Managing the dose escalation of biologics in an era of cost containment: the need for a rational strategy###

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

| Citation          | Shahwan, K.T., and A.B. Kimball. 2016. “Managing the dose escalation of biologics in an era of cost containment: the need for a rational strategy###.” International Journal of Women’s Dermatology 2 (4): 151-153. doi:10.1016/j.ijwd.2016.09.003. http://dx.doi.org/10.1016/j.ijwd.2016.09.003. |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Published Version | doi:10.1016/j.ijwd.2016.09.003                                                                                                                                                                    |
| Citable link      | http://nrs.harvard.edu/urn-3:HUL.InstRepos:33029909                                                                                                                                               |
| Terms of Use      | This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA |
Managing the dose escalation of biologics in an era of cost containment: the need for a rational strategy

K.T. Shahwan, MD a, A.B. Kimball, MD, MPH b,*

a Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA
b Department of Dermatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

ABSTRACT

Although biologic medications have demonstrated great efficacy for the treatment of psoriasis, a subset of patients fails to respond and others lose response later in the course. In treating a patient who has failed to respond to biologic therapy, clinicians must decide between dose escalation, switching biologics, and adding or switching to a non-biologic systemic drug or phototherapy. Although dose escalation is perhaps the simplest strategy and generally well-tolerated, it confers a tremendous cost burden because doubling the dosage is likely to double the wholesale price. We call for the development of rational strategies for the pricing of dose escalation in order to minimize this phenomenon. We also call for increased transparency surrounding negotiated pricing to ensure that all patients have access to the most effective, affordable treatment options available.

Introduction

Over the past decade, biologic therapies against TNF-α, IL-17, and IL-12/IL-23 have revolutionized the treatment of chronic inflammatory diseases including psoriasis. Although these medications have demonstrated favorable efficacy and side effect profiles, a subset of patients fails to respond and others lose response over time. Even patients who have treatment success often desire to escalate their dose (Langley et al., 2015).

The prevalence of non-responders, defined as the failure to achieve a 75% reduction in Psoriasis Area and Severity Index (PASI) scores by week 12-16 of therapy, ranged from 51-66% for etanercept (Papp et al., 2005; Tyring et al., 2006), 20-32% for adalimumab (Menter et al., 2008; Saurat et al., 2008; Thaçi et al., 2010), 24-34% for ustekinumab (Leonardi et al., 2008; Papp et al., 2008), 18-33% for secukinumab (Langley et al., 2014), and 11-19% for ixekizumab (Gordon et al., 2016) in Phase III clinical trials. When treating a patient who has failed to respond to biologic therapy, which in the United States has usually been preceded by systemic medications per insurers’ appropriateness criteria, clinicians must decide between dose escalation, switching biologics, and adding or switching to a non-biologic systemic drug or phototherapy. In this era of renewed focus on cost and quality, this decision becomes increasingly important, especially because psoriasis patients may be taking these drugs for several decades.

Although dose escalation is perhaps the simplest strategy and has been shown to be well-tolerated in the majority of patients, even when outside labeling by the U.S. Food and Drug Administration (FDA; Brezinski and Armstrong, 2012), it confers a tremendous cost burden because doubling the dosage also doubles the wholesale price (RedBook Online). For example, the maintenance dose of etanercept is 50 mg weekly (Papp et al., 2005; Tyring et al., 2006), which costs approximately $53,909 per year in the United States. Increasing the dose to 50 mg twice weekly doubles the cost to $107,818 per year. Transitioning to another biologic, such as adalimumab or ustekinumab, is a far more cost-effective strategy with an annual cost that is approximately equivalent (RedBook Online; Table 1).

This issue is further complicated by the weight-based dosing of ustekinumab. For patients who weigh ≤ 100 kg, the maintenance...
dose is 45 mg every 12 weeks (a cost of $39,311 per year), which can later be escalated to 90 mg every 12 weeks if necessary (a cost of $78,622 per year). Patients who weigh more than 100 kg, however, initiate the higher dose from the beginning. Escalating to 90 mg every 8 weeks may improve efficacy in these patients, however, this dose is not FDA-approved and costs approximately $117,933 per year (Leonardi et al., 2008; Papp et al., 2008; RedBook Online).

Interestingly, treatment with secukinumab is designed to avoid dose escalation. All patients are initiated on 300 mg weekly for 5 weeks, followed by 300 mg every 4 weeks, which may later be decreased to 150 mg every 4 weeks in some patients. The annual cost of maintenance therapy for patients who remain on the 300 mg dose is approximately $57,033. Although this is one of the more expensive options, there is at least the reassurance that the cost will not double in the future due to dose escalation. In addition, the annual cost for patients who maintain the 150 mg dose is only $28,517, because even though the 150 mg and 300 mg dose packages are the same price, patients could theoretically get around this by purchasing the 300 mg package and administering the contents as two separate 150 mg doses (Langley et al., 2014; RedBook Online).

### Table 1

| Cost of biologic drugs used to treat psoriasis, including the initial year of therapy, maintenance dosing, and escalated dosing |
|---------------------------------------------------------------|
| **Initial Dosing**                                            | **1st Year Cost of Therapy** | **Maintenance Dosing** | **Annual Cost** | **Escalated Dosing** | **Annual Cost** |
| Etanercept 50 mg twice weekly for 3 months, then 50 mg weekly | $67,386                     | 50 mg weekly           | $53,909         | 50 mg twice weekly   | $107,818        |
| Adalimumab 80 mg once, then 40 mg every other week ≤ 100 kg | $58,045                     | 40 mg every other week | $53,899         | 40 mg every other week | $107,798        |
| ≥ 100 kg: 90 mg at Week 0 and Week 4, then every 12 weeks  | $117,933                    | 90 mg every 12 weeks  | $78,622         | 90 mg every 12 weeks | $117,933        |
| Ustekinumab ≤ 100 kg: 45 mg at weeks 0 & 4, then every 12 weeks | $70,195                     | 300 mg every 4 weeks  | $57,033         | 300 mg every 4 weeks  | $28,317         |
| > 100 kg: 90 mg at Week 0 and Week 4, then every 12 weeks  | $83,714                      | 80 mg every 4 weeks  | $59,093         | 80 mg every 4 weeks  | $28,317         |
| Secukinumab 300 mg weekly for 5 weeks, then 300 mg every 4 weeks | $70,195                     | 300 mg every 4 weeks  | $57,033         | 300 mg every 4 weeks  | $28,317         |
| Ixekizumab 160 mg once, then 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks | $83,714                     | 80 mg every 4 weeks  | $59,093         | 80 mg every 4 weeks  | $28,317         |

Notes: Prices reflect average wholesale prices and may not include negotiated rebates or other discounts. Actual patient copays may be discordant with health system costs.

* The 150 mg package is the same price as the 300 mg package, but the 300 mg package could theoretically be split into two 150 mg doses to decrease costs.

---

**Fig. 1.** Treatment algorithm for patients with psoriasis who fail to respond to initial biologic therapy. Treatment options for patients who fail initial biologic therapy or lose response over time include dose escalation, addition of a systemic drug or phototherapy, or transition to a different biologic.
These considerations could lead to treatment algorithms designed to minimize costs, which favor switching biologics over dose escalation (Figure 1). Unfortunately, although this is more affordable, there are potential clinical consequences such as the development of anti-drug antibodies (Hsu and Armstrong, 2013), which can limit a patient’s future treatment options. Switching to a biosimilar will also become an option in the future as these drugs emerge on the market. Unfortunately, they are only expected to decrease costs by 20-40% (Rumore and Vogenberg, 2016), and their long-term safety and efficacy have yet to be determined. Another option is to add or switch to a systemic medication such as methotrexate, which carries the risk of cumulative toxicity (Cather and Crowley, 2014). Starting methotrexate at the time of biologic initiation may also improve response and prevent the need for dose escalation later on, however clinicians should keep in mind the trade-off between any potential cost reduction and the safety profile of methotrexate.

In this era of increasingly hard choices, we have to fight to preserve access for our patients. Biologic drugs are expensive to develop, and the United States subsidizes these drugs for the rest of the world, making it an immense challenge to control prices. However, some patients may be best served by dose escalation, and we need to maintain affordability. There should also be more transparency around cost. In some cases, dose escalation may actually be cheaper because of negotiated pricing, but it is difficult for physicians and even health care systems to get access to this data.

In conclusion, biologics have demonstrated great success in the treatment of psoriasis, but carry with them a substantial cost burden. This is especially true for patients who fail to respond to starting doses, because dose escalation typically doubles the price of the medication. As a result, clinicians may be compelled to switch to a different biologic without first attempting to increase the dose. Moving forward, our field should support efforts to develop rational strategies for the pricing of dose escalation in order to minimize this phenomenon. These strategies would be substantially improved as well if there were increased transparency surrounding negotiated pricing, which would help ensure that all patients have access to the most effective, affordable treatment options available.

References

Brezinski EA, Armstrong AW. Off-label biologic regimens in psoriasis: a systematic review of efficacy and safety of dose escalation, reduction, and interrupted biologic therapy. PLoS One 2012;7(4):e33486.

Cather JC, Crowley JJ. Use of biologic agents in combination with other therapies for the treatment of psoriasis. Am J Clin Dermatol 2014;15(6):467–78.

Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med 2016;375(4):345–56.

Hsu L, Armstrong AW. Anti-drug antibodies in psoriasis: a critical evaluation of clinical significance and impact on treatment response. Expert Rev Clin Immunol 2013;9(10):949–58.

Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al. Secukinumab in plaque psoriasis–results of two phase 3 trials. N Engl J Med 2014;371(4):326–38.

Langley RG, Lebwohl M, Krueger GG, Szapary PO, Wasfi Y, Chan D, et al. Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate-to-severe psoriasis: results from the PHOENIX 2 study through 5 years of follow-up. Br J Dermatol 2015;172(5):1371–83.

Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008;371(9625):1665–74.

Menter A, Tybring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. J Am Acad Dermatol 2008;58(1):106–15.

Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary PO, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008;371(9625):1675–84.

Papp KA, Tybring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 2005;152(6):1304–12.

RedBook Online [Internet]. Truvien Health Analytics: Micromedex Solutions. 2015; 2016 [cited 2015 September 11; 2016 July 13]. Available from http://micromedex.com/products/product-suites/clinical-knowledge/redbook.

Rumore MM, Vogenberg RF. Biosimilars: still not quite ready for prime time. P T 2016;41(6):366–75.

Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008;158(3):558–66.

Thaçi D, Ortonne JP, Chimenti S, Chisilain PD, Argengerer P, Kragballe K, et al. A phase IIIb, multicentre, randomized, double-blind, vehicle-controlled study of the efficacy and safety of adalimumab with and without calcipotriol/betamethasone topical treatment in patients with moderate to severe psoriasis: the BELIEVE study. Br J Dermatol 2010;163(2):402–11.

Tybring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 2006;367(9504):29–35.