Assessing the Long-term Effects of Biologics

Despite being somewhat new to dermatology, biologics are not “new” drugs. One expert shares thoughts on the future of biologics in psoriasis management.

Although immunosuppressive agents are still discussed as though they are new in dermatology, biologics have been with us for about a decade; they have figured largely in other specialties even longer. And yet there may be something to the tendency to view these agents as “new.” Despite the prominent coverage of biologics at conferences and in dermatology publications, not all dermatologists are comfortable prescribing them, and prescriptions written for biologics (in dermatology) are not drastically on the rise. In fact, the majority of prescriptions for biologics are written by a relatively static group of dermatologists constituting a small portion of dermatology physicians. In spite of the biologics’ popularity at the podium and in journals, these prescription patterns indicate there are still legitimate concerns about them among dermatologists. These concerns are centered primarily on the implications of long-term use of biologics, both in terms of safety and efficacy.

Safety

Long-term data is difficult to build for drugs that have already been approved, as it makes little economic sense for pharmaceutical companies to fund more trials. “It’s very important that a drug is efficacious, which is why many trials are designed for durations of about 12 to 16 weeks,” explains Craig Leonardi, MD, Clinical Assistant Professor of Dermatology at St. Louis University. If the condition treated does not improve during that time, or if significant safety concerns are raised, the agent will not meet the standard for approval. “Follow-up studies are important, but when it comes to approval, trials are not powered or designed to examine long-term safety,” says Dr. Leonardi.

Importantly, long-term studies with biologics have been conducted in other specialties, such as rheumatoid arthritis, and found little in the way of adverse events for long-term biological use. Dr. Leonardi served as chief investigator of a three-year study of efalizumab (Raptiva, Genentech) for the long-term control of psoriasis. Results showed that efalizumab’s safety profile remained stable over 36 months, with no new and no increase in common events. Regarding efficacy, patients’ psoriasis improved over 18 months, and was then sustained for the following 18 months.

This study and some others in rheumatology and sporadically in dermatology have helped physicians conceptualize long-term concerns for biologics. Primarily, existing data show us that there are no new blips on the adverse events radar in the long-term, Dr. Leonardi suggests. And now that biologics are normalized in Crohn’s disease, rheumatoid arthritis, and other immunological conditions such as psoriasis, researchers can identify trends in long-term safety for drugs such as etanercept (Enbrel, Amgen Wyeth), infliximab (Remicade, Centocor), and adalimumab (Humira, Abbott). “These safety profiles are built over time, and while they are not as precise as clinical trials, they help researchers and physicians understand long-term safety a great deal,” says Dr. Leonardi.

Nevertheless, recent events have stirred some debate in the medical community. The Food and Drug Administration (FDA) has given pimecrolimus (Elidel, Novartis) and Protopic (tacrolimus, Astellas) boxed warnings due to theoretical risk of lymphoma. Some dermatologists fear that heightened concern over pimecrolimus may lead to more patients questioning biologics, but Dr. Leonardi remains confident in patients’ trust in physicians. “The boxed warning reflects the agency’s concern over not just pimecrolimus, but of biologics in general,” he notes. But this isn’t nec-
With regards to lymphoma, and congestive heart failure,” he says. “The latter occurs less frequently, but its severity is not something to be taken lightly, which is why boxed warnings are more common with biologics.” The boxed warning shouldn’t surprise dermatologists, says Dr. Leonardi, since it legitimates everything they’ve been saying about the drug, and about biologics for a long time.

Dr. Leonardi notes that dermatologists treat biologic agents very seriously, and are known to exhaust precautions when it comes to safety. “There are different classes of biologics, and different buzz words to identify each category’s safety profiles, but physicians must not forget that these are immunosuppressive medications, and therefore the potential risk of adverse events is built-in,” says Dr. Leonardi.

But the advantages of biologics are in plain sight, and Dr. Leonardi assures that the many strengths of biologics allow them to thrive in a clinical setting, so long that physicians take proper precautions and don’t “fire and forget.” Compared to other systemic medications, biologics make a lot more sense, according to Dr. Leonardi. Systemic agents, such as cyclosporine and methotrexate, are more taxing from a management perspective, as patients often require blood tests, liver biopsies and more frequent visits.
Systemic treatments also they also come with a more defined set of risks.

Efficacy and Economy

While issues of safety tend to be discussed in greater capacity at conferences and in published studies, Dr. Leonardi points to some interesting trends on the efficacy front that deserve mention. “Some biologics seem to lose their effectiveness over time, particularly the TNF antagonists, in which there is often a slow erosion of disease control over a long-term period,” says Dr. Leonardi. These trends are not necessarily easy to identify if you’re looking at week-to-week or monthly results of therapy, he notes. Instead, they happen over longer periods of time. Dr. Leonardi therefore recommends keeping a chart of the patient’s history with psoriasis and response to treatment. “Performing PGA and BSA tests for surface area is very beneficial in that the physician can get a sense of a patient’s improvement on a visual evaluation, and then refer back to previous notes,” Dr. Leonardi explains. If treatment appears to be waning with a given biologic, you can add a second therapy or transition to a different agent.

“It’s important to have a sense of the overall pattern, rather than simply focusing on if improvement from the outset is maintained,” notes Dr. Leonardi. “Identifying the appropriate method of action at a given moment in therapy is essential, as we should never become too complacent,” he says. This method also works because it allows you to discuss the conditions and effects of the disease with your patients, which should provide a basis for choosing subsequent modes of treatment.

From a broader perspective, the efficacy of biologics as a class will likely continue improving, if only because the market is growing. Within the next couple of years, notes Dr. Leonardi, dermatologists may have access to two more biologics—Centocor’s ustekinumab (which is currently in Phase 3 trials) and Abbott’s ABT-874—with more potentially in the pipeline.

“There are a huge number of biologics being investigated right now, all with the potentially of treating psoriasis in a uniquely different way,” Dr. Leonardi estimates.

Aside from the documented efficacy of biologics, they are more viable and sustainable from an economic standpoint, as well. There are a slew of medications on the market for psoriasis, all of which treat the disease in a different way, and all of which are beneficial in their own respective ways, “But biologics represent a viable modality for aggressively treating psoriasis, and it can be administered by the hundreds in a practice,” Dr. Leonardi says.

Juxtaposed to other common psoriasis treatments, biologics are the most feasible for moderate to severe cases. “For example, light treatments, although potentially effective, are economically viable for a vast majority of patients, when you consider the amount of treatment required, and how that affects patients’ co-pays and commutes,” notes Dr. Leonardi. Adding that biologics are desirable in dermatology practice for reasons beyond efficacy, Dr. Leonardi explains that he can manage hundreds of patients at his practice with two medical assistants. Biologics can take care of more patients with less staff and in less time because of less monitoring, and therefore they often represent an ideal modality for physicians and patients.

Taking Precautions

The growing field of long-term biologic data is encouraging, especially with newer biologics on the horizon. Nevertheless, Dr. Leonardi recommends that physicians keep their minds set in the present, emphasizing caution and safety measures to maximize the safety and efficacy of biologics.

First is to build a referral base, so that if you do have concerns about secondary infections, you have a solid foundation of communication with specialized physicians who could speak to those concerns. “Although dermatologists aren’t trained to understand the nature of certain malignancies and infections that may result from treatment with biologics, it is incumbent upon them to familiarize themselves with these diseases and conditions, along with having a reliable referral base for patients,” Dr. Leonardi asserts. He also suggests performing age-appropriate analyses and keeping a track record of a patient’s medical and treatment history. Notes as simple as whether the patient received the flu vaccine seem like minor details, but are important to compile, especially when you’re deciding how to treat the patient’s psoriasis.

Prescreening for PPD, HIV, and hepatitis also represent more thorough explorations of the risk/benefit ratio for a given patient, he says. “It’s important to be as proactive as you can be, while acknowledging some limitations of pre-screenings and risk-benefit ratios,” says Dr. Leonardi. “The best thing that physicians can do is make informed decisions based on thorough investigation and the available information.” And when it comes to prevention of secondary infections and other adverse events, maintaining a proactive approach to reducing these effects and maximizing efficacy is essential.

Dr. Bagel is on the speakers bureau for Abbott Labs, Genentech, Astellas, Amgen, Stiefel, and Warner-Chilcott.