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CLINICAL REPORT

Inosiplex for Treatment of Alopecia Areata: a Randomized Placebo-controlled Study

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Treatment of alopecia areata remains unsatisfactory. We decided to test if systemic therapy with inosiplex (Isoprinosine®), an immunomodulator could influence the disease. Thirty-two subjects with recalcitrant alopecia areata, aged 16–48 years (mean 30.3±5.1 years), were randomized into two treatment groups of 16 subjects each. They were assigned to receive either oral inosiplex (group 1), or placebo (group 2) on a double-blind basis. Inosiplex dosage was 50 mg/kg/day in five divided doses for 12 weeks. Of the 15 evaluable patients in group 1, 5 (33.3%) had full remission, 8 (53.3%) responded partially and 2 (13.3%) did not respond. Of the 14 evaluable patients in the placebo group, none had full remission, 4 (28.5%) responded partially and 10 (71.4%) did not respond. The therapeutic difference between patients receiving active and placebo therapy was statistically significant (χ^2=7.82, p<0.01). Compared with placebo, oral inosiplex showed considerable efficacy in alopecia areata with insignificant side-effects. Larger studies are required, however, before inosiplex may be recommended as an efficacious and safe alternative systemic form of therapy for recalcitrant alopecia areata. ***Key words: alopecia areata; Isoprinosine; inosine pranobex; immunomodulation; systemic therapy.***
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Alopecia areata (AA) is a chronic non-scarring hair loss process with an unpredictable course. It accounts for about 2% of new dermatology outpatient attendances, equally affecting males and females most commonly of young age (1). Treatment remains unsatisfactory and recurrences are common. Systemic immunotherapy with inosiplex (Isoprinosine®, inosine pranobex), although initially promising, was later abandoned (2–5). We performed a randomized, double-blind, placebo-controlled trial with inosiplex in patients, who had been unresponsive to other treatments.

MATERIALS AND METHODS

Thirty-two subjects with recalcitrant AA (15 women and 17 men, mean age 30.3 ± 5.1 years) entered this study from 2000 to 2003. All patients had received other therapies, such as topical, intralesional and systemic corticosteroids, minoxidil and anthralin. Based on patient reports, the duration of disease varied from 11 to 34 months. Twenty-one patients had patchy AA, 9 had ophiasis and 2 had alopecia totalis. Patients in both groups were matched for age, sex, duration of disease and extent of involvement. No statistical significant difference between the two groups was noted.

The protocol was approved by the ethics committee of our hospital. Informed consent was obtained. Evaluation at entry included: disease history, clinical examination, blood counts, biochemistry profile and anti-thyroid antibodies. Eligibility criteria was a clinical diagnosis of AA with at least 12 months duration, lesions refractory to at least one conventional therapy, patients in good health with no contraindications for inosiplex administration, no history of local or systemic therapy, or immunosuppressive/immunomodulatory treatment within 12 weeks from study entry.

The patients were randomized using simple randomization. Subjects were assigned identification numbers (1–32) in order of recruitment, which corresponded with consecutive numbers derived from a random number table. Subjects with table numbers 0–4 were assigned to receive oral inosiplex (group 1), while subjects with table numbers 5–9 were assigned to receive placebo (group 2) given in an equal number of tablets that were identical in appearance, on a double-blind basis. The starting point of the random number table was determined so as to establish two treatment groups of 16 subjects each. Inosiplex dosage was 50 mg/kg/day, given in the form of 500 mg tablets (Isoprinosine®, Uni-Pharma Athens, Greece) in five divided doses for 12 weeks. No other topical or systemic medication was administered during the study period.

Response was evaluated by bidimensional measurements of the lesions, mapped on a schematic diagram of the scalp. The measurements were expressed as a single parameter, which was the area of the hair loss in cm^2. This study was performed at entry, every 4 weeks thereafter and at the end of therapy. Clinical evaluation was blinded. Complete response was defined as the total hair regrowth; partial response was considered as a hair regrowth equal or greater than 50%, i.e. at least 50% reduction of the affected area. No response was considered less than 50% hair regrowth. The reappearance of lesions after complete response was considered as relapse. Complete responders were followed monthly for 12 months. Partial responders and non-responders were administered other treatments. Statistical analysis involved the χ^2 test (Yates' correction included) for the comparison of proportions. The level of significance was fixed at 5%.

Toxicity was monitored, on a monthly basis, both clinically and through laboratory tests, which included complete blood counts and biochemistry profile. In case of significant toxicity, treatment was discontinued.

RESULTS

Twenty-nine patients were evaluable for response and toxicity. Three patients were withdrawn from the study

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due to poor compliance (1 subject of group 1 and 2 of group 2). The primary endpoint for evaluation of efficacy was the completion of the 12-week treatment. Of the 15 evaluable patients in group 1, 5 (33.3%) responded with complete hair growth, 8 (53.3%) responded partially and 2 (13.3%) did not respond. Of the 14 evaluable patients in group 2, none had complete hair growth, 4 (28.5%) responded partially and 10 (71.4%) did not respond. The therapeutic difference (percentage of responders) between patients receiving active and placebo therapy was statistically significant ($\chi^2 = 7.82$, $p < 0.01$). An intention to treat analysis was also performed. The therapeutic difference remained significant ($\chi^2 = 8.031$, $p < 0.01$) even when all 32 cases were considered.

In order to avoid recurrences, the dosage was slowly tapered to half (the initial dose in group 1 was 50 mg/kg daily) and was kept for the following 6 months. During that period no recurrences were noted.

Inosiplex was generally well tolerated. The safety analysis included all 32 subjects entered. Uric acid was examined as a baseline and monthly thereafter; mild elevations were detected in 6 patients in group 1 without any associated clinical effects. Patients did not mention any other side-effects. No clinical or laboratory abnormalities were noted in subjects of group 2. None discontinued treatment due to side-effects.

DISCUSSION

The results of this study support the effectiveness of inosiplex in the treatment of AA. Considering the potential of AA to resolve spontaneously, it cannot be ruled out that some of the responses were actually spontaneous remissions. However, this possibility seems less likely since the effectiveness of inosiplex was documented in comparison with placebo. But of course even a significance level of $p<0.01$ cannot totally be excluded to have arisen by chance.

The aetiopathogenesis of AA remains controversial (1). Association with classic autoimmune disorders (6), increased prevalence of organ-specific auto-antibodies, antibodies to pigmented hair follicles or to multiple structures of anagen hair follicles (7), an increase in the ratio of helper to suppressor cells (8), and induction of AA on severe combined immunodeficiency mice by transfer of T lymphocytes cultured with follicular homogenates (9) are all evidence supporting the immune-mediated pathogenesis for AA. Other proposed causal factors include genetic predisposition, infectious agents, cytokines, emotional stress, intrinsically abnormal melanocytes or keratinocytes, and neurological factors (10–13).

Inosiplex (Isoprinosine®) is a synthetic compound formed from the p-acetamido-benzoate salt of N,N dimethylamino-2-propanol and inosine in a 3:1 molar ratio (14). It is an immunomodulating agent, which has been reported to exert several immunopharmacological effects. Inosiplex is a potentiator of both T lymphocyte and phagocytic cell function (15, 16). It also enhances mitogen-dependent and antigen-dependent lymphocyte DNA synthesis (17, 18). It induces the appearance of phenotypic markers of differentiation on immature precursor T cells, augments helper or suppressor T cell functions and increases the production of lymphotoxin (19). Therapeutic investigations have focused primarily on viral illnesses, such as herpes simplex virus infections, subacute sclerosing panencephalitis, genital warts, influenza, zoster, hepatitis A or B and HIV infection (19).

Previous experience with inosiplex in the treatment of AA is limited. Galbraith et al. (2) treated 9 patients with alopecia totalis associated with T-cell function defects with inosiplex. All 9 developed enhanced T-cell function and 7 had clinically significant hair regrowth. Lowy et al. (3) treated 14 patients with AA, including cases of total AA associated with immunological abnormalities. Nine of them responded to inosiplex therapy. Of the responders, 7 had auto-antibodies prior to treatment that decreased or disappeared after treatment. Of 24 patients with alopecia totalis and associated defects of cell-mediated immunity treated with inosiplex on a double-blind basis, 11 patients were identified as responders with the majority of them exhibiting enhanced immune function (4). In contrast, Berth-Jones & Hutchinson (5) investigated treatment of alopecia totalis with a combination of inosiplex and diphencyprone compared with each treatment alone. They did not find any therapeutic value of inosiplex in alopecia totalis.

Existing data indicate that inosiplex is an immunomodulating agent that augments cell-mediated immunity. Since defects of cell-mediated immunity have been incriminated in the pathogenesis of AA, the restoration of such defects possibly explain the efficacy of inosiplex in AA. Furthermore, it can be speculated that inosiplex may exert its beneficial effect by decreasing the auto-antibody titres in patients with AA.

Although other treatments had failed in our patients, inosiplex in some cases clearly arrested rapid deterioration, providing a satisfactory cosmetic result, and most importantly without any side-effects. More and larger studies are required though before inosiplex might be considered as a therapeutic option in AA.

Conflicts of interest: None reported.

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