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Dapsone versus topical immunotherapy in alopecia areata

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Summary Twenty-seven patients with severe alopecia areata were treated with dapsone. The results of a mean treatment duration of $10 \pm 0{\cdot}5$ months are reported, and compared with the results of long-term topical immunotherapy obtained previously at the same institute. The efficacy of dapsone proved to be markedly inferior to that of topical immunotherapy. The percentage of patients showing regrowth of hair during treatment with dapsone was comparable with the occurrence of spontaneous regrowth of hair reported in the literature.

Alopecia areata (AA) is a disorder of unknown cause, although evidence for an autoimmune aetiology continues to mount.[1] Various therapies have been reported to be effective: photochemotherapy,[2] topical and systemic corticosteroids,[3,4] topical and oral cyclosporin A,[5,6] topical and oral minoxidil,[7,8] and isoprinosine.[9] None of these treatments, however, has produced a substantial regrowth of hair in the majority of patients. During the last decade, controlled studies have shown conclusively that the treatment of AA by topical immunotherapy using the contact allergen diphenylcyclopropenone (DCP) is effective.[10,11] Disadvantages of topical immunotherapy are that it requires close supervision, and the treatment is time-consuming for the patients and medical staff.

In 1990 Knauber and Zaun[12] reported that treatment of AA with dapsone was as effective as topical immunotherapy. However, no consensus has been reached on the value of dapsone for patients with AA.[13] The purpose of the present study was to analyse the effectiveness of dapsone in AA, and to compare the results with the response to topical immunotherapy obtained at the Nijmegen Institute.[10,14]

Methods

Between January 1992 and August 1993, 27 patients with severe AA were treated with dapsone. Between March 1986 and October 1989, a group of 139 patients with severe AA had been treated with DCP at the Nijmegen Institute.[10] Informed consent was obtained from all patients.

Included in both groups were patients suffering from severe AA. Pregnant women and those wishing to become pregnant were excluded. Patients with cardiopulmonary disease were excluded from treatment with dapsone. Table 1 summarizes the composition of the two treatment groups. Eleven patients in the dapsone treatment group had been treated previously with topical immunotherapy. In eight of these patients, topical immunotherapy had been successful initially, but a relapse had occurred during prolonged treatment. The details of patients treated with DCP have been reported previously.[10,14]

Dapsone was started at a daily dosage of 100 mg. If side-effects such as nausea, headache, sleep disturbance, anaemia or methaemoglobinaemia occurred, the dosage was reduced to 50 mg daily, or the drug was stopped. This dosage was continued until cosmetically acceptable hair growth had appeared. The dosage was then slowly reduced to the minimum effective level. If, after 12 months, no hair growth had occurred, therapy was stopped. Before treatment, we checked the full blood count, and performed renal and hepatic function tests. These parameters, and the methaemoglobin level, were monitored during treatment. Topical immunotherapy was carried out according to standardized procedures.[10,14]

Hair regrowth was recorded as follows: if some regrowth of hair occurred the response was designated as 'hair growth', and if the regrowth was complete the response was recorded as 'complete hair growth'.

Results

Data on hair growth during treatment with dapsone are summarized in Tables 2–4. Of the seven patients with the patchy type of AA, four showed complete regrowth. Fourteen patients in the dapsone-treated group showed sporadic hair growth on the scalp. Of these 14 patients,

Table 1. Composition of study populations

Treatment	Number of patients	Sex (M/F)	Duration of AA (years)	Type of AA
Dapsone	27	15/12	⩽ 1: 2 (7%) 2–9: 15 (56%) 10–39: 10 (37%)	Patchy: 7 ST/T/ST–U/U: 20
DCP[10,14]	139	66/73	⩽ 1: 36 (26%) 2–9: 54 (39%) 10–39: 47 (34%)	Patchy: 44 ST/T/ST–U/U: 85 Diffuse/ophiasis: 10

ST/T/ST–U/U, subtotal/total/subtotal universalis/universalis; AA, alopecia areata.

Table 2. Patient data during dapsone therapy

Age	Duration of disease (years)	Severity	Earlier treatment	Hair growth scalp	Hair growth body	Complete hair growth	Duration of dapsone therapy (months)
Female patients ($n = 12$)							
31	25	U	top. imm.	–	–	–	7
37	5	ST–U	top. imm.	+	+	+	10
33	22	U	PUVA, top. imm.	+	+	+	8
46	2	U	t.s.	–	–	–	12
32	5	P	PUVA, t.s.	+	–	+	10
57	6	ST–U	PUVA, t.s., s.s., top. imm.	–	–	–	9
54	11	U	t.s.	+	–	–	9
29	11	U	minoxidil	–	–	–	9
22	20	P	top. imm., t.s.	+	–	+	12
41	3 months	P	–	+	–	+	8
42	14	ST–U	PUVA, t.s.	+	+	–	11
52	42	P	PUVA, top. imm.	–	–	–	5
Male patients ($n = 15$)							
20	2	ST–U	–	–	–	–	4
21	6	U	t.s., top. imm.	+	–	–	12
31	2	U	s.s.	+	+	–	12
18	9	ST–U	–	–	–	–	12
46	33	U	–	–	–	–	12
40	2	U	–	+	–	–	12
55	4	U	top. imm.	–	–	–	4
22	7	P	t.s.	–	–	–	6
41	33	U	PUVA	–	–	–	11
38	14	U	PUVA, top. imm.	+	+	–	16
25	3	P	t.s.	–	–	–	6
28	1	ST–U	–	+	–	–	12
36	2	ST–U	PUVA	+	+	–	12
26	6	P	t.s., top. imm.	+	–	+	12
28	5	U	PUVA, top. imm.	–	–	–	10

ST/T/ST–U/U, subtotal/total/subtotal universalis/universalis.
P, patchy hair loss confined to scalp. Complete hair growth in the patchy group refers to the scalp only.
t.s., topical steroids.
s.s., systemic steroids.
top. imm., topical immunotherapy.

Table 3. Hair growth during treatment

Treatment	Type of AA	No. of patients	Hair growth	Complete hair growth (%)
Dapsone	Patchy	7	4	4 (57·1)
	ST/T/ST–U/U	20	10	2 (10·0)
DCP[10,14]	Patchy	44		34 (77·3)
	ST/T/ST-U/U	85		33 (38·8)
	Diffuse/ophiasis	10		3 (30·0)
Spontaneous[15,16]	Patchy	20		12 (60)
	Totalis	138	47	14 (10)

ST/T/ST–U/U, subtotal/total/subtotal universalis/universalis; AA, alopecia areata.

eight also noticed sparse hair growth all over the body, which subsequently disappeared. In the totalis/universalis group, 10 patients showed some hair growth, but only two had complete regrowth. In these two patients the hair growth appeared after 1 and 5 months, and therapy was stopped at 10 and 8 months, respectively, because of headache and fatigue. It is notable that the hair growth was unaffected by discontinuation of dapsone. Table 4 summarizes the duration of the DCP and dapsone treatment phases. It can be seen that improvement during dapsone therapy initially occurred after $2{\cdot}2 \pm 0{\cdot}6$ months in 14 patients, and that cosmetically acceptable regrowth was seen after $10 \pm 0{\cdot}7$ months in six patients. No significant correlation was observed between the dosage of dapsone and its clinical efficacy. Notably, those patients in the totalis/universalis group who had regrowth of hair received dapsone 50 mg daily.

Topical immunotherapy with DCP was continued for a year in 139 patients.[10,14] If, after this duration of therapy, cosmetically acceptable regrowth had not occurred, treatment was stopped. Data on hair regrowth during immunotherapy are presented in Tables 3 and 4. Of the 44 patients with the patchy type of AA, 34 had complete hair regrowth, and of the 85 patients with subtotalis/totalis type of AA, 33 had complete hair regrowth. As topical immunotherapy is initiated on one side of the scalp, a unilateral response can be interpreted as a therapeutic success, and a bilateral response as spontaneous regrowth. Of the 139 patients, 107 had a unilateral response and none showed a bilateral response.

A period of topical immunotherapy of approximately 3 months was required before signs of regrowth occurred, and at least 6 months for complete regrowth. A comparison of the effectiveness of dapsone with topical immunotherapy revealed that complete regrowth occurred in 22 and 50% of the patients, respectively. It can be concluded that topical immunotherapy is significantly more effective than dapsone (Fisher's exact test: $P \leqslant 0{\cdot}006$).

Side-effects are listed in Table 5. In two of 27 patients treated with dapsone (7%), the dose was reduced because of an increase in methaemoglobin ($\geqslant 5\%$). In 10 patients the dose was lowered to 50 mg because of a reduction of haemoglobin of more than 1·6 g% in 2 weeks. Liver and renal function tests remained normal during treatment. Three patients complained of shortness of breath, and two had headache. One patient had a sleep disorder, another had nausea, and fatigue was reported by three patients. In addition to the cutaneous side-effects, sleep disturbance proved to be a significant problem during topical immunotherapy.

Discussion

The results of this study indicate that treatment of long-lasting AA with dapsone is less successful than topical immunotherapy (Fisher's exact test: $P \leqslant 0{\cdot}006$). As the present investigation was not a placebo-controlled study, the response to dapsone has to be interpreted in the light of the spontaneous recovery rate in alopecia areata.[15,16] The two patients who had complete regrowth

Table 4. Duration of treatment phases (months, mean ± SEM)

	Treatment period	Duration until first improvement	Duration until full remission
Dapsone	20	$2{\cdot}2 \pm 0{\cdot}6$	$10 \pm 0{\cdot}7$
Diphenylcyclopropenone[10]	43	$3{\cdot}2 \pm 0{\cdot}2$	>6

Table 5. Side-effects

Side-effects during treatment with dapsone (%)		Side-effects during treatment with diphenylcyclopropenone[10] (%)	
Nausea	1 (4)	Mild contact eczema	139 (100)
Vomiting	—	Severe eczema/blister formation	81 (58·3)
Headache	2 (7)	Disseminated contact eczema	11 (7·9)
Weakness	—	Urticaria	7 (5·0)
Fatigue	3 (11)	Swelling of the scalp	1 (0·7)
Dizziness	1 (4)	Oedema of the eyelids/face	5 (3·6)
Shortness of breath	3 (11)	Erythema multiforme-like eruption	2 (1·4)
Sleep disorder	1 (4)	Lymphadenopathy	139 (100)
Anaemia	10 (37)	Sleep disturbance	48 (36·9)
Methaemoglobinaemia	2 (7)	Headache	3 (2·3)
Cyanosis	1 (4)		
Leucopenia	—		
Agranulocytosis	—		
Hepatotoxicity	—		
Nephrotoxicity	—		
Peripheral neuropathy	—		
Dapsone hypersensitivity syndrome	—		

of hair during dapsone therapy were treated with a low dose (50 mg daily), and did not relapse following discontinuation of dapsone. Hence, spontaneous recovery could be the explanation for the favourable course in both patients.

Table 3 includes the observations of Tosti *et al.* with regard to spontaneous regrowth in patients with the patchy type of AA. Complete regrowth in this group occurred in 60% of the patients.[15] In the patients with patchy AA treated with dapsone in the present study, four of seven (57%) had a cosmetically acceptable hair regrowth. In patients with AA totalis/universalis, Muller and Winkelmann reported complete regrowth without treatment in 10%.[16] This is equivalent to the proportion of our dapsone-treated patients in whom complete regrowth occurred. Hence, these data cast considerable doubt on the therapeutic efficacy of dapsone in AA.

The pathogenesis of AA is still unclear, but there is considerable evidence that an immunological mechanism is involved. Numerous reports have documented the frequent coexistence of AA with other autoimmune disorders,[17] and its association with circulating autoantibodies against various tissues.[18,19] In addition, more generalized disturbances in the immune status of patients with AA have been reported.[20,21]

Peribulbar accumulation of lymphocytes occurs in AA, and these consist predominantly of T-helper cells,[22] with a CD4/CD8 ratio of approximately 4 : 1.[23] Class I and II MHC antigens are expressed by the hair matrix cells and subinfundibular epithelium, and an increased number of Langerhans cells occurs in the peribulbar and intrabulbar regions.[24] Topical immunotherapy with DCP results in a change of the CD4/CD8 ratio from 4 : 1 to 1 : 1.[25] The number of Langerhans cells is markedly reduced, as is the expression of class I and class II MHC antigens.[24]

Dapsone has potent anti-inflammatory actions, and is an effective treatment for dermatitis herpetiformis, pustular dermatoses and vasculitis. It interferes with the chemotaxis of polymorphonuclear leucocytes and the respiratory burst of these cells.[26] There is little information about the effect of dapsone on T-cell function. It has been demonstrated by Wozel that phytohaemagglutinin-induced T-cell transformation is inhibited by dapsone.[27] However, T cell-mediated diseases show a poor response to dapsone therapy. The negative results of dapsone therapy in AA lend support to the supposition that AA is a T-cell-mediated disease.

In conclusion, the results of the present study do not provide any justification for the treatment of AA with dapsone, as its efficacy remains doubtful and its side-effects may be troublesome.

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