Clinical and Experimental Dermatology 1991; 16: 172–175.

Treatment of alopecia totalis with a combination of inosine pranobex and diphencyprone compared to each treatment alone

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Accepted for publication 28 *September* 1990

Summary

Recent developments in alopecia areata have included the use of oral inosine pranobex and the introduction of diphencyprone as a contact sensitizer. Good results have been claimed for these treatments even in severe forms of the disease. We performed a study to investigate the efficacy of a combination of these treatments in the most severe form of alopecia areata.

Thirty-three patients suffering from alopecia totalis were enrolled. Subjects were divided into three groups matched for age and sex. One group received treatment with inosine pranobex (50 mg/kg/day) for 6 months. The second was sensitized to diphencyprone and treated for 6 months by maintenance of contact allergic dermatitis on the scalp. The third received both treatments.

There was no evidence of response to inosine pranobex in any of the 22 subjects who received this treatment. Only two of 22 patients responded to diphencyprone.

Patients with long-standing alopecia totalis contemplating diphencyprone therapy should be advised that the chances of success are only around 10%. Inosine pranobex does not appear to improve the response rate.

There have recently been three encouraging reports of the use of the immunomodulatory agent inosine pranobex (inosiplex, Isoprinosine or Imunovir) in alopecia areata.[1,3] This treatment appeared free from adverse effects. The majority of patients studied appear to have had severe disease and response rates ranged from 32 to 78%.

It has long been recognized that the induction of contact allergic dermatitis on the scalp of patients affected by alopecia areata (AA) may effect regrowth of hair. The most favoured sensitizer at present appears to be diphencyprone (diphenylcyclopropenone).[4] Apart from the inconvenience of the scalp dermatitis and the occasional development of vitiligo in the treated area,[5] this treatment appears to have been safe and free from adverse effects. Reported reponse rates have varied widely, however, particularly in the severe forms of the disease, alopecia totalis (AT) or universalis (AU). Happle *et al.*[6] treated 27 patients, 22 of whom had AT, and reported a response in 23. In contrast Ashworth *et al.*[7] reported that only one of 17 patients with AT responded.

In view of the wide variations in reported response rates, and since it was clear that a significant proportion of patients with severe disease failed to respond to either of these treatments alone, we investigated the response rates to these treatment modalities used both separately and simultaneously, in alopecia totalis.

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Methods

Subjects

Thirty-three patients with AT of at least 12 months' duration under review at the Leicester Royal Infirmary were recruited for the study. The overall mean duration of AA was 20 years, and the mean duration of AT was 13 years. Fifteen of the subjects had AU. Subjects on systemic steroids or any other systemic or topical treatment which might in any way affect the outcome of the study were excluded. Each subject was required to give signed, witnessed, informed consent. Subjects were allocated to one of three groups, in such a manner that the groups were closely matched for age and sex (see Table 1). Allocation to groups was otherwise random except that one patient with a history of gout was entered into Group 1 to avoid exacerbating his hyperuricaemia.

Treatments

Group 1. After confirmation that the baseline serum urate was within the normal range this group received

Table. 1. Patient data

Parameter	Group 1 Inosine pranobex ($n=11$)	Group 2 Diphencyprone ($n=11$)	Group 3 Both treatments ($n=11$)
Mean age (years)	40	39	40
(range)	(21–57)	(18–62)	(17–66)
Sex (M/F)	5/6	5/6	6/5
Number with alopecia universalis	4	7	4
Mean duration of alopecia (years)	21	23	17
(range)	(7–39)	(2–40)	(2–44)
Mean duration of totalis (years)	15	15	9
(range)	(2–31)	(2–38)	(1–21)

oral inosine pranobex (50 mg/kg/day divided into three doses), for 6 months.

Group 2. Solutions of diphencyprone were prepared in a mixture of industrial methylated spirit 95% and propylene glycol (9:1 by volume). A 1% solution was applied to the right side of the scalp weekly until sensitization developed. Subsequently, applications of variable concentration, sufficient to maintain minimal irritation of the scalp were continued weekly to the same side. If an unequivocal regrowth of hair was obtained on that side, treatment was continued on both sides.

Group 3. This group received both the above treatments.

Assessment and monitoring

On entering the trial each patient was asked specifically about hyperuricaemia and gout.

Response to treatment was assessed after 1, 2, 4 and 6 months, by noting the proportion of the scalp covered in terminal hair. Photographs of the scalp were taken on each occasion. Responses were graded into three categories; none, poor (a response which was of no cosmetic value, less than 20% of terminal scalp hair regrown), and good (a response of cosmetic value, between 20 and 100% terminal scalp hair regrowth).

Compliance with oral medication was confirmed at each visit by questioning, and by observing a rise in the serum urate.

A full blood count, serum urate and routine biochemistry (SMAC) were performed at each assessment. Prior to starting treatment, and after 6 months on treatment, assays were performed for the following organ-specific auto-antibodies; thyroid microsome, thyroglobulin, parietal cell, mitochondria, smooth-muscle and anti-nuclear factor.

Results

Compliance

Compliance with oral medication appeared remarkably complete. Biochemical monitoring revealed the expected rise in serum urate in all subjects in this group during treatment. One patient in this group was lost to follow-up after 1 month. No response had been achieved.

The two patients who failed to sensitize to diphencyprone discontinued treatment before the end of the study, one at 2 months and one at 4 months. Compliance was otherwise extremely good. In all those patients who were sensitized, an inflammatory reaction was maintained on the scalp for 6 months without interruption.

Sensitization

Times taken to achieve sensitization varied. Five patients responded to the first application of diphencyprone, one required five applications. Only two patients failed to sensitize at all, one of these was receiving inosine pranobex. The mean number of weekly diphencyprone applications required to obtain sensitization was similar in the two limbs of the study where diphencyprone was employed (2·4 applications in Groups 2 and 2·1 in Group 3). Concentrations of diphencyprone required to maintain erythema varied from 1 to 0·001%.

Response to treatment

The overall response rate was low (Table 2). Only two subjects responded with a good regrowth of hair, one of whom was treated with diphencyprone and the other with combined treatment. In both of these cases male pattern alopecia was 'unmasked' by the treatment so that regrowth was incomplete, but they were nonetheless

Table 2. Response to treatment

Response	Group 1 Inosine pranobex ($n=10$)	Group 2 Diphencyprone ($n=11$)	Group 3 Both treatments ($n=11$)
Poor	0	1 (9%)	2 (18%)
Good	0	1 (9%)	1 (9%)
Total	0	2 (18%)	3 (27%)

pleased with the result. Three patients developed a poor response, one on diphencyprone alone and two on both treatments. All responses developed only on the side of the scalp treated with diphencyprone until the opposite side was also treated. No patient on inosine pranobex alone developed any regrowth of terminal hair.

Auto-antibodies

A total of 27 auto-antibodies were detected in 18 different patients. There was no consistent trend towards a change in titres during the study, either overall or when each limb of the study was examined individually.

Adverse events

Patients reported no adverse effects from inosine pranobex. Diphencyprone produced occasional unexpectedly severe eczematous reactions on the scalp but these were generally well tolerated by the subjects. Cervical adenopathy was an occasional cause of anxiety to patients. One patient who responded to treatment developed vitiligo in the distribution of application of the diphencyprone (Fig. 1).

Biochemical and haematological monitoring did not reveal any adverse changes, except that serum urates occasionally exceeded the normal range marginally in patients on inosine pranobex.

Discussion

We are not able to confirm any therapeutic value of inosine pranobex in AT. This finding appears to conflict with the results of Galbraith *et al.*[1,3] and of Lowy *et al.*[2]

In an uncontrolled study. Galbraith *et al.*[1] reported 'clinically significant hair regrowth' in seven of nine patients with AT. In a subsequent investigation they performed a randomized, placebo-controlled, double-blind, cross-over study of inosine pranobex in AT.[3] Thirty-four patients were enrolled and 25 completed the study. Measurable growth of terminal hair occurred, apparently in response to active treatment, in 11 of the 25 subjects. Two patients regrew hair spontaneously (within 4 weeks of commencing treatment), and three developed

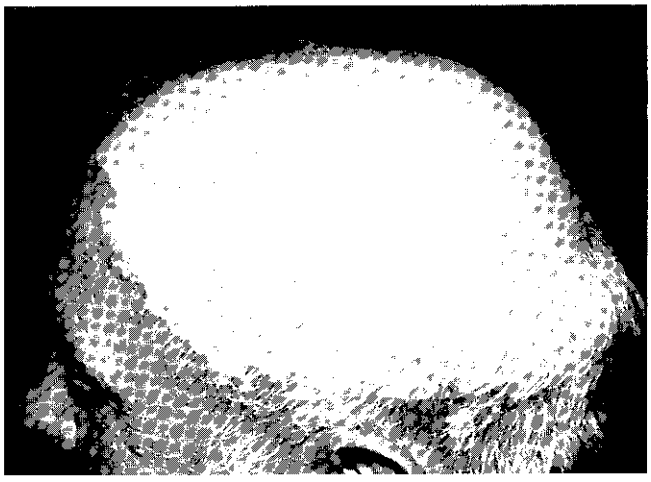

Figure 1. Vitiligo affecting the treated area in a patient who responded to diphencyprone. The treatment unmasked male pattern alopecia.

regrowth during the placebo phase. In both these studies, subjects were selected who demonstrated abnormal lymphocyte function, which we have not examined.

Lowy *et al.*[2] treated 14 patients with AA and AU in an open manner and reported a clinical response in nine of the 14 subjects and total regrowth of hair in five. The patients studied by this group were less severely affected by the disease than our own. Three of the five patients showing total regrowth had only AA. These authors reported a reduction in titre or complete disappearance of auto-antibodies following treatment. We did not detect such a trend.

In all three of these studies groups of patients with AT were treated with inosine pranobex at identical or lower dose rates, than those used in our study. Responses all developed within the period of treatment covered by our study. However, in all these studies the mean duration of alopecia was somewhat less than in ours, and the subjects were younger. The main differences between these previous studies and the present study are therefore in patient selection.

Several reports have been published of successful treatment of AA and AT by induction of contact allergic dermatitis.[4-12] This may be partly a non-specific response to inflammation, as induction of irritant dermatitis has also been effective.[13] However, allergic dermatitis appears more effective than irritant dermatitis when the two are compared.[7,10] Agents used to induce contact sensitization have included dinitrochlorobenzene,[8] squaric acid dibutyl ester,[12] diphencyprone[4-7,11] and *Primula*.[9] Diphencyprone has the advantages of a negative Ames test and a convenient shelf life.

All patients who exhibited a response to diphencyprone demonstrated a sharp mid-line boundary to the area of regrowth corresponding to the edge of the treated area. This disappeared once the other side was treated. It

is therefore most unlikely that this regrowth was spontaneous.

The overall response rate of our patients to diphencyprone was low when compared to some other studies. MacDonald Hull and Norris[4] reported that 39% of subjects with long-standing AT regrew cosmetically acceptable hair after treatment with diphencyprone. The overall duration of the disease in their subjects was similar to that in our own, but they did not report the duration of total alopecia in those subjects with AT. Happle *et al.*[6] reported a response in 23 of 27 patients, 22 of whom had AT. These authors did not provide any indication of the duration of the alopecia. Orecchia and Rabiosi[11] reported that only one of 26 patients with AA, AT and AU responded in a satisfactory manner. Ashworth *et al.*[7] recently reported a satisfactory response in only one of 17 patients with AT and this is the only previous study to examine exclusively AT and AU.

The low response rate to diphencyprone in this study was not due to a failure to sensitize, as all but two of our subjects demonstrated a dermatitis. It was not due to an inadequate duration of treatment, since most patients reported to respond to diphencyprone in previous studies, did so within the duration of the present study.

In contrast to some other studies, our subjects were clearly located at the most severe end of the disease spectrum, since all had complete AT of long duration and 15 had complete AU (see Table 1). Whilst response rates as high as 89% have been reported with AA,[4] the response rate in AT seems to be lower. The severity of the disease in the patient population investigated would therefore appear to be a possible explanation for the low response rate in our study.

The current investigation had the advantages that the patient population was relatively homogeneous in terms of disease severity and each treatment was controlled against two others. We observed a low response rate to each treatment used alone as well as in combination. There was no suggestion that inosine pranobex affected the process of sensitization to diphencyprone. It therefore seems unlikely to have been an interaction between the two treatments which resulted in such a low response rate.

When selecting patients for treatment with diphencyprone, consideration should be given to the likelihood of obtaining a worthwhile benefit. Our results indicate that AT is much less likely to respond than AA. The low response rate in AT should be explained to patients before this treatment is commenced. Unfortunately inosine pranobex did not improve the poor results in this group.

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