Time to Raise the Bar to Psoriasis Area Severity Index 90 and 100

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The current objective criterion for primary endpoints in clinical trials for psoriasis is Psoriasis Area Severity Index 75, as defined by the Food and Drug Administration and clinical trials sponsored by pharmaceutical companies. However, with the advent of the next generation of psoriasis therapeutics—the anti-interleukin-17 agents—we have seen landmark Psoriasis Area Severity Index response rates surpassing those of the tumor necrosis factor inhibitors and the interleukin-12/23 inhibitor, stimulating us to now consider the utilization of Psoriasis Area Severity Index 90 and 100 as the new therapeutic benchmarks. In this article, we discuss the published and latest-breaking results on efficacy, safety, and patient-reported outcomes of the anti-interleukin-17 agents that justify our reasoning for dermatologists to now increase therapeutic efficacy expectations to Psoriasis Area Severity Index 90 and 100.

Major milestones in systemic biologics for psoriasis are illustrated in Figure 1. Fifteen years ago, clearance was once deemed an unrealistic expectation.[1] In 2003, the United States Food and Drug Administration approved the first biologics for psoriasis: alefacept and efalizumab. These medications were known for their achievement in Psoriasis Area Severity Index (PASI) 50 response,[2, 3] which has been argued to be a clinically significant endpoint in the past.[4] Over the following years, the tumor necrosis factor (TNF) inhibitors etanercept, infliximab, adalimumab and the first interleukin (IL)-12,23 inhibitor ustekinumab were introduced. This generation of agents allowed for a higher expectation to what serves as the therapeutic benchmark today: PASI 75.

Now, the latest generation of biologics—the anti-IL-17 agents—are expanding our frontier in therapeutic strategy once again. Secukinumab was the first-approved in January 2015 in 300 and 150 mg doses, while ixekizumab and brodalumab are undergoing phase 3 trials. As of May 22, 2015, Amgen, Inc. has discontinued its collaboration with AstraZeneca in the co-development and commercialization of brodalumab due to events of suicidal ideation and behavior in the brodalumab program. AstraZeneca has yet to make a decision regarding the future development of brodalumab. For the purposes of this viewpoint, we continue to include brodalumab's clinical trials results as we highlight the benefits of increasing our therapeutic benchmark to PASI 90 and 100. Multiple studies have demonstrated their ability to achieve never-before-seen significant, rapid, and sustained PASI 90 and 100 response rates, while secukinumab and ixekizumab maintain favorable safety profiles similar to that of the anti-TNF and anti-IL-12,23 agents.[5, 6, 7, 8] It is now time for our expectations to reflect this new attainable goal by raising the bar for therapeutic efficacy to PASI 90 and beyond. All clinical trials should begin using PASI 90 and 100 as primary endpoints, and dermatologists should now accept these new therapeutic goals to expect more highly and rapidly effective therapies for psoriasis patients. The notion of increasing to PASI 90 has been contemplated before,[9, 10] but now the evidence to incorporate this new standard is compelling.

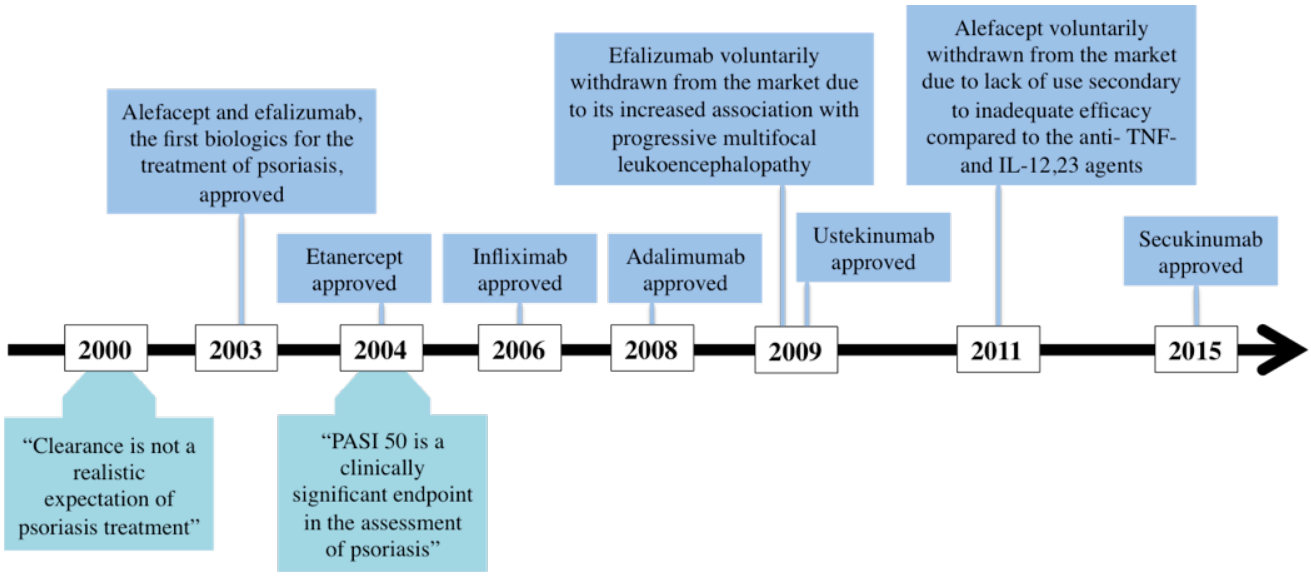
Improvement in Patient-related Outcomes

All of the anti-IL-17 agents have published results on the association between their impressive clinical responses and improved patient-reported outcomes (PROs). Secukinumab trials showed that PASI 90 response had a higher probability than PASI 75 at achieving meaningful improvements in patient-reported psoriasis symptoms.[11] For ixekizumab-treated subjects, groups that achieved PASI 100 and PASI 90-<100 responses had significantly greater health-related quality of life (HRQOL) and pruritus improvements than the PASI <75 and even PASI 75-<90 groups.[12] Significantly more brodalumab-treated subjects with PASI 100 compared to PASI 75-<100 response reported no psoriasis symptoms and more of the PASI 100 subjects reported no impairment in HRQOL.[13] Since these results were at 12-16 weeks, we await longer duration results, but adalimumab[14] and infliximab[15] reports have demonstrated similar findings. Moreover, it is imperative to ensure that treatment goals are clinically relevant to patient satisfaction, which serves as a major driver in selecting therapy. There are times when a more modest, bust still clinically significant improvement in psoriasis may be acceptable to patients, given that the alternative agent is cheaper, easier to administer, or safer. Nevertheless, it is important to note that PASI 90 and 100 responses have resulted in significantly greater improvements in Dermatology Life Quality Index (DLQI) than PASI 75.[14] A multicenter cross-sectional study showed that patients with clear skin were more likely to report no impact of psoriasis on quality of life than those with almost clear skin.[16]

Higher and Faster Response Rates Compared With the Previous Generation of Biologics

Numerous clinical trials have already completed or begun active head-to-head comparisons between anti-IL-17 agents and the previous generation of biologics, shown in Table 1. So far, published results show the superiority of secukinumab and brodalumab in PASI responses and PROs over etanercept and ustekinumab, respectively.[11, 17] Additionally, preliminary results show secukinumab's superiority in achieving PASI 90 over ustekinumab.[18] Trials comparing ixekizumab to etanercept are currently ongoing. All of these comparisons substantiate the importance of measuring PASI 90, as it identifies a distinct efficacy disparity between the current and new generation of biologics. These efficacy disparities demonstrate better PROs in

FIGURE 1. Timeline of major Food and Drug Administration milestones in psoriasis systemic biologics and PASI publications.



patients with greater PASI improvement scores. Furthermore, the PASI 90 benchmark is able to identify significant efficacy disparities within the same agent. Secukinumab's 300 mg dose showed more favorable PASI 90 and 100 response rates and correspondingly greater DLQI improvement compared with the 150 mg dose, supporting recommendations for its 300 mg dose.[5]

Conclusions and Areas for Further Research

As we become more proficient at treating psoriasis with significantly higher and faster PASI responses, our benchmarks for therapeutic success must evolve as well. Given that anti-IL-17 agents have already demonstrated significant superiority over etanercept and ustekinumab and that the first of the anti-IL-17 agents is now approved with sustained efficacy and safety after 2 years,[19] we must now increase our clinical efficacy expectations to PASI 90 and beyond. Of course, as we continue to strive for patient-centered care, management should remain multi-dimensionally catered to individual patients' preferences on efficacy, cost, convenience, and safety. We encourage dermatologists and third-party payers, however, to recognize the significant improvement in PROs in PASI 90 and 100 responses compared with PASI 75 and the significantly higher and faster response rates of the anti-IL-17 agents compared with the previous generation of biologics. Even in the longest duration of reported results for ixekizumab (60 weeks), significantly high proportions of patients maintained robust response rates and favorable safety profiles.[20] With consistent long-term results of these agents, PASI 90 and 100 should become the new benchmarks of therapeutic success for future systemic agents to be effectively compared

Disclosure

Dr. Wu received research funding from AbbVie, Amgen, AstraZeneca, Coherus Biosciences, Dermira, Eli Lilly, Janssen, Merck, Novartis, Pfizer, Regeneron, Sandoz, and Sun Pharmaceutical Industries; he is a consultant for AbbVie, Amgen, Celgene, Dermira, Eli Lilly, Pfizer, and Sun Pharmaceutical Industries. The other authors do not have any potential conflicts of interest.

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TABLE 1.

Head-to-Head Psoriasis Clinical Trials Between Secukinumab or Ixekizumab and the Previous Generations of Biologics			
ClinicalTrials.gov Number	Experimental Arm(s)	Active Comparator(s)	Study Duration (weeks)
NCT01358578	Secukinumab 300 mg and 150 mg	Etanercept 50 mg	52
NCT02074982	Secukinumab 300 mg	Ustekinumab 45/90 mg*	52
NCT01597245	Ixekizumab 80 mg	Etanercept 50 mg	60
NCT01646177	Ixekizumab 80 mg	Etanercept 50 mg	264
NCT01708603	Brodalumab 140 mg and 210 mg	Ustekinumab 45/90 mg*	260
NCT01708603	Brodalumab 140 mg and 210 mg	Ustekinumab 45/90 mg*	260

*Ustekinumab 45/90 mg: weight-based dosing per label recommendation

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