Seventeen Cases of Alopecia Areata: Combination of SADBE Topical Immunotherapy with Other Therapies

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Abstract

Topical immunotherapy is effective for severe alopecia areata. However, there are patients with alopecia areata refractory to topical immunotherapy alone. We tried SADBE (squaric acid dibutylester) topical immunotherapy combined with topical dry ice cryotherapy, carpronium chloride (a parasympathetic nerve stimulant) and/or oral cepharanthin (a biscoclaur alkaloid) in alopecia areata refractory to topical SADBE. Seventeen patients with alopecia areata (3 multiple, 3 ophiasis, 5 totalis and 6 universalis) were treated with SADBE in our department in 1999 to 2001. In 3 cases (2 multiple and 1 universalis) out of the 17 cases, cosmetically acceptable regrowth of hair was observed in several months with topical SADBE alone. In the other 14 cases, the SADBE therapy alone for several months (mean: 6.9 months) resulted in no or poor regrowth of hair. However, with subsequent combination therapy of topical SADBE for several months (mean: 7.6 months), satisfactory regrowth of hair was observed in 6 of the 14 cases. Our cases indicate that combination therapy of topical SADBE with other therapies can be a choice for alopecia areata which is refractory to topical SADBE therapy alone.

Key words: SADBE; dry ice; carpronium chloride; cepharanthin

Introduction

Alopecia areata is a non-scarring alopecia that appears equally in males and females of any age, although children and adolescents are more commonly affected. The disorder is usually characterized by limited alopecic patches on the scalp. However, more severe forms may affect the entire scalp (alopecia totalis) or body (alopecia universalis).

Alopecia areata has been known to be linked with certain human leukocyte antigen (HLA) class II alleles and other autoimmune diseases, indicating a probable autoimmune etiology (1, 2). T lymphocytes are possibly involved in the pathogenetic mechanism of the disease (3).

Topical corticosteroids are widely used in mild cases. Topical anthralin and minoxidil may also be clinically effective. Topical immunotherapy with squaric acid dibutlyester (SADBE) or diphencyprone (DPCP) for the treatment of severe alopecia areata has been used. There have been no major side effects reported since its initial use. Topical SADBE has about 30% to 90% (4–6) and DPCP has at least a 40% success rate (2, 7) for cosmetically acceptable regrowth in extensive alopecia areata. Topical SADBE acts as an ideal immunogen because it is not found in the natural environment and is not mutagenic by the Ames test, unlike other topical

sensitizers such as dinitrochlorobenzene (6, 9). However, there is no adequate treatment for patients with severe alopecia areata refractory to topical immunotherapy. Herein,

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we tried combination therapy of topical SADBE with topical dry ice cryotherapy, carpronium chloride (a parasympathetic nerve stiumlant) and/or intake of cepharantin (a biscoclaur alkaloid) in alopecia areata which is refractory to SADBE topical immunotherapy alone.

Case Reports

Seventeen patients (8 males and 9 females) with alopecia areata (3 multiple, 3 ophiasis, 5 totalis and 6 universalis) had been treated with SADBE in our department between 1999 and 2001. The average duration of hair loss prior to treatment with SADBE was more than 4.3 years. Before consultation with us, they were refractory to other forms of treatment, such as topical or oral steroid, immunosuppressants, glycyrrhizin, cepharantin, cryotherapy, PUVA or carpronium chloride. Initially, these patients were each sensitized with a 1% solution of SADBE in acetone on a 1 □ 1 cm area of the upper arm. They were asked to return 2 weeks later, and the treatment was started with varying concentrations of SADBE ranging from 10^{8} to 10^{2}%. Subsequently, the concentration and frequency of SADBE treatment that maintained a mild contact dermatitis on the site of application was prescribed. SADBE treatment was done with informed consent of the patients along with the local ethics committee of our hospital. Criteria for effectiveness in the treatment were determined by regrowth of terminal hair. In 4 out of the 17 cases, oral cepharanthin (3–30 mg/day) was prescribed at the beginning of topical SADBE, because of severity. In 3 cases (2 multiple and 1 universalis), regrowth of hair was observed in a few months. However, in the other 14 cases, topical SADBE for several months (mean: 6.9 months) resulted in no or poor regrowth of hair. Then, we tried combination therapy of topical SADBE with topical dry ice cryotherapy (Dry)

(applied every week or two weeks), topical carpronium chloride (Carp) (a parasympathetic nerve stimulant) and/or oral cepharanthin (Ceph) (3–30 mg/day) in these 14 cases. In detail, with topical SADBE, "Dry + Carp + Ceph" was done in 9 cases, "Dry" in 2 cases, "Dry + Carp" in 1 case, "Dry + Ceph" in 1 cases, and "Carp" in 1 case. The contents of combination therapies were mainly decided by severity of symptoms. (In more severe patients, the number of therapies combined with topical immunotherapy was increased.) After the combination therapies for several months (mean: 7.6 months), regrowth of hair was observed in 6 cases of the 14 cases (Fig. 1). In these successfully treated 6 cases, "Dry + Carp + Ceph" was done in 4 cases, "Dry + Ceph" in 1 case, and "Carp" in 1 case. The results are summarized in Table 1.

Fig. 1. Clinical features in case 9. A: Three months after topical SADBE alone. No hair regrowth was observed. B: Six months after topical SADBE combined with topical dry ice cryotherapy, topical carpronium chloride and oral cepharanthin. Eczematous reaction was enhanced. C: Three months after Fig. 1B, satisfactory regrowth of hair was observed on the whole scalp.

Combination of Topical SADBE with other Therapies

Discussion

As in many other reports, our patients treated with SADBE were recalcitrant to more common therapies. In the present report, total effective rate with simple or combinational topical SADBE was estimated as 53% (9/17 cases). Especially, combination of topical SADBE with other forms of therapy seemed to be effective in patients refractory to SADBE topical immunotherapy alone. The effective rate was in a range of those of simple topical SADBE in the literature (4–6). Although our report is not a case-controlled study and based on a small number of patients, it is indicated that a combination of SADBE topical immunotherapy and other therapies can be a choice for alopecia areata refractory to SADBE topical immunotherapy alone. Topical dry ice cryotherapy, carpronium chloride or cepharanthin therapy are each effective and have been used for alopecia areata. Topical dry ice may evoke superficial tissue damage and vasodilation after vasoconstriction. Carpronium chloride may stimulate parasympathetic nerves and dilate blood vessels. Cepharanthin is a kind of biscoclaur alkaloid widely used for alopecia areata in Japan. The pharmacological action of cepharanthin in alopecia areata is still unknown;

however, cepharanthin may act as an immunomodulator (10). Together, the effectiveness of the combination therapy of topical SADBE in our study would be ascribable to enhancement of inflammatory reaction or modifying perifollicular immunoreaction resulting in regrowth of hair.

The therapeutic action of contact dermatitis caused by topical SADBE in treatment of alopecia areata is not fully understood, although some data of topical SADBE in animal models with alopecia areata have been published recently. Immunohistochemical studies of topical SADBE in alopecia areata C3H/HeJ mice revealed that treatment with SADBE increased the CD4+/CD8+ ratio of the infiltrated T-lymphocytes from approximately 1:2 untreated alopecia areata to 1:1 treated alopecia area-

Table 1. Summary of 17 cases with alopecia areata

Case (Year)	Age (Years-old), Clinical type	Concominant therapies and effectiveness	Gender, AD History
1	1 totalis	S (12M) ineffective□SD (7M) ineffective	9, Male, (+)
2	>10 universalis	S (2M) ineffective□SDCaCe (10M) ineffective	15, Male, ( )
3	>5 ophiasis	SCe (2M) ineffective□SDCaCe (2M) ineffective	28, Female, ( )
4	>6 multiple	S (2M) effective	30, Male, ( )
5	>3 ophiasis	S (10M) ineffective□SDCaCe (3M) effective	13, Female, ( )
6	1 universalis	S (5M) effective	21, Male, ( )
7	>20 universalis	S (3M) ineffective□SDCaCe (8M) ineffective	53, Female, ( )
8	4 universalis	SCe (4M) ineffective□SDCaCe (9M) ineffective	13, Male, (+)
9	0.5 totalis	S (6M) ineffective□SDCaCe (9M) effective	19, Female, ( )
10	>7 universalis	SCe (4M) ineffective□SDCaCe (8M) ineffective	36, Male, ( )
11	3 universalis	S (14M) ineffective□SDCaCe (7M) effective	13, Male, ( )
12	4 multiple	S (11M) ineffective□SCa (10M) effective	17, Male, (+)
13	8 totalis	S (6M) ineffective□SDCaCe (14M) effective	25, Female, ( )
14	6 totalis	S (13M) ineffective□SD (7M) ineffective	26, Female, ( )
15	3 ophiasis	SCe (9M) ineffective□SDCe (4M) effective	10, Female, ( )
16	10 totalis	S (1M) ineffective□SDCaCe (8M) ineffective	21, Female, ( )
17	2 multiple	S (4M) effective	29, Female, ( )

Effective therapies are underlined. [S: SADBE, D: dry ice, Ca: Carpronium chloride, Ce: Cepharantin, AD: atopic dermatitis, M: duration (months) for therapies]

ta, and reduced abberant expression of MHC class II (11). From this point of view, the combination therapy of topical SADBE could be evaluated in future.

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