A Level Approach to Psoriasis Therapy
large array of effective therapies having acceptable safety profiles is pushing the step-wise approach for treating psoriasis into a historic curiosity. While not by any means extinct, the paradigm of topicals, then UVB, and finally systemic agents is relinquishing ground as manifest by the recent publication of guidelines suggesting a more equitable and therapeutically optimal approach: all effective therapies should be considered equally based upon recalcitrance of disease, severity of disease, comorbidities, and patient selection and ability. However, the physician is as much a part of the process of treatment selection as the patient. A summary of the treatment options coupled with appropriate screening and monitoring recommendations should aid physician and patient alike when evaluating potential therapies.

Rethinking Long-Standing Options
The recommendation to consider all treatment options on a somewhat level plane aims not necessarily to decrease the role of one group of agents or increase the role of another, though presumably shifts in usage will occur as physicians adapt their approach to patients. Certainly each available therapy has intrinsic strengths and weaknesses. I’ll begin by briefly reviewing the therapies with which dermatologists are most familiar.

Topical Therapies. Topical therapies are still used and may be the only option available to some patients with extensive, severe, or recalcitrant psoriasis. Corticosteroids are and will probably continue to be the mainstay of topical therapies given their historic use, prevalence, and cost. All dermatologists are aware of the possible adverse events associated with topical corticosteroid use, but we do not know the safety limits based upon their potential for systemic effects. Likewise, topical retinoid use has a poorly defined safety profile in terms of systemic absorption. Only vitamin D analogues, calcipotriol specifically, have set limits for safe topical application: 200gm weekly for the average adult. The latter is specifically related to limiting the risk of hypercalcemia resulting from percutaneous absorption of a drug that may alter calcium metabolism and absorption.

Systemic Therapy. Systemic therapy has a natural division: small molecules administered orally and biologics administered parenterally. Very limited data are available on the safety and efficacy profile of the commonly available small molecules: methotrexate, acitretin (Soriatane, Connexis), and cyclosporine, despite several decades of availability.

It is worth considering the circumstances surrounding the emergence of these agents as therapeutic options for psoriasis. Historic opportunity rather than prevarication saw the small molecules brought to practice at a time when the demand and requirements of clinical studies were modest. Consequently, most of what we know about these agents is based upon sparse, small, limited, short-term clinical studies and case reports. Clinicians must be vigilant against teratogenicity and monitor for pregnancy, with the most stringent screening and monitoring conditions applied to acitretin. A long half-life makes Soriatane a poor choice of therapy for young women of childbearing potential. Chronic therapy with Soriatane requires episodic monitoring of serum lipid levels and liver function, whether it is used as monotherapy or in conjunction with other agents, including phototherapy.

We all believe methotrexate is very effective for treating psoriasis but there is precious little evidence to support our beliefs. Moreover, not exceptional is the questionable requirement for a test dose of methotrexate prior to introduction of a therapeutic dose. Controversy surrounds the use and monitoring of the longest-available systemic agent. This controversy results not only from lack of large clinical studies to provide guidance but also from the changing diagnostic tools available. Hepatotoxicity and cirrhosis especially are the focus of routine monitoring and liver biopsies. However, it is important to note the fact that pulmonary fibrosis and cytopenias are the primary causes of mortality. Unfortunately, the latter are unpredictable: pulmonary fibrosis and cytopenia may occur at any time during therapy, even following decades of treatment, even at low doses.

Of the traditional agents, cyclosporine requires the most frequent monitoring and detailed attention to possible drug interactions. Metabolized through Cyp450A3, cyclosporine is
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responsible for significant metabolic interactions with commonly prescribed drugs and likewise is subject to altered metabolism via interaction with Cyp450A3 by other drugs. Hypertension is a common occurrence in patients treated with cyclosporine. The greatest challenge in offering treatment for cyclosporine-induced hypertension is that most antihypertensives are metabolized by Cyp450A3 or reduce renal function, thereby exacerbating renal toxicity.

The Biologics

The newest options for the treatment of psoriasis, the biologic agents have attracted a significant amount of attention due to their reportedly high efficacy. Because early reports emphasized dramatic improvements in psoriasis, these drugs quickly came to be viewed as “heavy hitters.” The assumption, unfortunately, is that “heavy duty” drugs must be associated with heavy risks. While such assumptions were often justified in the past, they no longer broadly apply in today’s drug development arena. Of course there are risks associated with these agents, but on balance, they may not be worse and in fact may be preferable to risks associated with older topical and oral agents. Plus, we have a better knowledge of and understanding of the risks associated with these newer agents than those with many older therapies.

Any parenterally administered agent may be associated with injection site reactions, though these are uncommon and are rarely significant. There are no direct organ toxicity risks associated with any of the approved biologics. Alefacept (Amevive, Astellas) has been associated with decreased CD-4 counts, and patients require weekly blood monitoring.

Because of their immunosuppressive action, biologic agents are not appropriate for patients with active or recently-treated malignancies, including skin cancers or active systemic infections. Anti-TNF-alpha agents are contraindicated for patients with congestive heart failure, demyelinating disorders, and untreated latent tuberculosis. One recent report suggested higher-than-expected risks for cancer and infectious diseases among patients treated with adalimumab (Humira, Abbott; approved for psoriatic arthritis, not yet approved for psoriasis) and infliximab (Remicade, Centocor; just approved for psoriasis), however, many experts note that the methodology likely over-estimated these risks. The study focused on patients with rheumatoid arthritis.

Importantly, the biologic agents have been monitored in large patient groups worldwide with etanercept (Enbrel, Amgen/Wyeth) and infliximab (Remicade) each with a 10 year history of use in rheumatoid arthritis, psoriatic arthritis, and other indications.

It is difficult to reliably compare the efficacy of the various biologic agents in a head-to-head fashion. Subtle differences in study protocols preclude direct comparisons. Nonetheless, these agents as a group demonstrate significant improvement in PASI scores among treated patients. Ongoing studies coupled with clinical use are helping clinicians to identify patterns of response so as to optimize treatment and identify appropriate candidates for biological therapy. Alefacept seems to have the slowest onset of action (eight to 12 weeks). Results from infliximab may be most dramatic, however the agent must be given via three-hour infusions, which may influence its use. Concomitant psoriatic arthritis (PsA) would suggest use of TNF-antagonists which have documented efficacy for PsA.

Putting it Together

Given our understanding—as limited or extensive as it may be—of the risks and benefits associated with the various therapeutic options, clinicians faced with a psoriasis patient should weigh the options carefully. No longer should we relegate patients to a trial of topical corticosteroids knowing with reasonable certainty that improvements, if any, will be minimal. Nor must we initiate a trial of oral therapy simply because that is what we always did in the past. Instead, we must assess comorbidities, concurrent medications, and risks on a case-by-case basis. Given the risks associated with the agents, one might conclude that a biologic agent represents a better treatment option than Soriatane for a woman of child-bearing potential. Conversely, Soriatane may be a better choice than a biologic for a patient who recently underwent excision of a melanoma.

Whereas the previous approach to treatment emphasized topical agents for limited body surface area involvement, a clinician may reasonably pursue use of biologics in a patient with so-called “limited involvement”—cases of severe palmar or plantar plaques vividly illustrate this point.

Important to the treatment selection process is patient screening. Obtaining a thorough history is critical to identify comorbidities, additional symptoms such as joint complaints, and concurrent medications. Keeping an open mind about treatment options, query patients about relevant facts that would influence treatment selection, such as history of congestive heart failure or cancer, before ruling any therapeutic option in or out.

Once you have identified appropriate options and begun to discuss these with the patient, then undertake a screening more specific to the therapy under consideration. Has the patient been diagnosed with tuberculosis or hepatitis B? Is he or she HIV positive? Patient response to specific screening questions may change the course of treatment.

In terms of topical therapies or biologics, determine if the patient can apply or administer these agents as necessary. In
the case of efalizumab (Raptiva, Genentech), etanercept, or adalimumab, can/will the patient self-inject? Can/will they present to the office as needed for IM injection of alefacept or infliximab infusion?

Finally, the patient must understand the risks and benefits associated with the specific therapy chosen and be willing to comply with the specific required screenings, as discussed above.

Making the Switch
The outmoded step-wise approach to treatment selection was based on presumed safety relative to disease severity, and for the most part, ignored issues like impact of the disease on function and quality of life, patient convenience and compliance, and long-term management. By encouraging clinicians to assess the possible utility of the range of treatment options, the current approach to therapy recognizes that we cannot simply tell a patient that the current BSA doesn’t justify a particular treatment. If after a reasonable trial with a particular therapy a patient is experiencing minimal or no clearance, it is incumbent upon clinicians to recommend trial of another agent that is reasonably expected to provide benefit. Importantly, this switch does not necessarily imply a “step-up” as considered in the old model. Rather, weighing the patient’s unique characteristics and disease profile as well as their experience with the failed therapy, the clinician can recommend the agent he or she feels is most likely to provide benefit.

Paradigm Shift
The notion of the paradigm shift has become trite, but in psoriasis care, we truly are witnessing a therapeutic revolution. While the relatively new class of biologics receive much credit for changing the face of psoriasis care, the fact of the matter is that the real change is coming through physicians themselves. The availability of generally safe, very effective agents—whose mechanism of actions, risks, and benefits are reasonably well-known—certainly facilitated the shift. However, this development alone does not explain our evolving approach.

In the past few years, the dermatology community has benefited from improved understanding of the nature of psoriasis as a chronic disease and enhanced knowledge of the disease’s potential impact on quality of life and functioning. We have expanded our treatment target from intervention to long-term management. The collective result of these changes in the past few years has been the recognition that the once-standard step-wise approach to psoriasis care simply does not apply to real-world clinical practice or patient experience. To pigeon-hole patients into a treatment “level” that may not provide the degree or speed of clearance or convenience that they require simply is not fair.

On a very personal note, I have had the great privilege of using all the systemic and biologic therapies available to us in relatively large cohorts of patients. I continue to treat patients with topicals, phototherapy, methotrexate, Soriatan, and cyclosporine, but I am far more comfortable treating patients with biologicals. This comfort is a reflection of our better understanding of the harm-benefit ratio for the biologics. Certainly, no available treatment is perfect. Each has its own unique risks and benefits. Although we are hindered by incomplete knowledge regarding many of the available therapies, we do have experiential evidence available to support the traditional agents as reasonable treatment choices.

As clinicians, we must recognize the “quality” of evidence available to us. Some clinicians continue to adhere to a “wait-and-see” approach to biologics, anticipating long-term data. A conservative approach is valid but we should recognize that much of the data already available for biologics are actually more reliable than published data for the traditional oral agents.

Consider each patient individually. Don’t attempt to match the patient to a treatment level. Help the patient to identify the treatment that best matches his or her individual needs.

Some Thoughts on Light Therapy
Photochemotherapy is an important therapeutic option in psoriasis, though its popularity has waxed and waned in recent years. The general discussion here has not included an in-depth discussion of phototherapy, though clinicians should consider it an acceptable treatment option that may provide benefit for certain patients either alone or in combination with other therapies. Physicians and patients must be familiar with documented risks regarding melanoma and other skin cancers potentially associated with phototherapy. These risks can be significantly minimized with appropriate use of light therapy and long-term monitoring, but communication and patient education are a crucial element of therapy.