IMIQUIMOD *IN VIVO* MODEL MIMICS PSORIATIC CONDITIONS IN MICE

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Psoriasis is a recurrent inflammatory disease mainly involving the skin, that affects about 3% of the population. Current treatment options targeted to specific cytokines (TNF-α, IL-23 and IL-17) are of choice in patients with moderate-to-severe forms of the disease. However, topical treatments used for milder forms of psoriasis (corticoids, vitamin D analogs and retinoids) have important limitations. Among the different preclinical animal models used throughout the years, the imiquimod-induced psoriasiform dermatitis has emerged as the most convenient one, due to its reproducibility and ease to perform. Particularly, this model is considered translational into the clinic since it reproduces many significant signs of the human disease, including histopathology of lesions and strong activation of the immune system.

Imiquimod is a TLR7/8 ligand and potent immune activator, authorized for the topical treatment of virus-associated skin abnormalities as well as (pre)cancerous skin lesions such as actinic keratoses and superficial basal cell carcinomas. One of its adverse side effects includes psoriasis induction or exacerbations. Therefore, it was determined that 5% imiquimod application on mice rapidly induced a dermatitis critically dependent on the IL-23/IL-17 axis, considered pivotal in the pathogenesis of psoriasis (1).

Although there are small variations in the days (5 or 6) of topical application, most investigators use the commercial cream Aldara 5% (Meda AB). Both approaches, preventive and once dermatitis is established (4 days), are commonly used. We have successfully used this model to evaluate the benefit of topical application of small molecules, such as Benzo[b]thiophen-2-yl-3-bromo-5-hydroxy-5H-furan-2-one (BTH), which inhibited the release of some of the key psoriatic cytokines such as TNF-α, IL-8, IL-6, and CCL27 through the downregulation of NF-κB in normal human keratinocytes (2). BTH pretreatment ameliorated the course of the disease, significantly reducing scaling and erythema exclusively at the site of application (suggesting a local effect). Histological analysis of punch biopsies showed a reduction of epidermal thickening in BTH-treated skin. BTH pretreatment also reduced the dermal leukocyte infiltrate, significantly decreased IL-23 levels and hindered STAT3 (Tyr705) and p65-NF-κB (Ser536) phosphorylation. As expected, topical treatment with the reference compound dexamethasone also ameliorated all the above-mentioned parameters. However, in contrast to BTH, the effect of dexamethasone was extensive to the skin beyond the delimited application site, causing dermal atrophy, a characteristic side-effect of topical corticoids.

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Reference:

1. van der Fits L, *et al*. *J Immunol*, 182: 5836-45 (2009)
2. Andrés RM, et al. J Invest Dermatol. 133:2362-71 (2013).

Short Curriculum Vitae:

Mª Carmen Montesinos is tenured professor of the Department of Pharmacology at the University of Valencia. Graduated in Pharmacy, her doctoral thesis dissertation versed on the antioxidant activity of phenolic derivatives. After completing a postdoctoral stay at the New York University Medical Center to study cell signaling in human neutrophils, she remained at this institution until reaching the position of Assistant Professor. She has substantially investigated the physiological effects of the activation of adenosine receptors and their involvement in promotion of wound healing and in the anti-inflammatory effect of anti-rheumatic drugs. Currently, her research focuses on the study of the pathological processes involved in inflammatory skin diseases in order to improve current therapeutic options.