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Chapter 2

A Review of Possible Triggering or Therapeutic Effects of Antimicrobial Vaccines on Psoriasis

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Additional information is available at the end of the chapter

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Abstract

Psoriasis is a chronic, immune-mediated disease resulting from interactions of genetic background with environmental triggering factors, such as trauma, infections and drugs. Dendritic cells, activated T-cells toward a Th1 and Th17 response and inflammatory cytokines [tumor necrosis factor (TNF)-alpha, IL-6, -12, -17, -22 and -23] are the key factors in psoriasis pathogenesis. Patients diagnosed with psoriasis are at increased risk of infection due to the nature of disease and immunosuppressive therapies. Vaccination is recommended to prevent infections in patients with psoriasis. Additionally, vaccines such as *Mycobacterium vaccae*, live attenuated varicella zoster virus and Leishmania amastigotes have been reported to induce improvement in psoriasis patients. It has been suggested that vaccines, targeting molecules in the immunopathogenesis of psoriasis, may be a new treatment option for psoriasis patients without any serious side effects. However, induction or worsening of the psoriasis and psoriatic arthritis followed by some vaccines (e.g., influenza, rubella, tetanus, BCG) has also been reported in the literature. In this review, we focus on the vaccines in psoriasis in terms of their both triggering and therapeutic effects.

Keywords: psoriasis, antimicrobial vaccination, recommended vaccines, triggering vaccines, therapeutic vaccines

1. Introduction

Psoriasis is a chronic, immune-mediated disease with a prevalence of 2–3% in adult population. Psoriatic arthritis affects approximately 11% of psoriasis patients, and cardiovascular disease is increased [1]. Psoriasis disease is caused by the interactions of genetic background with various environmental triggering factors. HLA-Cw6 allele in PSORS1, the most associated

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gene with psoriasis, encodes a major histocompatibility complex I allele that is the major factor for antigen presentation of intracellular peptides to the immune system [2].

Several environmental factors, such as trauma (Koebner effect), infections, obesity, smoking and some medications, play a role in the onset of psoriasis. Guttate psoriasis is related to streptococcal throat infections as two-thirds of patients have a history of throat infection nearly 2 weeks before the eruption [3, 4]. A homology between streptococcal M protein and human keratin 17, which is upregulated in the skin of psoriasis, has been reported. In the basis of this finding, T-cells cross-reacting with human keratin and streptococci have been detected in HLA-CW6-positive psoriasis patients, raising the possibility that psoriasis is an autoimmune disease [5].

In the initial phase of the disease, certain dendritic cell (DC) populations such as plasmacytoid DCs (pDC) and dermal myeloid DCs are activated and produce the key psoriasis effector cytokines IL-12 and IL-23. Self-DNA or self-RNA from damaged keratinocytes and the antimicrobial peptide LL37 stimulate pDCs, through Toll-like receptor (TLR) 9 or TLR7/8 and IFN-alpha production is triggered. The stimulation of pDCs is followed by differentiation and activation of myeloid DCs, which express cytokines IL-12, tumor necrosis factor (TNF)-alpha, TGF-beta and IL-6. These cytokines induce T-cells to polarize into Th1 and Th17 subtypes, with suppressing of regulatory T-cells [1, 2, 6, 7]. CD4+ T-cells secreting IL-17 are classified as a different T-helper population called Th17 cells, which are critical in psoriasis pathogenesis. Th17 cells produce IL-17A and IL-17F, and Th1 cells produce TNF-alpha, IFN-gamma, IL-12, IL-22 and IL-23 that promote the pathological changes in psoriasis skin lesions [2, 8].

For psoriasis patients with localized disease, topical treatments including corticosteroids, vitamin D derivatives, tazarotene, anthralin, tar, calcineurin inhibitors, keratolytic agents and urea are the first-line therapy [9]. Phototherapy is a mainstay option particularly for patients resistant to topical treatments with widespread disease [10]. In cases with moderate-to-severe psoriasis resistant to any of these treatments, conventional systemic therapy is done with methotrexate (MTX), cyclosporine, fumaric acid esters and acitretin. In patients who have failed to respond to conventional systemic therapies and phototherapy or the person is intolerant to, or has a contraindication to these treatments, biologic immunotherapy is used. There are several agents such as TNF-alpha inhibitors (etanercept, infliximab and adalimumab) and ustekinumab that are available in the treatment of psoriasis [11].

Vaccination is a proven way of reducing the incidence of serious or life-threatening infectious disease in general population and in patients with immune-mediated inflammatory disease. Vaccines are recommended for psoriasis patients due to their susceptibility to infections [12]. The data emphasize that especially some types of vaccines may trigger an exacerbation of psoriatic skin lesions or induce improvement in psoriasis [1, 13].

In this review, we aim to summarize the vaccines in psoriasis in terms of their both triggering and therapeutic effects.

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2. Vaccines recommended for psoriasis patients

Patients diagnosed with psoriasis are at risk of infections owing to the nature of disease and immunosuppressive therapies [12, 14]. Therefore, the medical board of the National Psoriasis Foundation recommends vaccinations in compliance with recommendations of the Advisory Committee for Immunization Practices to prevent infections [12]. Types of vaccines can be categorized as live and inactivated vaccines (**Table 1**) [12, 14].

Live vaccines, which contain attenuated natural pathogens, are contraindicated in immunocompromised patients and should be given 2 or 4 weeks before the immunosuppressive therapy. Additionally, immunosuppressive medications should be stopped generally 3 months before the immunization with live vaccines [12, 14]. However, a few reports suggest that some live vaccines such as yellow fever vaccine in patients receiving MTX may be safe [15]. More research is needed for safety of live vaccines in immunocompromised patients [12, 15]. Inactivated vaccines are safe for patients on immunomodulatory therapy due to their noninfectious content but vaccine response may be suboptimal [12, 14, 16]. It has been reported that the antibody response ratio following seven-valent conjugate pneumococcal vaccination was significantly higher in controls when compared to patients treated with MTX or MTX combined with TNF inhibitors. On the other hand, in the same study, patients treated with TNF inhibitors as monotherapy had numerically lower but not significantly different antibody levels, compared to controls [17]. In a study, ustekinumab did not impair the immune response to pneumococcal and tetanus toxoid vaccines in psoriasis patients [18]. In another study, efalizumab caused a nearly threefold decrease in the antibody response to tetanus toxoid vaccine while not changing the immune response to pneumococcal polysaccharide vaccine [19]. Immune responses to pneumococcal polysaccharide vaccine in patients with chronic plaque psoriasis treated with alefacept were similar to those seen in healthy subjects [20].

Inactivated or inert vaccines	Live vaccines
Salk poliomyelitis vaccine	Vaccinia/smallpox
Most influenza vaccines (injectable)	Rotavirus
Hepatitis A	Measles-mumps-rubella
Hepatitis B	Yellow fever
Human papillomavirus	Oral poliomyelitis
Diphtheria-tetanus-pertussis	Varicella zoster vaccine
Haemophilus influenza type b conjugate vaccine	Herpes zoster
Pneumococcal	Intranazal influenza virus
Meningococcal	BCG
Rabies	Oral typhoid
Parenteral typhoid	
Anthrax	
Japanese encephalitis	

Table 1. Types of vaccines.

In a study assessing the seasonal 2012 influenza vaccination among patients with psoriatic arthritis and psoriasis, usage of TNF-alpha blockers or disease-modifying antirheumatic drugs did not affect the response rate [21]. Annual immunization with inactivated influenza vaccine is recommended for psoriasis patients on immunosuppressive treatment due to high mortality rates of seasonal influenza [12, 22]. In a French study on 1308 psoriasis patients, Sbidian et al. reported that 19% of patients received the 2009 monovalent H1N1 vaccine. Only 33% of the patients treated with biologics were vaccinated [23]. The vaccination rate of influenza vaccine in 2010/2011 was found 28% among 1299 patients with psoriasis or psoriatic arthritis in Germany. Thirty-eight percent of the patients were on biological therapy at the time of vaccination [22]. Despite the recommendations, the vaccination coverage was low in psoriasis patients in both studies [22, 23].

Zoster vaccine, a live attenuated vaccine, is recommended for use in immunocompetent individuals 60 years of age or older to reduce the risk and severity of herpes zoster (HZ) [12]. Increased incidence of HZ has been reported in psoriasis patients receiving combination treatment with biologic medications and MTX while biologic or systemic agents as monotherapy did not increase the risk of HZ [24]. Zhang et al. reported that zoster vaccination was not related to increased risk of HZ in patients with immune-mediated disease including psoriasis under biological therapy [25, 26]. However, it was emphasized that infliximab increases the risk of HZ in most of the cohort studies while the risk of HZ in patients receiving etanercept, adalimumab or ustekinumab therapy is not clear [27]. Yun et al. indicated that the use of biologic agents and systemic steroids in patients with autoimmune and inflammatory diseases increased the risk of HZ [28]. Consequently, HZ vaccination should be considered for patients who are going to receive biological agents especially infliximab and combination treatment with MTX therapy. Additionally, the vaccine should be administered before initiation of the immunosuppressive therapy [24, 27].

As a conclusion, it has been reported that immunization status, including *Haemophilus influenza*, hepatitis A and B, human papillomavirus, influenza, *Neisseria meningitides* and *Streptococcus pneumoniae* should be assessed in all patients with moderate-to-severe psoriasis [12]. Recommendations for vaccination of patients diagnosed with psoriasis are given in **Table 2** [12, 14].

Type of vaccine	Before therapy	On therapy
Inactivated vaccines		
Influenza	Vaccinate with inactivated or live attenuated vaccine	Annual inactivated influenza
Human papillomavirus	Recommended for male and female < age 26 years	Same
Hepatitis A	For selected individuals at high risk (diabetes, liver disease, injecting drug users, homosexual men, employees or residents in institutional settings)	Same, test for serology after vaccination
Hepatitis B	For individuals at high risk and without evidence of disease and immunity	Use high-dose vaccine, test for serology after vaccination
Pneumococcal	Immunization with 23-valent pneumococcal polysaccharide vaccine	Immunization with 13-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide vaccine if not given prior

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Type of vaccine	Before therapy	On therapy
Haemophilus influenza type b	Unvaccinated individuals can be vaccinated	Same
Diphtheria-tetanus-pertussis	Booster is recommended every 10 years and for high-risk wounds, offer before therapy	Same
Meningococcal	For selected individuals at high risk (asplenia, complement deficiency, group living situation)	Same
Poliomyelitis	For selected individuals at high risk (healthcare workers or laboratory personnel)	Same
Live vaccines		
Varicella zoster	Test for serology before initiation of therapy, if negative, offer vaccination	Contraindicated
Herpes zoster	1 dose for adults ≥50 years	Contraindicated
Measles-mumps-rubella	Assessment of immunization by history and serology before initiation of therapy, if negative, offer vaccination	Contraindicated

Table 2. Recommendations for vaccination of patients diagnosed with psoriasis before or on systemic immunosuppressants.

3. Triggering effect of vaccines on psoriasis

As mentioned above, basis on a genetic predisposition, various environmental factors may cause development of psoriasis in patients who are in latent period. Physical or chemical factors, infections and various types of medications are the most important among these, and they may affect the course of psoriasis by many different mechanisms [13]. Triggering vaccines on psoriasis and psoriatic arthritis are summarized below.

3.1. Koebner effect

Various types of skin trauma with subsequent development of new psoriasis lesions about 10 days later are known as 'Koebner-phenomenon' [29]. In a study evaluating the relation between 'Koebner-phenomenon' and intradermal antigens, 30 psoriasis patients and 20 control subjects were firstly determined for Koebner status and then were tested with intradermal injections of purified protein derivative, Candida, mumps, mixed respiratory vaccine and saline control solutions. Two psoriasis patients were Koebner positive and developed psoriasis at all five injection sites. Besides, in five Koebner negative patients, local psoriasis lesions were observed in at least one injection site of different antigens. These findings were interpreted that some psoriatic patients may have individually specific sensitivity to different antigens to trigger the cellular immune response in psoriasis [30].

Additionally, in a recent placebo-controlled study, evaluating the 'nontypeable Haemophilus influenza protein vaccine', a psoriasis case was reported to be associated with injection of saline placebo at 114 days post-dose 3 in the placebo group indicating the Koebner effect [31].

3.2. BCG vaccination

BCG is a live attenuated strain of *Mycobacterium bovis*, which has been used as local immunotherapy for bladder cancer since 1976 [32]. In 1955, a psoriasis case was described following BCG vaccination under the name of 'psoriasis vaccinalis' [33]. A male with psoriatic arthropathy after BCG immunotherapy for bladder carcinoma and a psoriasis case after BCG vaccination are the other early reports associated with BCG vaccination [34, 35]. Koca et al. also defined a 7-year-old boy with guttate psoriasis-like lesions developed 1 week after the BCG vaccination [35]. Takayama et al. presented a 6-month-old girl with psoriatic skin lesions initially appeared on the vaccination site 1 month after the BCG vaccination. In that case, expression of activated phospho-Stat-3 was found in the epidermal keratinocytes of the lesional skin. Mycobacterial heat shock proteins have been reported to stimulate IL-6, which promotes the development of Th17 cells. Thus, the authors speculated that BCG vaccination might mediate the generation of IL-22-producing Th17 cells and lead to activation of epidermal Stat-3 and psoriatic skin lesions [36]. In addition, an 80-year-old man with bladder carcinoma was reported with erythrodermic pustular psoriasis triggered by intravesical BCG immunotherapy. The similar mechanism with Th1 and Th17 cells generation after BCG vaccination was thought to play an important role in the pathogenesis of psoriasis [32].

3.3. Tetanus-diphtheria (Td) vaccination

A case of 50-year-old psoriasis patient in remission was described as guttate psoriasis 1 week after the Td vaccination [37]. Td vaccine has shown to induce IL-6 production, which stimulates Th17 cells, having a key role in psoriasis pathogenesis [37, 38]. It was suggested that this mechanism was the triggering cause in this case [37]. In a case-control study evaluating the potential risk factors for the onset of psoriatic arthritis, exposure to rubella (OR = 12.4, 95% CI = 1.2–122.14) and tetanus (OR = 1.9, 95% CI = 1.0–3.7) vaccines was reported at a higher frequency in psoriatic arthritis group as compared to the psoriasis group without arthritis [39].

3.4. Influenza vaccination

Shin et al. described a 26-year-old woman with multiple erythematous scaly macules scattered on the extremities and trunk compatible with guttate psoriasis following injection of an inactivated split-virus influenza A/H1N1 vaccine without adjuvant [40]. Güneş et al. reported 43 patients suffering from psoriasis in that 36 of them had exacerbation of pre-existing psoriasis while disease first appeared in the remaining seven patients after influenza vaccination in the 2009–2010 season. Thirty-seven of these patients had mixed plaque type and guttate psoriasis, three of them suffered from palmoplantar psoriasis, and another three of them had scalp psoriasis. Although there is the lack of control group and follow-up evaluations in that study, they suggested that their observations may support the association between influenza vaccination and the development of psoriasis due to the short-time onset of psoriasis after vaccination and the lack of other possible triggers [13].

There is also a cross-sectional study investigating a total of 1125 cases for the onset or flare of psoriasis occurring within 3 months following the 2009 monovalent H1N1/seasonal vaccination

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through a national survey in France. The overall influenza vaccine coverage was found 19% in this population. Ten patients were reported with a psoriasis of new onset (n = 7) or with a worsening of previously diagnosed psoriasis (n = 3) within a median time period of 8 days after vaccination. Due to the uncertainties about the actual number of psoriatic patients undergoing vaccination, underestimation of the incidence due to underreporting and underdiagnosis and the lack of control group, the data could not provide a definitive conclusion about an association between vaccination and the psoriasis. However, the authors claimed that even if it is not a very strong risk, influenza vaccination is associated with psoriasis flare [41].

In another study, the effects of seasonal influenza vaccination in psoriatic arthritis patients under anti-TNF-alpha therapy were evaluated. 1 month after the vaccination (T1), patients (n = 25) had statistically significant increase in tender joint count (TJC) (p = 0.009) and erythrocyte sedimentation rate (ESR) (p = 0.046) as compared to baseline. Statistically significant difference was observed only in TJC (p = 0.01) 3 months after the vaccination (T3). Additionally, vaccinated patients showed a significant increase in TJC (p = 0.004), ESR (p = 0.007), Health Assessment Questionnaire (p = 0.023), patient global assessment (p = 0.013) and physician global assessment (p = 0.026) when compared to nonvaccinated patients (n = 25) at T1. At T3, similar findings were observed for only ESR (p = 0.006) and physician global assessment (p = 0.013) when data were analyzed between two groups. In conclusion, the authors suggested that influenza vaccine may have a short lasting triggering effect on psoriatic arthritis patients [42].

3.5. Adenovirus vaccination

In a retrospective study, which evaluated the possible side effects related to adenovirus types 4 and 7 in military recruits, psoriasis (21 versus 7 cases) was found more frequently (RR = 2.44, 95% CI = 1.13–5.31) in the vaccinated group (n = 100,000) when compared to unvaccinated group (n = 100,000) [43].

4. Therapeutic effects of vaccines on psoriasis

Both conventional systemic treatments and biologic agents are related to serious side effects. The biologic immunotherapy agents act by inhibiting over-expressed T-cell activity by reducing T-cell numbers, T-cell trafficking or immune deviation and blocking the activities of proinflammatory cytokines, which may lead to severe infections, myelodegenerative and autoimmune disorders [29]. Additionally, over the past few years, various John Cunningham virus (JCV) associated brain syndromes have been reported as a result of increased usage of the immunomodulatory medications [44]. The progression in the enlightenment of the immunopathogenesis of psoriasis may provide new therapeutic options that do not have immunosuppressive side effects. Vaccination is a progressing therapy option for psoriasis and the other chronic inflammatory disorders such as multiple sclerosis, rheumatoid arthritis and atherosclerosis, which are termed as noncommunicable diseases [1, 45, 46]. It has clearly demonstrated that vaccines have the ability to activate effectors such as dendritic cells and T lymphocytes, which are also

involved in psoriasis pathogenesis [41]. Noncommunicable disease vaccines target cells, proteins or other molecules that are related to these disorders and modulate the immune system, similar to traditional vaccines [45].

Approximately two-thirds of guttate psoriasis patients and a quarter of chronic psoriasis patients have an association with streptococcal throat infections. Fry et al. claimed that vaccination against Streptococcus pyogenes as well as the other possible microorganisms that trigger psoriasis may be a new way to prevent psoriasis [3, 4]. It has also been suggested that psoriasis may benefit from development of a T-cell receptor peptide vaccine [47].

As we mentioned before, IL-17 has been shown to play an important role as a proinflammatory cytokine in psoriasis. IL-17 is demonstrated as a 'target antigen' for the treatment of autoimmune disorders and psoriasis in preclinical experiments in animal models and in clinical trials [48]. Dallenbach et al. showed that immunization with Qβ-IL-17, a virus-like particle-based vaccine, generated IL-17-specific IgG in mice. In order to evaluate the role of hypermutation and affinity maturation, they mutated the hypermutated antibody back to germline sequence, producing a set of two antibodies with VH regions differing in three aminoacids, but recognizing the same epitope. They showed that both the hypermutated and the germline antibody significantly neutralized IL-17 and blocked its biological activity *in vivo*. They also demonstrated that both antibodies were able to reduce imiquimod-induced psoriatic skin inflammation, indicating that vaccination against IL-17 may be a new therapeutic option for psoriasis [49].

Over-expression of ß-defensin 2, known as a skin antimicrobial peptide, has been reported to be associated with psoriasis [50]. In a recent study, serum ß-defensin 2 levels have been found to correlate with IL-17A levels and psoriasis area severity index (PASI) scores in psoriatic patients [51]. Additionally, García-Valtanen et al. demonstrated that ß-defensin 2 improves the DNA vaccine efficacy due to its adjuvant-like effects besides its antiviral and immunomodulatory properties in a study of zebrafish. They claimed that this psoriasis-related peptide might be used as an adjuvant in DNA vaccination to improve the efficacy of viral vaccines [50].

The TNF-alpha-induced protein 3 (TNFAIP3) is an anti-inflammatory factor that inhibits NF-κB activation in T-cells. In a few studies, it was reported that expression of TNFAIP3 mRNA was significantly higher in patients with mild psoriasis than in the patients with severe psoriasis, suggesting that TNFAIP3 gene may be a 'target' molecule for psoriasis therapy [52, 53]. There are also reported studies, which are mentioned below, about the usage of vaccines on psoriasis.

4.1. Mycobacterium vaccae

Mycobacterium vaccae, a nonpathogenic organism usually applied as a heat-killed suspension, has been used as an adjunct immunotherapy for tuberculosis and leprosy [54]. The immunotherapy trials began after discovery of the therapeutic effect of *M. vaccae* injection in psoriasis skin lesions of leprosy patients with concomitant psoriasis [55].

A placebo-controlled study in patients with chronic plaque psoriasis evaluated the potential beneficial effects of *M. vaccae* immunotherapy. The study group of 31 patients received a dose of *M. vaccae*, and placebo group of 24 patients were given a dose of tetanus toxoid. The mean PASI values at both 3 and 6 months for the *M. vaccae* group were significantly lower than their

entry values ($p < 0.001$ and $p < 0.005$), while the tetanus toxoid group did not reach this significance at any time. The failure of the patients to return for follow-up visits and the selection of tetanus toxoid as a placebo were the problems of the study. In spite of these limitations, the authors claimed that the study showed a significant improvement ($p < 0.005$) in the PASI after a single injection of *M. vaccae* [56]. A subsequent study of 24 patients, PASI scores of whom showed significant reduction ($p < 0.001$) at 12 and 24 weeks in comparison with the initial PASI score after two intradermal inoculations of *M. vaccae*, confirmed these findings [56].

A study performed on 36 patients with psoriatic arthritis randomized the patients to receive two intradermal injections of 50 μg delipidated, deglycolipidated *M. vaccae* (PVAC) or placebo and followed up them for 24 weeks. The psoriatic arthritis response criteria at either 12 or 24 weeks were achieved by 50% (9/18) in both placebo and PVAC group. There was only a significant change in the visual analogue scale over time between the two groups. The mean score had decreased by 19.2 mm in the PVAC group and increased by 4.8 mm in the placebo group ($p = 0.006$). Consequently, the authors claimed that PVAC was not an effective immunotherapy for psoriatic arthritis [57]. Likewise, a placebo-controlled study did not show a clearly efficacy of PVAC in the treatment of psoriasis patients, because 75% PASI was similar among the studied groups at week 12 [55].

Mycobacterium w is a nonpathogenic, rapidly growing, cultivable strain of atypical mycobacteria and has been used as an adjuvant immunotherapy for leprosy, tuberculosis and human immunodeficiency virus, like *M. vaccae* [58]. The efficacy of Mycobacterium w in psoriasis was also evaluated by some trials [58, 59]. In a study of 36 psoriasis patients, 24 of them were in the study group and received two doses of 0.1 ml of heat-killed Mycobacterium w at 3 weekly intervals. The remaining 12 patients in the control group were given of normal saline at the same weeks. The study showed marked improvement (>50% reduction in PASI score) in the four of 24 cases (16.6%) and moderate improvement (25–50% reduction) in 15 cases (62.5%) at the end of the 4 months. No improvement was seen in the 4 of 24 patients, and the disease got worse in 1 patient. There were no significant side effects, although five patients had new lesions at the site of injection [59]. On the other hand, in another study that included 45 psoriasis patients who received a total of four doses of Mycobacterium w, the percentage reduction of PASI score was only 33% at the end of 12 weeks. Additionally, at the beginning of the study, PASI scores showed increase in nine patients, four of whom were severe and received an alternative therapy [58]. The results were in contrast to findings of the prior study by Rath et al. [58, 59].

The mechanism of mycobacterium immunotherapy leads to improvement in psoriasis is not known exactly. Lehrer et al. suggested that the decreasing effect of TNF-alpha might cause clinical improvement in psoriasis patients treated with *M. vaccae* immunotherapy [56]. According to Dalbeth et al., increased IL-10 levels after the PVAC injection may lead to improvement in psoriasis due to inhibition of T-cell function and reduction of IFN-gamma and TNF-alpha production [57].

4.2. Leishmania amastigotes

In a trial about a vaccine for cutaneous leishmaniasis, O'Daly et al. observed 100% clinical remission of a psoriatic lesion in one patient after third vaccination. After this discovery,

they performed an open-label, single-center study to evaluate the leishmaniasis vaccine (AS100®) in 2770 psoriasis patients. When baseline PASI values were compared with the post-treatment values, PASI 100 was achieved in 23%, PASI 75 in 45%, PASI 50 in 13%, PASI 10 in 9% and <PASI 10 was determined in 3% of patients. The most common adverse effects were pain and nodule formation, which were injection side related. The other systemic adverse effects were considered as mild and moderate in severity. Similar results were observed in a second, double-blind, placebo-controlled study, performed by the same group [60]. In a subsequent study, O'Daly et al. evaluated further purified vaccines, resulting in seven chromatography fractions per four Leishmania species. They suggested that three fractions from *L. brasiliensis* and four fractions from *L. chagasi* demonstrated the maximal therapeutic effect on psoriasis [61]. O'Daly et al. also revealed that regarding to PASI values, certain lymphocyte subtypes decreased in peripheral blood cells suggesting migration from the blood to the skin while others increased suggesting activation by unknown antigens. After injection seven doses of AS100 vaccine, lymphocyte subtypes CD3+CD8−, CD8+CD3−, HLA+CD8−, CD8+HLA+ and CD4+CD8− increased as PASI values decreased and clinical improvement was seen, while CD8+CD3+, CD8+HLA−, CD19 and CD8+CD4+ decreased in peripheral blood cells. These results suggested that treatment with Leishmania antigens leads lymphocytes to traffic between blood and skin and activates T-cells in skin plaques, contrary to current treatments killing T-cells in psoriasis patients [62]. Another open-label, single-center study conducted by O'Daly et al. showed clinical remission in patients with psoriatic arthritis after the average number of 9.9 ± 4.8 doses of AS100 treatment [63].

4.3. Live attenuated varicella vaccine

A placebo-controlled study was conducted by El-Darouti et al. to evaluate the adjuvant effect of live attenuated varicella vaccine (Varilrix®) in patients with resistant severe psoriasis after their observation of improvement in one patient with severe psoriasis following a chickenpox infection. Study group received four doses of Varilrix® once every 3 weeks before low-dose cyclosporine (2.5 mg/kg/day) while control group received four doses of subcutaneous saline as placebo. Study group demonstrated significantly higher improvement in their PASI values. According to El-Darouti et al., the hypotheses explaining the mechanism of live attenuated varicella vaccine on psoriasis are given as below [64]:

- The stimulating effect of varicella zoster virus on the humoral response by Th-2 cells and subsequent downregulation of the Th-1 response,
- The inhibitory effect of IFN-alpha on Th-17 cells by peripheral blood cells exposed to varicella zoster virus antigen,
- The upregulation of regulatory T-cells that have inhibitory effects on psoriasis after receiving varicella vaccine.

Subsequently, El-Darouti et al. reported that live attenuated varicella vaccine is effective in psoriasis when used with low-dose cyclosporine by acting possibly on the Th17/ regulatory T-cells balance [65].

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5. Conclusion

Vaccination is an effective tool for reducing the incidence of serious or life-threatening infectious disease [45]. Patients diagnosed with psoriasis are at risk of infections due to the nature of disease and immunosuppressive therapies [12, 14]. For this reason, the medical board of the National Psoriasis Foundation recommends vaccination for patients diagnosed with psoriasis in compliance with recommendations of the Advisory Committee for Immunization Practices [12]. Besides, vaccines such as *M. vaccae*, live attenuated varicella zoster virus and Leishmania amastigotes have been reported to be effective in the treatment of psoriasis. Vaccines, regulating the inflammatory response in psoriasis, may be a new therapeutic option for psoriasis patients without any serious side effects. On the other hand, the data emphasize that especially some types of vaccines may trigger an exacerbation of psoriatic skin lesions. The very low incidence of psoriasis following vaccination reveals the safe profile but some authors recommend the follow-up of such individuals [13]. Further large-sized and controlled clinical research studies need to be carried out to confirm the relationships between psoriasis and the vaccination.

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