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Journal Watch

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Three different patterns of CD4 recovery in a cohort of Chinese HIV patients following antiretroviral therapy – a five-year observational study

Int J STI AIDS 2015;26:803-9.
Naftalin CM, Wong NS, Chan DP, Wong KH, Reidpath DD, Lee SS.

CD4 T-cell count is an important marker for monitoring the function of immune system and progress of HIV disease. Low baseline CD4 count before HAART has been shown to be a strong predictor of mortality and AIDS. The aims of this study were to define and classify the CD4 trajectories after initiation of HAART and explore the factors which might be associated with the specific CD4 response patterns in Chinese HIV infected adults.

Clinical data for all infected HIV-1 Chinese patients were reviewed during the study period from June 1998 to December 2012. To evaluate the CD4 recovery pattern after HAART, those who were (1) aged ≥16, (2) had more than three CD4 and plasma HIV RNA measurements, (3) had CD4 data at the beginning and month 60, (4) had been on first HAART for >60 months and (5) had achieved sustained HIV RNA suppression (<500/mL) throughout the five years were selected.

Total 1070 clinical records were screened and 135 met all the inclusion criteria. Of these, 90.4% were men and the median age was 38.1 years when HAART was started. Overall, 26 (19.3%) were "poor responders" defined as having no significant net gain of CD4 trajectories from 0 to month 60 or in which the increase in CD4 was ≤100/uL and final CD4 was ≤350/uL. There were 76 (56.3%) "satisfactory responders" defined by final CD4 was persistently ≥350/uL an increase CD4 persistently ≥100/uL above baseline within the first 24 months and then levelling off at 25 to 60 months. There were 33 (24.4%) "continuing responders" defined as apart from increase of CD4 ≥100/uL from baseline and a final value ≥350/uL, there being a continuing rise of ≥100/uL between 25 to 60 months. Patients aged 35 or above at diagnosis were more likely to be " poor responders " (80.8%) than "continuing responders" (39.5%) (OR=0.15, 95% CI=0.05-0.51 p=0.002). Baseline CD4 ≥150/uL was a significant predictor for "poor responders" (OR=3.04, 95% CI=1.13-8.17 p=0.03). Patients with AIDS before HAART were the main predictor for distinguishing between "poor responders" and "continuing responders" (OR=3.94, 95% CI=1.36-11.45 p=0.01). The authors concluded that categorisation of HIV patients by their CD4 trajectory may help in the prediction of immunological outcome.

Transactional sex and prevalence of STIs: a cross-sectional study of MSM and transwomen screened for an HIV prevention trial

Int J STD AIDS 2015;26;879-86.
Solomon MM, Nureña CR, Tanur JM, Montoya O, Grant RM, McConnell JJ.

Research has suggested that male transactional sex (TS) such as men who have sex with men (MSM) and transgender women (TW) are the key populations for HIV transmission. The aim of this study was to explore the degree to which engagement in TS, identity and gender may be associated with HIV and STIs or their risk factors in MSM and TW. Transactional sex included all compensated sex defined by exchange of money,

gifts, shelter or drugs for sex with a partner in the last six months. It is also classified as (1) ever been paid for sex; (2) self-identified sex-worker; (3) never been paid for sex.

A total of 6.2% cases were self-identified sex-worker and 45.9% as ever been paid for sex. Despite the fact that more half of case had participated in TS, only 7.2% reported that all three of their last three sexual partnerships were transactional. Therefore, the authors claimed that TS is widely prevalent but for most only occasionally practiced among MSM and TW. The never been paid group (compared to ever been paid) had a later sexual debut and later anal sexual debut (first sex: ever been paid: 13.5 years vs. never been paid: 14.5 years, $p=0.001$ and first anal sex: ever been paid: 14.9 years vs. never been paid: 16.0 years, $p=0.008$ respectively). The never been paid group had also higher levels of education ($p<0.001$) and had higher monthly income ($p=0.005$). They were also less likely to have encountered forced sex ($p=0.004$), have over 150 lifetime sexual partners ($p<0.001$) and STIs ($p=0.007$). The self-identified sex-workers, when compared to ever or never been paid groups had lower education level ($p<0.001$), more frequently as bisexual ($p<0.001$) and less likely to have had an HIV test ($p<0.002$).

Compared to the MSM group, TW reported to have earlier first sexual experience (age at sexual debut: TW: 12.8 years vs. MSM: 14.3 years, $p<0.001$), earlier anal sexual debut (TW: 13.1 years vs. MSM: 16.1 years, $p<0.001$), left school at an earlier age ($p<0.001$) and higher incidence of recreational drugs abuse (TW: 47.3% vs. MSM: 36.6%, $p<0.024$). TW had more lifetime sexual partners (TW: 24.8% vs. MSM: 6.4%, $p<0.001$) and were more likely to have and STIs and HIV (TW: 16.8% vs. MSM: 12.5%, $p<0.201$) although not significant.

The authors concluded that transactional sex and being a transgender women are associated with a higher prevalence of sexually transmitted infections.

Can oral nonsteroidal anti-inflammatory drugs play a role in prevention of basal cell carcinoma? A systemic review and metaanalysis

J Am Acad Dermatol 2016;74:108-19.
Muranushi C, Olsen CM, Green AC, Pandeya N.

Regular use of non-steroidal anti-inflammatory drugs (NSAIDS) has been shown to reduce the risk of various kinds of cancers including some keratinocyte skin cancers. However, its role in preventing basal cell carcinoma (BCC) is still yet to be determined.

In this study, a search of PubMed, Web of Science and EMBASE up to 3 December 2014 was performed. Cohort, case-control studies and intervention studies examining the effect of oral aspirin or non-aspirin NSAIDs on BCC were included and a random effects meta-analysis model was used to obtain the pooled estimates. A total of 11 studies were included. Overall, a 10% reduction in BCC were noted among users of any NSAIDs (aspirin or non-aspirin), RR=0.9 (95%CI 0.84-0.97). Similarly an inverse association was observed in aspirin (RR=0.95; 95%CI 0.91-1.00) and non-aspirin NSAIDS (RR=0.93; 95%CI 0.86-1.02) users which was not statistically significant. Greater reduction was observed among high risk patients with a history of skin cancer or at high-risk of actinic keratosis. However, the authors emphasised that there were several limitations on the included studies. Most studies were based on pre-existing data, hence lacking the information on ultraviolet exposure, exact NSAIDs dosage and skin type. Also, NSAIDs bought over-the-counter cannot be assessed. Furthermore, the timing of NSAIDs use and diagnosis of BCC were not evaluated. Finally, the indications for NSAIDs, which may be a potential confounding factor for skin cancer development, were not assessed in these studies.

The authors concluded that NSAIDs use may help preventing BCC, especially in high risk patients. However, larger randomised controlled trials are required to confirm
the finding.

Comorbid autoimmune diseases in patients with vitiligo: A cross-sectional study

Gill L, Zarbo A, Isedeh P, Lim HW, Hamzavi I.
J Am Acad Dermatol 2016;74:295-302.

Vitiligo is well-known to be associated with autoimmune disease. However, its burden had not been well-studied in large scale studies. In this cross-sectional study, the authors reviewed all the records of vitiligo patients in Henry Ford Health System in Detroit, MI between January 2002 and October 2012. Patients with at least two visits and a diagnosis confirmed by a dermatologist were included. The prevalence of various diseases was compared with the prevalence of the US population, or world prevalence if US data was lacking.

A total of 1098 patients with vitiligo were identified, in which 20% had at least one concommittent autoimmune disease. Older age, later age of onset, extensive disease and longer duration of disease were possible associations. Thyroid disease was the most common disease association, with a 15-fold increase in prevalence of clinical thyroid disease observed when compared to the normal population, and females were at higher risk. This was followed by alopecia areata, which was a less frequently reported association in previous studies, and was also shown to have a significantly higher prevalence in vitiligo, especially in non-white patients. Other associated diseases included inflammatory bowel disease, pernicious anaemia, systemic lupus erythematosus, Guillain-Barre syndrome, discoid lupus, linear morphea, myasthenia gravis and Sjogren syndrome.

This study was limited by the single institution data and lack of a control group. However, based on the results, the authors recommended screening for thyroid function and look for symptoms and signs of systemic lupus erythematosus and neurological diseases and performed relevant investigations accordingly in managing patients with vitiligo.

Possible role of proenkephalin in psoriasis

Nagui NA, Ezzat MA, Abdel Raheem HM, Rashed LA, Abozaid NA.
Clin Exp Dermatol 2016;41:124-8.

Psoriasis is a chronic, systemic, inflammatory skin condition affecting predominantly skin and joints. The exact aetiology is still unknown, but is widely accepted to be multi-factorial in nature with components of genetic predisposition and various endogenous and exogenous factors. Proenkephalin (PENK) is an endogenous opioid polypeptide hormone that acts on specific opiate receptors found on nerve, mucosa and immunological cells. PENK receptors are normally expressed on skin cells. Upon activation, the cellular activities of keratinocytes and melanocytes will be altered. In previous studies, the expression of PENK has been shown to be increased in the skin of psoriatic patients. With background function in the immune system, it is postulated that PENK could have been regulated by immunological stimuli. The authors in the current study had assessed the possible roles of PENK in the patho-mechanism of psoriasis in order to identify the correlation between PENK expression and disease severity.

Twenty subjects with psoriasis and the same number of healthy controls were recruited into the study. Serological levels of PENK were compared between psoriatic patients and normal controls while tissue PENK levels obtained in the skin biopsies were compared between lesional and non-lesional skin among patients with psoriasis. In the current study, serum PENK levels were significantly higher in psoriatic subjects as compared to healthy controls (mean±SD, 264±120.59 versus 117.41±23.48) ($p=0.03$). Also, the tissue PENK level was significantly higher in the lesional than the non-lesional skin among psoriatic subjects (mean±SD, 129.33±33.96 versus 48.85±18.19) ($p=0.02$). However, the serological and tissue PENK levels did not correlate with disease severity, as denoted by the Psoriasis Area and Severity Index (PASI). The authors

concluded that PENK could be implicated in the pathogenesis of psoriasis, and development anti-PENK drugs may be one of the future directions in improving the current management of psoriasis.

Serum 25-hydroxy vitamin D level in patients with pemphigus and its association with disease severity

Moravvej H, Mozafari N, Younespour S.
Clin Exp Dermatol 2016;41:142-7.

In the past decade, there have been studies demonstrating the key roles of vitamin D in the pathogenesis and disease progression of many autoimmune disorders, including immunoblistering conditions. In the current study, the authors investigated the serological levels of 25-hydroxy vitamin D (25[OH]D) in patients with pemphigus to identify the correlation between the vitamin D level and its clinical characteristics.

In the study, 52 patients with pemphigus were recruited, with another 56 healthy controls (age and gender matched) enrolled. Only subjects who were newly diagnosed with pemphigus or those with relapse after treatment cessation for more than six months were included. Serological 25 (OH)D and parathyroid hormone (PTH) levels were measured accordingly. Other demographic data, body mass index (BMI), body surface area (BSA) involvement and background Pemphigus Area and Activity Score (PAAS) were also analysed. In the current study, there was no significant difference in serological level of vitamin D between patients with pemphigus and normal controls. However, among patients with pemphigus, significantly lower levels of vitamin D were observed in patients with more BSA involvement (OR=1.07, 95% CI 1.01-1.13, p=0.02) and higher total PAAS (OR=1.36, 95% CI 1.11-1.66, p<0.01). Otherwise, no significant association was identified between vitamin D levels and age, BMI, the season of sampling or smoking habit.

The authors concluded that vitamin D deficiency is a common finding in patients with pemphigus, particularly those with extensive and severe disease. Active screening may be considered and vitamin D supplements may improve disease control in pemphigus. However, the true beneficial effects of vitamin D supplements in reducing the severity of pemphigus remains to be elucidated in future interventional studies.

Sentinel lymph node biopsy in Merkel cell carcinoma: a 15-year institutional experience and statistical analysis of 721 reported cases

Gunaratne DA, Howle JR, Veness MJ.
Br J Dermatol 2016;174:273-81.

It has been known that Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous neuroendocrine cancer that often metastasises to the regional lymph nodes. With the help of sentinel lymph node biopsy (SLNB) of regional lymph nodes in patients without clinical apparent disease, the accuracy of staging can be improved. However, the accuracy of SLNB and its prognostic implications have not been well-studied.

The authors conducted a search of the Medline and Embase databases up till April 2015 concerning published data investigating the positive and false negative rates of SLNB in MCC. A total of 36 published studies between 1997 and 2015 comprising 692 patients were identified. A further 29 patients were recruited from the authors' institution leading to a total of 721 patients analysed. Among this cohort, SLNBs were performed at 736 regional sites with 29.6% cases found to be positive. There were regional metastases in 45 cases despite a negative SLNB, (false negative rate of 17.1%). The regional recurrence rate was not affected by adjuvant regional radiotherapy in patients with a negative

SLNB (p=0.31), being in line with recent findings that regional therapy can be safely omitted in patients with a negative SLNB. Distant relapse occurred more frequently in cases with positive than in those with negative SLNB (17.6% vs. 7.3%, p<0.001).

In summary, the authors suggested that SLNB can help with the management of MCC. Adjuvant regional radiotherapy may not be needed in negative SLNB. Distant relapses were more common in patients with positive SLNB.

The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-controlled study

Nemoto O, Furue M, Nakagawa H, Shiramoto M, Hanada R, Matsuki S, et al.
Br J Dermatol 2016;174:296-304.

The sensation of itch is thought to be due to the cytokine interleukin-31 (IL-31). Few studies have investigated the safety and efficacy of blocking the IL-31 signal in humans for the reduction of pruritus in atopic dermatitis (AD). CIM331 is a humanised antihuman IL-31 receptor A (IL-31RA) monoclonal antibody, which binds to IL-31RA in order to inhibit the subsequent IL-31 from signalling.

The efficacy, the pharmacokinetics, safety, and tolerability of CIM331 in healthy Japanese and white volunteers, and Japanese patients with AD was investigated in this randomised, double-blind, placebo-controlled phase I/Ib study, in which CIM331 was given as a single dose subcutaneously. The primary outcomes were tolerability and safety. There were no serious adverse events (AEs), deaths, or discontinuations due to AEs found in the study. There was also no dose-dependent increase in the incidence of AEs in the study. An increased creatine phosphokinase was more common in the CIM331 groups, while among the healthy volunteers, all AEs occurred once in the placebo groups. In patients with AD, the pruritus visual analogue scale score was reduced by about 50% at week 4 with CIM331 with an increase in sleep efficiency and decrease the use of hydrocortisone butyrate. On the other hand, the pruritus visual analogue scale score was only reduced by 20% with placebo.

In summary, a single subcutaneous administration of CIM331 was well-tolerated in patients with AD and healthy volunteers as well as decreasing sleep disturbance, topical use of hydrocortisone and pruritus.

Clinically amyopathic dermatomyositis: clinical features, response to medications and malignancy-associated risk factors in a specific tertiary-care-centre cohort

Galimberti F, Li Y, Fernandez AP.
Br J Dermatol 2016;174:158-64.

In amyopathic dermatomyositis (CADM) the cutaneous manifestations of DM are present but there is no muscle involvement.

The clinical features, response to drugs, and malignancy-associated risk factors in patients with CADM from a single tertiary-care centre were investigated in this study. A retrospective review of 44 patients with CADM with clinical and serological data prior to the start of treatment was performed. In the study, 18% of all patients with DM were CADM. Most CADM patients showed improvement with the first prescribed treatment, although most required additional medications for control. In addition, patients with malignancy-associated CADM were found to be more readily to have a cutaneous response with the first prescribed treatment than patients without malignancy (p=0.04). Interestingly, absence of malignancy was found to be associated with periungual erythema photosensitivity

(p=0.03 and p=0.02, respectively). Malignancy was found in six out of 44 patients.

The authors concluded that CADM is a significant subclass of DM. This study found differences in cutaneous manifestations and response to first treatment among patients with CADM with and without malignancy. This might suggest differences in pathophysiology among CADM subsets.

Increased risk of cutaneous squamous cell carcinoma after vismodegib therapy for basal cell carcinoma

Mohan SV, Chang J, Li S, Henry AS, Wood DJ, Chang AL.
JAMA Dermatol. Published online February 24, 2016. doi:10.1001/jamadermatol.2015.4330.

One form of the newer targeted treatment modalities of advanced basal cell carcinomas (BCCs) is smoothened inhibitor (SI), a hedgehog pathway inhibitor. It has been reported that cutaneous squamous cell carcinoma (CSCC) may develop after initiation of the SI vismodegib, the first SI to be approved by the US Food and Drug Administration for the treatment of advanced BCCs. However, there is still lack of evidence regarding this risk. This case-control study investigated the risk of developing a non-BCC malignancy after SI exposure in patients with BCC.

A total of 180 patients with BCC were identified. Fifty-five cases were exposed to vismodegib (cases), and 125 cases were not exposed (controls). The risk of developing a non-BCC malignancy for patients exposed to vismodegib was increased (hazard ratio 6.37; 95% CI, 3.39-11.96; $p<0.001$). The median number of years between vismodegib initiation and the development of CSCC was 0.6 years (range, 0.1-2.0 years). The most common type of non-BCC second malignancy in both the cases and controls was CSCC. Larger prospective studies to confirm the findings of this case-control study are warranted.

The exact mechanism by which hedgehog inhibition may increase the risk of CSCC is unknown. Hedgehog pathway inhibition has been shown to activate the RAS/MAPK pathway. In view of the association between RAS pathway dysregulation and multiple human cancers, hedgehog pathway inhibition, such as vismodegib therapy, could promote the development of CSCC and other secondary cancers. Regarding the increased risk for CSCC after vismodegib therapy, the author stressed the importance of continued skin surveillance after initiation of vismodegib treatment in patients with advanced BCCs.

Risk of nonmelanoma skin cancer associated with the use of immunosuppressant and biologic agents in patients with a history of autoimmune disease and nonmelanoma skin cancer

Scott FI, Mamtani R, Brensinger CM, Haynes K, Chiesa-Fuxench ZC, Zhang J, et al.
JAMA Dermatol 2016;152:164-72.

Immunosuppressive therapies (methotrexate, thiopurines, and tumour necrosis factor α) are the current standard treatments of rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). These medications are associated with dermatologic malignancy, in particular nonmelanoma skin cancer (NMSC) or squamous cell tumours. For patients with a prior history of malignancy, there are limited data regarding the effect of these medications on the risk of cancer recurrence or a second primary tumour. This is a retrospective cohort study investigating the risk of a second NMSC in patients with RA or IBD exposed to methotrexate, thiopurines, or biologic agents.

A total of 6,841 subjects with RA and 2,788 with IBD were studied. The incidence rate of a second NMSC per 1000 person-years was 58.2 (95% CI 54.5-62.1) and 58.9 (95% CI 53.2-65.2) in patients with RA and IBD respectively. It was found

that in patients with RA, methotrexate used in conjunction with other medications was associated with an increased risk of a second NMSC (hazard ratio [HR] 1.60; 95% CI 1.08-2.37). Also, the risk of NMSC increased with one year or more of methotrexate usage (HR 1.24; 95% CI 1.04-1.48). Compared with methotrexate alone, the addition of anti-TNF drugs was significantly associated with risk of NMSC (HR 1.49; 95% CI 1.03-2.16). Among individuals with IBD, thiopurines and anti-TNF agents usage were not statistically significant for the association with an increased risk of a second NMSC.

In conclusion, methotrexate use was associated with an increased risk of a second NMSC in RA, with increasing risk with longer duration of exposure. Anti-TNF therapy may further increase the risk of a second NMSC, particularly when used in conjunction with methotrexate to treat RA. Further long-term studies examining the association between thiopurines and anti-TNF agents and the risk of a second NMSC in patients with IBD are required. These data emphasise the need for intensive NMSC surveillance in patients with RA receiving methotrexate and / or anti-TNF agents with prior history of NMSC.