ESC European Society of Cardiology

European Heart Journal - Case Reports (2022) **6**, 1–6
https://doi.org/10.1093/ehjcr/ytac187

CASE SERIES
Other

Transient injection site reaction to alirocumab during immune system activation: a case series

Sarah Bär [1], Irene Räber[2], Konstantinos C. Koskinas[1], Christoph Schlapbach[3], and Lorenz Räber [1]*

[1]Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [2]Dermatologie Thun, Thun, Switzerland; and [3]Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Received 23 February 2022; first decision 18 March 2022; accepted 28 April 2022; online publish-ahead-of-print 5 May 2022

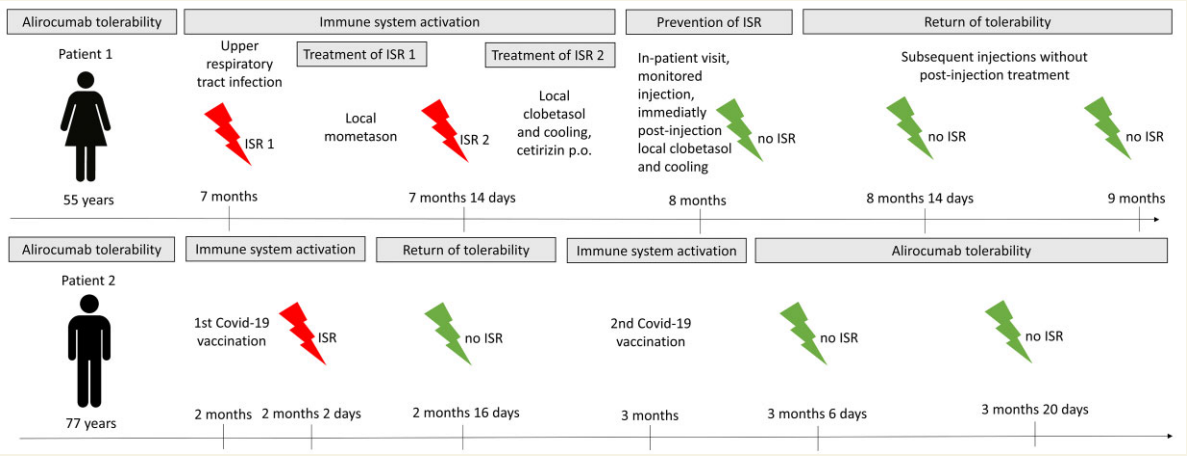
Background Injection site reactions (ISRs) are known side effects of the proprotein convertase subtilisin kexin 9 (PCSK9) inhibitor alirocumab. Transient ISR to alirocumab after a long phase of good tolerability have not been reported previously.

Case summary A 55-year-old woman (Patient 1) and a 77-year-old man (Patient 2) were treated with alirocumab for the management of dyslipidaemia. Both patients tolerated the treatment without side effects for 7 and 2 months, respectively. After an upper respiratory tract infection in Patient 1 and a first COVID-19 vaccination in Patient 2, both patients suddenly developed ISR with erythema, calor, and itching upon 2 (Patient 1) and 1 (Patient 2) subsequent injection(s), respectively. Symptoms resolved with local steroids, oral antihistamines, and cooling. After termination of the presumed immune system activated state, alirocumab was well tolerated again in both patients without recurrence of any ISR upon repeated applications.

Discussion These are the first cases to report transient ISR to a PCSK9 inhibitor, possibly triggered by activation of the immune system, after prolonged good tolerability. Based on the transient and benign nature of the reaction, such patients should be encouraged to continue supervised treatment, as tolerability may return after resolution of the pro-inflammatory state.

* Corresponding author. Tel: +41 31 632 09 29, Email: lorenz.raeber@insel.ch
Handling Editor: David Oxborough
Peer-reviewers: Adam Hartley; Tina Khan
Compliance Editor: Reshma Amin
Supplementary Material Editor: Katharine Kott

Graphical Abstract



ISR, injection site reaction.

Keywords PCSK9 inhibitor • Alirocumab • Injection site reaction • Inflammation • Case report

ESC Curriculum 3.1 Coronary artery disease • 8.3 Dyslipidaemia • 8.6 Secondary prevention

Learning Points

- Injection site reactions to proprotein convertase subtilisin kexin 9 inhibitors may occur transiently during immune system activation (triggered by infection or vaccination), even after initial good tolerability.
- Following proper treatment, tolerability may return after resolution of the pro-inflammatory state and patients should therefore be encouraged to continue treatment.

Introduction

Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors are approved for the treatment of dyslipidaemia in patients with inadequately treated low-density lipoprotein cholesterol (LDL-C) levels on maximally tolerated statin doses and ezetimibe.[1,2] Proprotein convertase subtilisin kexin 9 inhibitors are being prescribed to an increasing number of patients globally, since current European Society of Cardiology (ESC) guidelines recommend more stringent LDL-C goals across higher risk categories for atherosclerotic cardiovascular disease.[1,2] Proprotein convertase subtilisin kexin 9 inhibitors are generally well tolerated with an excellent safety profile.[3–5] However, potential side effects include injection site reactions (ISR), which occur in ~2.4–4.9% of patients.[3] Injection site reaction to biological therapies such as antibody treatment consists of localized erythema at the injection site, which can be accompanied by warming, swelling, and itching.[6,7]

We report the cases of two patients who tolerated the PCSK9 inhibitor alirocumab well for several months but developed transient ISR during a presumed activation of the immune system; following appropriate treatment, the reaction did not reoccur after termination of the suspected pro-inflammatory state. To our knowledge, these are the first cases to report a potential association between immune system activation and transient ISR to alirocumab.

Timeline

Patient 1		Patient 2	
Timepoint	**Event**	**Timepoint**	**Event**
0	Initiation of alirocumab 150 mg s.c. biweekly on the top of rosuvastatin 20 mg after STEMI and LDL-C above target	0	Initiation of alirocumab 150 mg s.c. biweekly for secondary ischemic stroke prohpylaxis in addition to

Continued

Continued

Patient 1		Patient 2	
Timepoint	**Event**	**Timepoint**	**Event**
	value (4.1 mmol/L) within the PACMAN-AMI RCT (NCT03067844)		ezetimibe 10 mg due to statin intolerance and LDL-C above target value (4.2 mmol/L)
0–7 months	Good tolerability of alirocumab	0–2 months	Good tolerability of alirocumab
7 months	Upper respiratory tract infection	2 months	First COVID-19 vaccination into the right deltoid muscle
7 months	First ISR to alirocomab at the right thigh (*Figure 1*) Treatment with local mometason	2 months 2 days	ISR to alirocumab at the left deltoid muscle (*Figure 2*) No specific treatment
7 months 7 days	Resolution of ISR symptoms, persistence of mild cough and fatigue	2 months 4 days	Spontaneous resolution of ISR symptoms
7 months 14 days	Second ISR to alirocumab at the left thigh Treatment with local clobetasol, oral cetirizine, and cooling	2 months 16 days	Alirocumab injection at the right deltoid muscle without any adverse event
7 months 21 days	Resolution of ISR and respiratory symptoms	3 months	Second COVID-19 vaccination into left deltoid muscle
8 months	In-patient visit for alirocumab injection at the abdomen with immediate application of local clobetasol and cooling with no subsequent reaction	3 months 6 days	Alirocumab injection at right deltoid muscle without any adverse event
8 months 14 days to 9 months	2 alirocumab injections at home into right thigh and left thigh, respectively, without any adverse event	3 months 20 days	Alirocumab injection at left deltoid muscle without any adverse event

ISR, injection site reaction; LDL-C, low-density lipoprotein cholesterol; RCT, randomized-controlled trial; STEMI, ST-elevation myocardial infarction.

Patient 1

A 55-year-old woman was treated with daily rosuvastatin 20 mg and bi-weekly subcutaneous (s.c.) alirocumab 150 mg for secondary prevention after ST-segment elevation myocardial infarction and marked dyslipidaemia [total cholesterol (TC) 5.8 mmol/l, LDL-C 4.1 mmol/l) in a clinical trial setting (PACMAN-AMI trial, NCT03067844). Her past medical history was notable for recurrent unprovoked pulmonary embolism. Allergic and atopic anamnesis was unremarkable. Besides lipid-lowering therapy, the patient received angiotensin-II-receptor-antagonist, metoprolol, clopidogrel, and phenprocoumon.

The lipid-lowering therapy was initially well tolerated without any side effects. After 7 months, the patient suffered from an upper respiratory tract infection with cough, rhinitis, and fever. A COVID-19 polymerase chain reaction test was negative. At the next alirocumab injection during the recovery phase of the upper respiratory tract infection, a localized erythema with diffuse borders, warming, and itching occurred at the alirocumab injection site at the right thigh within a few hours after drug administration (*Figure 1*). No other skin lesions were present, vital signs were stable, and there were no signs of systemic allergic reaction.

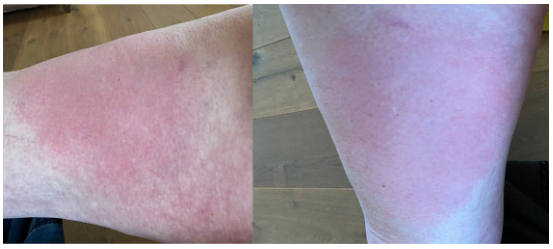


Figure 1 Injection site reaction of Patient 1.

The main differential diagnoses of sudden onset local itching erythema include irritative contact dermatitis, allergic contact dermatitis, and skin infections. The patient denied any new clothes, washing powders, shower gels, body lotions, or other cosmetic agents, potentially causative for the skin reaction. She denied recent travelling, or other affected persons in her environment. The regional and temporal relationship with alirocumab injection favoured the diagnosis of ISR, an established side effect of PCSK9 inhibitors.[3–5]

The patient was treated with local mometason (corticosteroid class III), which led to resolution of the symptoms within 7 days. At the timepoint of the next alirocumab injection 14 days afterwards, the patient still suffered from persisting mild cough and fatigue. Upon alirocumab injection, repeated ISR with larger erythema, swelling, slight pain, and strong itching occurred within minutes. The second episode of ISR was treated with local clobetasol (corticosteroid class IV), oral cetirizin, and cooling. Symptoms resolved again within 7 days. Treatment with alirocumab was not discontinued, as, also during the second episode, no signs of systemic allergic reaction had been present. For the next alirocumab application, an in-patient visit was scheduled to perform the injection under medical observation. At the scheduled visit, the patient was free of any infectious symptoms. She injected alirocumab s.c. at the lower abdomen immediately followed by application of local clobetasol and cooling. Vital signs remained stable and there were no signs of local or systemic allergic reaction during 30 min of observation. The patient was discharged and followed-up by daily phone calls for the next 3 days. No allergic

reaction occurred. The patient continued alirocumab at the regular biweekly intervals without any prophylactic post-injection treatment, and subsequent alirocumab administrations were not followed by any adverse local or systemic reaction.

Patient 2

A 77-year-old man with recurrent ischaemic cerebrovascular events and dyslipidemia developed statin intolerance with myalgias and had a TC of 5.8 mmol/l and an LDL-C of 4.2 mmol/L under ezetimibe 10 mg. PSCK9 inhibitor therapy with biweekly alirocumab 150 mg s.c. was initialized and tolerated well throughout 2 months. Allergic and atopic anamnesis was unremarkable.

After 2 months, the patient received the first dose of COVID-19 vaccination (tozinameran 0.3 ml, ©Pfizer) administered into to the right deltoid muscle. He experienced no signs of local or systemic symptoms upon vaccination. Two days later, he routinely injected alirocumab at the left deltoid muscle. An itching erythema occurred within a few minutes upon drug administration (*Figure 2*). No other skin lesions were present, and vital signs were stable, and there were no signs of systemic allergic reaction. He denied any new clothes, washing powders, shower gels, body lotions, or other cosmetic agents, denied recent travelling, signs of systemic infection, or other affected persons in his environment. Therefore, an alirocumab-induced ISR was postulated.

The patient did not apply any specific treatment and did not seek medical attention for his condition. Symptoms resolved spontaneously within 2 days. The next injection at the right deltoid muscle was well tolerated without any adverse effect. After the 2nd COVID-19 vaccination (tozinameran 0.3 ml, ©Pfizer), the patient waited 6 days before injection of the next dose of alirocumab, and no ISR occurred. Thereafter, continued treatment with alirocumab did not cause further ISR.

Discussion

Injection site reaction are established side effects of PCSK9 inhibitors occurring in 2.4–4.9% of patients.[3–5] In the largest trial of alirocumab, ODYSSEY OUTCOMES, ISR occurred in 3.8% of alirocumab-treated patients, leading to drug discontinuation in 7.2% of affected patients.[4] Pathophysiologically, ISR can be divided into two groups according to the mechanism of reaction to excipient(s) or the drug itself: irritative reactions and allergic reactions.[6,7] In irritative reactions, the causative agent triggers an unspecific activation of the innate immune system, leading to a rapid response, usually within minutes/hours after contact with the irritant.[6–8] In allergic reactions, the immune system responds to non-self-antigens or to self-proteins/-peptides, which have been modified by exogenous chemicals rendering them immunogenic (haptenization). This is followed by activation of both the innate and adaptive immune system involving IgE, IgG, complement, or T cells and can be divided into two phases: the initial sensitization phase, where the skin comes into contact with the chemical for the first time, and the elicitation phase occurring after a second encounter with the causative agent.[8] Type I allergic reactions are immediate (within minutes) reaction mediated by mast cells, IgE, and histamine. Type IV allergic reactions are delayed (within >12–24 h) reactions mediated by T cells, cytokines, and cytotoxicity.[6–8] Injection site reaction to other biological drugs have been reported to manifest during the first 1–2 months of treatment initiation and up to 1 week after injection.[9] The mean duration of reaction is 3–5 days.[10] Clinically, it is difficult to differentiate irritative from allergic ISR without further laboratory analyses or histology. However, 'recall ISR' at previous injection sites upon repeated stimuli by the agent at other locations is a typical hallmark of allergic ISR.[11]

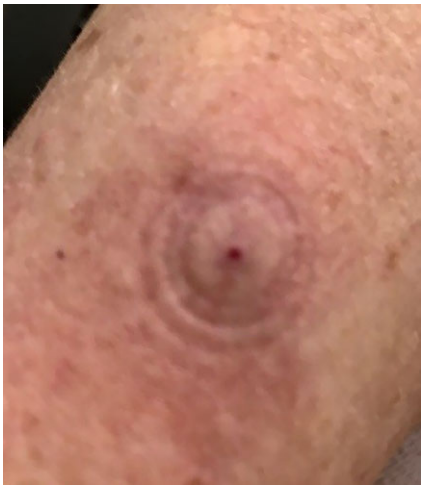


Figure 2 Injection site reaction of Patient 2.

For both types of ISR, the presence of a pro-inflammatory milieu, e.g. in the context of concomitant infections, can substantially lower the threshold for local immune reactions.[8,12] As both of our patients tolerated alirocumab initially well and showed only transient ISR during an acute activation of the immune system (upper respiratory tract infection and COVID-19 vaccination), we hypothesize that the presence of a pro-inflammatory milieu during alirocumab injection might have facilitated immune reaction against the drug (or excipients) resulting in transient ISR. Epicutaneous patch testing would be necessary to further investigate cutaneous contact sensitization to the drug or its excipients. Since both patients were able to continue therapy, we refrained from a further allergic work-up. Notwithstanding this limitation, the clinical course in both patients supports our assumptions. Patient 1 had an ISR after injecting alirocumab during an upper respiratory tract infection, which was still to some extent ongoing (mild cough, fatigue) during the second ISR but was no longer present at the time of the next (third) injection, upon which no ISR occurred. During the third alirocumab administration, immediate application of clobetasol and cooling after the injection might have prevented a third ISR;[6] however upon subsequent injections without any post-injection treatment after complete resolution of infection symptoms, no ISR recurred. Patient 2 showed an ISR upon injecting alirocumab 2 days after the first COVID-19 vaccination but not upon prolonging the interval between the second COVID-19 vaccination and alirocumab administration to 6 days. Thus, a temporal relationship between activated immune system and ISR can be established in both patients.

Injection site reactions are generally managed with local steroids, cooling, as well as oral antihistamines and systemic steroids, as needed.[6,13] Furthermore, it was shown that the incidence of ISR

can be reduced by proper skin sterilization techniques, room temperature of the injective agent, alternation of injection sites, and avoidance of sensitive skin locations,[6] all of which were applied in the presented patients at all time points. Therefore, the only changing condition was the presence of a pro-inflammatory state.

Proprotein convertase subtilisin kexin 9 inhibitors are expected to be prescribed to an increasing number of patients globally, as recently, LDL-C goals in patients with dyslipidemia have been lowered, necessitating more frequently the addition of PCSK9 inhibitors.[1,2] As ISR is one of the most frequent complications of PCSK9 inhibitors[4,5] and immune activation states occur frequently, this case series may address an important topic that should raise awareness among physicians managing patients on PCSK9 inhibitors by highlighting that unnecessary treatment cessation with these intensive LDL-lowering drugs (with associated increase in residual cardiovascular risk) should be avoided in the context of transient, and fully reversible ISR.

The strengths of the current case series are the clear temporal relationship between ISR and immune system activation in two individual patients and the close follow-up of both patients. Limitations are the lack of allergic work-up, laboratory analyses of immune parameters such as complement activation or circulating immune complexes, and histological investigations of the ISR; therefore, a definite causal relationship between presumed immune system activation and ISR cannot be firmly established, and the distinction between irritative and allergic ISR was not possible. Furthermore, widespread clinical extrapolations cannot be made on the basis of this small case series and our findings merit further large-scale investigation in the future, including immunological and histological profiling of patients with transient ISRs in the context of immune system activation. This should also be performed for the second clinically approved and widely used PCSK9 inhibitor, evolocumab.

To the best of our knowledge, these are the first two cases to report on transient ISR to alirocumab during presumed immune system activation after initial good tolerability for several (up to 7) months. Based on the transient and benign nature of the reactions, such patients should be encouraged to continue treatment under proper supervision and following appropriate therapy, as tolerability may return after resolution of the pro-inflammatory state.

Lead author biography

Sarah Bär is a Cardiology fellow at Bern University Hospital Inselspital, Switzerland. Her research focuses on coronary atherosclerosis and coronary artery disease imaging.

Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case series been obtained from the patients in line with COPE guidance.

Conflict of interest: S.B. reports research grants to the institution from Medis Medical Imaging Systems, Bangerter-Rhyner Siftung, and Abbott, outside the submitted work. K.K. has received honoraria/speaker fees from Amgen and Daiichi Sankyo. L.R. reports research grants to the institution from Abbott Vascular, Biotronik, Boston Scientific, Heartflow, Sanofi, Regeneron, Medis Medical Imaging Systems, and speaker or consultation fees by Abbott Vascular, Amgen, AstraZeneca, Canon, Occlutech, Sanofi, Vifor, outside the submitted work. C.S. has received honoraria as adviser for Abbvie, LEO Pharma, Lilly, and Novartis and has received research funding from PPM Services/Nogra Pharma. I.R. reports no conflicts of interest.

Funding: None declared.

References

1. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglu L, Wiklund O. ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2019;**2020**:111–188.
2. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida J-M, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B, De Backer G, Regitz-Zagrosek V, Aamodt AH, Abdelhamid M, Aboyans V, Albus C, Asteggiano R, Bäck M, Borger MA, Brotons C, Čelutkienė J, Cifkova R, Cikes M, Cosentino F, Dagres N, De Backer T, De Bacquer D, Delgado V, Den Ruijter H, Dendale P, Drexel H, Falk V, Fauchier L, Ference BA, Ferrières J, Ferrini M, Fisher M, Fliser D, Fras Z, Gaita D, Giampaoli S, Gielen S, Graham I, Jennings C, Jorgensen T, Kautzky-Willer A, Kavousi M, Koenig W, Konradi A, Kotecha D, Landmesser U, Lettino M, Lewis BS, Linhart A, Løchen M-L, Makrilakis K, Mancia G, Marques-Vidal P, McEvoy JW, McGreavy P, Merkely B, Neubeck L, Nielsen JC, Perk J, Petersen SE, Petronio AS, Piepoli M, Pogosova NG, Prescott EIB, Ray KK, Reiner Z, Richter DJ, Rydén L, Shlyakhto E, Sitges M, Sousa-Uva M, Sudano I, Tiberi M, Touyz RM, Ungar A, Verschuren WMM, Wiklund O, Wood D, Zamorano JL, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida J-M, Capodanno D, Cosyns B, Crawford CA, Davos CH, Desormais I, Di Angelantonio E, Franco Duran OH, Halvorsen S, Richard Hobbs FD, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B. ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**2021**:3227–3337.
3. Guedeney P, Sorrentino S, Giustino G, Chapelle C, Laporte S, Claessen BE, Ollier E, Camaj A, Kalkman DN, Vogel B, De Rosa S, Indolfi C, Lattuca B, Zeitouni M, Kerneis M, Silvain J, Collet J-P, Mehran R, Montalescot G. Indirect comparison of the efficacy and safety of alirocumab and evolocumab: a systematic review and network meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2021;**7**:225–235.
4. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema J. W, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby J-F, Tricoci P, White HD, Zeiher AM. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;**379**:2097–2107.
5. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**376**:1713–1722.
6. Thomaidou E, Ramot Y. Injection site reactions with the use of biological agents. *Dermatol Ther* 2019;**32**:e12817.
7. Corominas M, Gastaminza G, Lobera T. Hypersensitivity reactions to biological drugs. *J Investig Allergol Clin Immunol* 2014;**24**:212–225.
8. Esser PR, Martin SF. Pathomechanisms of Contact Sensitization. *Curr Allergy Asthma Rep* 2017;**17**.

9. Mocci G, Marzo M, Papa A, Armuzzi A, Guidi L. Dermatological adverse reactions during anti-TNF treatments: focus on inflammatory bowel disease. *J Crohns Colitis* 2013;**7**:769–779.
10. Thielen AM, Kuenzli S, Saurat J-H. Cutaneous adverse events of biological therapy for psoriasis: review of the literature. *Dermatol Basel Switz* 2005;**211**: 209–217.
11. Zeltser R, Valle L, Tanck C, Holyst MM, Ritchlin C, Gaspari AA. Clinical, histological, and immunophenotypic characteristics of injection site reactions associated with etanercept: a recombinant tumor necrosis factor alpha receptor: Fc fusion protein. *Arch Dermatol* 2001;**137**:893–899.
12. Martin SF, Esser PR, Weber FC, Jakob T, Freudenberg MA, Schmidt M, Goebeler M. Mechanisms of chemical-induced innate immunity in allergic contact dermatitis. *Allergy* 2011;**66**:1152–1163.
13. Bourke J, Coulson I, English J, British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for the management of contact dermatitis: an update. *Br J Dermatol* 2009;**160**:946–954.