Psoriasis specialists share their experiences combining psoriasis therapies, including biologic, topical, and systemic agents.

By Ted Pigeon, Associate Editor
Due to the chronic nature of psoriasis, physicians are required to explore a growing field of treatments that includes topical, systemic, and light-based therapies. While some agents, such as topical creams and steroids, have been used and studied for a long time, biologics represent a relatively new treatment modality, both in terms of their unique mode of delivery and their methods of action. Although many trials thus far have focused on the use biologics as monotherapy for treatment of psoriasis, these agents may also be used in combination with older, more established therapies. Since dermatologists are adept at combining a variety of agents to treat psoriasis, biologics present unique opportunities as well as difficulties in pioneering an emerging area of combination therapies.

Combination approaches involving biologic therapies represent a sensitive issue. Reasons for this may stem from the fact that almost all clinical trials involving biologics have examined their effects as a monotherapy, notes Alan Menter, MD, Chair of the Division of Dermatology at Baylor University’s Medical Center in Dallas. By virtue of their relative newness, there has been little time to fully explore biologics in combination with other agents. “Unlike many other therapies, biologics haven’t been around for 50 years,” says Neil J. Korman, MD, PhD, Professor of Dermatology at Case Western Reserve University in Cleveland, OH and Clinical Director of the Murdough Family Center for Psoriasis. Though there could be future clinical trials involving combinations, they are not likely because after approval funding for these trials is harder to come by, Dr. Korman says.
Combinations with Biologics

But this hasn’t prevented dermatologists from exploring off-label uses for various biologic therapies in combination. Dr. Menter notes that the overall absence of major clinical trials of biologics in conjunction with other therapies poses difficulties with regards to future study and understanding of these agents. “Many physicians who have ever treated psoriasis know that monotherapy may not be the final answer for every psoriasis patient,” he observes.

Topicals and Phototherapy
Perhaps the agents most commonly combined with biologics are topical therapies. “Roughly 70 percent of psoriasis patients receiving biologics are also using some kind of topical treatment for resistant localized areas, as well,” notes Dr. Menter. There is a diverse field of topical therapies that dermatologists have been using for many years, from steroids to topical vitamin D3 preparations, and these generally have reliable safety profiles.

Since the skin at different areas of the body has different characteristics, there are more difficult-to-treat areas (such as the scalp or intertriginous areas). By nature of their delivery as infused agents, biologics cannot necessarily be used to specifically target hard-to-treat areas. That’s where topical therapies—steroids, in particular—may come in. “For scalp psoriasis, it often helps to apply a high potency topical steroid on an intermittent basis,” says Dr. Menter. He further notes that tacrolimus (Protopic, Astellas) and pimecrolimus (Elidel, Novartis) are effective in intertriginous and facial areas in conjunction with biologics.

Another more pragmatic use for topical agents, according to Leon Kircik, MD, Associate Clinical Professor of Dermatology at Indiana University Medical Center and Medical Director of Derm Research PLLC and Physicians Skin Care in Louisville, KY, is after the initial decision to commence with biologic therapy. “Sometimes, approval to use biologics may take several weeks,” he says. “Therefore, once the decision is made to treat with a biologic, you can start a patient off with a topical steroid immediately.” After biologic therapy starts, the patient and physician can decide whether they wish to continue with the topical agent or taper it off.

Another effective combination approach associated with minimal additional safety concerns is phototherapy, especially in biologics that require extra time to take effect, according to Dr. Kircik. “In these instances, adding ultraviolet light—either narrowband UVB or PUVA, depending on patient profile—can be extremely helpful and relatively risk-free,” he says. While the choice of light therapy may differ depending on that profile, Dr. Kircik notes that etanercept (Enbrel, Amgen/Wyeth) is effective in conjunction with either PUVA or NB-UVB. He also observes that several recent clinical studies have shown that patients receiving alefacept (Amevive, Astellas) or efalizumab (Raptiva, Genentech) with UVB exhibit a jump in clinical response, especially over the first four to six weeks of treatment.1,2

According to Dr. Korman, adding phototherapy to biologic therapies that are losing efficacy or don’t meet the expectations of patients may be beneficial in increasing clearance and patient satisfaction. Furthermore, according to Dr. Menter, phototherapy is usually quite effective when patients experience flare-ups, as some do from time to time. However, he points out that the main problem with phototherapy isn’t safety or efficacy, but access. “Patients often need two to three treatments a week for several weeks, which just isn’t feasible for a great deal of patients who come long distances for treatment,” he says. Therefore, effective as it may be, long-term narrowband UVB therapy may be difficult to sustain for a number of patients.

Systemic Combinations
While certain systemic combinations with biologics may yield increased efficacy, Dr. Korman reminds that the best way to approach such combinations is cautiously. “Many dermatologists may not want to combine biologics with systemic agents due to the potential risks and the many uncertainties,” he says. Dr. Kircik echoes that concern, noting that dermatologists traditionally wouldn’t use two immunosuppressive agents at the same time. Though there are safety and efficacy data for systemic and biologic treatments individually, there is less data regarding the use of these agents in combination, he notes, particularly for combinations with T-cell inhibitors, such as alefacept and efalizumab. “While there have been studies in psoriatic arthritis patients treated with TNF inhibitors where about one half of patients have been concurrently treated with methotrexate, there is limited data on T-cell inhibitors in conjunction with systemic agents to warrant extensive combination treatment,” say Dr. Korman.

Unexpected Conveniences
One distinct advantage of biologics is that once a patient is established on a given therapy, lab work need only be done once every two or three months, as opposed to most systemic treatments, which often require labs every four to six weeks. This may reduce the expense of more frequent labs, as well as enhance convenience.
Dr. Menter observes that low-dose retinoids, such as acitretin (Soriatane, Connetics) in conjunction with any of the five biologics can yield significant efficacy for the right patient. Their limitation is that they can only be used in very specific patients. For example, Dr. Menter says, retinoids should never be used in women of childbearing potential, but when used in low dosages (10-25mg a day) they may be valuable for maintenance therapy in combination with biologics. Soriatane may be used when transitioning patients from one therapy to another, according to Dr. Kircik. “If you are stepping down a patient’s dosage of a biologic or changing therapies altogether, Soriatane can ensure efficacious transition during this period,” he points out. Moreover, Dr. Kircik notes that the primary advantage of acitretin is that it can be used in combination with any biologic since it is not an immunosuppressive treatment and everybody except females of childbearing age can be on it as long as they tolerate it.

**Desire For Data**

Data indicate that risks associated with systemic agents are prevalent, though adverse events are of variable severity. When considering systemic combination therapy with biologics, one point to keep in mind, Dr. Korman says, is that most data concerning any systemic therapy come from studies that examined them as monotherapies. “Safety profiles for systemic therapies are well-documented,” he says, “and while a well-planned course of systemic therapy for the appropriate patients may not likely result in side effects, physicians should keep in mind that there isn’t a great deal of data on systemics in combination with one another.”
One recent study found that retinoids have the highest adverse event rate of the psoriasis therapies, though most of these were considered minor. Cyclosporine is associated with more significant adverse events. Another recent review co-authored by Dr. Korman examines the extent to which toxic effects are associated with targeted immunotherapeutic agents used across various specialties. Dr. Korman and his fellow researchers noted that the use of biologic agents in combination with each other and/or the use of biologics in combination with other potent immunosuppressive therapies can cause serious adverse events. These include both infections and malignancies, which is why Dr. Korman sounds a note of caution about considering combination therapy. According to Dr. Menter, possible infections include tuberculosis and other bacterial infections. “Sometimes, infections may become very severe and require systemic antibiotics,” says Dr. Menter. “In these cases, withdrawal from biologics for one week may be necessary, but that withdrawal should not last more than two weeks to reduce risk of destabilizing the psoriasis.”

These findings serve as a reminder that a cautious approach to systemic combinations is integral to their efficacy and safety. Given that adverse events are a very real concern when treating with systemic agents, clinicians should screen their patients thoroughly before commencing with combination therapy with systemic agents. “Physicians should always be aware of the risk/benefit ratio,” says Dr. Korman. “Risking damage to the immune system for the sake of better efficacy can result in adverse events far greater than psoriasis, which is why more dermatologists are using these combinations for shorter amounts of time and adding it in and overlapping where necessary,” he observes.

Given concerns about risks and adverse events, many combination therapies are best reserved for transitioning therapies, as mentioned above, or in extenuating circumstances, Dr. Korman suggests. “Often times, the decision to use systemic therapy in conjunction with biologic therapy comes based on the patient’s previous experience with treatment,” he notes. “Patients who have been on topical formulations for an extended time to no avail or have been mismanaged in the past are often the best candidates for systemic combinations because they can be offered significant improvements,” he adds.

“There are a variety of potential combinations that can be mixed-and-matched depending on severity of the disease and quality-of-life, which will differ from patient-to-patient,” says Dr. Menter. “Psoriasis affects patients differently, so the willingness to try combination therapy with biologics will likely depend on a number of factors,” he notes.

Proceeding Cautiously

As safety profiles continue to emerge from new and forthcoming data, researchers are also exploring the specific relationships between psoriasis and obesity, depression, metabolic syndrome, etc. The combined influence of these various factors plays a role in treatment decisions, especially with regard to biologics. Some dermatologists approach biologics with trepidation when it comes to comorbidities and the associated risks of certain biologics, but findings are often equivocal. For example, before starting treatment with infliximab, a patient must consult with a cardiologist due to concerns regarding a possible correlation between infliximab and heart disease (as well as the likelihood that patients are at increased risk for heart disease simply by having psoriasis). But Dr. Menter suggests that the anti-inflammatory effect of infliximab may actually reduce cardiac risk. “Nevertheless,” he says, “it’s wise to be on the conservative side when it comes to patients who may be prone to heart disease until more data emerges.”

While topical and light-based therapies make for good adjunctive agents for use with biologics, dermatologists bear a responsibility to their patients to walk the tight wire of exploring the potential of systemic combinations in a cautious manner. In the meantime, education is paramount, Dr. Menter reminds.

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