

# Low Dose Cyclosporine and Prednisolone Combination in the Treatment of Diffuse Alopecia Areata and Alopecia Universalis<sup>†</sup>

## DİFÜZ ALOPESİ AREATA VE ALOPESİ ÜNİVERSALİS TEDAVİSİNDE DÜŞÜK DOZ SİKLOSPORİN VE PREDNİZOLON KOMBİNASYONU

Atilla ÖZCAN\*, Mustafa ŞENOL\*, Serpil ŞENER\*,  
Yelda KARINCAOĞLU\*, Sezai ŞAŞMAZ\*, Başak KANDİ\*

\* Dept. of Dermatology, Medical School of İnönü University, Turgut Özal Medical Center, Malatya, TURKEY

### Summary

Alopecia areata is a nonscarring and refractory hair disease. The exact etiology is unknown and the treatment is difficult. The aim of this study was to determine the efficacy of low dose cyclosporine and prednisolone combination in the treatment of diffuse alopecia areata and alopecia universalis. Eight patients with diffuse alopecia areata and 12 patients with alopecia universalis were included in the study. The oral dose of cyclosporine was 2,5 mg/kg/day and the prednisolone dose was 20 mg/day for meanly 6 months. Cosmetically acceptable hair regrowth was observed in all alopecia areata patients and in 6 patients with alopecia universalis. Recurrences were determined 3 and 6 months later from the cessation of therapy in 2 responsive patient with alopecia areata and 6 patients with alopecia universalis.

The treatment of diffuse alopecia areata and alopecia universalis with this combination is a safe and efficacious regimen, but recurrence rates are significantly high after the cessation of therapy, especially in patients with alopecia universalis.

**Key Words:** Alopecia areata, Cyclosporine, Prednisolone

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### Özet

Alopesi areata, sebebi tam olarak bilinmeyen, özellikle difüz ve üniversal formları tedaviye oldukça dirençli, nonskatrisyel bir alopesi türüdür. Bu çalışmada, düşük doz siklosporin ve prednizolon kombinasyonunun etkinliğini belirlemek amacıyla; diğer tedavilere dirençli 8 difüz ve 12 üniversal alopesili hastaya; yaklaşık 6 ay süreyle, 2,5 mg/kg/gün siklosporin ve 20 mg/gün prednizolon tedavisi uygulandı. Difüz alopesili hastaların tamamında ve üniversal alopesili hastaların yarısında kabul edilebilir kozmetik sonuçlar elde edildi fakat, tedavinin kesilmesinden 3-6 ay sonra, 2 difüz ve 6 üniversal alopesili hastada rekürrens oluştu.

Difüz ve üniversal alopesi areata tedavisinde, düşük doz siklosporin ve prednizolon kombinasyonunu, güvenilir ve etkili bir tedavi seçeneği olmakla beraber, özellikle üniversal tipte rekürrens sıklığı çok belirgindir.

**Anahtar Kelimeler:** Alopesi areata, Siklosporin, Prednizolon

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Alopecia areata (AA) is a nonscarring, recurrent, and refractory hair disease which can poten-

tially cause hair loss in any hair bearing area. The treatment is difficult especially if the disease is in diffuse or universal forms. The exact etiology of AA is unknown. However, recent hypotheses have suggested that immune abnormalities may be an important contributing factor (1-3).

We evaluated the role of low dose cyclosporine, an immunosuppressive drug, and prednisolone combination in the treatment of diffuse AA and alopecia universalis (AU).

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**Yazışma Adresi:** Dr. Mustafa ŞENOL  
İnönü Üniversitesi Tıp Fakültesi  
Dermatoloji AD  
44069, Malatya, TURKEY

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**Materials and Methods**

Twelve consecutive patients with AU and 8 patients with wide-spread AA were included in the study. Fourteen of the patients were men (8 AA and 6 AU) (Figure 1 and 2) and 6 of them were women (all AU). Patients were examined carefully and details of the disease and history were recorded.

In all patients; complete hemogram, urinalysis, serum biochemistry, and blood pressure were performed at the beginning and monthly afterwards. A chest rontgenogram and ophthalmologic examination were performed and repeated in every 3 months. Weights of the patients were also recorded. All patients had received various local or systemic

therapies before the study, but most of them were ineffective.

In every patient, prednisolone 20 mg/day and cyclosporine 2.5 mg/kg/day was administered orally for 6 months. Same dosage of prednisolone was continued during cyclosporine treatment and diminished gradually after cessation of cyclosporine. Recurrences were determined 6 months later from the cessation of therapy in responsive patients.

Response to therapy was evaluated as the percentage of terminal hair growth in affected areas. Cosmetical acceptability was defined as complete or at least 80% sufficient hair regrowth.



**Figure 1.** A patient with diffuse alopecia areata.



**Figure 2.** A patient with alopecia universalis.



**Figure 3.** The patient on Fig 1, after treatment.



**Figure 4.** The patient on Fig 2, after treatment.

**Table 1.** Epidemiologic properties of the patients and results of the therapy with cyclosporin and prednisolone

Type of alopecia	Sex (M/F)	Age (y) (range)	Duration (y) (range)	Number of atopics	Acceptable response	Recurrence
A. Areata	8/0	18-45	2-5	2	8/8	2/8
A. Universalis	6/6	17-36	3-6	2	6/12	6/6
Total	20			4	14/20	8/14

Nonresponsiveness was defined as vellus-type or no hair growth after 6 months of the therapy. The patients were assessed clinically every month and results were tabulated at 3rd and 6th months.

### Results

Complete or cosmetically acceptable hair regrowth was observed in all patients with AA (8 males) (Figure 3) and in 6 patients with AU (6 males) (Figure 4). No satisfactory hair growth was observed in 6 women with AU. Clinically significant responses became evident in first or second months of the combination therapy. Epidemiologic properties and atopic status of the patients and results of the therapy are shown in Table 1.

Hemogram, urinalysis, serum biochemistry, renal and hepatic function tests, creatinine clearance, serum electrolytes, chest x-ray, and ophthalmologic examination were all determined as normal in all patients. Serum lipid levels increased in second month of therapy in 2 patient with AA. Serum lipids returned to normal values by an appropriate diet and antilipid drugs. Acneiform lesions occurred in 4 patients and these lesions healed after cessation of the therapy.

Recurrence occurred in 2 patients with AA and 4 patients with AU at 3rd month and in 2 patient with AU at 6th month. So, recurrence occurred in all the responsive patients with AU and hair growth persisted in 6 of the responders with AA.

### Discussion

The cause of AA is unknown. A number of potential etiologies have been postulated over the past century, most popular one being that AA is an

autoimmune disease. Since the disease is likely to be complicated by concomitant autoimmune diseases such as SLE, Hashimoto disease, Sjögren syndrome, and to be of atopic constitution, AA is assumed to be related to immune abnormalities (2,4). Lymphocytic infiltrates have been observed around late anagen hairs as well as within the hair follicle in the acute progressive stage of AA. Inflammatory cells, primarily CD4+ lymphocytes and Langerhan's cells, are present in the peribulbar and perivascular areas and in the external root sheath of the follicular epithelia (5). Deposits of T cells and interleukins which related to immune abnormalities in the hair matrices of patients with AA have been reported (2). Anagen hair bulb keratinocytes normally lack expression of MHC class I and class II antigens (6). In AA, human leukocyte antigens (HLA)-A, HLA-B, HLA-C, and HLA-DR are all expressed on anagen hair bulbs. Expression of these antigens in AA would permit a long-standing interaction of cytotoxic T lymphocytes with hair matrix cells. Homing of T lymphocytes to lesions of AA may be regulated by adhesion molecules (7). E-selectin, endothelial leukocyte adhesion molecule-1 (ELAM-1), vascular cell adhesion molecule-1 (VCAM-1), and intracellular adhesion molecule-1 (ICAM-1) have all been described on endothelial cells in AA (8).

While the exact mechanism of action is unclear, cyclosporine affects the early phase of T-cell activation. It inhibits the interaction between antigen presenting cells and T cells required for the synthesis and release of interleukin 1 (IL-1). Cyclosporine also inhibits the transcription and release of IL-2, and the expression of IL-2 receptors, preventing primary T-cell activation and clonal expansion of activated T cells such as cytotoxic cells (9). Gupta et al found a significant decrease in

the perifollicular CD4/CD8 ratio early in the course and throughout the treatment in their patients with AA treated with cyclosporine (10). In some previous studies, large doses of cyclosporine (6.0-7.5 mg/kg) have been used, unfortunately high doses of cyclosporine could cause many side effects. In addition, a short period after the cessation of therapy, relapses have often been seen (3,11,12).

The mechanism of action of systemic steroids in AA is speculated to be immunomodulatory. Steroids decrease the production and/or secretion of IL-1, IL-2, and monocyte chemotactic factor. Systemic steroids have also been shown to induce a significant decrease in the peripheral helper/inducer T-cell population in atopic subjects as compared with controls (12,13). Various therapy regimens (60 mg/day or pulse doses) have been used in the treatment of AA (14,15). Side effects of high dose systemic steroid are relatively common. In addition, significant hair loss have rapidly occurred after discontinuation of large doses of steroid therapy (11).

Because many side effects were evident during the administration of high doses of cyclosporine and steroids, Teshima et al have used a combination consisting of low dose cyclosporine and prednisolone in the treatment of AA. They observed that serum concentration of cyclosporine elevated due to synergism with the steroid hormone through mutual competitive inhibition of hepatic microsomal enzymes. They suggested that hair continued to grow more than 6 months after cessation of cyclosporine in their all 6 cases (4).

In our study, complete or cosmetically acceptable hair regrowth was observed in our 8 patients with AA and 6 of the 12 patients with AU. Unfortunately, recurrence occurred in 2 patients with AA and 4 patients with AU at 3rd month and in 2 patients with AU at 6th month after the cessation of the therapy. In rest of the responders (6 patients with AA), hair growth persisted. Paquet et al did not observe any beneficial response and no histological changes were seen after a 3-month oral cyclosporine treatment in their patient with AA. They concluded that the inflammatory infiltrate of AA does not contain proliferating lymphocytes, apparently quiescent lymphocytes of AA could be less sensitive to cyclosporine than the proliferative

ones present in other inflammatory skin diseases (16). In another study, Shapiro et al observed that low dose cyclosporine and prednisone therapy was effective in only 25% of patients and remission was not durable after discontinuation of cyclosporine despite maintenance treatment with low dose prednisone (17).

We conclude that treatment of diffuse AA and AU with low dose cyclosporine and prednisolone combination is a safe and efficacious regimen, especially in men, but recurrence rates are significantly high after cessation of the therapy, especially in patients with AU. As concluded in some previous studies (16,17), women, especially with AU, are not good candidates for this regimen.

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