Actas Dermosifiliogr. 2013;104(4):304–310

ACTAS Dermo-Sifiliográficas

Full English text available at www.elsevier.es/ad

NOVELTIES IN DERMATOLOGY

Tofacitinib and Other Kinase Inhibitors in the Treatment of Psoriasis☆

K. Ortiz-Ibáñez, M.M. Alsina, C. Muñoz-Santos*

Servicio de Dermatología, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain

Received 28 August 2012; accepted 31 October 2012
Available online 11 April 2013

KEYWORDS
Psoriasis;
Small molecules;
Kinases;
Tyrosine kinase;
Janus kinase;
Tofacitinib;
Ruxolitinib

Abstract Protein kinases play a crucial role in the intracellular signaling pathways involved in inflammation and cell proliferation. Advances in our understanding of these metabolic pathways and of the role played by intracellular signaling in the pathogenesis of psoriasis have led to research in this area and the development of a new class of drugs for the treatment of psoriasis and other inflammatory processes. Since kinase inhibitors are small molecules, oral and topical treatments are possible. The future role of these molecules in the therapeutic arsenal used to treat psoriasis is as yet unknown because in most cases they are still in the early stages of research. The fact that these drugs may cost much less than biologic therapies could favor their approval in coming years. Tofacitinib, a Janus kinase inhibitor, is the drug that has reached the most advanced stage of research and has shown the most promising results.

PALABRAS CLAVE
Psoriasis;
Pequeñas moléculas;
Cinasas;
Tirosina cinasas;
Janus cinasas;
Tofacitinib;
Ruxolitinib

Tofacitinib y otros inhibidores de las cinasas en el tratamiento de la psoriasis

Resumen Las proteinas cinasas juegan un papel fundamental en las vías de señalización intracelular implicadas tanto en la proliferación celular como en la inflamación. El mejor conocimiento de estas vías metabólicas y del mecanismo patogénico de las señales intracelulares de la psoriasis está provocando el desarrollo e investigación de un nuevo grupo de fármacos en el tratamiento de esta enfermedad y de otros procesos inflamatorios. Los inhibidores de las cinasas son moléculas de pequeño tamaño que van a permitir un tratamiento vía oral o tópico. El futuro papel de estos fármacos dentro del arsenal terapéutico de la psoriasis está todavía por determinar ya que la mayoría de moléculas están en fases precoces de investigación. Su hipotético coste inferior al de los tratamientos biológicos pueda favorecer su aprobación en los próximos años. Tofacitinib, un inhibidor de las cinasas Janus, es el fármaco con investigación más avanzada y resultados prometedores.

☆ Please cite this article as: Ortiz-Ibáñez K, et al. Tofacitinib y otros inhibidores de las cinasas en el tratamiento de la psoriasis. Actas Dermosifiliogr. 2013;104:304–10.

* Corresponding author.
E-mail address: carlosmunozsantos@gmail.com (C. Muñoz-Santos).

1578-2190/$ – see front matter

Background

The introduction of biologic therapy in the last decade represented a major advance in the treatment of patients with moderate to severe psoriasis because it achieved a better response and was associated with lower toxicity than the systemic treatments previously used. However, a non-negligible percentage of patients (between 20% and 50%) respond insufficiently or not at all to biologictherapy.[1] There is therefore an interest in identifying new drugs that may be effective in a larger number of patients. The identification of a number of psoriasis susceptibility genes, and with it a better understanding of the pathogenesis of the intracellular metabolic pathways (especially those related to cell signal transduction), has generated new perspectives on the treatment of psoriasis. In contrast to the experience of recent years, it is very likely that the new paradigm for psoriasis treatment will come not from new biologic agents with extracellular activity but from compounds with the ability to inhibit certain intracellular proteins involved in the immune response. The ideal target protein upon which these drugs are intended to work is one that possesses essential immune-cell functions that are also critical for the functioning of other cells. The inhibition of this target protein should modify the immune response triggered in psoriasis without affecting relevant organs. However, in many cases, these same proteins participate in other biological processes, and occasionally, these drugs may interact with related enzymes of the same type, making it difficult to predict their effects and potential adverse events.

The most rapid advances achieved with this new class of drugs have been made in the field of oncology, leading to current research on various drugs that block cytoplasmic proteins involved in the immune response to psoriasis, and other inflammatory diseases such as rheumatoid arthritis and Crohn disease. Their small molecular size allows them to be administered orally or topically, thereby potentially lowering the cost of treatment when compared with current biological drug treatment. Although still in the initial phases, the development of these drugs has been very rapid, and several are on the verge of approval for the treatment of inflammatory diseases other than psoriasis. It is possible that a number of these drugs will be completely defined for the treatment of psoriasis in the next decade.

Protein Kinases

Among the molecules currently under development for the treatment of psoriasis are those that act against certain protein kinases, which are intracellular enzymes found in all cells. These kinases activate or deactivate other proteins through phosphorylation, with the resulting transmission and amplification of information essential for the control of cell physiology.[2] They exert this phosphorylation function through adenosine triphosphate molecules, and the majority of inhibitors act at this level. Protein kinases are essential for numerous membrane receptors, which do not have their own kinase activity and must interact with these proteins to transmit their signal from the exterior of the cell to the nucleus. The human genome encodes more than 500 different protein kinases, which are divided into 8 major didactic groups based on the sequence similarity of their catalytic domain (Table 1). The majority transfer phosphate groups to serine or threonine residues in a protein substrate. The most researched group in the field of psoriasis is the tyrosine kinase (TK) group.

Table 1 Classification and Basic Characteristics of Protein Kinases.

Group	Main Characteristic
AGC	Bound to protein G
CAMK	Regulated by calmodulin/calcium
CMGC	Cyclin-dependent
CK1	Casein kinases
RGC	Receptors associated with guanylatecyclases
STE	Mitogen-activated
TKs	Tyrosine kinases
TKL	Tyrosine kinase-like

Protein Tyrosine Kinases

Protein TKs (PTKs) are one of the primary groups of protein kinases and derive their name from their selective phosphorylation of tyrosine residues.[3] There are an estimated 90 PTKs divided into 2 large families: receptor PTKs (cell membrane receptors with intrinsic kinase activity) and cytoplasmic or nonreceptor PTKs (Table 2). The latter, in turn, are divided into 9 subfamilies.[4] Cytoplasmic PTKs are closely linked to essential cell functions such as the regulation of growth, division, differentiation, survival, and migration, as well as to the immune cell signaling system.[2,5] They play a role in the nucleus in regulating the cell response to chemical signals, such as those from inflammatory cytokines (e.g., tumor necrosis factor α [TNF-α]); pathogens, such as viruses; cell growth factors; and UV radiation. Cytoplasmic PTKs play an important role in the activation of lymphocytes, macrophages, neutrophils, and mast cells, and they also regulate diverse activities including hormonal activity, cell division, and gene expression.[6]

PTKs are clinically important because their activity is related to numerous diseases involving local inflammation, such as psoriasis and atherosclerosis, and other systemic inflammatory states, such as sepsis and septic shock. In addition, the expression of mutant or aberrant protein TKs may result in cancer due to uncontrolled cell division. Therefore, the blocking or inhibition of the activity of certain protein TKs represents an interesting therapeutic basis, for both neoplastic and inflammatory diseases. Numerous PTK inhibitor molecules have been developed that block the action of 1 or more protein kinases that, due to a particular mutation, are permanently activated in certain types of cancer. Initially, the development of protein kinase inhibitors was aimed at producing drugs with a high selectivity of action, although it has been subsequently shown that several of the compounds under development act on more than 1 kinase (multikinase inhibitors), and that each kinase can, in turn, act with various cytokines. In some cases, this relative lack of selectivity has been shown to be more of an