and tumour necrosis factor α. Furthermore, the neutralization of interleukin 27 led to a reduction in messenger ribonucleic acid levels of T helper 1 cytokine/chemokines including tumour necrosis factor α and induced improvement both clinically and histologically.

Interestingly, and in contrast to previous studies and the current work, Chen *et al*.[4] reported downregulation of interleukin 27 in both serum and tissue in moderate-to-severe psoriasis. They found that injecting interleukin 27 in imiquimod-induced psoriasis mouse models, decreased the severity of inflammation.[4] Several factors may have contributed to the discrepancy in results across various studies, including ethnic differences,[4] as well as differences in disease activity and stability of the patients recruited between studies, indicating that the function of the cytokine might dynamically change at different stages of disease progression.[4,5]

Our findings show that serum and tissue interleukin 27 is upregulated in psoriasis and this upregulation is negatively affected by the severity and extent of the disease. It may thus be speculated that interleukin 27 is initially upregulated at the onset of psoriasis, but this upregulation is dampened with increasing severity and extent of disease, leading to an inadequate protective role for this cytokine on tumour necrosis factor α induced cytokines in progressive and severe disease. Large scale molecular studies are needed to confirm the dual effect of interleukin 27, in addition to clinical trials that utilize interleukin 27 inhibitors as well as activators, to identify its exact contribution in the pathogenesis of psoriasis and in the various stages of disease progression.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

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Switching immune sensitizer agents in refractory alopecia areata as a valuable therapeutic strategy a retrospective case series

Sir,

Alopecia areata is an autoimmune hair disorder that can affect any hair-bearing region of the body. Treatments include topical, intralesional, and systemic medications.[1] When considering immunotherapy, guidelines suggest using diphenylcyclopropenone, with subsequent consideration of squaric acid dibutylester in nonresponders.[2]

After approval by the local research and ethical committee (DE21-00004), a retrospective analysis of cases from the

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Table 1: Clinical characteristics of the 10 patients from the immunotherapy clinic database

Characteristic										
Patient #	1	2	3	4	5	6	7	8	9	10
Gender	F	M	F	F	M	F	F	F	M	F
Age (years)	8	10	20	17	16	35	17	8	10	47
Personal medical history	Allergic rhinitis, generalised anxiety disorder	–	Vitiligo	Allergic rhinitis	–	–	Obesity, separation anxiety disorder, hypertriglyceridemia, hypothyroidism	Atopic dermatitis	Major depression	Syphilis
Duration (years)	4	5	19	3	11	20	15	2	4	7
# Episodes	1	1	2	1	1	1	2	1	1	2
Clinical variant of AA	AU	AU	AT	AT	AU	AT	AU	AS	AV	AT
Primary immune sensitizer	SADBE	SADBE	SADBE	SADBE	DPCP	DPCP	DPCP	SADBE	DPCP	DPCP
# Application treatments	72	80	41	47	44	45	18	35	49	26
Secondary immune sensitizer	DPCP	DPCP	DPCP	DPCP	SADBE	SADBE	SADBE	DPCP	SADBE	SADBE
# Application treatments	23	70	120	32	35	83	30	37	39	35
SALT score prior to primary sensitizer	S_5	S_5	S_4	S_4	S_5	S_5	S_5	S_4	S_2	S_4
SALT score prior to secondary sensitizer	S_5	S_5	S_3	S_4	S_4	S_4	S_3	S_3	S_2	S_3
Reason to switch to secondary contact sensitizer	Tolerance, relapse with first sensitizer	Tolerance, relapse with first sensitizer	Minimal response, lack of cosmetically acceptable outcome	Lack of response with first sensitizer	Tolerance, relapse with first sensitizer	Lack of response with first sensitizer	Development of urticaria	Minimal response, lack of cosmetically acceptable outcome	Lack of response with first sensitizer	Minimal response, lack of cosmetically acceptable outcome
Final SALT score	S_5	S_5	S_1	S_4	S_4	S_1	S_1	S_1	S_1	S_1
Response category after switch	Non responder	Non responder	Partial	Non responder	Non responder	Excellent	Partial	Partial	Partial	Partial

SALT: Severity of Alopecia Tool, S: SALT score, AA: Alopecia areata, AU: Alopecia universalis, AT: Alopecia totalis, AS: Sisaipho, AV: Alopecia vulgaris, SADBE: Squaric acid dibutyl ester, DPCP: Diphenylcyclopropenone

immunotherapy clinic database of the dermatology department at the Dr. José Eleuterio González University Hospital of the U.A.N.L., in Monterrey, Mexico was conducted. Patients who had been treated with both diphenylcyclopropenone and squaric acid dibutylester were identified. Medical records were examined and several variables were evaluated [Table 1]. Informed consent had been obtained prior to treatment. Patients were sensitized with 2% diphenylcyclopropenone or squaric acid dibutylester in a 5 cm^2 alopecic patch. After eight hours the immune sensitizer was removed and the patient returned to the clinic three weeks later for treatment starting with a low concentration such as 0.001% and gradual increments according to the patient´s response and tolerance.

Assessment of therapeutic regrowth was based on the Severity of Alopecia Tool (SALT): S0 = no hair loss, S1 = <25% hair loss, S2 = 25–49%, S3 = 50–74%, S4 = 75–99% and S5 = 100% hair loss. Clinical response was classified as excellent (>75% reduction in SALT score), partial (reduction 25–74%), and minimal response (reduction of <25%). Patients were classified as non-responders when the SALT score remained unchanged.[3,4] If there was no hair regrowth, nor a cosmetically acceptable outcome, patients were switched to a second sensitizer, depending on which one they received initially. Ten patients treated with both agents were identified from a total of 54 patients treated at the immunotherapy clinic from September 2009 to November 2020, seven females and three males, ages ranging from 8 to 47 years. The alopecia areata pattern was universalis in 5 (50%), totalis in 3 (30%), sisaipho in 1 (10%) and vulgaris in 1 (10%).

The SALT score before squaric acid dibutylester as initial treatment was S_5 in two patients and S_4 in three. The SALT score at the time of switching, was S_5 in two, S_4 in one and S_3 in two. Two initially responded to the primary sensitizer but developed tolerance, two had a minimal response and one had

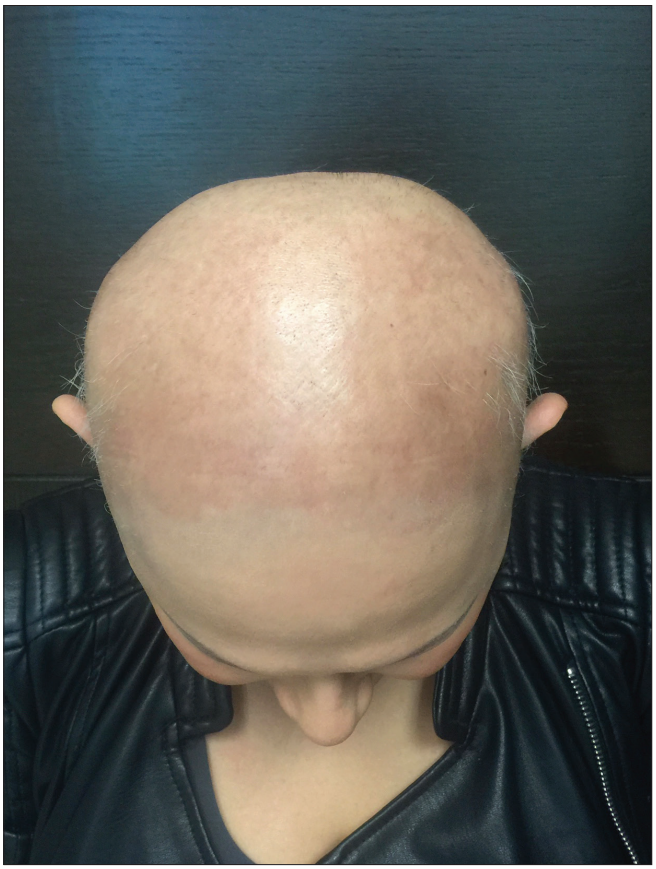

Figure 1a: 35-year-old woman with alopecia areata universalis. Baseline after four treatment applications with primary contact sensitizer diphenylcyclopropenone, SALT score S5

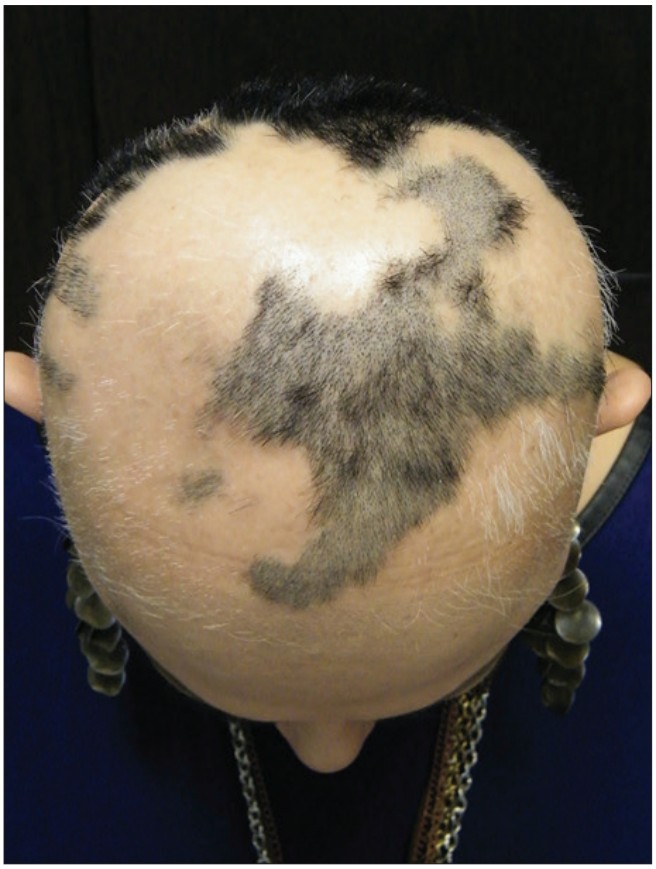

Figure 1b: Same patient, SALT S4 after 40 treatments with diphenylcyclopropenone, prior to switching to squaric acid dibutyl ester as secondary contact sensitizer

Figure 1c: Patient after switching to squaric acid dibutyl ester as secondary contact sensitizer. SALT S1 after receiving 20 treatments

Figure 1d: Patient after receiving 36 treatments with squaric acid dibutyl ester, still SALT S1, thought with better cosmetic results

Figure 1e: Follow-up of same patient after 80 treatments with secondary contact sensitizer (squaric acid dibutyl ester), SALT score S1. Minimal lesions remained. Excellent cosmetic results

no improvement. When switched to secondary agent, three continued to be unresponsive and two improved from S_3 to S_1 achieving a partial response.

Before treatment with diphenylcyclopropenone as the first sensitizer, the SALT score was S_5 in three, S_4 in one and S_2 in one. The SALT score at the time of switching to squaric acid dibutylester was S_4 in two, S_3 in two and S_2 in one. One patient developed tolerance to diphenylcyclopropenone, one had minimal improvement, two had lack of response and one was switched to squaric acid dibutylester because of urticaria. Four improved to S_1, including the latter achieving an excellent response in one and a partial response in the other three, thus one continued to be unresponsive.

Switching was done after 18–80 treatments corresponding to 5–20 months. Side effects were observed in all patients, the most common being pruritus and erythema. Patients showing benefit with the second sensitizer, continue to have adequate disease control and are scheduled every 2–3 months for immunotherapy of limited affected areas.

Alopecia areata is a chronic relapsing disease with an unpredictable course. Patients with <40–50% patchy scalp involvement may present spontaneous regrowth within one year from onset without treatment. In more severe cases, topical immunotherapy has been used with encouraging results.

Information is lacking regarding the real benefit and expectations when treating with a secondary agent when unresponsive to a first sensitizer.[1] Van der Steen *et al.* reported the use of squaric acid dibutylester in 15 patients who developed tolerance to diphenylcyclopropenone showing total regrowth in three and cosmetically acceptable regrowth in four, helping almost half of re-treated patients.[5]

In our study, six patients had excellent outcomes achieving a final S[1] score and remarkable cosmetic results [Figures 1a–e]. Although an S0 score was not achieved, and limited lesions remained, the quality of life was strikingly improved. While more studies are required to reach definitive conclusions, it seems that trying a second sensitizing agent after an initial failure to respond, might help nearly half of re-treated patients according to our experience and the Van DerSteen report.[5]

Immunotherapy continues to be a first-line therapeutic alternative due to its excellent safety profile and adequacy for long-term use. It seems that there is a potential value in re-treatment with a second contact sensitizer in non-responders or in those who have developed tolerance. Based on our small study, we could suggest that switching to squaric acid dibutylester might provide better results than switching to diphenylcyclopropenone.

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Declaration of patients consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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