Psoriasis: from basic and clinical research to the development of new treatments

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Abstract

Psoriasis is an incurable cutaneous disease that affects 2.9% of the Mexican population, and it is therefore important for the impact of translational medicine on the development of anti-psoriatic drugs to be analyzed. In this review, current etiopathogenic concepts of the disease are discussed, and articles on drugs under development published between 2005 and 2017 are reviewed; in addition, a critical analysis on future perspectives for the development new treatments is presented. The use of translational medicine bi-directional strategies has allowed to significantly increase the number of available anti-psoriatic therapies. Eighteen new investigational drugs were found. Characterization of antigens responsible for immune activation, identification of predictive biomarkers with pharmacologic efficacy, and the development of more representative disease models, as well as the integration of pharmacogenomic aspects to translational medicine strategies were identified as relevant aspects that should be incorporated in the development of new therapeutic options.

KEY WORDS: Psoriasis. Pharmacological targets. Drugs. Translational medicine.

Introduction

Psoriasis is an incurable cutaneous disease of inflammatory nature, characterized by erythematos plaques. It is estimated to affect 2 to 3 % of the world population; it is less common in equatorial than in Nordic regions.1 In Mexico there are few epidemiological studies on the disease, and thus the real magnitude of the problem remains unknown. At a symposium celebrated in 2009 in Dallas, Texas, the prevalence in Mexico was estimated to be 2.9 %;2 which would be equivalent to more than 3 million affected Mexicans. The incidence of death directly related to psoriasis is low, but its physical and psychological manifestations make it incapacitating, comparable to cancer, diabetes and depression.3

Current anti-psoriatic treatments are essentially directed to the management of symptoms and include phototherapy, as well as topical and systemic medications aimed at:4

- Inhibiting keratinocyte hyperproliferation (vitamin D analogues).
- Normalizing keratinocyte differentiation process (vitamin D analogues, retinoids).
- Decreasing immunocyte recruitment and activation (cyclosporine A, biotechnological medications).
- Neutralizing pro-inflammatory cytokines (biotechnological medications).

However, their long-term use is limited by efficacy loss, toxicity and elevated costs. As a consequence, from 31 to 70 % of patients with psoriasis are highly dissatisfied.6 The pharmaceutical industry is increasingly interested in the development of new treatments.

In recent years, the term “translational medicine” has been born, which refers to a new paradigm based on the need to integrate scientific knowledge that is generated from basic research to the development of treatments with clinical impact (bench-to-bedside). It is a bidirectional concept, where the new findings derived...
Esquivel-García R, et al.: *Psoriasis and translational medicine*

from clinical research serve as the basis for the generation of scientific hypotheses used in fundamental science (bedside-to-bench). Within this model, knowledge derived from genomics, proteomics, medicine and pharmacology is used in order to more deeply know the pathophysiology of diseases, define possible pharmacological targets and obtain promising molecules, thus providing a realistic vision oriented to the transfer of knowledge between different areas of knowledge, in order to generate increasingly effective drugs.

Psoriasis is an excellent example of the importance of translational medicine for the development of new treatments. In fact, the first anti-psoriatic treatments, such as phototherapy or cyclosporine, were developed based on an empirical approach that started from clinical evidence. This entailed the generation of etiopathogenic hypotheses subsequently elucidated in basic research.\(^6\)

Currently, the development of treatments for psoriasis has undergone a paradigm shift, promoted by greater knowledge about the causes of the disease, which has been shown with the launch onto the market of biotechnological medications aimed at neutralizing specific chemokines and cytokines.

The purpose of this review is to analyze the impact of translational medicine on the development of anti-psoriatic drugs. The pathophysiology of psoriasis is examined based on current concepts. In addition, the scientific literature on new drugs under development and their pharmacological targets is explored in order to offer an updated view of the pharmaceutical development in this pathology. Finally, a critical analysis of future perspectives in the development of new treatments for this disease is presented.

**Current etiopathogenic concepts of psoriasis**

The etiology of psoriasis is complex and multifactorial, since it involves a complex interaction between constitutive cells of the skin and immune system innate and adaptive responses (Fig. 1).\(^7\) The first hypotheses considered that the primary defect that caused the disease involved keratinocytes. In fact, hyperproliferation of these cells is considered to be a distinctive characteristic the pathology until today. Psoriatic keratinocytes rapid division comparatively to normal ones (7 to 10 days versus 28 to 50 days) entails an increase in epidermal thickness and changes in the expression of differentiation markers.\(^8\) The granular layer of the skin, where keratinocyte terminal differentiation begins, is diminished or absent in psoriatic skin, with a corneous layer formed by undifferentiated cells.\(^8\)

In recent years, the role of the immune system in psoriasis has been revealed, which has helped for the pathophysiological bases of the disease to be understood. Psoriatic lesions are characterized by increased T lymphocyte infiltration. A patient with 20 % of body surface compromised with psoriasis will have an estimate of 8 billion T cells in blood, while 20 million will be located in the dermis and epidermis.\(^7\) Immunohistochemical studies confirm that the dermis harbors predominantly CD4 + T lymphocytes, macrophages and dendritic cells (DC), while CD8 T lymphocytes predominate in the epidermis.\(^7\) Despite the undeniable importance of the immune system in psoriasis, the debate on its primary cause continues and numerous doubts must be resolved, in particular with regard to identification of antigens (exogenous or endogenous) and their interaction with epidermal and immune cells in the context of skin lesions.\(^9\)

Genetic studies have identified 9 susceptibility loci for psoriasis (\(PSORS1\) to \(PSORS9\)). One of the main genetic determinants is \(PSORS1\), a 220 kb region in the major histocompatibility complex located at chromosome 6p21, which explains 35 to 50% of the disease inheritability.\(^10\) Other specific genes have also been identified in different populations; their polymorphisms have been associated with numerous immune processes, including keratinocyte differentiation, T cell proliferation, signaling pathways modulation, as well as leukocyte regulation and adhesion by T-helper cells (Th) 1 and 17.\(^11\) Recently, the participation of micro-RNA in the inflammatory regulation of the disease has also been highlighted.\(^12\)

**From basic and clinical research to the development of anti-psoriatic treatments**

The development of new treatments from a conventional point of view involves the following stages:
- Establishment of etiopathogenic hypotheses of the disease.
- Identification of pharmacological targets.
- Selection of therapeutic candidates.
- Chemical optimization of the selected compounds.
- Preclinical tests in experimental animals.
- Safety evaluation in human beings and establishment of pharmacokinetic properties (phase I).
- Efficacy tests (proof of concept, phase II).
- Multicenter clinical trials on a larger scale to assess safety and efficacy (phase III).
With this classical method, the transfer of knowledge is made from basic research to the clinical setting in a unidirectional sense.

The development of anti-psoriatic drugs throughout its history breaks with that model, since the transfer of knowledge has not always originated in basic science, but many hypotheses have emerged from clinical experience and have been able to be verified with fundamental research to then return to clinical scenarios. Thus, although the concept of translational medicine is relatively recent, its implementation in the development of anti-psoriatic treatments is not new.

In fact, one of the first changes regarding the paradigms on the pathogenesis of the disease occurred when an accidental observation demonstrated that transplanted patients who received cyclosporine showed improvement of their psoriasis. This clinical experience prompted the start of new investigations that showed that the action of this drug reduced the number of T lymphocytes, antigen-presenting cells, monocytes and macrophages. Consequently, T lymphocytes were considered to be therapeutic targets, which led to the development of a fusion protein that selectively blocked their activation without affecting keratinocytes. Curiously, translational medicine strategies were used that entailed the generation of new hypotheses building upon clinical experiences (bedside-to-bench).

Figure 1. Pathogenesis of psoriasis and involvement of new drugs under development. Psoriasis involves a complex interaction between neutrophils, dendritic cells (DC), T lymphocytes (Th1 and Th17) and keratinocytes. Keratinocyte activation by an initial lesion induces the production of antimicrobial peptides (AMP), promoting DCs to release cytokines (IFN-α, IFN-β, IL-12 and IL-23) involved in Th1 and Th17 lymphocyte differentiation, which produce mediators (IL-17A, IL-17F, IL-22, TNF-α and IFN-γ) that stimulate the generation of chemokines (CXCL and CCL) in keratinocytes, with consequent recruitment of more immunocytes in the skin. Some of the new anti-psoriatic drugs under investigation act on: a) blockade of the JAK/STAT signaling pathway (baricitinib, MOL4239, BCX-4208); b) inhibition of enzymes such as PDE4 (AN2728) and PNP (BCX-4208); c) blockade of TLR receptors (IMO-8400); d) inhibition of the TrkA receptor (CT327); e) SIRT1 activation (SRT2104) and A3AR (CF101). 2-DG = 2-dexosiguanosine, A3AR = adenosine A3 receptor, cAMP = cyclic adenosine monophosphate, D1P = deoxyribose-1-phosphate, JAK = Janus kinase, NF-κB, nuclear factor kappa light chain enhancer of activated B cells, NGF = nerve growth factor, PNP = purine nucleoside phosphorylase, STAT = signal transducer and transcription activator, SRT1 = sirtuin-1, TLR = Toll-like receptors, TrkA = tropomyosin kinase A.

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The hypothesis that considered T lymphocyte activation as a central event in the etiology of the disease was subsequently confirmed with the performance of experiments where the transfer of knowledge was carried out bi-directionally (bench-to-bedside/bedside-to-bench). In one of them, immunosuppressed mice were used, which were grafted unharmed skin from patients with psoriasis. This skin acquired characteristics of psoriatic plaque after the leukocyte injection. To test the same hypothesis, specific antagonists (anti-CD80 antibodies and CTLA4-Ig fusion protein) of surface molecules implied in the activation of T lymphocytes were used. These were clinical experiments coupled with basic research that led to the elucidation of signaling pathways linked to the pathogenesis of the disease.

In those days, the idea that the presence of a network of cytokines generated by lymphocytes in genetically predisposed individuals had an influence on keratinocyte hyperproliferation was spread. As a consequence, biotechnological products were designed to block the action of said cytokines. An example of this was daclizumab, a monoclonal antibody that targets the IL-2 receptor and the launch onto the market of two new agents aimed at inactivating T lymphocytes: alefacept and efalizumab. Although efalizumab was later withdrawn for generating serious adverse effects, its use was another proof of the importance of T lymphocytes in this pathology. In the 1990s, tumor necrosis factor (TNF) had already been shown to be found at high concentrations in psoriatic plaques. Remission of skin lesions in patients with psoriatic arthritis after the use of an anti-TNF agent (etanercept) provided evidence of the relevant role of this cytokine and the innate immune response in psoriasis. Subsequent clinical trials, complemented with cell and molecular biology tools, confirmed that anti-TNF agents also had effects on the proliferation of other lymphocytes, Th17. These translational medicine bidirectional approaches contributed to the identification of key mediators in the disease, allowing the launch onto the market of drugs with higher selectivity for specific cytokines.

Although the first anti-TNF drugs emerged at the beginning of the 21st century (etanercept, adalimumab, infliximab), new pharmacological strategies have enabled the development of other novel anti-TNF agents. That is the case of certolizumab pegol, which differs from other anti-TNF drugs for its structure. This drug is composed of a Fab fragment of a humanized murine monoclonal anti-TNF antibody combined with two polyethylene glycol molecules, which increases its half life period to approximately 14 days, with higher tissue distribution. By being free of the Fc portion, certolizumab pegol does not form immune complexes or induce antibody or complement-mediated cytotoxicity. In addition, it possesses higher affinity for TNF than other drugs such as infliximab and adalimumab, without inducing apoptosis in healthy individuals’ T lymphocytes and monocytes.

The importance of Th17 cells in psoriasis was also established using translational medicine approaches. Firstly, the existence of this group of IL-17-producing cells, their impact on inflammatory autoimmune diseases and their important presence on the skin and peripheral blood of individuals with psoriasis was shown in animal models and in patients. Other investigations demonstrated that Th17 cells activation was influenced by IL-23 and that this shared the p40 subunit with IL-12. These basic science studies combined with clinical verifications allowed the establishment of a new paradigm in the physiopathology of the disease, which was related to the IL-23/IL-17 axis. The logical consequence of these investigations was the development of two antibodies against the p40 subunit: ustekinumab and briakinumab, as well as inhibitors of IL-17 or its receptor (secukinumab, ixekizumab, brodalumab).

A thorough analysis of what happened two decades ago with the generation of new drugs for psoriasis allows understanding the impact of translational medicine in this process. In fact, the success of biotechnological agents was due to the conduction of investigations where hypotheses were established in biological models with the possibility to move quickly to the clinical field, while this clinical experience served as a basis to refine etiopathogenic concepts. This bidirectional process has guaranteed success in the generation of treatments and, although many of them were dropped half way through (anti-IL8 antibody, anti-CD5 antibody, anti-L selectin antibody), there is no doubt that this strategy has allowed the launch of new drugs onto the market, contributing to improvements in patient quality of life.

New anti-psoriatic drugs under development

Deeper understanding of the cellular and molecular events involved in psoriasis etiology of has allowed a considerable leap to occur regarding the number of drugs under development that are associated with new therapeutic targets (Fig. 1). Those that activate or block
phosphodiesterase 4, the tropomyosin kinase A receptor, purine nucleosides phosphorylase, adenosine A3 receptor, sphingosine-1-phosphate receptor and the family of Janus kinases, among others, stand out (Table 1).

Future perspectives in the development of new anti-psoriatic drugs

The use of translational medicine strategies in the development of anti-psoriatic drugs has allowed to significantly increase the number of those available for this pathology in the last 20 years. The launch onto the market of biotechnological products was a milestone in the approaches to the development of this type of drugs, since it consciously combined a bidirectional strategy where knowledge derived from basic science was quickly incorporated into clinical research, while clinical experience served as the basis to accept or refute basic science hypotheses. Therefore, it is not surprising that there are 18 anti-psoriatic drugs associated with new targets, which are being developed by multiple pharmaceutical companies in the world.

Despite these encouraging news, psoriasis remains an incurable disease and there are still several aspects that can hinder the future development of drugs, whose integration with translational medicine approaches should be deepened. As an example, the following could be enumerated:

- Characterization of specific antigens responsible of immune response activation.
- Identification of biomarkers predictive of toxicity, pharmacokinetics and pharmacological efficacy.
- Development of in vivo and in vitro models that are more representative of the disease.
- Integration of genomic aspects to the process of drug discovery.

There is much that remains to be understood about the causes of this disease, as well as on the influence
of genetic markers on the response to new treatments, but surely the bidirectional transfer of knowledge will allow the future introduction of new individualized options where the cooperation between all stakeholders (scientists, doctors, patients) will be necessary for the paradigm shift.

References


