
Apremilast in psoriatic arthritis

G. Schett

Department of Internal Medicine 3,
University of Erlangen-Nuremberg,
Erlangen, Germany.

Georg Schett, MD

Please address correspondence to:

Dr Georg Schett,

Department of Internal Medicine 3,
Rheumatology and Immunology,
University Clinic of Erlangen-Nuremberg,
Ulmenweg 18,
91054 Erlangen, Germany.

E-mail: georg.schett@uk-erlangen.de

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ABSTRACT

Apremilast is a small molecule inhibitor of phosphodiesterase (PDE) 4 approved for the treatment of psoriatic arthritis (PsA). The efficacy and safety of apremilast in PsA have been demonstrated in four phase III trials. The compound has been approved for the treatment of moderate to severe PsA in the United States and in Europe. Apremilast also shows efficacy in psoriatic skin disease. Its mode of action is based on an increase of immune-regulatory cAMP in immune cells, which is mediated through the inhibition of the cAMP-degrading enzyme PDE4. Higher levels of cAMP inhibit cytokines involved in the pathogenesis of psoriasis, such as TNF-alpha or IL-23, resulting in clinical improvement.

Introduction

Although chronic inflammation of joints is shared by psoriatic and rheumatoid arthritis, the two diseases show profound differences in several respects: psoriatic arthritis (PsA) and rheumatoid arthritis (RA) differ in (i) their immune pathogenesis, (ii) the presence *versus* absence of an interleukin-6 driven acute phase response, (iii) the involvement of the enthesial compartment in PsA but not RA and (iv) the presence *versus* absence of bone proliferative responses. It is therefore not surprising that responses to anti-inflammatory drugs differ between PsA and RA. One important example of differences in therapeutic response is the sensitivity of the disease to conventional disease-modifying anti-inflammatory drugs (DMARDs). Methotrexate (MTX) is considered the anchor drug in rheumatoid arthritis, while its effect in PsA is confined to subtypes of the disease, such as polyarticular disease, while it is less efficient in oligoarticular or axial disease. Furthermore, other conventional DMARDs applied in RA, such as leflunomide, sulfasalazine and hydroxychloroquine are not widely

used in patients with PsA, and have not been rigorously studied in this patient population.

An important development in the field of conventional DMARD treatments in PsA is apremilast, now approved in the United States and in Europe. Approval of apremilast for the treatment of moderate to severe PsA was the final step of a long preclinical and clinical study programme involving more than a thousand patients affected by PsA.

Apremilast as inhibitor of phosphodiesterase 4

Apremilast is a small, chemically synthesised substance with a molecular weight of 460 gram per mole. Its detailed molecular name is ((S)-N-{2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl}acetamide). In earlier studies, apremilast was often referred to as “CC-10004.” Apremilast was synthesised to block the catalytic site of the enzyme phosphodiesterase 4 (PDE4). This enzyme is a member of a family of enzymes, called phosphodiesterases (PDEs), with the common function to hydrolyse and degrade cyclic adenosine monophosphate (cAMP) (1).

The various forms of PDEs differ in their tissue distribution and cellular expression pattern. PDE4 is expressed widely in haematopoietic cells (both myeloid and lymphoid cells), and in some non-haematopoietic cells, such as keratinocytes (2). In leukocytes, PDE4 plays an important role in degrading cAMP (3). When initially screened for PDE4 inhibition, apremilast was found to inhibit PDE4 activity very potently with an IC₅₀ in the nanomolar level (4, 5).

Role of cAMP in the regulation of cytokine synthesis

cAMP is a “second messenger” which plays a key role in the regulation of inflammation (6). The cAMP signalling pathway is used by various G-protein

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coupled receptors, such as histamine receptor, α - and β -adrenergic receptors and prostaglandins. An increase in intracellular cAMP concentrations inhibits the production of cytokines. Actual cAMP concentration in cells depends on the activity of adenylate cyclases that produce cAMP, as well as PDEs that degrade cAMP (6). Hence, blockade of PDE4 by apremilast increases intracellular cAMP levels and promotes anti-inflammatory actions by modulating cytokine production by leukocytes and some non-haematopoietic cells.

Apremilast inhibits cytokine production

In monocytes, apremilast inhibits TNF- α production induced by challenge of cells with lipopolysaccharide in a dose-dependent fashion (5, 7, 8). Furthermore, production of IL-12, as well as chemokines such as CXCL9 (MIG), CXCL10 (IP-10), and CCL4 (MIP1 α) from human peripheral blood monocytes, also is inhibited by apremilast (5, 9). Furthermore, the production of matrix metalloproteinase (MMP)-3, which is involved in tissue remodeling in synovitis and in cartilage damage, and therefore important in inflammatory arthritis, is inhibited by apremilast (10). Therefore, PDE4 inhibition may interfere with pro-inflammatory pathways at more than one point. However, not all monocyte-derived cytokines are inhibited by apremilast: For instance, the expression of the anti-inflammatory cytokine IL-10 is not inhibited, but even slightly enhanced (11).

In neutrophils, PDE4 is involved in the production of IL-8, leukotriene B₄, and superoxide anions mediating the degranulation and chemotaxis of neutrophils. PDE4 also mediates the adhesion of neutrophils by inducing expression of the integrin Mac-1, which mediates adhesion to vascular endothelium (12). Apremilast effectively blocks the production of IL-8 from neutrophils. Since psoriatic disease is characterised by the accumulation of neutrophils, forming, for instance, Munro's microabscesses in the skin, inhibition of neutrophil chemotaxis by apremilast may add to its function in clinical inhibition of psoriasis and PsA.

In T lymphocytes, several experiments suggest that PDE4 plays a role in T cell activation and cytokine production. Importantly, PDE4 is associated with the CD28 surface receptor, an essential molecule for co-activation of T cells (13). PDE4 influences the production of IL-2, IL-4 and IFN- γ by T cells (14) and overexpression of PDE4 results in augmented cytokine production after T cell activation. Conversely, apremilast downregulates production of IL-2 (5), IFN- γ (5), and IL-17 by T cells (14). The later effect appears important, especially in PsA and psoriatic skin disease, as IL-17 blockade has emerged as a powerful treatment for these diseases, in addition to TNF inhibition.

Some functions of apremilast also have been described in non-haematopoietic cells expressing PDE4. For instance, apremilast inhibits TNF- α production from UV-treated keratinocytes, which disrupts the pathological tissue response of psoriatic skin. By contrast, apremilast has no significant effect on normal keratinocyte proliferation or viability.

Apremilast in arthritis

In preclinical models, treatment of collagen-induced arthritis with apremilast in DBA1 mice resulted in a reduction of clinical and histopathology signs of arthritis. (15). *Ex vivo* experiments indicated that apremilast inhibited T-cell proliferation, IFN- γ production, and TNF- α production of lymph node cells from mice with arthritis. Similar results were seen in experimental arthritis induced by monoclonal antibodies against type II collagen, in which apremilast significantly blocked synovial inflammation, cartilage damage and bone erosion (15).

The clinical efficacy and safety of apremilast in patients with PsA was documented in a randomised controlled phase 2 study (16). In this study, 40 mg of apremilast per day showed efficacy in the treatment of signs and symptoms of PsA over placebo. Efficacy was similar in patients who received concomitant MTX treatment and those who received apremilast as monotherapy. Furthermore, apremilast showed significant efficacy in patient related outcomes in PsA patients, including physical func-

tion and quality of life (17). In addition, the initial phase 2 study revealed no laboratory abnormalities after administration of apremilast and no other safety issues. Mild diarrhoea was observed in a subset of patients, which, however did not lead to discontinuation of therapy (16).

Efficacy of apremilast in the phase III study programme

The successful phase II study led to a large phase III study programme in PsA, consisting of four individual randomised, placebo-controlled studies, termed Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) (18). In these studies, which included patients with active PsA, consistent clinical efficacy in reducing the signs and symptoms of PsA was seen after treatment with apremilast administered at an oral dose of 30 mg twice-daily. The primary endpoint, an American College of Rheumatology (ACR) 20 response, compared to placebo was seen in 40% of patients treated with apremilast compared to only 20% of control patients. The ACR20 responses observed in the PALACE study programme are similar to those observed for ustekinumab in two trials. ACR responses with apremilast, however, appear somewhat lower than responses observed with inhibitors of TNF- α or interleukin-17, although "head-to-head" trials have not been conducted to date.

Improvement of signs and symptoms observed with apremilast did not reach maximum levels after 16 weeks of treatment. Hence, data from the PALACE 1 study showed that the magnitude of response to apremilast further increased with longer duration of treatment (19). After 52 weeks continuous treatment, 55% of the patients receiving 30 mg of apremilast twice daily achieved an ACR20 response, while 25% of the patients had an ACR50 response and 14% an ACR70 response.

The majority of apremilast-treated patients also showed improvement in physical function, with clinical meaningful reduction of HAQ scores (more than 0.13 units decrease) in 60% of the patients (19). Also, quality of life scores improved during treatment with

apremilast, suggesting that the effect on signs and symptoms are associated with a better health state in patients with PsA. This latter observation is also attributed at least in part to a significant effect of apremilast on enthesitis and dactylitis, which are hallmarks of PsA and substantially affect the patients' health state. Hence, the median change in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) after 52 weeks of apremilast treatment was 67%. Furthermore, 38% of the patients showed complete disappearance of clinical signs of enthesitis and in 63% of the patients dactylitis completely resolved.

Tolerability and safety of apremilast

Mild nausea or diarrhoea have been reported during the first two weeks of treatment with apremilast but usually resolves without intervention despite continued treatment at the same dose (18, 19). Headache may occur in a minority of the patients. Fewer than 2% of patients discontinue apremilast because of diarrhoea or nausea. Apremilast appeared as a safe drug during the phase III trial programme, with no laboratory abnormalities observed and no serious adverse events related to the drug.

If this promising safety pattern of apremilast is confirmed in usual clinical care, it is an important advantage for its wider use in patients with PsA, which are often affected by substantial comorbidity. Apremilast treatment also is associated with mild but significant weight loss. PsA patients lose about two kilogrammes in body weight, when treated with apremilast and 17% of the patients manage to decrease in more than 5% of body weight. The reason for this effect is unknown, but not related to diarrhoea. Whether apremilast has direct positive effect on fat metabolism or whether it indirectly affects body weight by improving the capacity for physical activity remains to be determined. This finding is interesting as PsA patients often suffer for concomitant obesity and metabolic syndrome.

Summary

Apremilast has been approved for the treatment of active PsA based on clinical efficacy and a favourable safety profile.

This development is an important milestone in the treatment of this severe joint disease, since the role of conventional DMARDs in PsA is limited compared to rheumatoid arthritis. MTX does appear efficacious only in a subset of PsA patients, but never reached the status of an "anchor drug" like in rheumatoid arthritis. Importantly, MTX has no effect on enthesitis and dactylitis. Moreover, other conventional DMARDs have not been widely-used in PsA because their benefits have not been promising. Therefore, the successful development of an oral drug in PsA is a major step forward towards better disease control of this severe joint disease.

The ideal use of apremilast in clinical practice remains to be determined. However, it appears as an attractive option when MTX is inefficacious or there is intolerance to it. In certain conditions, e.g. in patients with dominant enthesitis, where MTX has limited efficacy, apremilast may even be considered as first-line treatment. Also, the high safety makes apremilast an attractive therapeutic option before treatment with biological DMARDs is considered.

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