New Drugs and New Molecular Entities in Dermatology

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Objective: To identify and analyze the possible reasons that so few drugs with new molecular entities (NMEs) are first developed for “dermatologic diseases,” especially diseases treated primarily by dermatologists.

Design: Systematic review and analysis. IMS Health (the pharmaceutical industry worldwide product database) was searched using the terms first launch, topical, and skin/dermatological for the preceding decade. These terms were used for inclusion but not exclusion so that intravenous and oral agents were also identified if they were for skin or dermatologic use. The US Food and Drug Administration (FDA) New Molecular Entities Drug and New Biological Approvals Web site for the 10 years from 1999 to 2009 was examined for approval of dermatologic agents. To determine the frequency of drug development for dermatologic drugs compared with other fields, the total number of NMEs by therapeutic category for the 5-year period 2005 to 2009 was assessed.

Results: Worldwide, the total number of NMEs for diseases treated primarily by dermatologists for almost a decade was 13. Using the FDA Web site, 5 NMEs for diseases treated primarily by dermatologists were approved in 10 years.

Conclusions: The major factors precluding NME development for dermatologic diseases seem to be (1) the economic potential of dermatologic drugs, (2) the benefit-to-risk relationship, (3) the limited number of surrogate end points and “soft” semiquantitative end points, and (4) the limited or inadequate basic knowledge of the pathophysiologic characteristics of skin diseases.

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METHODS

An IMS Health (the leading provider of market intelligence to the pharmaceutical industry) worldwide product database search was conducted using the search terms first launch, topical, and skin/dermatological. These terms were used for inclusion but not exclusion so that intravenous and oral agents were also identified if they were for skin/dermatologic use. The search was confined to the decade preceding the search.

The FDA Web site titled “NME Drug and New Biologic Approvals,” which lists NME approvals by year for the 10 years from 1999 to 2009, was searched using the same terms. To determine the frequency of NME development for dermatologic drugs compared with those developed in other fields, the total number of NCEs (worldwide) by therapeutic category for the 3-year period 2005 to 2010 was assessed.

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IT IS WIDELY RECOGNIZED IN DERMATOLOGY that the unique feature of many “new” drugs resides in incremental changes such as a new vehicle, a new concentration of the active agent, or even a new combination of known active agents. (The US Food and Drug Association [FDA] also considers a drug to be “new” if it is for a new indication or made by a different manufacturer.) While often quite useful in clinical practice, these new drug formulations are considerably different from drugs that have a new active agent or novel mechanism of action and create a truly novel therapeutic category. Such agents are known as new molecular entities (NMEs), and such new drugs are often called NME drugs.

According to the FDA, an NME is an active ingredient that has never before been marketed in the US in any form. New molecular entity is a term which is generally recognized world-wide and is replacing the term new chemical entity (NCE). The abbreviations NME and NCE will be considered as interchangeable and, as is customary, will include drugs and biologic drugs. Among those concerned with dermatologic drug development, it is believed that few NME drugs are developed primarily for dermatologic conditions or perhaps more accurately for diseases treated primarily by dermatologists.

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RESULTS

In this worldwide search from January 2000 to February 2010, 22 agents met the search criteria. Two of these 22 were excluded because they were administered by nasal spray for nondermatologic uses. Of the 20 for dermatologic use, 12 were anti-infective agents (6 antibiotics, 3 antiviral agents, and 3 antifungal agents). However, 5 of the 6 antibiotics were for intravenous administration to treat methicillin-resistant Staphylococcus aureus infections and were unlikely to be used by most dermatologists. Two of the 20, epidermal growth factor gel and fibroblast growth factor spray, were wound-healing agents for the treatment of chronic wounds only infrequently treated by dermatologists. Considering only those agents likely to be used by dermatologists removes 5 of the antibiotics and both growth factor wound treatments, leaving the total number of NMEs worldwide for almost a decade at 13. Of these 13, 2 were biologic drugs (etanercept [Enbrel; Amgen Inc, Thousand Oaks, California] and Amevive [Astellas Pharma US, Deerfield, Illinois]), 2 were photosensitizing agents (aminolevulinic acid hydrochloride [Levulan stick; DUSA Pharmaceuticals, Wilmington, Massachusetts] and methyl 5-aminolevulinate hydrochloride [Metavix; TCI America, Portland, Oregon]), and 1 was a topically applied antioxidant for hair loss.

Using the FDA Web site titled “NME Drug and New Biologic Approvals,” which lists NME approvals by year for the 10 years from 1999 to 2009, we found 268 NME drug approvals in the United States. Of these, 5 were NME drugs for diseases treated primarily by dermatologists (Levulan-Kerastick [DUSA Pharmaceuticals] for actinic keratoses, Solage [Stiefel, a GlaxoSmithKline Co, Research Triangle Park, North Carolina] for solar lentigens, Bexarotene [Eisai, Woodcliff Lake, New Jersey] for cutaneous T-cell lymphoma, Elidel [Novartis, Basel, Switzerland] for atopic dermatitis, and Stelara [Johnson & Johnson, New Brunswick, New Jersey] for psoriasis). In addition we found 12 NME drugs for skin indications treated by many types of physicians, for example, drugs for scabies, perianal warts, invasive bacterial skin infections, and Sjogren syndrome, and over-the-counter agents, such as Abreva (Avanir Pharmaceuticals, Aliso Viejo, California) for herpes simplex and a sunscreen.

The total number of NCEs for all categories during the 5 years was 119 (range, 21-26 per year) (Table). Of the 119 total, 4 NCEs were for dermatologic drugs. The average for each therapeutic category was 8.5 NCEs. The number of dermatologic NCEs was the same as the number for musculoskeletal disease.

This study demonstrates that the number of NCEs developed for dermatologic disease and for diseases treated primarily by dermatologists is remarkably small. Considering that skin diseases are among the most common of all diseases (eg, acne affects almost 85% of people 12-24 years of age, seborrheic dermatitis affects 3%-5% of the population worldwide, dandruff is experienced by an estimated 15%-20% of the US population, and skin cancer is the most common cancer). Nearly 37% of primary care patients have a skin disease. Given the burden of skin disease cared for by dermatologists and nondermatologists, it is somewhat surprising how few NMEs are developed for skin diseases, in particular, the diseases treated most commonly by dermatologists.

Our analysis indicates that 4 major factors contribute to development of few NMEs for skin disease: the economic potential of dermatologic drugs, the risk-to-benefit relationship, few surrogate end points, and inadequate basic knowledge of the pathophysiologic mechanisms of skin disease. A major reason that few companies undertake the development of NMEs solely or even partly for dermatologic diseases is that the economic return from dermatologic drugs (especially topical products) is relatively small compared with markets for drugs for other diseases, such as cardiovascular diseases. This has been especially true for the past 2 to 3 decades, during which the primary strategy of the largest pharmaceutical companies, so-called Big Pharma, has been the identification and development of new drugs that have potential sales of $1 billion or more. Commonly referred to as “blockbusters,” these drugs have provided the economic base of the industry and their prices are justified by the high cost and long time (> $800 million and 15 years, respectively) needed to develop NME drugs. Generally, the greatest revenues have been generated by drugs, usually NMEs, for heart disease and other “serious” or life-threatening diseases. For example, atorvastatin (Lipitor; Pfizer, New York, New York) has been the worldwide and US sales leader every year since at least 2003, with 2009 worldwide sales...
of $12.45 billion. The antiplatelet drug clopidogrel (Plavix; sanofi-aventis US, Bridgewater, New Jersey) has been either number 2 or 3 worldwide and in the US for some years with 2009 worldwide sales of $9.29 billion.\textsuperscript{9}

With the exception of the recently introduced biologic drugs that are used for psoriasis, drugs for dermatologic diseases have produced relatively low revenues even when the number of potential patients is large. For example, the only 2 topical drugs that surpassed the $200 million mark in 2007 were imiquimod (Aldara; Graceway Pharmaceuticals, Bristol, Tennessee) and clindamycin 1%, benzoyl peroxide 5% (BenzaClin; sanofi-aventis US).\textsuperscript{3} These drugs are indicated for the treatment of acne vulgaris, basal cell carcinoma, or genital warts and acne vulgaris, respectively.\textsuperscript{10,11} Accutane (Hoffman-La Roche Inc, Nutley, New Jersey), an oral drug for severe acne, achieved one of the highest annual sales totals in the dermatology product category with peak US sales of $200 million mark in 2007 were imiquimod (Aldara; Graceway Pharmaceuticals, Bristol, Tennessee) and clindamycin 1%, benzoyl peroxide 5% (BenzaClin; sanofi-aventis US).\textsuperscript{3} These drugs are indicated for the treatment of acne vulgaris, basal cell carcinoma, or genital warts and acne vulgaris, respectively.\textsuperscript{10,11} Accutane (Hoffman-La Roche Inc, Nutley, New Jersey), an oral drug for severe acne, achieved one of the highest annual sales totals in the dermatology product category with peak US sales of $200 million in 2000.\textsuperscript{12,13} Some categories of drugs, such as oral antifungal and topical antibacterial drugs, which are used by dermatologists as well as many other physicians, are able to attain sales in the range of $500 million. However, with the recent exception of the biologic drugs for treatment of psoriasis, the products that are somewhat exclusive to dermatology rarely command annual sales of over $100 million. In fact, most of these drugs have annual sales below the $50 million mark.\textsuperscript{3}

Regarding the biologic drugs, which tend to be approved for a number of inflammatory diseases, one of which is psoriasis, Enbrel had total sales of $3.3 billion in 2009,\textsuperscript{14,15} and its sales for psoriasis treatment were reported to be $1.1 billion in 2008.\textsuperscript{16}

The basic question that has rarely been addressed is “what accounts for dermatologic drugs producing such relatively low revenues?” In some cases, the small number of people having a certain dermatologic disease, such as xeroderma pigmentosum, might be the explanation. However, as noted herein, many skin diseases are in fact among the most common of all diseases. Although not formally investigated, it seems that the perceived unimportance of common skin conditions somehow results in the drugs’ inability to command reimbursement that yields an economic return that encourages investment in unique drugs for dermatologic conditions. Whatever the cause or causes, the end result is that the potential revenue from dermatologic drug sales has generally not been sufficient to stimulate or economically justify the high cost of developing new and novel (NME) drugs.

Evaluating a benefit-to-risk relationship (ratio) is a normal but informal calculus in the physician’s thinking and evaluation of therapeutic and preventive interventions. As used by the FDA, the phrase is applied to suggest that there is a mathematical precision to what is actually a highly subjective process in which the different values of regulators, lawyers, physicians, scientists, lawmakers, businessmen, and public interest groups are synthesized into binding judgments as to whether and how a drug will be made available in the market place. For example, people with terminal cancer most often have a different view of the ratio than advisory committees. The AIDS community was notably successful at changing the regulatory calculus in the late 1980s and early 1990s. The AIDS community’s activism even led to new regulations that allowed FDA approval ahead of formal phase 3 studies for life-saving therapies. As suggested herein, the benefit-to-risk ratio is a considerable hurdle to the approval of drugs for non-life-threatening conditions, such as dermatologic disease. Unfortunately, many physicians other than dermatologists tend to be dismissive of the severity of skin disease. Because skin disease does not often kill or obviously cripple, it is easily underrated in the conference rooms where decisions about the benefit-to-risk ratio and regulatory approval are made. Hence, believing that the benefit obtained from treating skin diseases is minimal, the regulatory tolerance for toxic effects and adverse effects is much lower than it is for diseases that kill, cripple, or cause more dramatic and easily identifiable morbidity.

When considering the possibility of using surrogate end points for regulatory approval, it is important to appreciate that certain well-accepted clinical end points are really substitute or surrogate end points used for convenience. For example, one of the real aims of antihypertensive drugs is to prevent strokes, but studies of stroke prevention would require an impractically larger commitment of time and numbers of participants than are required to study blood pressure control, which has been demonstrated to correlate with stroke prevention. Obtaining regulatory approval would be faster and less costly if measuring inhibition of epidermal proliferation or upper dermal blood flow were an accepted end point for a dermatologic NCE rather than psoriasis remission. Certainly, electing to develop an NCE drug for a dermatologic condition would be more attractive should there be more validated surrogate end points that would result in a more predictable, and possibly a simpler, development path. At least part of the reason that surrogate markers have been validated for cardiovascular and other diseases is the attention that has been put into research both in the private and government sectors.

In order to understand the effect that not having surrogate end points has on the development of generic topical drugs, one must be aware of the fairly easy regulatory pathway deliberately created to make generic drugs readily available with the minimum of development costs. To obtain regulatory approval, manufacturers of systemic generic drugs do not have to perform clinical trials to prove that the generic drug is effective at treating the intended disease. Rather, oral or systemic generic drugs are approved based on demonstrating that blood levels of the generic drug are more or less (±20%) the same as the blood levels of the pioneer or original drug—so called bioequivalence. Thus, blood levels, not clinical efficacy, are measured, the assumption being that if the drug exposure is similar, the efficacy and safety will also be similar. By their nature, most topical treatments are not intended to act systematically; thus, blood levels are not even desired and are therefore not a useful surrogate end point. This does not mean that the regulatory standards are different for topical drugs but rather that the method of demonstrating bioequivalence is more complicated and thus more costly for topical drugs. Because blood levels will not be useful, topical generic drugs have the special problem of having to be proven to be bioequivalent by costly clinical trials showing efficacy in patients with the indicated condition.
The vasoconstrictor assay end point is a major exception to the general lack of surrogate end points in topical drug development. With the recent exception of topical generic steroids for treatment on the scalp, vasoconstriction of normal skin in response to application of a corticosteroid has proven to be an acceptable surrogate for approval of topical anti-inflammatory corticosteroid generic drugs. Many attempts to find other surrogate end points for topical treatments, such as measuring the amount of drug in stratum corneum samples stripped by pressure-sensitive tape, have unfortunately not yet proven sufficiently reproducible to allow their use as surrogates in developing topical drugs. The role surrogate end points might play in the development of topical NCE drugs will clearly depend on the surrogate end point being disease related rather than drug related. For example, reducing the number of S aureus infections in the skin of patients with atopic dermatitis might be a useful surrogate for developing an antimicrobial drug for treating atopic dermatitis. However, it would not be useful for developing an anti-inflammatory treatment of atopic dermatitis because it would be a drug-specific rather than a disease-specific surrogate.

Many of the most medically important end points used in studying the efficacy of agents for dermatologic disease, such as the amount or intensity of symptoms (eg, pruritus) or signs (eg, redness or scaling), are difficult, if not impossible, to measure by objective means; thus, their inability to be quantified makes the end points “soft” or semiquantitative. Their measurement requires subjective assessment that may contribute to greater variability, which increases the number of participants and the cost of regulatory trials owing to the need to accommodate wider statistical variability. Even measures such as the extent or percentage of the body surface involved are not made mechanically or with totally reproducible methods. Counting of lesions, such as inflammatory papules in acne studies, is clearly subject to many variables, such as when a lesion is visibly clear or minimally present. Such imprecision of end-point detection and measurement forces studies of treatments for these conditions to use a larger number of participants, requires a documented training of the investigators, and results in higher cost than would be encountered in developing drugs for diseases with objective end points (eg, serum cholesterol levels). Also contributing to this general problem, at least with regard to the development of topical drugs, is the imprecise nature of the amount of an agent that is applied to a given surface area on each occasion and other variables, such as absorption through diseased skin in various stages and at differing body sites. While the degree to which such factors affect dermatologic drug development has not been fully elucidated, they are clearly special challenges not encountered in developing drugs for treating diseases of many other organs.

Knowledge of the pathophysiologic basis of disease is an important element in the development of new medical treatments for diseases of most organs, including skin. While very difficult to document, it is our impression that the amount of funding and the number of investigators working on developing the fundamental pathophysiologic knowledge needed to identify targets and strategies for new drug development is lower in the skin disease area than in many other areas. For example, the 2010 appropriation for the National Institute of Arthritis and Musculoskeletal and Skin Diseases was $538.8 million compared with $5 billion for the National Cancer Institute, $3 billion for the National Heart, Lung, and Blood Institute, $4.5 billion for the National Institute of Allergy and Infectious diseases, and $2 billion for the National Institute of General Medical Sciences. Disparities in funding result in disparate numbers of investigators, ultimately both in the private and government sectors. The relatively low level of effort aimed at understanding skin disease pathophysiologic mechanisms does not reflect an inherent difficulty in studying skin disease but, we believe, is consequent to a societal (governmental) judgment as to where investment will best “pay off.” The relatively lower investment in skin research ultimately also contributes to the low number of NCE drugs developed for dermatologic diseases.

Although difficult to quantify and fully document, it seems that the major reasons for the relatively low number of NMEs aimed at dermatologic disease, especially those conditions treated primarily by dermatologists, are the relatively poor economic potential of dermatologic NMEs; the difficulties occasioned by the relatively poor benefit to risk relationship of nonlethal diseases; the lack of surrogate end points, such as blood pressure and cholesterol measures and “soft” end points; and the relatively small basic science efforts in determining skin pathophysiologic mechanisms. Because ultimately the likelihood of developing NME drugs for dermatologic indications is so closely linked to the economics of drug development, the recent billion-dollar-plus revenues generated by the biologic drugs for psoriasis may in the near term result in more interest in NME development for dermatologic drugs. In addition, Big Pharma is moving away from the current “blockbuster” focus to a more diversified focus, which may include trying to reduce the risk of systemic therapies and increasing the chances of getting a new molecule through the development and approval process.

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Comparative Effectiveness Research

Comparative effectiveness research expands the scope of clinical research to compare different therapies against one another as a means to improve delivery of value-based health care. Typically, outcomes analysis of quality of life, disability, and death are used to compare the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor dermatologic conditions. Traditional efficacy research, used for approval of pharmaceuticals or devices, compares 1 or more treatment alternatives with placebo in a carefully selected population cared for in an ideal setting, thus answering the question of whether the intervention is effective and safe for human use.

In contrast, comparative effectiveness research seeks to answer a different set of questions including: (1) when to use the treatment (appropriate time), and (2) who should receive the intervention (proper patient selection). This research also considers patients from populations that are under less than ideal conditions. Thus, comparative effectiveness research seeks to replace the physician’s informed intuition of case management with data-driven, scientifically derived, “best-treatment” protocols. We at the Archives are interested in comparative effectiveness research using observational and clinical trial methods comparing different strategies provided by dermatologists in heterogeneous patient populations and heterogeneous health care settings.

The Archives of Dermatology, along with JAMA and other Archives Journals, will publish a theme issue devoted to comparative effectiveness research in early 2012. Priority will be given to studies using rigorous methodological designs that are generalizable beyond a single institution. Authors should consult the Instructions for Authors at http://www.archdermatol.com for guidelines on manuscript preparation and submission. Manuscripts must be received before October 1, 2011, to allow for appropriate consideration.

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