

Successful Treatment of Granuloma Annulare with Imiquimod Cream 5%: A Report of Four Cases

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Sir,

Granuloma annulare (GA) is a benign and usually asymptomatic granulomatous dermatosis characterized by erythematous, violaceous or skin-coloured necrobiotic papules, often fused into annular arrangements, that most commonly affect the extremities. Although it may resolve spontaneously, GA is frequently resistant to treatment. A variety of topical or systemic therapeutic modalities has been used in its management with varying success (1–3). To our knowledge, there is only one case report of imiquimod, a novel immune response modifier, being therapeutically active in GA (4). We therefore conducted a pilot study to evaluate the efficacy and safety of imiquimod 5% cream in the treatment of this disorder.

CASE REPORTS

Four patients (two women and two men aged 40–56 years) with a 24–36-month history of histologically confirmed GA

were included in the study (Table I). In all patients one (patients nos 1 and 2) or multiple lesions (patients nos 3 and 4) were localized on the extremities and had previously been treated with a variety of topical and systemic drugs that were ineffective. Topical and/or systemic treatment had been discontinued in all patients at least 6 months prior to the onset of imiquimod therapy. Routinely performed haematological, biochemical and serological investigations revealed no abnormalities. The treatment regimen was discussed with the patients, who gave their informed consent, and consisted of spot application of imiquimod 5% cream to the cutaneous lesions once daily. The medication was left on the lesional skin for 10–12 h without occlusion and was then removed by washing.

Patient no. 1 initially applied imiquimod three times/week in order to avoid, as she claimed, the occurrence of 'serious adverse reactions'. Five weeks after onset of this mode of therapy her lesions started to flatten and fade, but after two further weeks the therapeutic response was moderate. Thus, she decided to fully comply with the given guidelines and after 6 weeks of daily application she revealed a complete remission of her lesions. In patients nos 2, 3 and 4 the first signs of therapeutic response were clearly evident 2–3 weeks after onset

Table I. Characteristics and response to topical imiquimod treatment of four patients with granuloma annulare (GA)

Patient no.	Age (years)/sex	History of GA			Imiquimod 5% Treatment			
		Duration (months)	Previous treatment	Location of GA (no. of lesions)	Application	Duration (weeks)	Outcome	Follow-up
1	40/F	28	TS, OA, OS	Left foot (1)	3 × /week	7	Moderate response	–
					1 × /day	6	Complete remission	14 months, no recurrence
2	55/M	24	TS, OS, OA	Right hand (1)	1 × /day	7	Complete remission	10 months, no recurrence
3	56/F	36	TS, OS, D	Both hands (multiple)	1 × /day	8	Complete remission	12 months, no recurrence
4	47/M	32	TS, OS, RA	Right hand and forearm (multiple)	1 × /day	12	Complete remission	Recurrence after 10 days
					1 × /day	6	Complete remission	18 months, no recurrence

TS, topical steroids; OA, oral antimalarials; OS, oral steroids; D, dapsone; RA, all-*trans* retinoic acid.

of treatment in terms of reduction of erythema and infiltration. Patients nos 2 and 3 showed a complete remission after 7 and 8 weeks of daily imiquimod application, respectively. The lesions of patient no. 4 completely resolved after 12 weeks of treatment. However, 10 days after discontinuation of his treatment a relapse of GA was observed. Topical imiquimod was then restarted and resulted in a complete remission of the skin lesions after 6 further weeks of treatment. None of the patients experienced local or systemic side effects. Subsequent to discontinuation of treatment all patients have been followed-up for 10–18 months and revealed no recurrence.

DISCUSSION

GA is thought to represent a delayed-type hypersensitivity reaction (2) characterized by the occurrence of interferon-gamma-producing Th-1 lymphocytes that contribute to the activation of macrophages expressing tumour necrosis factor (TNF)-alpha and matrix metalloproteinases responsible for matrix degradation (5). Imiquimod, the first member of the imidazoquinoline family of immune response modifiers, was licensed for the treatment of external genital warts but also has proven favourable clinical efficacy in a variety of viral dermatoses and cutaneous neoplasms (6). It exerts its antiviral and antitumour effects, at least in part, through binding to Toll-like receptors on monocytes, macrophages and dendritic cells followed by secretion of proinflammatory cytokines (7) and reveals considerable direct proapoptotic activity against tumour cells (8). However, the question as to which of these effects of imiquimod are involved in the mechanisms of its therapeutic action in GA at the molecular level remains to be elucidated.

As far as we know, there is only one case report on the treatment of GA with topical imiquimod. Kuwahara et al. (4) reported on a 12-year-old girl with GA who was successfully treated with daily application of imiquimod for 6 weeks but provided no data with regard to the duration of the remission observed.

As GA is a self-limiting disease, the possibility that its complete remission in all patients was coincidental and unrelated to imiquimod therapy cannot be definitely ruled out. However, this possibility seems very unlikely in view of the refractoriness of their lesions over a period

of 2–3 years, the prompt response of GA to topical imiquimod (patients nos 2, 3 and 4), the dose-dependent response seen in patient no. 1 and the fact that the biopsy of the lesional skin, that might have influenced the course of the disease, had been performed in all patients at least 18 months prior to the onset of imiquimod therapy. The results of our study indicate that management of GA with topical 5% imiquimod cream seems to be an effective, well tolerated, easy and patient-applied treatment modality. Nevertheless, large-scale, double-blind, placebo-controlled studies are now warranted to fully explore the efficacy and safety of this promising compound in the treatment of GA.

Conflicts of interest: none reported.

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