Patient preferences for curettage followed by imiquimod 5% cream versus surgical excision for the treatment of non-facial nodular basal cell carcinoma: A discrete choice experiment

ZnO was found to be effective. Given its excellent safety profile,[10] topical STS appears as a promising treatment option for calcinosis cutis. However, the optimum composition and therapeutic effectiveness in a larger number of patients remain to be evaluated in future trials.

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Conflict of interest

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References

1 Bair B, Fivenson D. A novel treatment for ulcerative calcinosis cutis. *J Drugs Dermatol* 2011; **10**: 1042–1044.
2 Ma JE, Ernste FC, Davis MDP, Wetter DA. Topical sodium thiosulfate for calcinosis cutis associated with autoimmune connective tissue diseases: the Mayo Clinic experience, 2012–2017. *Clin Exp Dermatol* 2019; **44**: e189–e192.
3 Deen J, Byrom L, Robertson I. Calcinosis cutis associated with chronic sclerodermoid graft versus host disease: a case and review of the literature. *Case Rep Dermatol Med* 2020; **2020**: 9250923.
4 Saardi KM, Rosenstein RK, Anadkat MJ *et al*. Calcinosis cutis in the setting of chronic skin graft-versus-host disease. *JAMA Dermatol* 2020; **156**: 814–817.
5 Jiménez-Gallo D, Ossorio-García L, Linares-Barrios M. Calcinosis cutis and calciphylaxis. *Actas Dermosifiliogr* 2015; **106**: 785–794.
6 Badawi AH, Patel V, Warner AE, Hall JC. Dystrophic calcinosis cutis: treatment with intravenous sodium thiosulfate. *Cutis* 2020; **106**: E15–e17.
7 Sowers KM, Hayden MR. Calcific uremic arteriolopathy: pathophysiology, reactive oxygen species and therapeutic approaches. *Oxid Med Cell Longev* 2010; **3**: 109–121.
8 Howard RM, Smith GP. Treatment of calcinosis cutis with sodium thiosulfate therapy. *J Am Acad Dermatol* 2020; **83**: 1518–1520.
9 Brandt S. The clinical effects of zinc as a topical or oral agent on the clinical response and pathophysiologic mechanisms of acne: a systematic review of the literature. *J Drugs Dermatol* 2013; **12**: 542–545.
10 von Hodenberg C, Neufeld M, Wohlrab J, Meyer D, Ehrchen J, Sunderkötter C. Topical sodium thiosulfate: a reliable treatment for digital calcinosis cutis - a case series with six patients. *J Dtsch Dermatol Ges* 2020; **18**: 1181–1183.

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Patient preferences for curettage followed by imiquimod 5% cream vs. surgical excision for the treatment of non-facial nodular basal cell carcinoma: a discrete choice experiment

Dear Editor

To evaluate patient preferences for the treatment of non-facial nodular basal cell carcinoma (nBCC), a discrete choice experiment (DCE) was performed alongside a clinical trial that compared curettage followed by imiquimod 5% cream and surgical excision.[1] The attributes used to describe the treatment options were as follows: effectiveness,[2–8] cosmetic outcome[3] and waiting time and side-effects[3] (Table 1).

Table 1 Discrete choice experiment attributes and their levels

Attributes	Treatment options	
	Surgery	**Curettage + IMQ**
Cosmetic outcomes	**Good** Scar is barely visible	**Good** Treated skin has the same colour as normal skin
	Moderate Visible scar	**Moderate** Treated skin is slightly darker/lighter than normal skin
	Bad Clearly visible scar	**Bad** Treated skin shows strong discoloration/uneven surface compared to normal skin.
Chance of complete clearance one year after treatment (%)	98% 96% 94%	94% 90% 86%
Waiting time	0 weeks 4 weeks 6 weeks 8 weeks	0 weeks
Side-effects during and after treatment	**No side-effects** **Mild-moderate** Pain, but no need for pain medication/disturbing sleep **Severe** Pain with need for pain medication/disturbing sleep	**No side-effects** **Mild-moderate** Mild-to-moderate irritation, burning or redness, mild-to-moderate pain or superficial erosions **Severe** Severe irritation, burning or redness, pain, deep erosions. Flu-like symptoms

An efficient labelled design was created using Ngene software (version 1.1.1) (Choice metrics, Sydney, New South Wales, Australia) with information used from a pilot study. In total, 36 hypothetical choice sets were generated and blocked into three questionnaires with 12 choice sets.

Respondents were asked to choose either curettage and imiquimod or excision in a labelled design because the treatment differed in invasiveness and consequently had specific levels for each attribute.

Data analysis was performed using a multinominal logit (MNL) model with Nlogit software version 5. Based on the results of the MNL model, a simulation analysis was performed to examine the uptake of both treatments.

One hundred and ten patients completed the questionnaire from January 2016 until March 2017, all with informed consent. Median age was 67 (28–91) years old. Twenty-nine per cent of the respondents had experience with both treatments. Respondents preferred a higher level of effectiveness and no side-effects. Both a good and a moderate cosmetic outcome with curettage followed by imiquimod were positively valued. For excision, a good cosmetic outcome was positively appreciated, both moderate and bad cosmetic outcomes were considered negative. Severe side-effects are negatively valued in both treatments, while the attribute waiting time was not statistically significant (Table 2).

Overall, patients choose surgery in 60% and curettage and imiquimod in 40% of the choice sets. Patients from the clinical trial choose curettage and imiquimod in 57% of the choice options while those outside the trial choose this treatment in 29% of the choices. Patients having experience with both treatments almost equally made a choice for curettage and imiquimod (49%) or excision (51%).

Overall, patients preferred excision in 60% of the choice sets over curettage and imiquimod (40%). An explanation could be the inclusion of a large number (n = 69/63%) of patients from outside the clinical trial. The inclusion of the patients for the clinical trial was going slowly which led to the decision to include patients from outside the trial. However, patients that are willing to participate in a randomised trial often are open to new treatments. It seems plausible that patients outside the trial choose surgical excision more often since that is the standard care. Although this could introduce status quo bias which means that patients prefer what they have experienced, we think that including patients from in- and outside the trial resulted in a higher patient diversity that is a better reflection of the population with a nBCC. Still, this could also be considered a limitation because the groups are unevenly divided.

Our results represent the average preference weighing the importance of different aspects of treatment of nBCC: efficacy, side-effects, cosmetic outcomes and waiting time. The clinical trial showed a lower efficacy for curettage followed by imiquimod 5% cream (86.3%) as compared to surgical excision (100%).[1] However, since the 86.3% efficacy of curettage followed by imiquimod 5% cream is still high, recurrences can easily be detected and treated, and this minimal invasive treatment could still be a valuable option in specific cases. The DCE results show that there might be a place for curettage followed by imiquimod cream 5% for some patients. The findings should be seen as guidance in underlining the importance of discussing every aspect of a treatment with patients to make the decision that fits to their needs.

Table 2 Main effect multinomial model

	Whole sample ***N*** **= 110**	
	Regression	
	coefficient	**95% CI**
Constant	**1.332**	−7.32 to 9.98
Curettage followed by imiquimod 5% cream		
Effectiveness	**0.057**§	0.017 to 0.096
Cosmetic outcomes		
Good	**0.414**§	0.223 to 0.605
Moderate	**0.234**‡	0.050 to 0.419
Bad	**−0.649**§	−0.843 to −0.454
Side-effects		
No	**0.443**§	0.265 to 0.621
Mild-moderate	**0.090**	−0.090 to 0.270
Severe	**−0.533**§	−0.729 to −0.337
Excision		
Effectiveness	**0.073**†	−0.007 to 0.153
Cosmetic outcomes		
Good	**0.586**§	0.398 to 0.775
Moderate	**−0.263**§	−0.451 to −0.074
Bad	**−0.324**§	−0.509 to −0.138
Side-effects		
No	**0.480**§	*0.288 to 0.672*
Mild-moderate	**0.066**	−0.120 to 0.252
Severe	**−0.546**§	−0.723 to −0.369
Waiting time	**−0.014**	−0.090 to 0.063
Number of observations	**1320**	
Log-likelihood function	−762.67	

†Significance at 10% level. ‡Significance at 5% level. §Significance at 1% level.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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References

1 Sinx KAE, Nelemans PJ, Kelleners-Smeets NWJ, Winnepenninckx VJ, Arits A, Mosterd K. Surgery versus combined treatment with curettage and Imiquimod for Nodular basal cell carcinoma (SCIN): 1-year results of a non-inferiority, randomized controlled trial. *J Am Acad Dermatol* 2020; **83**: 469–476.

2 Bath-Hextall F, Ozolins M, Armstrong SJ *et al*. Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial. *Lancet Oncol* 2014; **15**: 96–105.

3 Tinelli M, Ozolins M, Bath-Hextall F, Williams HC. What determines patient preferences for treating low risk basal cell carcinoma when comparing surgery vs imiquimod? A discrete choice experiment survey from the SINS trial. *BMC Dermatol* 2012; **12**: 19.

4 Weston A, Fitzgerald P. Discrete choice experiment to derive willingness to pay for methyl aminolevulinate photodynamic therapy versus simple excision surgery in basal cell carcinoma. *Pharmacoeconomics* 2004; **22**: 1195–1208.

5 Wu JK, Oh C, Strutton G, Siller G. An open-label, pilot study examining the efficacy of curettage followed by imiquimod 5% cream for the treatment of primary nodular basal cell carcinoma. *Australas J Dermatol* 2006; **47**: 46–48.

6 Neville JA, Williford PM, Jorizzo JL. Pilot study using topical imiquimod 5% cream in the treatment of nodular basal cell carcinoma after initial treatment with curettage. *J Drugs Dermatol* 2007; **6**: 910–914.

7 Spencer JM. Pilot study of imiquimod 5% cream as adjunctive therapy to curettage and electrodesiccation for nodular basal cell carcinoma. *Dermatol Surg* 2006; **32**: 63–69.

8 Roozeboom MH, Aardoom MA, Nelemans PJ *et al*. Fractionated 5-aminolevulinic acid photodynamic therapy after partial debulking versus surgical excision for nodular basal cell carcinoma: a randomized controlled trial with at least 5-year follow-up. *J Am Acad Dermatol* 2013; **69**: 280–287.

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Restoration of collagen and elastic fibre networks following treatment of photoaged skin with Serènesse, a novel over-the-counter anti-ageing product

Chronic sun exposure induces profound changes to the dermal extracellular matrix (ECM) resulting in the loss of fibrillin-rich microfibrils (FRM)[1] and fibrillar collagen.[2] The gold standard topical treatment for photoaged skin is all-*trans* retinoic acid (tRA).[3] The 'Manchester Patch-Test' (MPT) assay was first developed in 2001 as a short-term, exaggerated-use patch-test protocol to test the potential efficacy of topical anti-ageing products.[4] Since its inception, the assay has provided evidence that some over-the-counter cosmetic 'anti-ageing' products, as well as topical retinoids, can induce FRM deposition at the dermal–epidermal junction (DEJ) of photoaged skin.[4–6] We used the MPT assay to assess the effect of a novel, over-the-counter topical anti-ageing product (Serènesse, CG Skincare Ltd, Manchester, UK) on the dermal collagen and elastic fibre network in photoaged skin. The study was performed on 10 healthy, photoaged volunteers (mean age 73.1 ± 3.9 years; 3 M; 7F) and approved by The University of Manchester Research Ethics Committee; all subjects gave written informed consent. Test substances (vehicle and Serènesse) were applied, under occlusion, to photoaged extensor forearm for 12 days; tRA (0·025%; Retin-A® cream; Janssen-Cilag Ltd, Beerse, Belgium; 20 μL) was used as a positive control and applied for 4 days. At the end of the test period, 3-mm punch, skin biopsies were obtained under 1% lignocaine local anaesthesia from each test site and analysed histologically.

Unlike treatment with tRA, occluded application of vehicle and Serènesse for 12 days did not induce significant acanthosis of the epidermis. Immunohistochemical assessment of photoaged baseline skin identified the characteristic Grenz zone adjacent to the DEJ[7]; application of vehicle produced no significant effect on FRM deposition and the Grenz zone persisted. In contrast, application of both Serènesse and tRA resulted in significant deposition of FRMs at the DEJ and a marked diminishment of the Grenz zone ($P < 0.001$ and $P < 0.01$ respectively; Fig. 1). Reductions in fibrillar collagens are a further histological consequence of chronic photodamage[8]; however, neither tRA nor vehicle had affected the abundance of mature fibrillar collagen. In contrast, application of Serènesse significantly increased the amount of regularly ordered mature collagen bundles within the papillary dermis ($P < 0.01$; Fig. 2); however, this was not associated with *de novo* deposition of pro-collagen (data not shown). Similarly, a failure to identify changes in matrix metalloproteinase activity by *in situ* zymography suggests that remodelling of the pre-existing collagen does not occur in response to application of either Serènesse or tRA (data not shown).

Here, we demonstrate that application of a novel, over-the-counter 'anti-ageing' product – Serènesse – restores the structural architecture of photoaged dermal ECM. This finding is particularly important as remodelling and degradation of these key matrix components, particularly in ageing, cause profound structural and functional decline to overall skin health.[9] Consumers purchasing cosmetic skincare products – particularly those purporting 'anti-ageing' properties – are presented with a broad choice but only limited data regarding their efficacy. However, the results from this study are indicative of structural change in the skin following the use of a non-prescription, anti-

