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Navigating Targeted Therapeutics in Dermatology: Biologics and Small Molecules

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ABSTRACT

Dermatology is entering an exciting era with new, targeted immune-modulating medications for treating a variety of dermatologic conditions including psoriasis, atopic dermatitis (AD), and hidradenitis suppurativa. Previously, mainstay treatments consisted of topical corticosteroids or broad systemic immunosuppressants. Recently, our understanding of cytokine signaling cascades has grown, presenting new opportunities to target skewed immune responses. Two major classes are biologics and small molecules. Herein, we highlight the similarities and differences between these two categories of targeted medications.

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Biologics

Biologics are monoclonal antibodies (ie, infliximab, adalimumab, ustekinumab, dupilumab, etc.) or fusion proteins (ie, etanercept) that have activity in the extracellular space. Infliximab and adalimumab bind to tumor necrosis factor-α (TNF-α) in the extracellular space, to decrease its concentration. Other biologics, like etanercept, pose as an extracellular decoy receptor to decrease TNF-α concentration. Biologics can also bind to the cell surface directly; for instance, dupilumab binds to the alpha subunit of interleukin-4 receptor (IL-4Rα). Biologics are large molecules, thus require subcutaneous or intravenous administration to achieve bioavailability.

Biologics have shown great efficacy in treating multiple dermatologic diseases, but tend to have decreased long-term efficacy, particularly in psoriasis. The median adherence to treatment (drug survival) for infliximab, etanercept, adalimumab, and ustekinumab in the treatment of psoriasis was 47 months, and 67% of discontinuations were attributed to loss of efficacy (drug tolerance).[1] Such drug tolerance is not fully understood, but the leading theory is anti-drug antibody (ADA) development. Humoral immunity is antibody-mediated and requires antigen-MHCII interaction, along with a co-stimulatory signal. MHCII receptors require a minimal length peptide segment in order to have an interaction. Owing to their large size, biologics can interact with MHCII and can therefore become immunogenic. Assays for ADA testing are expensive for regular clinical use, and results obtained by pharmaceutical companies are not often made public. Together, this makes it difficult to study the incidence and impact of ADA-induced drug tolerance. Lecluse et al tracked ADA levels in patients initiated on adalimumab for plaque psoriasis over 24 weeks, with ADA assays at weeks 12 and 24.[2] ADA were detected at the 12-week point. All patients with high anti-adalimumab titers had undetectable adalimumab trough concentrations and were non-responders. While all non-responders had low adalimumab trough concentrations, they did not all have detectable anti-adalimumab titers. This finding had subsequently been confirmed in additional studies.[3] Since ADA are not seen in all non-responders, additional factors such as inter-individual pharmacokinetic heterogeneity may be involved. Due to their large molecular weight, biologics are removed from circulation via proteolytic catabolism within the reticuloendothelial system (RES), not through renal clearance or hepatic metabolism.[3] Individual differences in the RES are likely a contributing component in drug tolerance. More research is needed to fully understand this multifaceted process of drug tolerance.

In addition to drug intolerance, biologics tend to require more complex and expensive manufacturing, and may require refrigeration and photoprotection.[4] Cost is an important consideration for the patient especially in the age of value-based medicine. The average wholesale acquisition cost of a 16-week course of apremilast or adalimumab in the US was $6,844 and $10,010, respectively.[5] Other components to consider in a cost-value analysis include treatment efficacy, patients' ability to return to productivity, and costs associated with changing treatment for low drug survival.

Small Molecules

Small molecule drugs (<1 kDa)[6] such as apremilast, tofacitinib, ruxolitinib, baricitinib have bioavailability with oral administration and easily cross the epidermal barrier through topical application. Their target is intracellular. Thus, they must passively move through the plasma membrane, if hydrophobic, or through channel-mediated transport, if hydrophilic. Within the intracellular space, they inhibit their target signaling pathway

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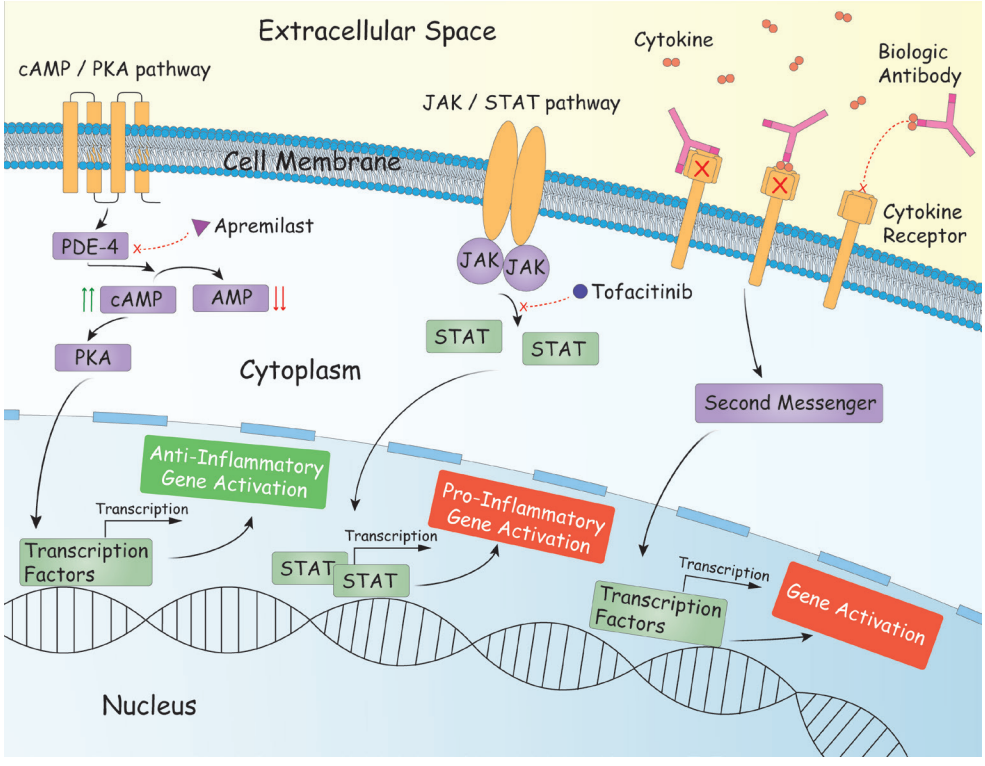
by modulating nuclear transcription. Unlike biologics, which require the RES system for drug clearance, small molecules undergo hepatic or renal clearance and may require decreased dosages for severe renal or hepatic impairment.

Apremilast is an oral formulation of an intracellular phosphodiesterase 4 (PDE-4) inhibitor approved for psoriasis and psoriatic arthritis. Crisaborole is a topical formulation approved for mild-moderate AD. PDE-4 is a cytosolic enzyme that degrades cAMP to AMP within inflammatory cells including dendritic cells, T-cells, macrophages, monocytes, and keratinocytes.[6,7] Increased cAMP leads to PKA activation, which phosphorylates transcription factors that prompt transcription of anti-inflammatory genes, including interleukin (IL)-10.[7] This process also inhibits nuclear factor-κB (NF-κB), which decreases production of pro-inflammatory mediators TNF-α, interferon (IFN)-γ, and IL-23.[7] Apremilast is metabolized through both CYP1A2 and non-CYP-mediated hydrolysis, to be cleared through urine and stool.[7]

Tofacitinib is an intracellular Janus kinase (JAK)-1 and JAK-3 inhibitor available in oral and topical formulations. JAKs are tyrosine kinases that bind to an activated intracytoplasmic cytokine receptor to activate STAT proteins. Activated STAT proteins undergo nuclear translocation to act as transcription factors that upregulate the expression of pro-inflammatory cytokines and growth factors. Tofacitinib inhibits intracellular signal transduction of IL-2, IL-4, IL-9, IL-15, and IL-21, together modulating various aspects of the immune response.[6] Small molecules are less likely to interact with MHCII due to their size, making ADA formation unlikely. Therefore, in theory, small molecule inhibitors should not develop the same drug tolerance response. However, research investigating the long-term drug survival of small molecule inhibitors is warranted.

Biologics and small molecules play an important role in the treatment of dermatologic diseases. It is important for dermatologists to recognize the similarities and differences between the two classes of drugs. Advantages of biologics include strong initial efficacy and proven safety profiles. Disadvantages include their subcutaneous or intravenous administration, storage requirements, and potential drug tolerance. Advantages of small molecules include their oral or topical formulation, and their lack of immunogenicity. Future head-to-head trials are needed to compare the efficacy and cost-value analyses of biologics to small molecules in treating dermatologic diseases. Additionally, as we move closer to an era of personalized

FIGURE 1. Molecular pathways of apremilast, tofacitinib, and biologic antibodies. Apremilast inhibits a second messenger in the cAMP/PKA pathway, increasing transcription of anti-inflammatory genes. Tofacitinib inhibits a second messenger in the JAK/STAT pathway, decreasing the transcription of pro-inflammatory genes. Biologic antibodies can either bind circulating and/or receptor-bound cytokines or cell-surface receptors to prevent the cascade that would cause gene activation.



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medicine, certain targeted drugs may be recognized as more effective in specific subpopulations within a disease. Already, some clinical trials are starting to perform genetic analyses prospectively and we are just now starting to understand the role epigenetics plays in drug metabolism.

DISCLOSURE

VYS is a stock shareholder of Dermveda, has served as a paid advisor for Sanofi, Novartis, SUN Pharma, Pfizer, Menlo Therapeutics, GpSkin, the National Eczema Association, and Global Parents for Eczema Research, is an investigator for AbbVie and Leo Pharma, and has received research funding from the Foundation for Atopic Dermatitis and Skin Active Science.

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