

## Journal Watch

Reviewed by JCY Chan 陳俊彥, SH Chan 陳上熙, CK Kwan 關志強, YK Lai 黎亦翹,  
MYM Wat 屈綺文

---

### **Is early detection of basal cell carcinoma worthwhile? Systematic review based on the WHO criteria for screening**

Hoorens I, Vossaert K, Ongenaes K, Brochez L.  
Br J Dermatol 2016;174:1258-65.

It had been noted that there has been an increase in the incidence of basal cell carcinoma (BCC) in the last 30 years. With a prolonged life expectancy, the incidence is expected to continue to increase. Basal cell carcinoma can cause significant morbidity and can impact on the public health budget due to the costs of the treatment.

A systematic review of the World Health Organization criteria was performed to look at whether earlier detection of BCC could reduce morbidity and cost. BCC grows in size gradually (median increase in diameter of 0.5 mm over 10 weeks). The delay in diagnosis ranged from 19 to 25 months which was significant. Several studies showed surgical complexity, treatment cost, the specific surgical procedure performed, such as Mohs micrographic surgery or surgical excision, reconstruction technique was determined by the size of the BCC. In one study, the cost per treatment for other non-surgical options was also affected by the size. Vismodegib was used only for locally advanced or metastatic BCC. It was found that delay in diagnosis and appropriate treatment were the most important underlying causes in the occurrence of giant BCC or metastatic BCC. Metastatic BCC represented a very small proportion of all BCCs, most of them being located in the facial region. The size of BCCs increases slowly over time, as shown by current

data. Choice of treatment and the associated cost depended mainly on the size of the BCC.

The authors concluded that the current study shows the need for early detection and adequate management of BCCs on the face.

### **Interventions for hidradenitis suppurativa: a Cochrane systematic review incorporating GRADE assessment of evidence quality**

Ingram JR, Woo PN, Chua SL, Ormerod AD, Desai N, Kai AC, et al.  
Br J Dermatol 2016;174:970-8.

There have been more than 50 different types of treatments that have been used to treat hidradenitis suppurativa (HS). The aim of the study was to summarise and evaluate randomised controlled trial (RCT) evidence for HS interventions in adults.

A search up till 13 August 2015 from the following databases was performed: five trials registers, Embase Medline, CENTRAL, LILACS and abstracts from eight dermatology conferences, in which extracted data, study eligibility and methodological quality were independently assessed by two authors. The primary outcomes were adverse effects of the interventions and quality of life.

Twelve trials, from 1983 to 2015, investigating 15 different interventions were selected. The median number of participants was 27 and the

median trial duration of these trials was 16 weeks. It was found that Adalimumab 40 mg weekly improved the Dermatology Life Quality Index (DLQI) by 4.0 points, being equivalent to the minimal clinically important difference for the scale, vs placebo (95% confidence interval -6.5 to -1.5 points). The quality of evidence was considered to be 'moderate' as the results were based on a single study. Adalimumab 40 mg given on alternate weeks was not effective in a meta-analysis of two studies of 124 participants. In a moderate-quality study completed by 33 of 38 participants, infliximab 5 mg/kg was shown to improve the DLQI score by 8.4 points after 8 weeks. However, Etanercept 50 mg twice weekly was ineffective. The remaining treatments, including topical and oral antibiotics, were investigated by relatively small studies, could not be recommended due to the defects of the studies. Therefore, more and larger RCTs were required to study the HS interventions. The use of a gentamicin sponge prior to primary closure did not improve the outcome.

### **The contributions of adjusted ambient ultraviolet B radiation at place of residence and other determinants to serum 25-hydroxyvitamin D concentrations**

Kelly D, Theodoratou E, Farrington SM, Fraser R, Campbell H, Dunlop MG, et al.  
*Br J Dermatol* 2016;174:1068-78.

It was known that the major source of vitamin D (vitD) for humans included solar ultraviolet B (UVB) radiation. This study investigated the ambient UVB radiation at wavelengths that induce vitD synthesis (vitD-UVB) in Scotland and the relationship with serum 25hydroxyvitamin D (25OHD).

Using the Tropospheric Emission Monitoring Internet Service database, the authors estimated the average vitD-UVB dose for each day of the year and for each postcode area in Scotland. The cumulative and weighted vitD-UVB (CW-vitD-UVB)

exposure at place of residence for each recruit was then calculated and plasma 25OHD was measured in 1964 healthy recruits.

The results showed that there was significant seasonal and geographical variation in vitD-UVB. It was found that plasma 25OHD was significantly associated with ambient vitD-UVB exposure at place of residence ( $P < 0.01$ ). There was an average increase in 25OHD of 1 ng/mL for every 1000 kJ/m<sup>2</sup> higher CW-vitD-UVB dose or for every 2.5 mcg of daily supplement received. In most cases, 25 OHD concentration was found to be adequate ( $> 16$  ng/mL) when CW-vitD-UVB dose was  $> 6000$  kJ/m<sup>2</sup>. This level of ambient radiation could only be found during summer in Scotland.

In summary, the ambient vitD-UVB could be a useful predictor of vitD level. Measurements of vitD-UVB mapped according to season and region could be used for estimation for vitD status or provide further information in epidemiological studies.

### **Clinical significance of serum soluble CD molecules to assess disease activity in vitiligo**

Speeckaert R, Lambert J, van Geel N.  
*JAMA Dermatol* 2016 Aug 24. doi: 10.1001/[jamadermatol.2016.2366](https://doi.org/10.1001/jamadermatol.2016.2366). [Epub ahead of print]

Vitiligo is a common T-cell-mediated autoimmune disease presenting as macular depigmentation due to epidermal melanocyte loss. Associations between immunological markers and vitiligo activity have been reported. Moreover, associations between soluble CD (sCD) molecules and several autoimmune disorders have been established.

CD25 is the  $\alpha$  chain subunit of the heterotrimeric interleukin 2 (IL-2) receptor, which is expressed on the surface of activated T cells. Soluble CD25 results from the proteolytic cleavage of the IL-2 receptor on activated T cells and is reportedly

elevated in the plasma and serum of patients with several lymphoproliferative and autoimmune diseases. CD27 is a type I transmembrane protein and member of the tumor necrosis factor receptor superfamily which is expressed on the surface of specific subsets of T cells. Serum sCD27 level has been used as a biomarker to monitor immune activation and disease burden in various inflammatory disorders. This is a cross-sectional study investigating the association between serum sCD levels and disease activity in patients with vitiligo.

Out of the 93 patients recruited in the present study and it was found that serum levels of sCD25 and sCD27 were elevated in patients with active vitiligo compared with patients with stable disease. In addition, sCD25 levels were found to be significantly lower in the serum of patients being treated with topical immunosuppressants (including steroids and calcineurin inhibitors) and the serum levels of sCD27 were significantly lower in patients with recent repigmentation. The findings suggest that these molecules may be used as biomarkers to monitor treatment response.

The author concluded that the findings of this study provide preliminary evidence that sCD25 and sCD27 may indicate the probability of disease progression in patients with vitiligo, thus suggesting a possible role as a biomarker. Future studies with consecutive blood sampling may determine their final usefulness as biomarkers in clinical practice.

### **Risk factors for degree and type of sequelae after involution of untreated hemangiomas of infancy**

Baselga E, Roe E, Coulie J, Munoz FZ, Boon LM, McCuaig C, et al.

JAMA Dermatol 2016 Aug 17. doi: 10.1001/jamadermatol.2016.2905. [Epub ahead of print]

Infantile haemangiomas (IH) may leave permanent sequelae that may cause disfigurement

after involution. The identification of risk factors for the development of permanent sequelae is therefore crucial for treatment decisions. The extent, characteristics, and predictive factors of permanent sequelae after involution of IH have not been well characterised. A multi-centre retrospective cohort study investigating the incidence of permanent sequelae of involuted IH and the respective predictive clinical features was therefore performed.

A total of 184 patients with IH who had not received any systemic treatment were recruited. The overall incidence of significant sequelae was 101 out of 184 (54.9%). It was found that the most common sequelae after involution of IH included telangiectasias (84.3%), fibrofatty tissue (47.1%), and anetodermic skin (32.6%). The least common were redundant skin (15.7%) and scar (12.8%). It was discovered that superficial and deep haemangiomas left significantly fewer sequelae than combined haemangiomas. Moreover, haemangiomas with a stepped or abrupt border of the superficial component resulted in more severe sequelae than those with a smooth border. Superficial haemangiomas with a cobblestone appearance or rough surface left more severe sequelae than those with a smooth surface. However, the association between locations of IH and their sequelae was not identified in this study due to the limited number of IH cases at any particular location.

More than half of the IHs will leave significant or severe sequelae if left to involute spontaneously according to the present study. The above findings may help clinicians in predicting the risk of sequelae and in the treatment decision-making process. The author suggested that a close follow-up during the first weeks of life is mandatory to detect early morphological changes that suggest a risk of significant sequelae and to consider therapy before unfavorable clinical features develop.

## **The risk of non-melanoma skin cancer in HIV-infected patients: new data and meta-analysis**

Zhao H, Shu G, Wang S.  
*Int J STI AIDS* 2016;27:568-75.

Non-melanoma skin cancer (NMSC) includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) the risk of which is increased among people with HIV /AIDS. The aims of this meta-analysis study were to update the incidence of NMSC among HIV-infected people and whether the association varied with gender and antiretroviral therapy (ART). Literatures satisfying the inclusion criteria were as follows: (1) cohort studies of adult people with HIV/AIDS and (2) collected data on incident cancer through cancer registry in MEDLINE (since 1966) and EMBASE (since 1974) were searched till February 2014 by two independent investigators and 189 potential articles were identified and 133 were excluded after the title and abstract review. A further 50 articles were excluded after full article review.

Six articles were included for meta-analysis in the study and 78,794 patients with HIV or AIDS were included. The results suggested that HIV/AIDS was associated with an increased risk of NMSC with the standardised incidence ratio (SIR) 2.76; 95% CI 2.55-2.98. The SIR for HIV/AIDS men was 3.36 (95% CI 1.08-12.22) and was 2.18 (95% CI 1.24-3.83) for HIV/AIDS women. Individuals receiving ART had a lower risk for NMSC with SIR 1.95 (95% CI 1.10-3.47) versus 2.11 (95% CI 1.44-3.12) for those not receiving ART.

There were several limitations of this study. Firstly, the cohort studies were subject to selection bias as HIV/AIDS patients might be under increased medical surveillance and secondly was the heterogeneity of the studies in terms of study design and the use of ART. Thirdly, as the studies were performed in Western countries, their findings might not be applicable to Asian countries. Finally, other important factors for the development NMSC including type of skin, family skin history of skin cancer, cumulative sun-

exposure, CD4 count, HIV RNA level could not be analysed in the study.

Finally, the authors concluded that HIV/AIDS appeared to be associated with a significantly increased risk of NMSC in both genders and the use of ART appeared to be beneficial in protecting against the development of NMSC.

## **Vaginal douching and association with sexual transmitted infections among female sex workers in a prefecture of Yunnan Province, China**

Luo L, Xu JJ, Wang GX, Ding GW, Wang N, Wang HB.  
*Int J STD AIDS* 2016;27:560-7.

Vaginal douching using liquid agents to clean the vagina for hygiene or therapeutic purposes is a common practice among FSW in China. Many women douche before or after sexual intercourse to alleviate the odour and to prevent STIs or pregnancy. Previous studies have shown that vaginal douching is linked to an increased risk of STIs, pelvic inflammatory disease (PID), cervicitis which, in turn may increase the risk of HIV acquisition. The aims of this study were to assess the association between vaginal douching and STIs, genital symptoms and knowledge of HIV/STIs among FSW in Yunnan Province China.

This was a cross-sectional study involving 837 FSWs. The inclusion criteria were (1) age  $\geq 16$ ; (2) self-reported to have sold sex for money within the previous three months; (3) agreed to test for HIV, STIs and use of illegal drugs. A total of 702 (83.9%) FSWs reported ever douching with any products of which, 89.9% reported using medical disinfectant, followed by 58.1% with water only, 27.9% with toothpaste, 16.7% with salt water, 4.0% with spermicide, 3.0% with soapy water and 0.9% with vinegar. The reasons for douching were "feeling cleaner (79.3%)"; "preventing STIs (77.5%)"; "cleaning vaginal discharge (36.3%)"; "preventing and curing odour (27.4%)"; "preventing pregnancy

(12.3%)" and "cleaning during menstruation (7.3%)".

FSWs who had more knowledge on HIV and STIs were significantly more like to douche (HIV: OR=3.14, 95% CI 1.80-5.47  $p<0.01$ / STIs: OR=2.62, 95% CI 1.66-4.12,  $p<0.01$ ). FSW who douched had a significantly higher prevalence of HIV (11.0%) than non-douchers (5.2%,  $p<0.05$ ) and significantly higher prevalence of HSV 2 (70.8%) than non-douchers (56.0%,  $p<0.05$ ). In contrast, FSW who douched had a lower prevalence of *N. gonorrhoeae* (10.6%) than non-douchers (16.4%,  $p>0.05$ ) and significant lower prevalence of *C. trachomatis* (26.9%) than non-douchers (35.1%,  $p<0.05$ ). The authors postulated that douching would wipe off or remove cervical discharge containing the indicators of infection.

In summary, vaginal douching is a common practice among FSWs in China and was found to be significantly associated with HIV and STIs.

### **Efficacy and possible mechanisms of topical tranexamic acid in melasma**

Kim SJ, Park JY, Shibata T, Fujiwara R, Kang HY.  
Clin Exp Dermatol 2016;41:480-5.

Melasma is often fairly resistant to topical and light-based treatments and is a common pigmentary disorder in Asians. Recently, tranexamic acid (TA; trans-4-aminomethyl cyclohexane carboxylic acid), a plasmin inhibitor, has been proven with clinical efficacy in the treatment of melasma. Tranexamic acid has been postulated to reduce the synthesis of melanin pigments by inhibiting the signalling between melanocytes and keratinocytes. Other possible mechanisms include reversion of the dermal changes in melasma by altering the abnormal vasculatures implicated in the disorder.

In the present study, the authors investigated the clinical efficacy of topical TA in melasma and the

possible mechanisms via histopathological confirmation. A total of 23 subjects (skin phototype III-IV; age, 34-60 years) with melasma were involved in the study. They were started on a 2% TA formulation (full face application) for a 3-month period. Clinical outcomes were defined by the modified Melasma Area and Severity Index (mMASI) and measurements from a calibrated chromometer. Skin biopsies were performed in ten subjects to evaluate the level of hyperpigmentation, vascular abnormalities and the expression of paracrine mediators related to the application of TA. In this study, 22 of 23 subjects had satisfactory clinical improvement in terms of significant reduction in the mMASI scores ( $p<0.05$ ). The degree of lightness (L-values) was significantly raised while the erythema (a-values) was reduced in both lesional and peri-lesional normal skin. No adverse event was recorded in the present study. Histopathologically, Fontana-Masson staining revealed a significant reduction in epidermal melanin content. Endothelin (ET)-1 was proven to be down-regulated after 3-month treatment with topical TA ( $p<0.05$ ). The number of CD31+ vasculatures and the expression of the vascular endothelial growth factor appeared reduced, but the difference did not reach statistical significance.

The authors concluded that topical TA is efficacious in reducing the pigmentation and erythema of melasma. The suppressive effects of TA in the expression of the ET-1 and hence vascular formation may be implicated.

### **Retrospective review of diphenylprone in the treatment of alopecia areata**

Lamb RC, Young D, Holmes S  
Clin Exp Dermatol 2016;41:352-8.

Alopecia areata (AA) is an organ-specific autoimmune disorder considered to be pivoted by CD8+ T-lymphocytes. Severe AA can lead to complete baldness and is associated with significant psychosocial impacts. Immunotherapy

with diphencyprone (DPCP) has been employed to treat severe AA and offers hope to patients with recalcitrant disease. However, the reported efficacy of DPCP has been variable. In addition, treatment responses appear unpredictable.

In the present study, the authors reviewed the use of DPCP in AA and identified the predictors for clinical outcomes. A single-centre, retrospective review of DPCP therapy in AA between year 1991 and 2010 was conducted. A total of 205 treatment courses were analysed, of which 162 (79%) treatment courses were completed for 133 subjects. A positive clinical outcome (defined by hair regrowth of any grade observed) was observed in 96 of 133 cases (72.2%). Excellent responses (more than 90% of hair regrowth) were observed in 15.8% of cases (21 out of 133). Clinical response with regrowth of vellus hair was identified in 20.3% (27 out of 133) and regrowth of sparse pigmented hair in 6.0% (8 out of 133). In this study, the extent of alopecia at baseline assessment and duration of disease prior to treatment correlated with unfavourable clinical outcomes ( $P < 0.05$ ). However, history of atopy, age and presence of nail changes were not statistically associated with the clinical effects of DPCP treatments.

The authors concluded that DPCP was generally a safe and effective treatment in AA, and the extent of alopecia at baseline and duration of disease are the most important predictors for clinical responses.

### **Oral tranexamic acid (TA) in the treatment of melasma: A retrospective analysis**

HC Lee, TG Thng, CL Goh.

*J Am Acad Dermatol* 2016;75:385-92.

Melasma is commonly found in Asians. Genetic predisposition, increased cutaneous vascularity and increased expression of angiogenic factors in the epidermis may play a role in its pathogenesis.

However, treatment of melasma is difficult and no treatment modality guarantees satisfactory results. Tranexamic acid (TA), commonly used as haemostatic agent, has been shown to be effective in modulating vasculature in melasma and in inhibiting melanin synthesis. However, large-scale studies are lacking.

In this retrospective study, the authors evaluated the efficacy and adverse effects of using oral TA for melasma. Patients with melasma who had visited a tertiary dermatological centre in Singapore and who had been treated with more than one dose of TA (usual regime 250 mg twice daily) were included. Those lost to follow-up, without clear documentation and lacked objective assessment by physician were excluded. Clinical outcome was defined as worsened, remained unchanged or improved. Physician Global Assessment was used to document the degree of improvement.

A total of 561 patients were included, the majority (91.4%) of which was female. The median duration of melasma before starting oral TA was six years. Ninety-five percent of them had failed other treatment modalities prior to TA, namely topicals and LASER/intense pulsed light treatment. Oral TA was added as an adjunct treatment and the median duration of treatment was four months. Only 10% received TA as monotherapy. Nearly 90% of patients had documented improvement, and the median time to initial response was two months. Patients who improved showed approximately 50% (median) lightening. Better responses were seen in patients without family history (90.6% vs 60%,  $p = 0.01$ ), older age of onset and longer duration of melasma ( $p < 0.05$ ). However, among those who responded, 27% of them relapsed seven months (median duration) after cessation of oral TA. Tranexamic acid was generally well-tolerated and only 7% of patients complained of transient gastrointestinal, neurological and menstrual side effects. However, one patient developed deep vein thrombosis and was later confirmed to have familial protein S deficiency.

The authors concluded TA is a good adjunct for those with refractory melasma and is generally well-tolerated. However, further large scale studies are required to evaluate whether this may be used as a first-line treatment option or monotherapy. This study was limited by its retrospective nature, lack of standardisation of treatment and follow up period and the lack of objective measurement of pigmentary changes.

### **Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults**

Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, et al.

*J Am Acad Dermatol* 2016;75:494-503.

Phosphodiesterase 4 (PDE4) is a key regulator in the cytokine production in AD. Blocking of PDE4 in monocytes in vitro has been shown to reduce the release of pro-inflammatory cytokines. Oral PDE4 inhibitors have recently been approved for the management of psoriasis and psoriatic arthritis but are associated with gastrointestinal side effects due to the non-selective inhibition. This novel topical PDE4 inhibitor, crisaborole ointment, can penetrate human skin effectively and inhibit PDE4 and hence suppress the release of cytokines locally without much systemic exposure as it is rapidly metabolised and inactivated on the body surface.

In this multicentre, randomised, double-blind, vehicle-controlled phase III trial, patients were randomly assigned to either crisaborole or vehicle arm given over a period of 28 days. Patients aged two years or older, with a clinical diagnosis of AD, involving a body surface area of 5% or more and a baseline Investigator's Static Global

Assessment (ISGA) score of mild or moderate were included. Those received systemic corticosteroids or biologic therapy within 28 days or topical TCS or TCI within 14 days and active skin infection were excluded. Primary efficacy was defined as clear or almost clear with a 2-grade or more improvement on ISGA score at day 29. Other treatment outcomes like time to success in ISGA score, percentage of patients achieving clear/almost clear, pruritus and improvement in signs of AD were assessed.

A total of 1016 and 506 patients were recruited. There were more crisaborole-treated than vehicle-treated patients who achieved ISGA score success (clear/almost-clear with more than 2 grade improvement) (32.5% vs 25.4%,  $p=0.38$  / 31.4% vs 18%,  $p<0.001$ ), with a higher percentage that achieved clear/ almost clear (51.7% vs 40.6%,  $p=0.005$ ; 48.5% vs 29.7%,  $p<0.001$ ). Moreover, crisaborole-treated patients were also shown to have significant improvement in pruritus score, improvement in clinical signs of AD and a greater reduction in severity of AD. Crisaborole is generally well-tolerated. Transient application-site pain was the only treatment-related side effect and was reported in 1% of patients. Discontinuation rate was low (1.2%) and was comparable to vehicle-treated counterparts. Gastrointestinal side effects, which were observed in systemic PDE4 inhibitors, were not significantly higher than in controls.

This study showed that crisaborole is a promising agent in patients with mild or moderate AD. It is effective in controlling disease severity, pruritus and other clinical signs with favorable safety profile. However, further studies are needed to evaluate its long-term safety, their efficacy in younger children (below age of 2) and to compare its efficacy with TCS/TCI.