CHAPTER 8

APREMILAST IN DERMATOLOGY

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Agents which increase intracellular cyclic adenosine monophosphate (cAMP) may have an antagonistic effect on pro-inflammatory molecule production so that inhibitors of the cAMP degrading phosphodiesterases have been identified as promising drugs in chronic inflammatory disorders. Although many such inhibitors have been developed, their introduction in the clinic has been hampered by their narrow therapeutic window with side effects such as nausea and emesis occurring at sub-therapeutic levels. The latest generation of inhibitors selective for phosphodiesterase 4 (PDE4), like apremilast, seems to have an improved therapeutic index. Apremilast shows promising activity in dermatological and rheumatological conditions. Studies in psoriasis and psoriatic arthritis have demonstrated clinical activity of apremilast. Efficacy in psoriasis is probably equivalent to methotrexate but less than that of monoclonal antibody inhibitors of tumour necrosis factor (TNF-α). Similarly, in psoriatic arthritis efficacy is less than that of TNF inhibitors. PDE4 inhibitors hold the promise to broaden the portfolio of anti-inflammatory therapeutic approaches in a range of chronic inflammatory diseases which may include granulomatous skin diseases, some subtypes of chronic eczema and probably cutaneous lupus erythematosus. We discuss apremilast on skin inflammatory responses and also their future role in clinical practice.[1-5]

Mechanism of action

The clinical symptoms of chronic inflammatory diseases are determined by a number of different inflammatory mediators. In psoriasis, for example, not only the well-recognized TNF is an important effector molecule, but IL-17, IL-22, INF-γ, IL-2, IL-36, CCL20, IL-8, chemokine CXCL10, IL-23, IL-1, IL-18, IL-12, VEGF, substance P, IFN-α, and many others contribute to the inflammatory response in the joint and skin. Conventional therapies have a broad range of action and inhibit, e.g. preferentially lymphocyte proliferation [cyclosporin (CsA), methotrexate] and lymphokine production (IFNγ, IL-17, IL-22, IL-2) or mainly target the hyperproliferation and abnormal differentiation of keratinocytes (dithranol, tar) or combine the latter with cytokine modifying properties (retinoids, vitamin D, glucocorticoids). Biologics currently used in the clinic target one specific mediator which supposedly plays a key role upstream in the disease-specific cytokine network. cAMP is a key intracellular second Messenger and also cAMP signalling is activated by a variety of G protein-coupled receptor ligands. The effects of cAMP are transduced by two ubiquitously expressed intracellular cAMP receptors, protein kinase A (PKA) and exchange protein directly activated by cAMP. cAMP can also bind to cyclic nucleotide-gated ion channels in certain tissues. The local pools of cAMP expression/PKA activation are generated in distinct subcellular compartments. This allows for precisely regulated activity essential for response specificity. cAMP activates and enables PKA to phosphorylate substrate proteins. PKA activates cAMP response element binding protein which is a cAMP-responsive element possessed by several immune-related genes including IL-2, IL-6, IL-10, and TNFα. cAMP can directly or indirectly inhibit nuclear factor kappa B (NF-κB) pathway activation events. Low intracellular cAMP may thus lead to the preferential expression of proinflammatory mediators. Intracellular concentration of cAMP is determined by the activity of adenylyl cyclases on the one hand and PDE on the other. PDEs are also expressed in distinct cellular compartments and functionally coupled to individual receptors-thus providing a way to control sub compartment cAMP levels in a stimulus-specific manner. Substances which increase cAMP in monocytes/macrophages are among the most potent inhibitors of IL-12 family members including IL-12/IL-23 p40.[1-3] This has been shown for cholera toxin, histamine, PGE2 and other mediators. Repression of cAMP greatly reduces the suppressive activity of human Treg. cAMP facilitates the functional activity of a transcriptional inhibitor called ICER (inducible cAMP early repressor) and this mechanism seems to be involved in the suppression of the key T cell growth factor IL-2 and other cytokines. In addition, immunosuppressive and anti-inflammatory actions of cAMP have been attributed in part to the ability of cAMP induced signals to interfere with the function of NF-κB. NF-κB activation is one of the master signalling pathways involved in inflammatory responses and a key target for anti-inflammatory drug design. Important cytokines downstream of NF-κB include TNFα, CCL20, IL-8; IL-1 family members (IL-36, IL-18, IL-1)

10 patients with inflammatory rosacea were administered apremilast, 20 mg orally twice daily, for 12 weeks. The primary end point was the total number of papulopustular lesions at baseline compared with the end of treatment and with follow up 1 month after treatment. When baseline scores were compared with those at the end of treatment, there was a statistically improvement in ratings on the lesions assessment. The authors concluded tha apremilast was well tolerated treatment agent for rosacea.[19]

8- Sarcoidosis:

One study points to a potentially beneficial effect of apremilast in cutaneous sarcoidosis and it will be interesting to further explore the activity of PDE4 inhibitors in granulomatous skin diseases including Melkerson Rosenthal syndrome for which the therapeutic options are limited at present. Although PDE4 selective inhibitors inhibit IL-12 and TNFα mixed PDE4/3/7 preparation may have improved activity on macrophages which are key cells in granulomatous diseases. Apremilast is a newphosphodiesterase type4inhibitor that blocks the synthesis of proinflammatory cytokinesandchemokines, such as tumor necrosis factor, interferon-γ, and the IL-2, IL-12, and IL-23. These cytokines are important in the initiation and perpetuation of sarcoidosis. In this study, all 15 patients wtih sarcoidosis received oral apremilast, 20 mg, twice a day. If adverse events were reported, the dosage was reduced to 20 mg orally once a day. Patients received 12 weeks of treatment and were seen 1 month later. Skin lesions were assessed in 2 ways:[1] by using the previously described Sarcoidosis Activity and Severity Index (SASI) 3 and[2] by comparing photographs of the index lesion initially and at week 12, with the photographs presented in random order. The SASI induration score3 decreased significantly with apremilast therapy the authors found apremilast effective for some patients with sarcoidosis who had persistent lesions despite multiple systemic treatments.[17]

9-Contact Dermatitis:

A study by Volf et. al assessing the efficacy of apremilast in treating recalcitrant allergic contact dermatitis (ACD). Ten patients with either ACD or AD were treated with apremilast 20 mg daily for twelve weeks. Ten percent of subject achieved EASI-75 and another 10% reached EASI-50. These results were not as promising as PDE4 inhibition in psoriasis treatment.[21]

Summary:

PDE4 inhibitors are a class of drugs which act intracellularly to down regulate inflammatory pathways and to promote innate antiinflammatory pathways. They have a potentially wide range of therapeutic uses in chronic inflammatory diseases. In particular, apremilast has already proven effective in psoriasis and the peripheral arthritis of psoriatic arthritis. Efficacy in psoriasis is probably equivalent to methotrexate but less than TNFα. In psoriatic arthritis efficacy is probably similar to methotrexate but less than TNFα. Apremilast appears to have a good safety profile and this, together with the oral dosing are likely to be major factors in the decision to use the drug. However, much will depend on the cost and long-term tolerability and safety.[31]

TABLE 1. The applications of Apremilast in Skin Diseases

1. Psoriasis
2. Contact Dermatitis
3. Atopic dermatitis
4. Lichen Planus
5. Sarcoidosis
6. Rosacea
7. Alopecia areata
8. Systemic lupus erythematosus and discoid lupus erythematosus
9. Psoriatic arthritis

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