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USHERING IN A NEW ERA OF PSORIASIS TREATMENTS

I often find myself counseling my patients about this being an "exciting time" to be a psoriasis patient. This is due to the fact that our knowledge of the disease has evolved at such a rapid pace, and, with it, our ability to clear the skin in both a safe and efficacious manner has become more advanced than ever before.

In my dermatology training, a dermatologist teacher of mine often used the metaphor of a tree when discussing treatment options for managing psoriasis with his patients. His rationale was quite simple: this metaphor was understandable to all patients of all backgrounds including those with lower health literacy. I have found this simplistic treatment discussion so useful in my own discussions with patients now that I am in independent practice that I often find myself "borrowing" it as an educational tool on a near-daily basis.

In this patient counseling discussion, I refer to some of the more traditional agents for psoriasis, including methotrexate or cyclosporine as cutting the trunk of the immune-system tree. As such, these medications are associated with a higher risk of side effects, including infections and immunosuppression[1]. These older treatments can also require extensive workup and monitoring

during treatment. They also often take between six to twelve weeks for optimal onset of action[2]. Unfortunately, by that time, we may often observe a loss of motivation on the part of the patient as they struggle with active disease that does not seem to be effectively managed according to their expectations of the therapy. Additionally, the patient may be lost to follow up before the medication has started to work and this can pose another challenge in the utilization of these older treatments. Patients (and physicians) are often nervous to try these agents which underscores the need for safer and more effective treatment options.

Around 15 years ago, therapies with monoclonal antibodies were introduced for the treatment of psoriasis and psoriatic arthritis. When describing these agents, often called "biologics", I liken them to cutting a large branch of the immune system tree. The early biologics include tumor necrosis factor alpha agents (i.e. adalimumab, etanercept and infliximab) and IL 12/23 inhibitors (i.e. ustekinumab). These drugs were welcomed by providers and patients alike with benefits including less frequent and cumbersome dosing, fewer adverse events, and a more potent and enduring efficacy profile[2].

Within the last 2-3 years, our understanding of psoriasis and psoriatic arthritis has grown by leaps and bounds. The therapeutic landscape has evolved with newer, more targeted and safer agents. With more specific drug targets, I equate their mechanism to simply cutting the twigs in the immune system tree that specifically drives psoriasis and/or psoriatic arthritis. The IL-23 inhibitors (i.e. risankizumab, tildrakizumab and guselkumab) and IL-17 inhibitors (i.e. ixekizumab, broadalumab and secukinumab) are examples of these modern targeted agents. Patients understand that with the more targeted nature of these medications, they can benefit from a more precise and cleaner safety profile.

In the psoriasis clinical trials of the 2000s, a realistic treatment goal was a PASI 75 by 12 weeks[3]. Today's newer agents aim for a PASI 90 or even PASI 100 – which is often obtainable both in trials and real-world studies[4,5,6]. We, as dermatologists, are in a unique position to offer clear or nearly clear skin to our patients where this was only a dream in the past.

With these more ambitious treatment goals, we are seeing success even in the harder to treat areas such as the scalp, genitals, nails and palmoplantar psoriasis. The psoriasis therapeutic landscape is competitive and with that comes the desire by many pharmaceutical companies to create therapies that not only clear the skin quickly, but also that may stand out as the "agent of choice" for these difficult cases. For example, secukinumab has marketed its efficacy in ankylosing spondylitis and nail psoriasis[7,8] and ixekizumab as the agent of choice for managing genital psoriasis[9].

The past twenty years have seen a true evolution within the psoriasis therapeutic landscape. The paradigm has shifted from a mentality of immunosuppression to that of more immunomodulation. Dermatologists that had previously been limited to a few rudimentary immunosuppressive agents now have a full armamentarium of tailored and precise treatment options. With this movement towards immunomodulation, comes a need to update our guidelines. Specifically, the diagnostic tests often ordered by specialists for patients prior to starting these agents. The previous recommendations were designed in an era of patients being initiated on methotrexate, cyclosporine or early biologics where infection and immunosuppression risk was very real. Today, the risk of these adverse effects is much lower with these targeted agents.

For example, past treatment options for a patient who had a history of tuberculosis or a solid organ malignancy may have been limited to oral retinoids and topicals. Now, due to more targeted immunomodulatory therapies where the mechanism of action is truly "anti-inflammatory" as opposed to "immunosuppressive" (i.e. PDE4 inhibitors and targeted

biologic agents), there are many safe and effective options available for treatment.

Another push towards updating our older recommendations for initiating biologic treatment in patients is the move toward examining healthcare needs through the lens of societal cost and burden, where the allocation of scarce health care resource and an eye on cost-effectiveness is becoming more important. In my experience, I have sometimes found TB skin testing, extensive laboratory investigations and radiologic imaging for every patient to be time consuming for the patient and inefficient for the healthcare system and often leads to false negatives. Thus, work-up should be patient-specific – low-risk patients may not need these tests which ultimately lead to attrition rates and loss to follow up. Certainly, higher-risk patient populations, such as immigrants, healthcare workers, homeless, indigenous populations, sex workers etc., should be investigated prior to starting biologics with tuberculosis testing, (TBST or Quantiferon assay), chest x-ray, stool cultures, hepatitis and HIV serologies and/or other viral titres.

There have been studies both in risankizumab and guselkumab in patients with proven latent tuberculosis (positive TBST or quantiferon gold assay[4,5]). In these trials, none of the 31 patients with latent TB went on to develop active tuberculosis despite the use of risankizumab,[5]. In the guselkumab clinical trials, some of the latent TB patients patients started the biologic agent prior to anti-TB treatment and still did not develop active disease[4]. In response to these studies, newly approved risankizumab is the first biologic agent where the label does not require tuberculosis testing (instead, leaving it up to the discretion of the provider)[10]. In the real world, it would certainly be clinically appropriate to have patients in higher risk groups undergo TB screening prior to initiation of treatment (i.e. indigenous populations or those living on reserves, homeless persons, and immigrants or high-risk travellers).

One final reason I tell my patients it is an exciting time to be a psoriasis patient is the growing level of support patients have access to outside their immediate care circle, such as: improved patient access to drugs through the industry-sponsored patient support programs, bridging and compassionate programs and even increased access to these newer therapies via the public reimbursement mechanisms, all of which have contributed to this exciting era of psoriasis therapies. The government's recognition of the impact of skin disease on quality of life and workplace performance is increasing, as is research in this field.

Ultimately, it is an exciting horizon for psoriasis treatment and management. We have more efficacious medications, with improved safety profiles and longer duration of effect. With these tailored and personalized treatment options we, as dermatologists, are in a position to really make an incredible difference in the lives of our patients.

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