistent with those reported in US epidemiologic and PSOLAR registry data, but due to limited safety data, further evaluation is needed as part of ongoing monitoring in post-market surveillance. Women with severe psoriasis do have a two-to-three-fold higher rate of spontaneous abortion than age-matched women without psoriasis.

Anti-TNF agents have been associated with activation of latent tuberculosis, but there was no evidence of tuberculosis reactivation in an integrated analysis of seven clinical trials of ixekizumab. To date, available data do not indicate that ixekizumab increases the risk of developing active or reactivated tuberculosis. However, prescribers need to evaluate patients for tuberculosis infection prior to initiating treatment with ixekizumab.

“Biologics have changed our patient’s lives. They do have some side effects, but proper management will help minimize any risks and maximize the benefits.”
In another report, Crohn’s disease and ulcerative colitis occurred infrequently (<1 percent) in ixekizumab-treated patients in a dataset culled from seven psoriasis trials, and no cases were reported in the double-blind treatment period of a psoriatic arthritis clinical trial (SPIRIT-1). Exposure-adjusted incidence rates of Crohn’s disease and ulcerative colitis with ixekizumab treatment are similar to those reported previously in patients with psoriasis.

**GUSELKUMAB SAFETY**

The Efficacy and Safety of Gusekumab, an Anti-IL23 Monoclonal Antibody, in Patients with Active Psoriatic Arthritis: a Phase 2a, Randomized, Double-blind, Placebo-controlled Study, demonstrated significant improvement of joint symptoms, physical function, psoriasis, enthesitis, and dactylitis. Gusekumab was well tolerated with no unexpected safety findings.

In the VOYAGE 2 trial, IL-23 blocker guselkumab demonstrated superior efficacy in psoriasis and patient-reported outcomes compared with placebo and adalimumab across multiple endpoints and time points through week 24. Gusekumab is well-tolerated in psoriasis patients, the study showed.

**BIOSIMILAR SAFETY**

In a randomized, double-blind, multicenter study comparing the efficacy, safety, and immunogenicity of a proposed adalimumab biosimilar (GP2017) with originator adalimumab in patients with moderate to severe chronic plaque-type psoriasis, researchers noted equivalent efficacy of GP2017 and originator adalimumab. Safety and immunogenicity profiles of GP2017 and originator adalimumab were also similar and consistent with clinical experience with originator adalimumab, the study showed.

**FIRST, DO NO HARM**

Biologics have changed our patient’s lives. They do have some side effects, but proper management will help minimize any risks and maximize the benefits.

Jerry Bagel, MD, FAAD, is director of the Psoriasis Treatment Center of Central New Jersey.

5. Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. https://seer.cancer.gov/