Chapter 14
43-Year-Old with Recurrence of Red, Scaly Rash

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A 43-year-old male with a 9-year history of well-controlled plaque psoriasis presented with concerns of progressive worsening of his psoriasis symptoms. His psoriasis had been well managed with adalimumab for the past 5 years with less than 1% body surface area affected. However, the patient states that new lesions formed on both upper and lower extremities in the past 4 months. The patient is compliant with his medication regimen and denies any interruptions in treatment. He does not complain of side effects from his medication. The review of systems did not reveal any pertinent positive or negative findings. He denies recent illness,

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trauma to the skin, or use of new medications. He has no other medical conditions and does not use any other medications. The patient has a maternal family history of psoriasis. The patient is a former smoker and denies the use of alcohol.

On physical examination, bilateral knees, dorsal hands, and elbows had erythematous, indurated papules and plaques with overlying silvery scales. Less prominent papules with fine scales were also found on the back and face. A total of 5% body surface area was affected.

Based on the case description, what is the best treatment recommendation for this patient?

1. Continue current regimen (adalimumab).
2. Add topical agent to current regimen.
3. Discontinue current regimen and prescribe alternate biologic agent.
4. Discontinue current regimen and recommend ultraviolet phototherapy.
5. Add methotrexate to current regimen.

Treatment

Add methotrexate to current regimen.

Discussion

The effectiveness in managing psoriasis has vastly improved since the emergence of biologic medications. However, biologic drugs tend to lose efficacy with extended use (Levin et al. 2014). Although the specific mechanism that causes the clinical decline is not completely understood, evidence suggests that an immune-mediated mechanism is partially responsible. Biologic drugs are recognized by the immune system as foreign and elicit a helper T-cell-dependent humoral response that leads to the development of antidrug antibodies (ADAs) (van Schouwenburg et al. 2013). ADAs are

considered to be either neutralizing or non-neutralizing. Neutralizing ADAs bind to the drug's active site and prevent it from interacting with its end target. Non-neutralizing ADAs may form immune complexes with the drug, thereby increasing drug clearance (Jullien et al. 2015). Nonetheless, both neutralizing and non-neutralizing ADAs likely alter the bioavailability, excretion, binding sensitivity, and ultimately the efficacy of biologic medications. In order to maximize the utility of biologic agents, additional studies must be conducted to find effective methods of reducing biologic drug immunogenicity and identifying risk factors for loss of response.

Treatment

Patients experiencing a loss of effect from biologic agents are managed differently depending on the severity of recurrence. A topical corticosteroid may be adequate if less than 3% of the body surface area (BSA) is affected. Apply the topical steroid BID for 2 weeks and alternate with a steroid-sparing agent BID for 2 weeks and repeat as needed. If recurrence involves more than 3% BSA, add methotrexate (7.5–25 mg weekly) to the patient's current medication regimen for 3–6 months. If symptoms do not improve, consider switching to a different biologic agent with a long-term drug survival (e.g., ustekinumab).

The theory that concurrent methotrexate use can be used to overcome loss of efficacy is supported by retrospective studies of infliximab and adalimumab. Vermeire et al. demonstrated that simultaneous methotrexate use reduces the risk of ADA formation (Vermeire et al. 2007). The group of patients using infliximab with concurrent methotrexate had a lower incidence of ADA formation (46%) compared to the infliximab monotherapy group (73%). Lower serum infliximab levels were also seen in patients not simultaneously using methotrexate. The evidence for concomitant methotrexate use in minimizing loss of biologic effect appears reassuring, although further studies are needed to clarify the exact mechanism and proper dosage.

In a 52-week randomized control trial, 71% of participants treated with adalimumab obtained a 75% reduction in their Psoriasis Area and Severity Index score (PASI 75) after 16 weeks (Menter et al. 2008). During the study, 9% of patients developed anti-adalimumab antibodies (AAAs). Forty-three percent of AAA-positive participants lost clinical response by week 52. In the 3-year open-label extension study, 83% and 76% of participants who received uninterrupted adalimumab therapy maintained PASI 75 at week 100 and week 160, respectively (Gordon et al. 2012). Asahina et al. further demonstrated the correlation of AAAs and poor clinical response. Patients with AAAs fared worse with significantly lower PASI 75 response (23% vs. 73% in AAA-positive patients vs. AAA-negative patient, respectively), PASI 50 response (39% vs. 87%), and PASI 90 response (0% vs. 52%) at week 16 and week 24 (Asahina et al. 2010).

The long-term efficacy of ustekinumab has been well established in two long-term studies (PHOENIX 1 and PHOENIX 2) (Kimball et al. 2013; Langley et al. 2015). In the PHOENIX 2 study, 63.1% and 72% of participants achieved a PASI 75 response by week 12 when administrated 45 mg or 90 mg of ustekinumab, respectively (Papp et al. 2008). About 5% of the participants developed anti-ustekinumab antibodies. Of note, from the group who attained PASI 75, only 2% of participants were found to have anti-ustekinumab antibodies. In contrast, 13% of patients with partial response were found to have anti-ustekinumab antibodies. The authors also noted that partial responders had trough serum drug levels two to three times lower than PASI 75 responders. To further assess the long-term efficacy of ustekinumab, participants who achieved PASI 75 at week 40 were given an every-12-week maintenance treatment to complete 244 weeks of treatment. Approximately 80% of the patients maintained a PASI75 response through 244 weeks of therapy (Papp et al. 2013).

Secukinumab has exhibited low immunogenicity in two 52-week studies. In the ERASURE study, 82% of participants who received 300 mg of secukinumab attained PASI 75

at week 12 (Langley et al. 2014). Similarly, the FIXTURE study showed a 77% response (Langley et al. 2014). Of note, 81% of patients in the ERASURE study maintained PASI 75 from week 12 to week 52. The FIXTURE study showed comparable results with 84% of patient maintaining PASI 75. The FIXTURE study detected anti-secukinumab antibodies in four patients (0.4% of 980 secukinumab-treated patients). None of the antibodies were neutralizing and were not associated with loss of efficacy. In the ERASURE study, anti-secukinumab antibodies were found in two patients (0.3%), one of which was a neutralizing ADA. However, neither patient experienced a loss of efficacy.

The long-term efficacy of ixekizumab is demonstrated in three 60-week phase 3 trials. In the UNCOVER-3 trial, 87% of patients achieved PASI 75 by week 12 (Gordon et al. 2016). The long-term efficacy of ixekizumab is demonstrated by the 83% of patients who maintained PASI 75 at week 60 with an every-4-week maintenance therapy. Anti-ixekizumab antibodies were found in 103 of 1150 patients (9%) in all three UNCOVER trials. The 19 patients with high titers (>1:1280) of antidrug antibodies had decreased clinical efficacy and collectively did not attain PASI 50 at week 12. However, patients with low to moderate titers had clinical efficacy that was comparable to their counterparts without detectable levels of ADAs.

In a large multicenter 24-week study, 49% of patients achieved PASI 75 by week 12 when administered 50 mg of etanercept twice weekly. Of the patients who achieved PASI 75 at week 12, 77% maintained a PASI 75 response at week 24 (Papp et al. 2005). About 2% of the participants developed anti-etanercept antibodies. The ADAs were non-neutralizing and did not have an effect on drug efficacy. In a longer randomized control study with an open-label extension, 47.3% of participants using etanercept 50 mg twice weekly achieved PASI 75 in the first 12 weeks of the study (Tyring et al. 2007). At week 96, the PASI 75 response was 51.1%. Anti-etanercept antibodies were found in 18% of the participants. Similar to the previous study, the ADAs were non-neutralizing with no appreciable effect on clinical response.

Intravenous infusions of infliximab may be challenging to patients. Additionally, infliximab is known to have a predilection for causing severe infusion reactions in patients with anti-infliximab antibodies (Baert et al. 2003). Patients with anti-infliximab antibodies also have a higher tendency to lose clinical efficacy. In the EXPRESS I study, only 39% of participants who developed anti-infliximab antibodies and achieved PASI 75 by week 10 were able to maintain PASI 75 to week 50 (Reich et al. 2005). In contrast, patients who tested negative for anti-infliximab antibodies, 81% were able to maintain PASI 75 until week 50. Patients with anti-infliximab antibody were also found to have lower serum infliximab concentrations and lower steady-state trough concentrations (Takahashi et al. 2013).

A prospective observational cohort study assessed the drug survival of biologic agents (Warren et al. 2015). Ustekinumab was shown to have a significantly higher survival rate in comparison to TNF inhibitors. Among the tumor necrosis factor (TNF) inhibitors, adalimumab has the longest drug survival time. When ineffectiveness was the reason for discontinuing therapy, the 3-year survival rate for ustekinumab was 89%, adalimumab 79%, infliximab 76%, and etanercept 55%.

Methotrexate was added to our patient's current regimen of adalimumab and was advised to follow-up in 2 months. He was also prescribed a high-potency topical corticosteroid to apply to more resistant lesions.

Key Points

- Biologic therapies lose efficacy over time. Although the exact mechanism is unknown, antidrug antibodies likely play a role in drug survival.
- Depending on the extent of clinical worsening, consider adding a topical corticosteroid, methotrexate, or substituting the current biologic with a more effective biologic agent.

- Further studies are needed to find successful methods of reducing biologic drug immunogenicity, identifying clinically relevant risk factors, and increasing the sensitivity and specificity of antidrug antibody detection assays.

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