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Scabies Vaccine as a New Breakthrough for the Challenge of Acaricides Resistance

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ABSTRACT
Scabies is first recorded as far back as 2500 years ago and considered as an ancient disease. It affects around 300 million people every year around the world, and its prevalence is as high as around 60% in children. Several amount of drugs have been used for the disease treatment, but conventional therapy become resistant throughout the year and it keep increasing. *Sarcoptes scabiei* mites are able to develop new means to avoid newer therapies. Hence, in order to eradicate them, radical solutions such as vaccination, are required. The treatments currently available for scabies can cause problems due to side effects and maybe the risk of treatment failure. The available coping methods like treating diagnosed individuals are ineffective and impractical. Resistance to mites and consumer rejection of livestock products containing drug residues are aggravating issues. Although there may be potential for immunological control, vaccine development or other immunotherapy modalities may be several decades away. The current therapy has faced some rising serious concerns such as developing resistance to classical scabicides among scabies mites and the ineffectiveness of current treatments associated with scabies (in suppressing skin inflammatory reactions and secondary bacterial infections). Treatment adherence difficulties, and the uncertainty of safety and efficacy in young and elderly, makes necessary to identify new treatments for scabies. Vaccination is the best alternative way because it is safe for the environment and consumers, and potentially more effective and inexpensive.

Keywords: *disease, immunodiagnostic, immunotherapy, scabies, resistance*

1. INTRODUCTION

Scabies emerged 2500 years ago and currently attacks 300 million people every year worldwide. *Sarcoptes scabiei* is a mite that causes scabies, attacks humans and at least 40 animal species. Losses caused by this disease is a form of public health problems and at the same time may lead to economic losses, which indicated by a high prevalence. The treatment methods available for treating diagnosed individuals are ineffective and impractical. The list of tropical diseases has been ignored by the World Health Organization (WHO). Effective control is performed on patients who have been infected with scabies by paying attention to the contact of the patient and his environment. However, control is difficult to achieve because of inaccuracies in diagnosis, inappropriate application of drugs, inadequate care, or poor patient compliance. In addition, dissatisfaction is also increasing due to the development of resistance to mites and consumer rejection of livestock products containing drug residues [1, 2].

Vaccination is the best alternative, but the availability of scabies vaccine still requires a very long process. Scabies is believed to be controlled by vaccination because animals recovering from scabies have immunity to mite reinfestation because mites internalize their host's immunoglobulin. The identification of protective antigens in scabies mites, which is the first step in making a vaccine, is constrained because of the protective nature of the unstable antigens and their very low concentration, and the difficulty of getting mites in sufficient quantities.

In this paper, we focus on the challenges in treatment with resistance that arises among scabies mites, and the need for further research to prophylactic scabies in the form of scabies vaccine.

1.1. Materials and Methods

This paper was synthesized by using a library comparison approach. Library research method was carried out in this paper. Several journals, books, both printed and electronic documents, and other sources and/or information that relate to the research was analysed and explored to collect the data. According to the generation assumptions, this paper collects from several literaturs that discusses the handling of scabies and emerging resistance. After that, we examined several studies about making vaccination in

several experimental animals. The conclusion assumptions were taken subjectively.

1.2. Our Contribution

The paper presents a new breakthrough to overcome acaricides resistance. Scabies vaccine is expected to challenge and reduce the global prevalence of scabies. This is based on some literature that can be implemented for benefits of human. Vaccination is the best alternative way because it is safe for the environment and consumers, and potentially more effective and inexpensive.

1.3. Paper Structure

The rest of the paper is organized as follows. Section 1 introduces treatment methods available for treating individuals diagnosed with scabies as ineffective and impractical. Section 2 explains the development of immunodiagnostics, vaccines and immunotherapy as a promising long-term strategy for controlling scabies in the concerned areas globally. Section 3 concludes that vaccination is the best alternative method because it is safe for the environment and consumers, and potentially more effective and inexpensive.

2. RESULTS AND DISCUSSION

2.1. Immune Response Mechanism

There are several recommendation options of scabies treatment that have been thoroughly discussed in the Cochrane review 2010 (The Cochrane Library 2010, Issue 2) to control the disease. The use of ivermectin has been experimented in the mass drug administration (MDA) program to control scabies in democratic communities globally [3]. For the last few years, scabies incidence in Germany has been diagnosed in a surprisingly frequent number, and acaricides use has risen immensely. Observations of ineffective treatment with permethrin are thought to be the cause of Sarcoptes mites developing resistance to this particular drug. [4].

On Figure 1, the mechanism of immune response to this mite infestation was revealed. Proinflammatory cytokines such as TNF-α, IFN-γ, TGF-β, IL-1β and IL-23 are secreted upon the respond of keratinocytes, langerhans cells and macrophages in the skin to mite antigens. This eventually caused the differentiation and recruitment of CD8+ T and CD4+ Th1 and Th2 cells into the skin. The differentiation of Th17 or Tc17 cells and IL-17 production are promoted upon cytokine milieus of IL-6, TGFβ and IL-23 secretions. IL-17 production by γδ T cells have also encouraged firmly by the roles of IL-23 and IL-1β, and their increased expression observed in CS may act in an amplification loop for IL-17 production, promoting inflammation and aggravating immune pathology. Tregs are induced by TGF-β and IL-2. The production of IL-10 and TGF-β by Tregs

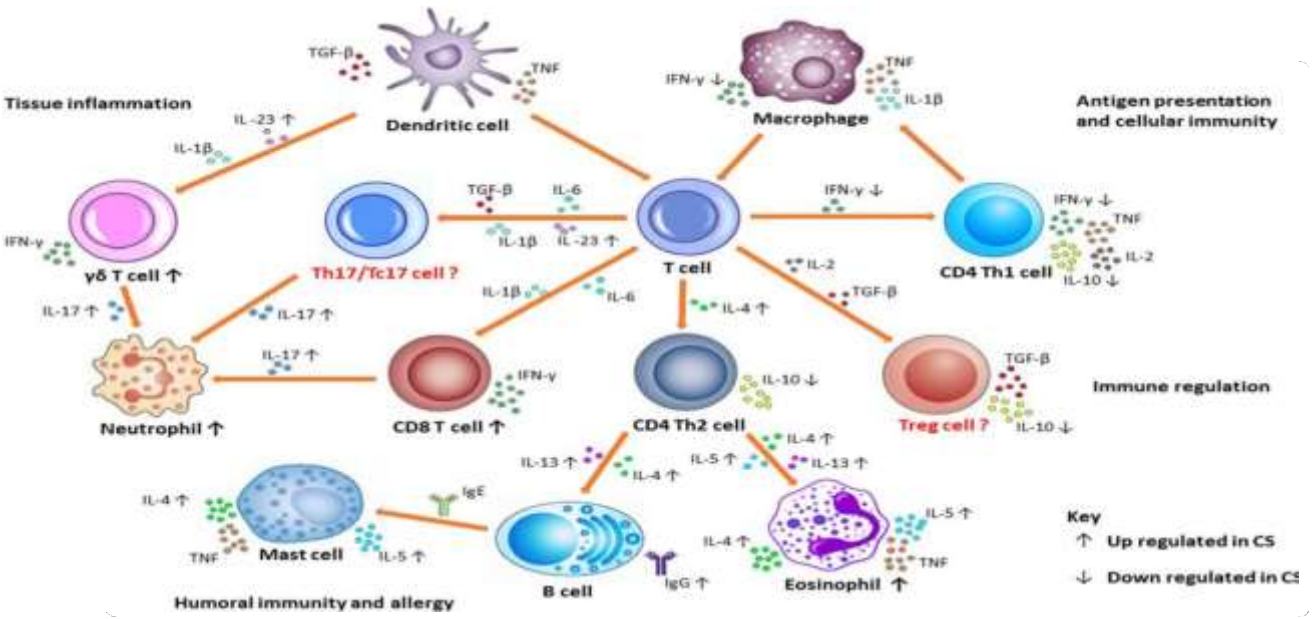

Figure 1 Current knowledge on immune mechanisms in scabies: The figure shows possible mechanisms of immune responses to scabies mite infestation (Source: [5])

may have had involvement in holding inflammatory response in scabies and suppress pathological inflammation in ordinary scabies, regulating innate and adaptive responses. Strong IFN-γ secretion in response to mite antigens indicates that immune responses to ordinary scabies appear to be Th1 oriented. A large amount of IgE and IgG secretions are resulted from immunoglobulin switching in B cells upon induced by the rising expression of the Th2 cytokines IL-4 and IL-3 in CS. IL-5 activates and promotes the maturation of eosinophils at the site of infestation, sustaining the local Th2 inflammatory responses. Mast cells are activated through IgE high-affinity receptor (FcεRI). These cells produce inflammatory mediators such as TNF, histamine, leukotrienes, IL-4, IL-5 and IL-13, supporting their involvement to allergic inflammation in CS. Cells highlighted in "red" and with "?" are not yet defined in scabies [5].

Permethrin resistance spread extensively to other ectoparasites. There have been reports regarding the increase of acaricide resistance that causing treatment failure. For the past 10 years, in vitro sensitivity data from Australian data of scabies mites show that the average survival time for leading acaricides (ivermectin and permethrin) has increased 2-3 folds. Acaricide is one that work the slowest (in vitro) in the Northern Territory, Australia according to the documentation of each failure case of permethrin treatment as a scabicide in the Indigenous community in Australia (after MDA) and elsewhere. Permethrin resistance to scabies mites has been confirmed in animal models and the possibility of any resistance mechanisms have also been recorded [6]. In Australia, *Sarcoptes scabiei* resistance to ivermectin in vitro and in vivo have been reported since the first case in 1994, as well as the record of treatment failures in clinical trials. Oral administration of ivermectin has been used since the 1980s (for mass treatment of onchocerciasis, and filariasis); the treatment for particular scabies is disapproved elsewhere but Japan, Brazil, France; only indicated if symptoms persist 3 weeks after the application of benzyl benzoate or permethrin; no ovicidal activity, hence repeated treatment is required; one report increased mortality among elderly patients during outbreaks of scabies in institutional settings on 1997. The lack of other studies that replicate this finding lead to the amount of criticism regarding the credibility of this report. MDA programs that encounter poor adherence increase the risk of developing resistance and targeted treatment for cases and contact indexes might be a better approach [7].

2.2. Vaccination

Sarcoptes scabiei mites can develop new ways to avoid newer therapies. Therefore, radical solutions, such as vaccinations, are needed to eradicate them. Many reports have been confirmed concerning immune animals after a past attack as it is known that the second infection is often milder than the first, hence vaccines might be effective. The data indicate that in order protective immunity to occur, vaccine that triggers type 1 T (Th1) response is needed, although the host immune response that targets mites is not yet fully grasp as of today. Antibodies (IgG, IgM, and IgE) are increased both in ordinary scabies (OS) and CS, although CS's is higher. Moreover, the total of IgA is also increased in CS but decreases in OS. In one report, goats with soluble *S. scabiei* protein produced specific IgG scabies in high level, although these goats could be exposed to reinfestation. In another report, high level of specific IgG and IgE were found in goats with previous infestation and they were resistant to reinfestation. Therefore, it is thought that the abundance of specific IgE might be an indicator of immunity, despite CS patients do not have protective immunity although they have very high IgE levels [8, 9].

Acaricides can be used for scabies treatment but they have developed a significant resistance and thus treatment failure to occur. In addition, the toxicity effects of these chemicals' unknown to humans and animals. Thus, vaccination for protection against infection by scabies mites is an attractive alternative to chemotherapy currently available. Vaccination against *S. scabiei* mites is a rational plan supported by several reasons. Scabies mites induce innate and adaptive immune responses in parasitized hosts. Adaptive responses involve the production of IgM, IgG and in some human hosts IgE and isotypes of IgA antibodies for antigens that are released by mites in the epidermis while they hide. Mites ingest serum antibodies as they dig and feed the lower epidermis as several reports mention that serum is a part of their diet. Systemic acaricides, like ivermectin, works by possibly swallowed by mites and resulted killing the mites on the skin. A study using antibodies labelled fluorescence showed that host antibodies were bound to the intestinal lining of live mites removed from the host. Stem antibodies that bind to intestinal cell molecules and digestive enzymes produced by these cells which are very important for the digestion and absorption of nutrients can inhibit this process and thus prevent the survival of mites. Likewise, host antibodies directed at molecules from mites that are very important to suppress host protective responses will inhibit the ability of mites to survive and form populations on the host skin because the host can now mount a successful protective response. Other revelation shows that vaccination can form protection against scabies mites. On the second infection the development of host antibody titters are faster and greater than those on the initial infection with scabies mites. In the following reinfection, the mites' level on recovering animals from scabies mite infection are decreased [10].

It was revealed by Arlian *et al.* that 8 dogs recovered from *S. scabiei* and they showed protective immunity after they were re-infused. As many as 7 of those dogs experienced short-term infections and recovered after some times without treatment. Rabbits have also been immunized with *S. scabiei* var's whole-body extract. Canis produces antibodies to more antigens than rabbits infected with this mite. The results of several vaccination tests have been published [11]. Tarigan *et al.* evaluated the protective effect of goat vaccination using fresh extracts from the whole body of scabies mites collected. Although it has been

known that protective immunity could develop in a *S. scabiei* infested animal, the attempt employed to goat by vaccinated them using fractions of soluble or insoluble mite proteins to induce their protective immunity was unsuccessful. Thus, indicates that the protective antigens of *S. scabiei* are prone to degradation or denaturation and have a very low concentration or antigenicity. After exposed with *S. scabiei*, 74.3% (26/35) of rabbits vaccinated with rSsCLP5 showed no indication of lesions [12]. From the data, it is demonstrated that rSsCLP5 is a quite suitable for a recombinant protein-based vaccine against *S. scabiei*. This study also provides a method for studying scabies vaccine using the rabbit as an animal model and a basis for screening more effective candidate proteins. Casais *et al.* [15] vaccinated rabbits with a mixture of recombinant Ssλ20ΔB3 and GST-Ssλ15 antigens derived from *S. scabiei* var. *hominis* mite [13]. These rabbits later after exposed to *S. scabiei* var. *cuniculi* (rabbit scabies mites) they showed high levels of specific IgG however were still unable to protect themselves from flea infestation. Studies showed that *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* house dust mites cross-reacted with antigens in *S. scabiei* extracts. This shows that vaccination with house dust mite extract can cause protection against *S. scabiei*. Besides, house dust mites are easy to cultivate in a large amount, meanwhile scabies mites are difficult to obtain in such amount for vaccines making purposes. Rabbits are successfully able to induce protective immunity against *S. scabies* var. *kanis* after immunized with a mixture of 50/50 extracts of *D. farinae* and *D. pteronyssinus*. This is shown by a noticeably decrease in the amount of parasitic load compared with unimmunized controls.

There are other studies that revealed protection against ectoparasites is exist. Thoraxial antigen of *Stomoxys calcitrans* has been used to enhance the immunoglobulin serum in young horses. Sheep and rabbits are vaccinated with scab mites associated with *Psoroptes sp* [14]. They are able to induce partial immunity to rabbit scab mite (*Psoroptes cuniculi)* infection after four immunizations with whole-body extracts. Compared to naturally infected rabbits, vaccinated rabbits show a comparable protection. As found in rabbits, sheep vaccination with a whole-body extract of sheep scab mite (*Psoroptes ovis*) provided noticeable protection against infection. Subsequent studies found that the specific fraction prepared by the parent extract anion exchanger chromatography provided greater protection than the other fractions and from the parent extract itself. However, the SDS-PAGE profile of the fraction shows that it contains a lot of protein so that the molecules responsible for increasing protection cannot be identified. Gu *et al.* [16] investigated the immune response induced in mice by *S. scabiei* var. DNA cuniculi vaccine that codes for paramyosin. DNA vaccines induce humoral and cellular immune responses characterized by the abundance of IgG, IgG1, IgG2a, IgE and IgM, increased secretion of IL-2, IL-4, IL-5 and IFNγ by splenocytes, and lymphocyte proliferation in the spleen. Paramyosin as a common protein often found in invertebrates, has high homology among species. These experiments provide the basis for further studies on the possibility of a DNA vaccine to protect from scabies. It is not determined whether this causes protective immunity [16].

A deterministic model, compartments, using Descartes signs rules and numerical simulations by Bhunu *et al.* [17] are able to show endemic balance and sufficiency of the current treatment to control scabies infection, or the necessity of vaccine. Assumed values for the main model parameters are not proven, and it is not clear what model is calibrated. In other words, the reliability and result produce by the model are impossible to assess. This model focuses on predicting the possibility of effect to scabies vaccination. This should be seen as a theoretical exercise and not an exercise that provides actual insight into the epidemiology of scabies or the effectiveness of any available intervention. Overall, all the data conclude that in order to protect human and animal from scabies mite's infection, vaccination is undoubtedly a realistic plan. Many reported scabies immunization failures are caused by several factors other than just antigen or antigen mix, they can be attributed to adjuvants, immunization schedules, antigenic doses, and delivery methods. Antigen or antigen key cocktails have not yet been identified and produced by recombinant technology. Moreover, all principal components of the immunization are necessary to be fixated on [17].

Mites also defend themselves against the host immune system. For example, proteases and serine, where serine can be found in the intestine and stool of *S. scabiei*, this has been shown to inhibit all three complementary pathways of the immune response. Serine works differently according to the site of intestine. On the inside, serine provides a defence mechanism against swallowed plasma, while on the outside they may act in weakening the skin's immune system, thereby contributing to increasing bacterial infections during scabies. In vitro research shows that proteases and serine provide a favourable environment for the growth of *Streptococcus pyogenes* and *Staphylococcus aureus* even in the presence of the complement. Currently, experiments are underway to develop an optimal scabies vaccine. Research has shown that although scabies antigen reacts to house dust mite extract and their proteins are homologous, it will require years to make a commercially effective vaccine [18].

Making vaccines for multicellular parasites is far more difficult than viral or bacterial vaccines. This is caused by the interaction between the parasite and its host which is very complex. Parasitic infestation runs chronic because the parasite has the ability to deceive the host immune system. Viral or bacterial vaccines can be made by simply inactivating or patenting the virus or bacteria in question and producing vaccines in large quantities is also relatively easy because it is easy and fast to propagate viruses or bacteria in an *in vitro* culture system. Multicellular parasite vaccine cannot be made by inactivating or patenting the parasite concerned. The parasitic vaccine is a subunit vaccine, made from one or several parasitic proteins that have the ability to induce immunity in animals immunized with it. Finding this protective protein requires a large number of parasites as starting material, sophisticated

equipment and high skills in protein biochemistry and many animals in testing its protection. Once identified, protective proteins must be produced using recombinant technology which also requires high expertise, large costs and a long time. Vaccines whose components use protective proteins originating from parasites (not recombinant) are unlikely to have commercial value because they are too expensive [14, 19].

3. CONCLUSION

The development of immunodiagnostics, vaccines and immunotherapy is a promising long-term strategy for controlling scabies in globally affected areas. Comprehensive understanding of the immune events in the skin and peripheral blood that occurs during scabies can provide many points where immunological interventions can cut off infection and target responses from pathology to immunity.

Vaccination is believed to be the best alternative treatment method, but the availability of scabies vaccine still requires a very long process. Scabies is believed to be controlled by vaccination because individuals who recover from scabies have immunity against mite reinfestation. Besides that, even though scabies mites only settle on the surface of the skin and do not suck blood, mites internalize their host's immunoglobulin. Scabies vaccine, like other ectoparasites vaccines, is a protective mite antigen subunit vaccine produced using recombinant technology. The identification of protective antigens in scabies mites, which is the first step in making a vaccine, is constrained because of the protective nature of the unstable antigens their very low concentration, and the difficulty of getting mites in sufficient quantities. The identification of protective antigens by conventional biochemical methods, even though have been used for several other parasites, are not sensitive enough for scabies mites. Identifying protective antigens among groups of proteins that have vital functions for mites and which can only be reached by the host immune system may be a better alternative. Gastrointestinal membrane proteins and mite allergens may be included in this group.

Vaccination is safe for the environment and consumers, and potentially more effective and inexpensive. The big obstacle in making vaccines is that large quantities of tobacco are difficult to produce and protective mite antigens used as the main component of vaccines are very unstable and are in very low concentrations. Identification of protective antigens by conventional fractionation methods has been done but has not given satisfactory results. Alternative methods for the isolation of protective antigens need to be sought.

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