Ten Years On
The Impact of Biologics on the Practice of Dermatology

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KEYWORDS

• Psoriasis • Biologics • Monoclonal antibodies • Cytokines • Clinical trials • Efficacy • Safety • Quality of life

KEY POINTS

- Evolving science has been translated into targeted and effective therapeutic tools that have enabled the dermatologist to control both the symptoms and underlying inflammation of psoriasis.
- The toolbox continues to expand with emerging knowledge on the pathophysiology of psoriasis, which will manifest in new therapeutic options that can better enhance patients' quality of life.
- The currently available biological therapies for psoriasis are etanercept, infliximab, adalimumab, and ustekinumab; each of these therapies displays differential properties based on their unique mechanisms of action, which target either tumor necrosis factor α or interleukin (IL)-12/23 cytokines, and each biologic has accumulated significant controlled clinical trial and long-term use data to support a positive benefit/risk profile in psoriasis.
- New, promising therapies are in development for psoriasis (brodalumab, ixekizumab, and secukinumab, which specifically target interleukin [IL]-17, and guselkumab and tildrakizumab, which specifically target IL-23); the IL-17 and IL-23 cytokines constitute part of the TH17 axis that is thought to be at the core of psoriasis pathogenesis.

THE POTENTIAL OF BIOLOGICAL THERAPIES FOR PSORIASIS

Psoriasis is a chronic, genetically defined, inflammatory condition that affects approximately 2% to 3% of the population worldwide. Men and women are affected equally, with the onset of disease usually before 40 years of age.[1] The disease manifests most notably with characteristic skin lesions, which are distinguished by red, scaly plaques most prevalent on the elbows, knees, and scalp, although any or all portions of the body surface may be affected. A proportion of patients with psoriasis (10%–30%) will also develop psoriatic arthritis (PsA).[1,2] In addition to its physical signs, psoriasis impacts health-related quality of life (HRQOL) to a degree that parallels other major

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systemic diseases.[3] Moreover, psoriasis is associated with disease states that potentially increase morbidity and mortality and lower QOL.[4] Evidence continues to accumulate to support the association of psoriasis with established comorbidities that increase the risk of cardiovascular-related disease, including components of metabolic syndrome, such as hypertension, diabetes, dyslipidemia, and obesity.[5–8] Data to support increased mortality in the psoriatic population continues to be collected and reported.[9]

The advent of biological therapies in the past 10 years has been paralleled by advances toward elucidating the pathogenic mechanisms of psoriasis.[10,11] The selective targeting of cytokines (ie, tumor necrosis factor-α [TNF-α], interleukin [IL]-12 and IL-23) or cell surface receptors (ie, leukocyte function antigen [LFA]-1 and LFA-3) through monoclonal antibodies has delivered clinical validation that a dysregulated immune system is at the core of psoriasis disease pathogenesis.[11] Indeed, the monoclonal antibody-based biological therapies have delivered a variety of clinical tools with which the dermatologist can, for the most part, control both the symptoms of psoriasis as well as the underlying systemic inflammation and associated comorbidities.[12] Evidence, however, continues to accumulate to support that the full potential of these magic bullets has not been realized because patients continue to be considerably undertreated globally.[13–15] In a series of US surveys performed by the National Psoriasis Foundation from 2003 to 2011, the proportion of patients with moderate to severe psoriasis who remain untreated has plateaued at approximately 30%.[13] Moreover, more than 20% of patients with moderate to severe psoriasis continue to be treated with topical therapies alone and more than 50% of patients are dissatisfied with their treatment.[14] In Brazil, similar discrepancies exist between actual clinical practice and the recommendations included in the relevant guidelines, thus negatively influencing optimal patient care.[15] The reasons for these inconsistencies include low awareness of therapy availability; lack of understanding of therapy use or monitoring; concerns over adverse effects; lack of effectiveness; and the inability to secure appropriate national insurance coverage or payment for the recommended biological therapies. This finding begs the question as to whether the much-heralded new era for disease management from 2003 has actually been fulfilled.[16] Consequently, this review revisits the rationale for the development of biological therapies, inventories the available therapies of today in terms of the clinical trial and postmarketing data sets, and also evaluates the impact of these agents on dermatology practice as it relates to the management of patients with psoriasis.

PERSPECTIVES ON THE DEVELOPMENT OF BIOLOGICAL THERAPIES

Biopharmaceuticals are biopolymers of organic molecules that are manufactured in living systems, such as animal or plant cells. They are derived from a combination of understanding of the fundamental biology of disease and advances in the technological engineering of proteins that target specific elements of cell processes. The Nobel Prize winners Kohler and Milstein[17] first reported such technology in 1975. Their discovery permitted the mass production of monoclonal antibodies as a consequence of the fusion of antibody-producing spleen cells to immortal myeloma cell lines. The psoriasis biologics currently available are based primarily on this antibody platform technology in the development of therapeutic tools that are protein structures that bind to specific receptors or cytokines.[18] Biologic drugs exhibit great variability in design and structure, features that lead to divergence in function and therapeutic benefit. For example, etanercept is a receptor/antibody fusion protein; infliximab is a chimeric mouse/human monoclonal antibody; however, adalimumab and ustekinumab are both fully human monoclonal antibodies (**Table 1**).[19–22] Their function, as well as interaction with the human body, is based not only on the amino acid number and sequence but also on posttranslational modifications (eg, folding and glycosylation) that are added by virtue of their manufacture in living systems. The uniqueness of each biological agent manifests in differences in binding specificity, affinity, and tolerability, features that can impact the clinical outcome.[23] However, most biological candidates deliver therapeutic effectiveness because of their selective mechanisms of action, which is derived from a significant understanding of the role of specific cytokine or cellular targets involved in the pathogenesis of disease. Consequently, biological therapies delivered hope for a solution to chronic psoriasis management while circumventing the safety limitations of traditional agents, thus offering patients continuous relief.[24]

CURRENT BIOLOGICAL THERAPIES FOR PSORIASIS

Consistent with the uniqueness of each biological agent in terms of structure and function, the approved biological agents for psoriasis display