Table 5 Follow-up results of patients with excellent response to Diphencyprone

Patients with maintenance therapy Relapse/total number (%)	Patients without maintenance Relapse/total number (%)	*P*-value
7/39 (17.9)	4/7 (57.1)	0.025

immune privilege as the main cause of AA, the anagen hair bulb represents an immune privileged site characterized by the absence of major histocompatibility complex (MHC) class I expression and the presence of immunosuppressive cytokines such as TGF-β (transforming growth factor β). Infections, follicular microtrauma or microbial superantigens may induce the release of the proinflammatory cytokine, IFN-γ, inducing the ectopic expression of MHC class I and class II molecules on follicular bulb cells. This, in turn, could lead to the induction of $CD8^+$ and $CD4^+$ T cells targeted to newly exposed follicular antigens, which are normally sequestered from immune recognition. This immune dysregulation could induce hair loss in AA through multiple mechanisms including: Direct cytotoxicity by $CD8^+$ T cells, natural killer cells (NK), or NK-T-cell activity; Antibody dependent cell-mediated cytotoxicity (ADCC); Apoptosis of hair follicle keratinocytes in a Fas–Fas ligand interactions and cytokine-induced inhibition of the hair cycle.[17]

Through its immune-modulating effect, immunotherapy reverses these changes. Skin treated with topical sensitizers shows a decrease in peribulbar CD4/CD8 ratio. There is a shift in the position of T lymphocytes from the perifollicular to the interfollicular area.

Also, there is a decline of intrabulbar CD6 +ve lymphocytes and Langerhans cells.[18] There is disappearance of class I and II MHC molecules normally present in areas affected with AA.[19]

The earliest theory suggested that immunotherapy may attract a new population of T cells into the treated area of the scalp, which could eliminate the antigenic stimulus present in AA. Another theory later proposed the concept of antigenic competition in which recruited suppressor CD8 T cells presumably exert a non-specific inhibitory effect on the immune response against hair follicles, thereby permitting hair growth.[20]

Immunotherapy may interfere with the initial or continued production of proinflammatory cytokines by the follicular keratinocytes.[21] All the above may lead to restoring relative immune privilege allowing the hair follicles to grow normally.

Most of the AA patients show localized patches of acute hair loss, where regrowth is observed spontaneously or with simple topical treatment within few months. In up to 15% of patients severe forms of disease can develop with total scalp (alopecia totalis) or scalp and body hair loss (alopecia universalis). Although spontaneous remission is possible in these cases, it occurs rarely and treatment is difficult.[22] We felt it was justified to apply DPC on the whole scalp from the beginning of therapy as all of our patients had extensive alopecia for over 6 months duration (with the exception of three cases) and also to avoid the poor cosmetic appearance of unilateral hair growth. In this study, excellent response (>75% growth of terminal hair) was achieved in 56.7% of cases in a median time of 12 months (95% CI 11.2–12.8 months). These results are similar to several studies conducted earlier[14,15,21,23] where the overall response rate ranged from 48% to 63% of cases.

In a study by Cotellessa *et al.*,[21] 48% of patients with extensive AA treated with DPC (42 with >90% and 14 with 30–90% area of scalp) showed regrowth of terminal hair all over the scalp after 6 months of therapy. Our results in these groups of patients are better probably due to the longer median treatment period in our case (12 months) in addition to higher percentage of DPC used in selected cases.

In our study, an excellent response was seen in 100% of patients with Grade 1 AA (25–49%) in a median time of 6 ± 0.4 months, 77% of patients with Grade 2 AA (50–74%) in a median time of 12 ± 0.8 months, 54% of patients with Grade 3 AA (75–99%) in a median time of 12 ± 0.8 months, 50% of AA totalis patients in a median of 12 ± 1.17 months and finally 41% of AA universalis patients in a median of 18 ± 5.5 months. Compared with previous reports, Wiseman *et al.*[23] reported >75% growth of terminal hair in 100% of patients with 25–49% AA, 88.1% of cases with 50–74% AA and 60.3% of cases with 75–99% of AA, which is similar to our results. In patients with AA totalis and Universalis, however, our results showing an excellent response in 50% and 41% of AA totalis and AA Universalis cases respectively are better than those reported by Wiseman *et al.*[23] in which >75% Terminal hair regrowth was seen in only 17.4% of cases; this may be explained by the larger sample size in our case comprising 66 patients compared with 35 in Wiseman's study.

Several factors that allow prediction of poor prognosis have been proposed in previous studies.[5,9,14,23,24] Weise *et al.*[24] demonstrated five factors of prognostic significance: presence of nail changes, personal history of atopy, duration of AA, extent of AA and age at the onset of disease. Different studies produced variable results as regard these prognostic criteria. Wiseman *et al.*[23] confirmed a positive correlation with the extent of AA and age at onset of disease, while Costellessa *et al.*[21] suggested a relation to duration of AA, nail changes and history of atopy. Hull and Norris[25] found no statistically significant differences in age or duration of alopecia between those who re-grew hair and those who did not. In our study, the only factor that affected the treatment outcome was the extent of AA at the onset of treatment (*P*-value = 0.038). Unlike previous reports, all other factors did not affect prognosis. A cause of this variation may be different method of assessment of response to DPC therapy.

Similar to other studies[21,23] reported, side-effects in our study included severe irritation and blistering in 14% of cases controlled by rest for one week, systemic antihistaminics and topical steroids and hyperpigmentation in 5.2% controlled by bleaching agents