

Journal Watch

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Which aeroallergens are associated with eczema severity?

Hon KLE, Leung TF, Lam MCA, et al.
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Eczema is a common disease in children. A variety of avoidance strategies, such as diet restriction, using air purifying machines, cleansing the mattress and pillows, avoiding pets and carpets at home, were adopted by their parents. However, aeroallergens are not adequately investigated in Chinese children. This study investigated the correlation between the presence of aeroallergen sensitization and the severity of eczema in the children. All skin prick tests (SPTs) done in patients >12 months old with eczema (total 119) were included during January 2005 to February 2006. Twelve patients who had SPTs done without eczema, urticaria and non-specific dermatitis were selected as the control. The severity of eczema over the preceding 12 months was determined by a Chinese version of the Nottingham Eczema Severity Score. The response of the SPTs was classified as 1+ (3-5 mm), 2+ (6-8 mm) and 3+ (≥ 9 mm).

Over 90% of the eczematous children had at least one positive response to SPT. The commonest sensitizing aeroallergens were *D. pteronyssinus* & *D. farinae* (70%), two common dust mites, followed by cat fur (34%) and cockroach (34%). The sensitization to dust mites was associated with the eczema severity (67% in mild group / 88% in moderate group / 97% in severity group; $p=0.001$). However, the association between the strength of SPTs response and eczema severity was not statistically significant. Sensitization to moulds, Bermuda grass, cockroach and dogs were less

prevalent and were not associated with eczema severity. Therefore, the authors concluded that specific avoidance strategies should be advised only in severely affected children who had a definitive history of eczema exacerbation by specific aeroallergens and who were not responsive to conventional treatment.

Postoperative electron beam radiotherapy for keloids: objective findings and patient satisfactory in self-assessment

Bischof M, Krempien R, Debus J, Treiber M.
Int J Dermatol 2007;46:971-5.

Keloids do not only cause cosmetic problems but also induce discomfort, pain and itchiness. Treatment is often difficult and disappointing because of a high chance of relapse. This study aimed to evaluate the role of post-operative radiotherapy in the management of keloids. During the 15 years (1987-2002) study period, 47 patients (male=16; female=31) with a total of 60 keloids were invited to answer the questionnaire addressing their satisfaction with cosmetic outcome, late effect and discomfort. The median follow-up time was 70 months (range 10 months to 13 years). The median length of keloid was 5 cm (range 2-21 cm). Keloids were mainly localized on the trunk (48%) and ear (18%). Eighty-one per cent of patients suffered from symptoms like pain and itchiness.

All keloids were excised and confirmed by histology. Then, they were subjected to 6-MeV electron plus 0.5 cm tissue equivalent bolus

material in radiotherapy as safety margin. The mean daily fraction was 4Gy (3-5Gy) up to the mean total of 16Gy (12-18Gy).

Four (4/60) keloids relapsed completely and five (5/60) keloids had limited relapse (<50% return of keloid). All relapses occurred at the high stretch-tension sites within 1 year. Twelve patients (26%) had grade 1 erythema and 29 patients (62%) had hypopigmentation. Two patients (4%) developed grade 1 telangiectasia. No malignancy was reported. Twenty-nine patients (62%) rated the treatment outcome as excellent or good and six patients (13%) described it as sufficient. However, there was a discrepancy in self-assessment outcome and objective findings. Twelve patients (25%) were not satisfied with the cosmetic outcome but only two of them relapsed completely and two had limited relapses. In contrast, one patient with complete relapse and two patients with limited recurrences rated their results as excellent or good. Thereby, the authors concluded that postoperative electron radiotherapy is effective in preventing keloid recurrence. Nevertheless, patients should be well counselled to avoid over-expectation of cosmetic outcome.

Addition of topical pimecrolimus to once-daily mid-potent steroid confers no short-term therapeutic benefit in the treatment of severe atopic dermatitis: a randomized controlled trial

Spergel JM, Boguniewicz M, Paller AS, et al.
Br J Dermatol 2007;157:378-81.

The treatment of severe atopic dermatitis is difficult and a synergistic effect is observed in vitro by combining topical pimecrolimus plus topical corticosteroid. The authors sought to assess the efficacy by comparing the outcomes of topical pimecrolimus BD (PC) + topical fluticasone (FT) daily with topical fluticasone (FT) alone. A two-week, double blinded and randomized study was conducted. Patients with severe atopic dermatitis

[modified Eczema Area & Severity Index (m-EASI) >7] were included. The study excluded patients with skin infection or other skin disorders. The patients needed to stop topical treatment for one week and systemic therapies for four weeks before starting the study.

Two target lesions with similar severity, size and location were selected. Each participant (total 45 participants) was randomized 1:1 to apply 1% pimecrolimus cream plus fluticasone (PC+FT) or vehicle plus fluticasone (V+FT). The investigators conducted the m-EASI and localized investigator global assessment (l-IGA) at day 1, 3, 5, 8 and 15 visit. The patients or the caregivers completed the Patients Self-Assessment of Disease Severity (PSA) daily.

There was no statistical difference ($p=0.262$) between the two treatment groups in terms of decline in m-EASI from baseline. In addition, time to clearance of the disease (l-IGA score of 0 or 1) in PC+FT arm (9.22 ± 4.5 days) and the V+FT arm (7.88 ± 3.8 days; $p=0.92$) was similar. The number of patients with clearance or near clearance of target sites treated with PC+FT (18 patients) was similar to the V+FT arm (17 patients; $p=0.508$). The change in PSA was similar in both treatment regimens. Thus, the authors concluded that this study did not find any short-term clinical benefit of the combination therapy in treatment of atopic dermatitis. Although long-term benefits are possible, additional studies are needed to address this possibility.

High-dose intravenous immunoglobulins for the treatment of autoimmune mucocutaneous blistering diseases: evaluation of its use in 19 cases

Segura S, Iranzo P, Martinez-de Pablo I, et al.
J Am Acad Dermatol 2007;56:960-7.

High-dose intravenous immunoglobulin (IVIg) has been used in difficult cases of autoimmune

mucocutaneous blistering diseases refractory to or contraindicated to prolonged use of high-dose systemic corticosteroids and immunosuppressive agents. The authors evaluated the outcome of the use of IVIg in 19 cases. A retrospective analysis of clinical response to monthly cycles of IVIg were performed in 10 patients with pemphigus vulgaris (PV), 2 with pemphigus foliaceus (PF), 4 with mucous membrane pemphigoid (MMP), 2 with epidermolysis bullosa acquisita, and one with linear IgA bullous dermatosis. Four of 19 cases presented a complete response (2 PV, 1 MMP and 1 epidermolysis bullosa acquisita). Five patients did not respond to the treatment (3 PV, 1 PF, 1 MMP). Ten patients had a partial response. They concluded that the effectiveness of IVIg was inferior to that previously reported. This difference could be attributed to the preparations employed (dose used and batch to batch variation), the different severity of the disease, or individual responses in each patient dependent on Fc receptor gamma polymorphisms. This study was limited by its retrospective non-controlled nature and its inclusion of a heterogeneous group of patients.

Treatment of pruritus with topically applied opiate receptor antagonist

Bigliardi PL, Stammer H, Jost G, et al.
J Am Acad Dermatol 2007;56:979-88.

Current topical treatments for pruritus are often ineffective. The authors conducted two separate studies to evaluate the efficacy of topically applied naltrexone, an opioid receptor antagonist, in the treatment of severe pruritus. Firstly an open pilot study was performed on 18 patients with different chronic pruritic disorders using a topical formulation of 1% naltrexone for 2 weeks. A punch biopsy was performed in 11 patients before and after the application of the naltrexone cream and the staining of epidermal μ -opioid receptor (MOR) was measured. Subsequently, a randomized, placebo-controlled, crossover trial was performed with the same formulation. Forty patients with localized and generalized atopic dermatitis with

severe pruritus were included. In the open study, more than 70% of the patients using the 1% naltrexone cream experienced a significant reduction of pruritus. More interestingly, the topical treatment with naltrexone caused an increase in epidermal MOR staining. The unregulation of the epidermal opioid receptor correlated with the clinical response. The placebo-controlled, crossover trial demonstrated clearly that the cream containing naltrexone had an overall 29.4% better effect compared with placebo. The formulation containing naltrexone required a median of 46 minutes to reduce the itch symptoms to 50% whereas the placebo requires 74 minutes. They concluded that the placebo-controlled study showed a significant advantage of topically applied naltrexone over the placebo formulation. This finding was supported by the biopsy results from the open studies, showing a unregulation of MOR expression in epidermis after treatment with topical naltrexone, especially in atopic dermatitis. These results clearly show potential for topically applied opioid receptor antagonist in the treatment of pruritus. This study was limited as only biopsy specimens in 11 patients were available. This means that a satisfactory statistical analysis of the changes of epidermal MOR staining was impossible. In addition, there were insufficient number of patients with nephrogenic pruritus and pruritic psoriasis to draw definitive conclusions.

Results of a randomized, double-blind, vehicle-controlled efficacy trial of pimecrolimus cream 1% for the treatment of moderate to severe facial seborrheic dermatitis

Warshaw EM, Wohlhuter RJ, Liu A, et al.
J Am Acad Dermatol 2007;57:257-64.

Seborrheic dermatitis is commonly treated with anti-inflammatory agents including topical corticosteroids. Pimecrolimus cream 1% also exerts anti-inflammatory activity by inhibiting T-cell cytokine production. The authors compared the efficacy and safety of twice-daily pimecrolimus

cream for treatment of moderate to severe facial seborrheic dermatitis. They performed a double-blind, vehicle-controlled, 4-week trial, randomizing patients with seborrheic dermatitis to use either pimecrolimus or vehicle (1:1). Clinical assessments (erythema [0-3] and scaling [0-3] combined to a total area score [0-6]) were performed at weeks 0, 2, and 4. Inclusion criteria included total area score 4 or greater and erythema 2 or greater. The pre-specified primary variable, change from baseline in total area score at week 4, was analyzed using a two-sample t test for intention-to-treat and per protocol populations. In brief, 96 adults of mean age 59.6 years, 88.5% male, were randomized (n=47 for pimecrolimus; n=49 for vehicle). At week 4, the mean change from baseline in total area score was 3.7 versus 3.3 for pimecrolimus and vehicle groups, respectively (intention-to-treat: $p=0.1913$; 95% confidence interval (CI) for difference [-0.195, 0.961]). Per protocol analysis (n=41 for pimecrolimus; n=46 for vehicle) indicated a significant difference between the two groups. The superiority of pimecrolimus was observed as early as week 2. No drug-related serious adverse events occurred. The most frequent drug-related adverse events were local, mild, and transient (pimecrolimus=26%; vehicle=12%). This study suggests that pimecrolimus cream 1% is an effective and well-tolerated treatment for moderate to severe facial seborrheic dermatitis. This study was limited as the patients recruited were primarily of male elderly patients.

Antiretroviral drug exposure in the female genital tract: implications for oral pre- and post-exposure prophylaxis

Dumond JB, Yeh RF, Patterson KB, et al.
AIDS 2007;21:1899-907.

Since the site of HIV inoculation in the context of sexual transmission is the genital tract, the authors hypothesized that oral antiretroviral drugs that achieved high concentrations quickly in the genital tract after the first dose would be the optimal

candidate for pre-exposure prophylaxis (PrPEP) and non-occupational post-exposure prophylaxis (nPEP). To evaluate the optimal antiretroviral candidates for PrPEP and nPEP, they conducted a single centre, open-label pharmacokinetic study in twenty-seven HIV-infected women.

Eleven commonly used antiretroviral medications in the three drug classes, NRTI (nucleoside reverse transcriptase inhibitors), NNRTI (non-nucleoside reverse transcriptase inhibitors) and PI (protease inhibitors), were selected. Blood plasma and cervicovaginal fluid drug concentrations during the first dose and at steady-state were measured.

For all antiretroviral drugs, genital tract concentrations were detected rapidly after the first dose. Median rank order of highest to lowest genital tract concentrations relative to blood plasma at steady state were: lamivudine (concentrations achieved were 411% greater than blood plasma), emtricitabine (395%), zidovudine (235%), tenofovir (75%), ritonavir (26%), didanosine (21%), atazanavir (18%), lopinavir (8%), abacavir (8%), stavudine (5%), and efavirenz (0.4%).

These findings support the use of lamivudine, zidovudine, tenofovir and emtricitabine as excellent PrPEP/nPEP candidates. Despite lower genital tract concentrations, atazanavir and lopinavir might be useful agents for these applications due to favorable therapeutic indices. Agents such as stavudine, abacavir, and efavirenz that achieve genital tract exposures less than 10% of blood plasma are less attractive PrPEP/nPEP candidates.

Syphilis screening and intervention in 500,000 pregnant women in Shenzhen, the People's Republic of China

Cheng JQ, Zhou H, Hong FC, et al.
Sex Transm Infect 2007;83:327-50.

To prevent mother-to-child transmission of syphilis,

the Shenzhen local government initiated a syphilis prevention and intervention programme in 2001. The authors sought to describe the epidemiology of syphilis among pregnant women in Shenzhen and also to evaluate the effectiveness of the programme.

All pregnant women who lived in Shenzhen for more than 3 months were eligible for syphilis screening by toluidine red unheated serum test (TRUST). Positive screening results were subsequently confirmed with *Treponema pallidum* particle agglutination (TPPA) test. Syphilis cases were managed according to PRC's Diagnostic Criteria and Management of Syphilis guidelines and the Guidelines for Prevention and Control of Congenital Syphilis by the US Centers for Diseases Control. Infants born to syphilis positive mother were followed up and screened for congenital syphilis by 19S-IgM FTA-Abs test.

During the four years of implementation (July 2002 and December 2005), 477,656 pregnant women (94.0%) were screened for syphilis. Two thousand two hundred and eight pregnant women (0.5%) were detected positive. Risk of syphilis was higher in those who were poorly educated, unemployed or "commercial or service personnel". Epidemiological and treatment data were collected from 2,019 syphilis cases, of whom 1,855 (91.9%) received treatment. Among 1,020 infants born to these women, 91 (9.0%) were confirmed to have congenital syphilis. Excluding the syphilis positive mother who did not have prenatal screening, the success rate of mother-to-child transmission intervention reached 99.1%.

These findings suggest that the screening and intervention programme in Shenzhen was successful. However, further work should be done to ensure earlier screening and treatment of pregnant women.

Methamphetamine use and risky sexual behaviors during heterosexual encounters

Zule WA, Costenbader EC, Meyer WJ, Wechsberg WM.

Sex Transm Dis 2007;34:689-94.

The association between methamphetamine use and sexual risk behaviors is less well-documented among heterosexual encounters than among men who have sex with men. This study examined the association between event-level of methamphetamine use and heterosexual risk behaviors.

A total of 703 out-of-treatment injecting drug users in North Carolina were recruited through street outreach. Using audio-computer assisted self interviews, data on 1213 heterosexual encounters were collected. Participants were asked a series of questions about the last time that they had sex (oral, vaginal and/or anal).

Methamphetamine was used in 7% of encounters. Methamphetamine use by either or both partners was significantly associated with an increased likelihood of anal intercourse (OR=2.41; 95%CI = 1.29-4.53), vaginal and anal intercourse (OR=2.41; 95%CI=1.22-4.77), and sex with a new partner (OR= 1.98; 95%CI=1.09-3.61). Furthermore, methamphetamine use by both partners was significantly associated with unprotected intercourse with a new partner (OR=5.20; 95%CI=2.09-12.93) and unprotected anal intercourse (OR=4.63; 95%CI=1.69-12.70).

The authors concluded that methamphetamine use during heterosexual encounters appears to increase sexual risk-taking, especially when both partners are using methamphetamine.

A single cycle of rituximab for the treatment of severe pemphigus

Joly P, Mouquet H, Roujeau JC, et al.

N Eng J Med 2007;357:545-52.

This is a prospective multicentre open trial in which 21 patients with severe pemphigus were recruited from 13 centres in France. The aim of the study was to determine the efficacy of a single cycle of rituximab. The inclusion criteria were: 1) patients' disease did not respond to an eight week course of 1.5 mg per kg body weight per day prednisone (steroid refractory disease), 2) patients had at least two relapses despite doses of prednisone higher than 20 mg per day (steroid dependent disease), 3) patients had contraindications to corticosteroid.

The diagnosis of pemphigus vulgaris or foliaceus was confirmed by histological feature of intraepidermal acantholysis and positive direct immunofluorescence deposition of IgG or complement C3 on the keratinocyte membrane.

The patients were treated with one cycle of four weekly infusions of rituximab at 375 mg per square meter body-surface area. Corticosteroid was continued at the initial dosage until the disease was controlled and then the steroid dosage was reduced gradually. Patients with contraindication to steroid were treated with rituximab alone. The primary end point was complete remission three months after treatment. The secondary end points were the rate of complete remission, the time from start of treatment to complete remission, the number of relapses, the length of time to each relapse and adverse effects.

Of 21 patients recruited, 14 had pemphigus vulgaris, 7 had pemphigus foliaceus. The mean proportion of body-surface area involved was 27%. All patients had severe oral mucosal involvement. Seven patients had one or more other mucosae involved. Five patients were treated with rituximab alone because of contraindication to steroid due to underlying conditions such as

poorly controlled diabetes, hypertension, severe infection, osteonecrosis of hip.

Eighteen patients (12 out of 14 with pemphigus vulgaris and 6 out of 7 with pemphigus foliaceus) had a complete remission at three months. Two patients with pemphigus vulgaris had a delayed remission at days 180 and 360. One patient with erythrodermic pemphigus foliaceus failed to respond to rituximab treatment.

Of the 20 patients with complete remission, nine had a relapse after a mean period of 18.9 months. Among nine relapse patients, three were treated with topical steroid, four were treated with a raised steroid dose and 2 were treated with a second course of rituximab. Both patients treated with a second course of rituximab had a complete remission. Eighteen patients were disease-free after a median follow up of 34 months. Eight patients did not receive corticosteroid. The mean dosage of prednisone needed for disease control was significantly reduced in corticosteroid-refractory disease and corticosteroid-dependent disease.

Two patients had severe side effects. One had pyelonephritis 12 months after treatment and the other died from septicemia 18 months after treatment. B-cell count decreased to 0/mm³ and remained undetectable in all but two patients until day 180. B-cells reappeared between day 180 and day 270. No major changes were noted in T-cell or natural killer cell. Anti-desmoglein 1 and anti-desmoglein 3 antibodies showed a dramatic decrease in 15 of 18 patients with complete remission at three months. Persistent high titers of antibodies were detected in two patients with delayed remission and one with failed response.

The authors therefore concluded that rituximab was effective in treating severe pemphigus with steroid-refractory or steroid-dependent diseases. Multiple cycles might not be necessary to achieve complete remission of the disease. However, the authors suggested restricting the use of additional

cycles for relapses that could not be controlled with conventional therapy.

It is important to be aware that rituximab treatment is associated with the side effect of severe infection which may result in mortality. It is not known whether the addition of intravenous immunoglobulin reduces the risk of serious infections.

Narrowband UVB phototherapy, alefacept and clearance of psoriasis

Legat FJ, Hofer A, Wackernagel A, et al.
Arch Dermatol 2007;143:1016-22.

This was a single centre prospective randomized study. It sought to determine if addition of narrowband UVB (NB-UVB) phototherapy would accelerate and improve the efficacy of alefacept in treatment of moderate to severe psoriasis.

Patients with moderate to severe plaque type psoriasis (PASI score >10) for more than six months were recruited from the authors' center in Austria in 2004. During the study period, the patients were given weekly intravenous alefacept injection (7.5 mg) for a total of 12 weeks. All patients were also treated with narrowband UVB (311 nm) phototherapy on a randomly selected body half (either left or right) three times per week until complete remission (defined as reduction of PASI to 3 or lower) of psoriasis on the treated body half.

The study end points were modified PASI, self-assessed visual analog scale rating of skin lesions and self assessed therapeutic efficacy. During the study, besides alefacept and NB-UVB phototherapy, no concomitant antipsoriatic treatment was allowed. Emollients were allowed to be used after UVB treatment had been given.

Fourteen patients (4 female and 10 male) were recruited. The mean disease duration was 22 years

(range 4-50 years) and mean age was 48 years. The mean total dose of NB-UVB delivered was 28.8 J/cm². Thirteen patients received all 12 injections of alefacept. Alefacept treatment was terminated in one patient whose CD4 lymphocyte count was below 250/ μ L for more than four weeks.

After the first 12 weeks treatment, the mean PASI on irradiated and non-irradiated body half were reduced by 81% and 62% respectively. The mean PASI for irradiated body half was significantly lower than non-irradiated counter-part. PASI 75 was observed more in irradiated body half (86%, 12 of 14) than the non-irradiated body half (43%). Complete remission (PASI \leq 3) was achieved more in irradiated body half than non-irradiated half (43% vs. 0%). PASI reduction of <50% and 25% was observed in two patients respectively. They both had a better response to combination therapy.

The patients' self-assessed visual analog scale for skin lesion severity and therapeutic efficacy were consistent with physician based PASI assessment. The self assessments showed combination therapy being more effective than alefacept alone. During the follow up period of 12 weeks after combination treatment completed, 10 patients (71%) remained clear or almost clear of psoriatic lesions and required no further phototherapy. The remaining 4 patients received at least 4 weeks NB-UVB phototherapy during follow up period and further reduction of PASI was observed.

The therapeutic effect of combination treatment was first noted within 2 to 3 weeks of treatment while the use of alefacept alone showed improvement 4 to 8 weeks after start of treatment in other studies. The adverse events to alefacept treatment were mild and short lasting. The most commonly reported event was fatigue. Other reported events were myalgia, arthralgia, headache, dizziness, nausea, diarrhea and fever. Most events occurred during the first week of alefacept and lasted for less than one day. Two patients had interruption of alefacept treatment

because the CD4 lymphocyte count fell below 250/ μ L. One patient had a CD4 lymphocyte count below 250/ μ L for more than 4 consecutive weeks and therefore alefacept was not restarted.

It was concluded that combination treatment of NB-UVB phototherapy with the biologic alefacept accelerated and improved the clearance of psoriatic skin lesions. In addition, combination therapy is a safe treatment in short term with few mild adverse events. However, long term side effects of this combination have yet to be determined, especially the risk of photocarcinogenic effect and serious infections. The comparison of combination therapy with phototherapy alone and the efficacy of combining other biologics with phototherapy also warrants further study.

Epidermal nevi treated by carbon dioxide laser vaporization: a series of 25 patients

Paradela S, Pozo J, Fernandez-Jorge B, Lozano J, Martinez-Gonzalez, Fonseca E.

J Dermatol Treat 2007;18:169-74.

This article studied the use of CO₂ laser vaporization in the treatment of verrucous epidermal nevi and to identify the factors that could influence long term results. Of 25 patients who were recruited from a centre in Spain, 24 patients had verrucous epidermal nevi and 1 had systematized nevus. Patients with inflammatory linear verrucous nevus and nevus unius lateris with epidermolytic hyperkeratosis were excluded.

The patients' mean age was 17 years old (range 3 to 41 years old). Sixteen were female and 9 were male. Eleven patients had small lesions of <20 cm², 10 patients had lesions 20-100 cm², 4 patients had extensive lesions >100 cm². The most frequent site of involvement was the trunk, followed by the neck, head and extremities.

The lesions were vaporized down to the superficial dermis with a CO₂ laser system (Frank Line SE 20-30W CO₂, Inter-medic) in superpulsed mode, focalized at 2W/cm². Seventy-six per cent of patients had multiple treatment sessions (mean number = 4, range = 1-28). Bleeding was controlled with application of saline soaked gauze compression. Postoperative care included application of occlusive dressing and antibiotic ointment.

The clinical outcome was assessed by the physician performing the procedure. Sixty-four per cent showed good results (almost complete removal of lesions without or with very superficial scar formation or minimum residual erythema), 32% showed moderate results (hyper- or hypopigmented shallow atrophic or slightly hypertrophic scars, partial removal or small recurrences of lesions), and 4% showed poor results (no remission or full recurrence of lesions or hypertrophic or keloidal scar). Good results were achieved in 92% patients with soft flattened nevi and in 33% patients with keratotic nevi. Five recurrences were noted and three of them had keratotic nevi. Mean follow up period was 28 months.

The hyperkeratotic level of the epidermis is the most important variable for the outcome. The result was less favourable in thickened lesions. Neither age of patient nor location of lesions was related to cosmetic outcome.

The authors concluded that CO₂ laser was an effective and safe treatment of verrucous epidermal nevi. In comparison with other laser therapies, CO₂ laser provided a more favorable outcome with fewer recurrences, but scarring risk was more common. Recent and flattened lesions had better cosmetic outcome. The use of superpulsed mode and lower energy fluence initially provided better cosmetic outcome and lower risk of scarring.