ACTA ABP BIOCHIMICA POLONICA

Vol. 70, No 4/2023
729–733
https://doi.org/10.18388/abp.2020_6426

Review

Imiquimod-induced psoriasis model: induction protocols, model characterization and factors adversely affecting the model

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Imiquimod-induced psoriasis is widely-employed to study disease pathogenesis and to screen drugs. While the original protocol was published more than a decade ago and has been rigorously used in research since then, a modified protocol was described recently with several advantages including milder systemic manifestations although the disease morphology is highly conserved. Being a toll-like receptor 7 and 8 agonist, IL-23/IL-17 axis predominates in imiquimod-induced psoriasis. In addition, different immunocytes were described to aggravate or supress the disease. This article aims to review the currently available protocols of imiquimod-induced psoriasis *in vivo*, to characterize the model as described in literature and to define the five important independent factors adversely influencing the model which researchers should pay attention to.

Keywords: animal model, B-cell, IL-17, IL-23, imiquimod-induced psoriasis, T-cell

Received: 14 July, 2022; revised: 15 May, 2023; accepted: 18 July, 2023; available on-line: 22 November, 2023

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Abbreviations: PASI, Psoriasis Area and Severity Index

INTRODUCTION

Animal models of psoriasis are categorized into four categories: the first category represents models resulting from spontaneous mutations, such as homozygous asebia ($Scd1^{ab}$/$Scd1^{ab}$) and flaky skin (Ttc^{fsn}/Ttc^{fsn}) mice where the latter model shares with human psoriasis acanthosis, parakeratosis, and corneal neutrophils infiltration. The second category represents genetically-engineered models where epidermal proteins like keratins and/or cytokines are modified to produce features resembling psoriasis. The third category includes humanized models or models generated by xenotransplantation where lesional skin biopsy or skin equivalent is transplanted to mice. A recently-described but frequently used model is the directly induced model, where imiquimod is used to produce an immunological reaction resembling the one seen in psoriasis, largely mediated by IL-23/IL-17 axis and TNF-α (Guerrero-Aspizua *et al.*, 2020; Jean & Pouliot, 2010; Jeong & Lee, 2018).

This article aims to review the model of imiquimod-induced psoriasis, highlighting the currently published two induction protocols and characterizing the model in terms of dominant cytokines and cellular infiltrate. It also tackles the five factors that may influence disease modelization.

THE ORIGINAL AND MODIFIED PROTOCOLS OF IMIQUIMOD-INDUCED PSORIASIS

Imiquimod was first described in the mid-1990s as an immunomodulatory agent that augments the innate and adaptive immune systems. It is a toll-like receptor-7 and 8 agonist. It obtained the US Food and Drug Administration approval to treat anogenital warts, facial actinic keratoses and superficial basal cell carcinoma (Hanna *et al.*, 2016). Topical application of imiquimod may induce psoriasis (Wu & Strutton, 2004).

Van der Fits and others (van der Fits *et al.*, 2009) were the first to employ imiquimod to modelize psoriasis *in vivo*. They applied 62.5 mg of imiquimod 5% cream (Aldara) daily, equivalent to 3.125 mg of active ingredient, on the shaved back and right ear of BALB/c and C57BL/6 mice for five or six consecutive days and they assessed the severity of psoriasis using modified Psoriasis Area and Severity Index (PASI). Signs of psoriasis start to appear within the first three days and severity steadily increases till the end of the experiment. Authors reported lack of difference between the two strains of mice. Imiquimod-treated skin shows the cardinal histopathological features of psoriasis such as acanthosis (Singh *et al.*, 2019), parakeratosis and hypogranulosis. Immunohistochemical staining shows infiltration of dendrocytes, neutrophils and $CD4^+$ cells. Imiquimod also induces IL-23 and augments IL-17A, IL-17F and IL-22 production (van der Fits *et al.*, 2009).

Horvath and others (Horvath *et al.*, 2019) further modified the original protocol. They applied 25 mg of imiquimod 5% cream in Finn chambers on the back of C57BL/6 mice daily. This protocol results in erythema after the second application and scaling and skin thickening after the third application. The modified protocol was reported to be comparable to the original one. On histological examination, features of psoriasis such as parakeratosis, acanthosis, Munro microabscesses and dilated blood vessels in the dermal papillae were observed among both groups. Consistently, immunohistochemical examination reveals overexpression of Ki-67 in both. However, the modified protocol minimizes systemic manifestations and allows for prolonged imiquimod treatments.

Imiquimod-induced psoriasis model is largely used to study disease pathogenesis and to screen drugs. The model was employed for drug screening in more than 100 publications. In the majority of studies, the experimental drug of interest was administered concurrently on the same day of psoriasis induction. In a limited number of studies, it was started a few days before (1–21 days) or after induction. Regarding the protocol of induction, majority of studies complied with the original duration described as five or six consecutive days; few, howev-

er, applied the cream for shorter (three to four days) or longer periods (vast majority for seven days, up to 15 days). Prolonged daily application of imiquimod cream results in tachyphylaxis where Ki-67 expression diminishes in alignment with spontaneous attenuation and disappearance of erythema and scaling at three to four weeks despite continuous application of the cream (Kataoka *et al*., 2018).

Some studies lack a positive control; but where a positive control was used, it is a topical or systemic preparation that matches the route of administration of the experimental agent. Topical control preparations include betamethasone, calcipotriol, clobetasol, dexamethasone, dithranol, methotrexate and tacrolimus. Systemic control preparations include cyclosporine orally, dexamethasone orally and intraperitoneally, etanercept, methotrexate orally and intraperitoneally and tacrolimus.

CHARACTERIZATION OF IMIQUIMOD-INDUCED PSORIASIS MODEL

Jabeen and others (Jabeen *et al*., 2020) characterized the model of imiquimod-induced psoriasis where they applied 62.5 mg of imiquimod 5% cream for eight days. Cutaneous concentration of imiquimod approaches 100 μg/g on day 2 and it doubles by six folds on day 8 corresponding with a pronounced worsening of redness, thickness, scaling and total modified PASI. Acanthosis is evident on day 8 compared with day 2, explaining the clinically apparent thickness. Dermal hypervascularity is also marked, explaining the progressive redness. In terms of cytokine profile, elevation of IL-1β, IL-6 and IL-17A was observed in skin and TNF-α and IL-17A in serum. Disease progression associates with elongation of spleen, enlargement of total area of lymph nodes, and loss of weight independently of food intake (Zhang *et al*., 2020).

Macrophages and dendrocytes were investigated in the current model of psoriasis. While plasmacytoid dendrocytes are absent in imiquimod-induced lesions, the model shows a biphasic cellular behaviour. During the early phase, neutrophils infiltrate the epidermis and monocytes predominate in the dermis. Whereas in the late phase, Langerhans cells are pronounced in the epidermis and macrophages in the dermis. Depletion of Langerhans cells results in massive neutrophil infiltrate during the late phase, suggesting a potential anti-inflammatory role of Langerhans cells (Terhorst *et al*., 2015). On the contrary (Xiao *et al*., 2017) concluded that Langerhans cell depletion attenuates psoriasis and downregulates psoriasis-associated cytokine gene expression. (Lee *et al*., 2018) found that resident and monocyte-derived Langerhans cells secrete IL-23. Depletion of these cells inhibits IL-22 and IL-17A secretion (Lee *et al*., 2018), diminishes gamma-delta T-cell infiltration (Lee, 2016) and ultimately, attenuates psoriasis (Lee *et al*., 2018). Parallelly (Yoshiki *et al*., 2014) found IL-23-secreating Langerhans cells to induce IL-17A-producing gamma-delta T-cells. Depletion of Langerhans cells decreases Th-17-related cytokines and ameliorates psoriasis. In contrast, Kusuba and others (Kusuba *et al*., 2016) found that depletion of neutrophils early during psoriasis induction inhibits the infiltration of dermal monocytes, whereas depletion of both, neutrophils and monocytes, significantly attenuates psoriasis (Kusuba *et al*., 2016).

While IL-17 receptor is expressed on different cells, including T-cells and keratinocytes, its importance is cell-specific. For instance, deletion of keratinocyte's IL-17 receptor reduces neutrophil infiltration and abolishes psoriasis; yet, this is not the case with T-cell-expressed receptor, emphasizing on keratinocytes' role in neutrophil chemoattraction (Moos *et al*., 2019). Likewise, IL-17 abrogation inhibits imiquimod-induced psoriasis (Ha *et al*., 2013). On the contrary (El Malki *et al*., 2013) found that in IL-17A receptor-knockout mice, imiquimod may still induce psoriasis independently of IL-17 pathway. The C-X-C motif chemokine receptor type-2 is involved in neutrophil chemoattraction as well. It promotes neutrophil-produced leukotriene-B_4 and augments neutrophil chemotaxis and infiltration (Sumida *et al*., 2014). Likewise, kallikrein-related peptidase-8 is elevated in psoriasis. If knocked out, the severity of imiquimod-induced psoriasis is comparable to wildtype, however, lesions lack neutrophil microabscesses (Iinuma *et al*., 2015).

IL-1 and IL-36α chemoattract neutrophils. Both molecules mediate human generalized pustular psoriasis which is accompanied by systemic symptoms such as fever and malaise. In the current model of psoriasis, mice also display systemic symptoms such as weight loss and generalized malaise, suggesting the contribution of IL-1 and IL-36α to model development. Deficiency of IL-1 receptor-1 or IL-36α variably attenuates psoriasis; however, deficiency of both absolutely abolishes the disease (Alvarez & Jensen, 2016). IL-36 role is further verified in IL-36 receptor-knockout mice where these are resistant to imiquimod (Goldstein *et al*., 2019).

Imiquimod-treated mice exhibit antihistamine-resistant itching that is largely driven by μ-opioid receptor located in the epidermis, the dorsal root ganglia, and the spinal cord. In alignment, naloxone, a μ-opioid antagonist successfully inhibits itching in imiquimod-treated mice (Takahashi *et al*., 2017). Itching is also mediated by sphingosine 1-phosphate receptor-3, which if knocked out, scratching behaviour improves (Hill *et al*., 2020). In addition, Oishi and others (Oishi *et al*., 2019) found imiquimod treatment to associate with expansion of mastocytes and overexpression of the nerve growth factor, the neurotrophic factor neurotrophin 3 and enkephalin precursor preproenkephalin (Oishi *et al*., 2019).

REGULATION OF IMIQUIMOD-INDUCED PSORIASIS

Imiquimod-induced psoriasis is negatively regulated by B-cells (Yanaba *et al*., 2013), regulatory T-cells (Choi *et al*., 2020; Oka *et al*., 2017), matrix remodelling associated-7 (Ning *et al*., 2018), indoleamine 2, 3-dioxygenase 2 (Elizei *et al*., 2018; Fujii *et al*., 2020), IFN regulatory factor-2 (Kawaguchi *et al*., 2018), IFN regulatory factor-5 (Nakao *et al*., 2020), dermokine β/γ (Tokuriki *et al*., 2016), IL-10 (Jin *et al*., 2018), IL-27 (Chen *et al*., 2017; Shibata *et al*., 2013), poly(ADP-ribose) polymerase-1 (Kiss *et al*., 2020), endogenous n-3 polyunsaturated fatty acids (Qin *et al*., 2014), L-selectin and ICAM-1 (Mitsui *et al*., 2015).

The regulatory role of B-cells, regulatory T-cells and IL-10 is evident in different studies. In a model of $CD19^{-/-}$ mice, exacerbation of psoriasis is attributed to the loss of IL-10-secreting regulatory B-cell subset (Yanaba *et al*., 2013). Likewise, depletion of regulatory T-cells disturbs the closely regulated gamma-delta T-cells, augments TNF-α and IL-17A secretion and aggravates the disease (Choi *et al*., 2020). Neutralization of IL-10 in imiquimod-induced psoriasis promotes epidermal thickening, increases neutrophil infiltration and accentuates IL-23/IL-17 axis (Xu *et al*., 2018). Likewise, knocking out IL-10 aggravates psoriasis macroscopically and mi-

croscopically, emphasising on its anti-inflammatory role in the disease (Jin *et al*., 2018).

FACTORS INFLUENCING IMIQUIMOD-INDUCED PSORIASIS

Five factors adversely modify the model of imiquimod-induced psoriasis: the brand of imiquimod 5% cream, mouse strain, mouse sex, stress and obesity.

The brand of the commercially available imiquimod 5% cream may interfere with the model. While (Singh *et al*., 2019) claimed generic formulations of imiquimod to produce a psoriasiform inflammation that is comparable to Aldara, Luo and others (Luo *et al*., 2016) found that in comparison with Aldara, Likejie creams mediates a milder form of psoriasis with a modified PASI of 3.25±1.56 (compared with 9.81±0.84 in Aldara), a less pronounced acanthosis with a Backer's score of 2.93±1.07 (compared with 6.47±1.50 in Aldara) and an epidermal thickness of 49.79±14.16 μm (compared with 85.62±17.55 μm in Aldara), concluding that different brands may adversely affect the successful establishment of the model (Luo *et al*., 2016).

In terms of the employed strain of mice, although van der Fits and others (van der Fits *et al*., 2009) described their protocol in two different strains, (Swindell *et al*., 2017) reported variation in modelization across six different strains of mice using a five-day course of 62.5 mg imiquimod 5% cream (Aldara). Microarray showed gene expression of imiquimod-induced psoriasis to largely overlap with that of human psoriasis. C57BL/6 mice, in particular, show the highest consistency, in contrast to MOLF/EiJ and 129X1/Sv mice where gene expression is opposite to human psoriasis. In terms of IL-17 gene expression, C57BL/6 mice highly express IL-17A, IL-17B, IL-17C and IL-17F. D'Souza and others (D'Souza *et al*., 2020) examined the psoriatic changes induced by imiquimod in two different strains: BALB/c and the Swiss mice and concluded that imiquimod induces psoriatic changes macroscopically and microscopically among both strains, although these are more pronounced in the Swiss mice.

In terms of sex differences, and compared with male mice, female mice develop severe psoriasis in response to imiquimod, resulting in a greater weight loss, significant distress and unexpected early death. Inductions in females may also mandate euthanization (Alvarez & Jensen, 2016). In contrast, the influence of patient's sex on the severity of psoriasis is controversial. While female patients were found to significantly display milder psoriasis than male patients in two studies conducted in Swaziland and Sweden (Guillet *et al*., 2022; Hagg *et al*., 2017), this was contradicted by a third study (Goldburg *et al*., 2022).

Wang and others (Wang *et al*., 2020) investigated the effect of stress on imiquimod-induced psoriasis in a model of mice with emotional stress. In comparison with a control group with psoriasis kept off stress, stress was found to prolong the disease, to upregulate IL-1β, IL-17 and IL-22 gene expression and to increase IL-1β, IL-12, IL-17 and IL-22 secretion. This should further explain the role of stress in human psoriasis. For instance, stressful events were found to proceed psoriasis onset and were reported to trigger the disease in 31-88% of patients. Stress was also observed to aggravate psoriasis where daily stressors may expand the disease and worsens pruritus (Rigas *et al*., 2019; Rousset & Halioua, 2018). This is evident in pediatrics as well, where childhood trauma is commoner in patients with psoriasis, and likewise, children with psoriasis score higher in anxiety scores (Wintermann *et al*., 2022).

Obesity is known to exacerbate psoriasis in humans. This is also evident in imiquimod-induced psoriasis model where obese mice display thicker psoriatic lesions compared with non-obese subjects. Diet restriction partially improves psoriasis and cytokine profile (Hong *et al*., 2019; Kanemaru *et al*., 2015) and consistently, leptin deficiency attenuates the disease (Stjernholm *et al*., 2017). The relationship between human psoriasis and obesity was vigorously studied. A metanalysis found the odd ratio of obesity in psoriasis is 1.66, and it can approach 2.23 in patients with severe disease (Armstrong *et al*., 2012). A systematic review did also conclude that seven out of nine studies found a statistically significant association between increased psoriasis severity and increased body mass index (Fleming *et al*., 2015). Such an association is attributed to a shared mechanism involving inflammatory mediators and adipokines (Jensen & Skov, 2016).

CONCLUSIONS

Imiquimod-induced psoriasis serves as an acceptable model to study IL-23/IL-17 axis and to screen pharmaceutical agents in psoriasis. While the model could be induced using two protocols, the original protocol described by van der Fits and others (van der Fits *et al*., 2009) is widely employed in different studies. To ensure consistency of results, researchers should take into account that variation in the brand of imiquimod 5% cream, strain of mice, sex of mice, exposure to stress and obesity may adversely modify the course of disease.

Declarations

Interest statement. Author declares no conflict of interest.

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