Autoimmunity Reviews 15 (2016) 664–667

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Modified immunotherapy for alopecia areata

Takashi Yoshimasu [a,b,*], Fukumi Furukawa [a]

[a] Department of Dermatology, Wakayama Medical University, Japan
[b] Department of Dermatology, Arida Municipal Hospital, Japan

ARTICLE INFO

Article history:
Received 19 February 2016
Accepted 25 February 2016
Available online 27 February 2016

Keywords:
Alopecia areata
Immunotherapy
SADBE
DPCP
Pulse

ABSTRACT

Squaric acid dibutylester (SADBE) is a commonly used contact sensitizer in immunotherapy for alopecia areata (AA). Severe contact dermatitis is induced by the currently high recommended sensitization dose of 1%–2% SADBE, often decreasing patient compliance. We assessed a modified immunotherapy for AA using SADBE at a starting concentration of 0.01% without sensitization. After one or two weeks of initial 0.01% SADBE application, the concentration of SADBE was increased gradually to 0.025%, 0.05%, 0.1%, 0.25%, 0.5%, 1% and 2% until the patients felt itching or erythema at the AA lesion site. The modified immunotherapy showed a response rate of 69.4% (25/36), equivalent to conventional immunotherapy using SADBE starting at 1%–2% sensitization. Furthermore, we investigated the combination therapy of SADBE and multiple courses of steroid pulses for AA. The response rate for combination therapy was 73.7% (28/38); however, the group receiving combination therapy showed a significant prevalence of severe AA compared with the group receiving modified immunotherapy only. We reviewed the efficacy and safety of modified immunotherapy without initial sensitization and combination therapy with immunotherapy and multiple courses of pulses for AA.

Contents

1. Introduction

Alopecia areata (AA) is a tissue-specific autoimmune disease of the hair follicle resulting in hair loss and is the most common human autoimmune disease [1]. The lifetime risk of AA is approximately 1.7% [2]. No current treatments have been widely accepted to have complete and satisfactory efficacy for AA. Among various treatments for AA, contact immunotherapy has been recommended in the British and Japanese guidelines for the treatment of AA [3,4].

Squaric acid dibutylester (SADBE) and diphenylcyclopropenone (DPCP) are commonly used contact sensitizers for AA immunotherapy. The exact mechanisms involved in immunomodulation therapy for alopecia are poorly understood. Severe contact dermatitis is induced by the currently recommended high sensitization dose of 1%–2% for these sensitizers; these effects often decrease patient compliance. Based on this situation, the current review discusses novel strategies for AA immunotherapy.

2. Immunotherapy can change autoimmunity in AA

The destruction of a hair follicle (HF) immune privilege site may contribute to the pathogenesis of AA, resulting in a predominantly CD8 + T-cell infiltrate at the location of the follicle [5]. The identification of disease-specific TCRs, intralesional CD8 + T cells, can serve as a basis for specific AA immunotherapy and may possibly also provide prognostic biomarkers [6]. In an AA model using C3H/HeJ mice, SADBE increased

* Corresponding author at: 811-1 Kimiidera, Wakayama City, Wakayama 641-0012, Japan. Tel.: +81 73 441 0661; fax: +81 73 448 1908.
E-mail address: yosshii8@jg8.so-net.ne.jp (T. Yoshimasu).

http://dx.doi.org/10.1016/j.autrev.2016.02.021
1568-9972/

the CD4+/CD8+ ratio from approximately 1:2 in untreated alopecia areata to 1:1 in treated alopecia areata [7].

On the other hand, the infiltration of interleukin (IL)-17 producing cells was seen in the development of AA [8,9]. Perifollicular $CD4^+$ cells and IL-17^+ T cells were reduced in number, while $CD8^+$ cells were increased in number after three months of treatment with SADBE [10]. It is suggested that the recruitment of specific $CD8^+$ cells mediated the contact allergy to SADBE, rather than CD4/CD8 switch correlated with hair growth [11].

3. Current immunotherapy for AA

Topical immunotherapy is based on the principle of inducing allergic contact dermatitis by applying potent contact allergens to the affected skin. These contact sensitizers act through immunomodulation of the skin and its appendages [12]. A topical sensitizer for AA was first reported in 1978 and allergic contact dermatitis using dinitrochlorobenzene (DNCB) was applied to induce hair growth [13]. This agent was later found to be mutagenic [14].

SADBE and DPCP are contact sensitizers still used for AA. The response rate of immunotherapy for AA is 50%–60% [15]. In less severe forms affecting less than 50% of the scalp, the response rate to SADBE is 80%, compared to 49% for severe forms affecting more than 50% of the scalp [16]. SADBE therapy also induced persistent benefits in a small portion of children with severe AA [17]. Furthermore, systemic action by SADBE was also reported, such as hair regrowth in areas distant from the SADBE application site [16]. On the other hand, the response rate of DPCP was 72.2% in the treatment of two hundred and five cases of AA [18]. Furthermore, topical immunotherapy with DPCP was effective in the treatment of chronic, extensive AA including AA totalis and AA universalis [19]. In treatments with SADBE and DPCP, there are conflicting reports on the best protocol for their administration. The difference in the response rate of the immunotherapy depends on the sensitization regimens for AA. Sensitization protocol, treatment area, treatment duration and definition of hair growth are different in each regimen [20–24].

Several prognostic factors including duration of disease, extent of alopecia, age at onset and nail changes may be able to predict the level of patient' responsiveness to treatment with SADBE [25]. Extensive AA at baseline and a longer disease duration predicts a poorer response to DPCP; on the other hand, atopic dermatitis is not a negative prognostic factor for DPCP [18]. A history of thyroid disease is a negative prognostic factor for both therapeutic success and relapse in DPCP treatment for AA [26]. Pigmentary complications caused by contact immunotherapy are associated with poor responsiveness for AA [27].

It is possible that initial sensitization with 1%–2% SADBE causes not only contact dermatitis but also other side effects. Hapten-induced lymphoadenosis benigna cutis (LABC) developed secondary to SADBE sensitization in AA patients [28–29].

It is necessary to establish more convenient and effective protocols for AA for use. The possibility of the self-administration of DPCP by patients was also suggested [18,26].

4. Immunotherapy without 1%–2% sensitization for AA

Severe contact dermatitis is induced by the currently high recommended sensitization dose of 1%–2% SADBE or DPCP, often decreasing patient compliance. Low-dose DPCP starting with 0.1% sensitization was effective for AA [30]. Initial concentrated SADBE sensitization was not required for a positive response in AA treatment [31]. SADBE sensitization regimens and reactions vary widely, and the absence of an initial eczematous reaction to sensitization did not predict a failed response with continued SADBE treatment [31].

5. Modified immunotherapy starting with 0.01% SADBE

We investigated a novel and convenient immunotherapy without the use of initial sensitization for AA. Our purpose was to investigate the efficacy and safety of modified immunotherapy for AA using SADBE at a starting concentration of 0.01%. Furthermore, we investigated the combination of SADBE immunotherapy and multiple courses of steroid pulses. SADBE treatment and pulse corticosteroid therapy for AA were both approved by the ethical committee of Wakayama Medical University. To exclude AA associated with other diseases, we carried out biological examinations including tests for serum zinc, serum iron, HBs antigen and hepatitis C antibody, a serologic test for *syphilis* and *Treponema pallidum* hemagglutination, a thyroid function test and a measurement of anti nuclear antibody. X-rays and electrocardiograms were analyzed before starting pulse corticosteroid therapy. We excluded children under 15 years of age from our study, because of the possible long-term side effects including growth retardation. The percentage of scalp hair loss was evaluated according to the AA investigational assessment guidelines [32].

After written informed consent was obtained, seventy-four patients with AA were enrolled in this study between 2008 and 2016. Thirty-six of 74 patients received the modified immunotherapy only. Thirty-eight of 74 patients received the combination therapy of modified SADBE treatment with pulse therapy. The AA group receiving modified immunotherapy only was treated with SADBE starting at 0.01% with no sensitization at the site of AA. From one week or two weeks after initial 0.01% SADBE application to the AA lesions, the concentration was gradually increased to 0.025%, 0.05%, 0.1%, 0.25%, 0.5%, 1% and a maximum of 2%, until an optimum concentration was reached where the patients felt itching or mild erythema which continued for four to five days. The concentration of SADBE was fixed at the optimum concentration and SADBE treatment was continued every one or every two weeks until terminal hair had grown on the entire head. If the patients felt severe itching or blistering at the application site of the immunotherapy, topical corticosteroids were applied and the concentration of SADBE was decreased one to two levels.

In the combination therapy group that received multiple pulses, the AA patients were treated with methylprednisolone at 500 mg/day intravenously on 3 consecutive days (—one course). If vellus hair was not seen within one month after the first course of pulse therapy, the patients received another course each month for up to three courses in total until vellus hair was seen. After pulse therapy was completed, modified immunotherapy was started for the combination therapy group.

The duration until vellus hair was detected was investigated after the start of immunotherapy in the modified immunotherapy group and after the start of the first pulse treatment in the combination therapy group. A clinically significant response to SADBE therapy was defined as a cosmetically acceptable response or greater than 75% terminal hair regrowth; however, if the patient experienced recurrence of alopecia, they were not deemed a good responder even if though they showed more than 75% regrowth hair. The efficacy and safety in each group were compared and statistical analysis was done using the *t*-test.

Results are summarized in Table 1. Vellus hair regrowth was detected at a median duration of 3.6 months (range: 1–9 months) after the start of modified SADBE therapy. In contrast, regrowth was detected at 2.5 months (range: 0.5–7 months) in the combination therapy group, which was a significantly faster response (Table 1). The response rate for the modified immunotherapy group was 69.4% (25/36). On the other hand, the response rate for the combination therapy was 73.7% (28/38); this group also included significantly more cases with severe AA compared to the modified immunotherapy only group. The final optimum concentration of SADBE in both groups showed no statistical difference.