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# Journal Watch

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## An indirect comparison of long-term efficacy of every-2-week dosing vs recommended dosing of ixekizumab in patients who had static Physician's Global Assessment >1 at week 12

Papp K, Maari C, Cauthen A, Gooderham M, Spelman L, Yamanaka K, et al.
Br J Dermatol 2020;183:52-9.

Ixekizumab is a monoclonal antibody that selectively targets interleukin (IL)-17A. Current recommended dosage for adult moderate-to-severe plaque psoriasis is: 160-mg loading dose at week 0, 80 mg every 2 weeks (Q2W) till week 12, then 80 mg every 4 weeks (QW4) for patients with high level response (static Physician's Global Assessment (sPGA) score of ≤1). This study investigated whether a more frequent dosing regimen (Q2W) beyond 12 weeks for adult psoriasis patients (aged 18 years old) will improve the efficacy outcome for suboptimal response patients (sPGA >1 at week 12). Data from the IXORA-P study for patients with sPGA >1 at week 12 treated with the Q2W regimen through week 52 were indirectly compared with similar patients from the UNCOVER studies treated with the Q2W/Q4W regimen.

There was a significantly higher percentage of patients in the Q2W group (64%) achieved sPGA ≤1 at week 52 than Q4W group (36%). The median time to sPGA ≤1 response was also shorter in Q2W group (8.1 weeks) than Q4W group (16.4 weeks). About 18% patients had antidrug antibody in this 52-week study but did not have significant impact on response in any dose group. There were no clinically significant differences in adverse events between patients with sPGA ≤1 and patients with sPGA >1 at week 12.

In conclusion, most patients maintained high levels of response through week 52 on Q2W/Q4W labelled ixekizumab psoriasis dose. Dose escalation for patients with suboptimal response beyond 12 weeks from Q4W to Q2W result in an extra 30% patients with complete or almost complete clearance of psoriasis at week 52.

## Secukinumab for patients failing previous tumour necrosis factor-α inhibitor therapy: results of a randomized open-label study (SIGNATURE)

Warren RB, Barkner JNWB, Finlay AY, Burden AD, Kirby B, Armendariz Y, et al.
Br J Dermatol 2020;183:60-70.

Secukinumab is a human monoclonal antibody against interleukin (IL)-17A, a cytokine responsible for development of psoriasis. A randomised, open-label study in 53 dermatology centres of United Kingdom and Ireland with a study period of 72 weeks. It studied the effect of secukinumab for moderate-to-severe chronic plaque psoriasis patients who had failed TNF-α inhibitor therapy. Patients were randomised to receiving subcutaneous secukinumab 300 mg or 150 mg at baseline, then weekly from week 1 to 4 and 4-weekly afterward. The study recruited 235 adult patients (≥18 years old). A significant response was observed for both 300 mg and 150 mg secukinumab groups with Psoriasis Area and Severity Index (PASI 75) response from baseline to week 16 to be 65.3% (77/118) and 44.3% (51/115) of patients respectively. About 77% (54/70) patients achieved PASI 75 after 72 weeks in 300 mg secukinumab group. There was an improvement of Dermatology Life Quality Index (DLQI) from baseline to week 16 in 54% of patients

in the 300 mg secukinumab group with mean decrease of DLQI of 17 after 72 weeks.

The safety profile was favourable with the most common side effects being headache and nasopharyngitis and a higher incidence of candida infection. No cases of Crohn disease, ulcerative colitis, or tuberculosis were reported. It was therefore concluded that secukinumab is highly effective and safe for psoriasis patients who had failed TNF-α inhibitor therapy.

## Surgery versus combined treatment with curettage and imiquimod for nodular basal cell carcinoma: One-year results of a noninferiority, randomized, controlled trial

Sinx KAE, Nelemans PJ, Kelleners-Smeets NWJ, Winnepenninckx VJL, Arits AHMM, Mosterd K.
J Am Acad Dermatol 2020;83:469-76.

To investigate whether curettage enables deeper penetration of imiquimod into nodular basal cell carcinoma (nBCC), a multicentre, randomised, controlled non-inferiority trial comparing conventional surgical excision of nBCC with curettage of nBCC then daily application of 5% Imiquimod cream for five days per week over 6 weeks was performed. Patients with primary nBCC of 4 mm to 20 mm, confirmed by a 3-mm biopsy, were recruited. Exclusion criteria were recurrent BCC or aggressive histopathological subtypes. The primary study endpoint was the proportion of patients with no evidence of treatment failure at one year.

A total of 145 patients were included in the trial between January 2016 and November 2017. One year after treatment, 86.3% patients treated with curettage and imiquimod cream and 100% treated by surgical excision were free from treatment failure respectively. The absolute difference was -13.7% (95% CI-21.6% to -5.8%; 1-sided P=0.0004), thus favouring surgical excision. At 3 months after treatment 6.8% of the curettage and imiquimod group had residual tumour at three months compared to 0% in the surgical excision group. Moderate to severe pain was report in a lower percentage (13.5%) of patients treated with curettage and imiquimod cream than those treated excision (27%). However, the difference did not reach significance. Although investigator-reported cosmetic outcome with curettage and imiquimod was significantly better than after surgical excision, patient rating of the cosmetic outcome for both modalities were similar patient ratings of cosmetic results for other sites except the head and neck were similar in both treatment groups. In contrast, patient ratings for nBCCs located on the head and neck reported a significantly better cosmetic result with curettage and imiquimod than with surgical excision.

It was concluded that surgical excision was significantly more effective than curettage and imiquimod in this study. Curettage and imiquimod may lead to better cosmetic outcome especially over the head and neck region.

## No evidence of increased cancer incidence in children using topical tacrolimus for atopic dermatitis

Paller AS, Folster-Holst R, Chen SC, Diepgen TL, Elmets C, Margolis DJ, et al.
J Am Acad Dermatol 2020;83:375-81.

Due to the theoretical possibility of increased risk of cutaneous or other cancers from the immunosuppressive effect of topical calcineurin inhibitors (TCI), United States (US) and European regulators issued warnings against continuous long-term use of topical tacrolimus and pimecrolimus. However, as there is no clear epidemiological evidence supporting a causal relationship, the APPLES trial (A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety of Tacrolimus Ointment for the Treatment of Atopic Dermatitis) examined whether topical treatment with tacrolimus 0.03% or 0.1% ointment increases children's long-term risk of malignancy.

Children with atopic dermatitis who had used tacrolimus ointment for over six weeks before age 16 were recruited. Patients with a past history of cancer were also recruited. During the study period, there were no restrictions on treatment. The amount

of TCI used by the patient after enrollment was not quantified. The study duration was planned for 10 years and an independent Endpoint Review Committee reviewed all potential cancer events.

There were 8071 patients enrolled from 9 countries of which 2125 patients (26.7%) completed the study. The mean age at enrollment was 7.1 years and the mean time between first use of tacrolimus and enrollment in APPLES was 1.8 years. The mean age of first exposure to tacrolimus and pimecrolimus was 5.7 years and 4.8. years respectively. The estimated mean TCI exposure before enrollment was 885 grams of tacrolimus ointment. There were six incident cancer events in six individuals of which one was a spitzoid melanoma. No nonmelanoma skin cancers or incident lymphomas were observed. The observed rate of all incident cancers, which was 6 events per 44,629 person-years, which was similar to the expected rate of a population matched by age, sex, race, and country of origin.

In conclusion, this study found no evidence that tacrolimus ointment increases cancer risk in children with atopic dermatitis.

## Clinical outcomes of once-daily darunavir in treatment-experienced patients with darunavir resistance associated mutations through 48 weeks of treatment

Rolle C-P, Marquez O, Nguyen V, Hinestrosa F, DeJesus E, et al.
Int J STD & AIDS 2020;31:958-66.

Darunavir (DRV) is approved for once-daily use in HIV patients with no DRV resistance-associated mutations (RAMs) and twice-daily use in those with DRV RAMs. Studies have suggested that once-daily DRV remains effective in the presence of 1-2 DRV RAMs whereas three or more DRV RAMs are needed for DRV resistance. As there are few data regarding the long-term use of once-daily DRV in patients with DRV RAMs, this observational study evaluated the 48-week clinical outcomes of 22 treatment-experienced patients with 1 DRV RAMs that were switched to once-daily DRV boosted with either ritonavir (DRV/r) or cobicistat (DRV/c). The safety parameters were analysed throughout the study and the primary endpoint was HIV-1 RNA <50 copies/ml at week 48.

Of the 22 patients suitable for analysis, 18 (82%) had baseline HIV-1 RNA <50 copies/ml. The median number of historical DRV RAMs at baseline was two and the median age of the sample was 53 years. At week 48 after switching to once-daily boosted DRV, 20 (91%) cases had HIV-1 RNA <50 copies/ml, and 2 (9%) cases had HIV-1 RNA of >50 copies/ml who were found to have suboptimal adherence. No adverse drug reactions were observed throughout the 48-week study period.

It was concluded that virological control was achieved by once-daily DRV in patients with one historical DRV RAMs and that it was a well-tolerated and safe treatment option. Further studies are required.

## 2019 UK National Guideline for consultations requiring sexual history taking: Clinical Effectiveness Group British Association for Sexual Health and HIVS

Brook G, Church H,Evans C, Jenkinson N, McClean H, Mohammed H, et al.
Int J STD & AIDS 2020;31:920-38.

This updated version of the 2013 guidelines provides guidance in consultations requiring sexual history taking. The updated version contains new recommendations for managing cases of female genital mutilation (FGM), online testing, transgender (and non-binary) individuals and chemsex. In contrast to previous versions, the recommendations are given without assuming a specific gender identification. Gender terminology has also been updated in line with the British Association for Sexual Health and HIV. Although primarily intended for use in the UK Sexual Health/Sexual and Reproductive Healthcare service settings, but it can also be applied or adapted for sexual health assessments in other settings.

## Evaluation of risk of bullous pemphigoid with initiation of dipeptidyl peptidase-4 inhibitor vs second-generation sulfonylurea

Lee H, Chung HJ, Pawar A, Patorno E, Kim DH.
JAMA Dermatol. doi:10.1001/jamadermatol.2020.2158.

Several recent studies have reported an elevated risk of bullous pemphigoid in patients with type 2 diabetes treated with dipeptidyl peptidase-4 (DPP-4) inhibitors. This study characterised the incidence rate of bullous pemphigoid associated with DPP-4 inhibitor use compared with second-generation sulfonylureas.

This cohort study used data from two large commercial insurance claims databases and Medicare data from January 1, 2006, to December 31, 2016. Patients with type 2 diabetes who initiated treatment with DPP-4 inhibitors or second-generation sulfonylurea were included. The primary outcome of the study was bullous pemphigoid which was identified using ICD-9 or ICD-10 diagnosis codes.

A total of 870 709 patients (49% male; 51.0% female) were newly started on DPP-4 inhibitors (mean [SD] age, 63.7 [9.7] years) and 1 910 304 patients newly started on sulfonylurea (48.2% male; 51.8% female; mean [SD] age, 64.8 [10.2] years) were recruited. The incidence rate of bullous pemphigoid per 1000 person-years was 0.42 per 1000 person-years in the DPP-4 inhibitor group vs 0.31 per 1000 person-years in the sulfonylurea group (HR, 1.42; 95%CI,1.17-1.72). Higher rates per 1000 person-years for DPP-4 inhibitor vs sulfonylurea groups were seen in those who were treated with linagliptin (1.20 vs 0.55;HR, 1.68; 95%CI, 1.16-2.43), 65 years or older (0.79 vs 0.49; HR, 1.62; 95%CI, 1.32-1.99), and white (0.93 vs 0.54; HR, 1.70; 95%CI, 1.30-2.24).

It was concluded that there was an increased risk of bullous pemphigoid among DPP-4 inhibitor users compared with second generation sulfonylurea users. Although DPP-4 inhibitor-associated bullous pemphigoid is rare, clinicians should be aware of this possibility in DPP-4 inhibitors, particularly in older and white patients and in those taking linagliptin.

## Assessment and treatment outcomes of persistent radiation-induced alopecia in patients with cancer

Phillips GS, Freret ME, Friedman ND, Trelles S, Kukoyi O, Azael Freites-Martinez A, et al.
JAMA Dermatol 2020;e202127. doi:10.1001/jamadermatol.2020.2127.

A retrospective cohort study of patients with persistent radiation-induced alopecia (pRIA, defined as incomplete hair regrowth 6 months following radiotherapy completion), with primary central nervous system (CNS) tumors or head and neck sarcoma was conducted at two tertiary care hospitals and cancer centres between January 1, 2011 to January 30, 2019. Trichoscopic images, standardised clinical photographs of the scalp, and radiotherapy treatment plans were used to assess the radiation dose-response relationship, clinical and trichoscopic features, and response to topical minoxidil.

There were 7 (10%) cases with head and neck sarcoma and 64 (90%) cases with CNS tumour, giving a total of 71 patients. The median age was 27 years (range 4-75 years). Alopecia severity was grade 1 in 40 of 70 patients (56%), and grade 2 in 30 patients (43%). The pattern of alopecia was diffuse in 13 of 54 [24%] cases, localised in 29 of 54 [54%] cases, and mixed in 12 of 54 [22%] cases. The degree of alopecia was more severe with proton irradiation (OR, 5.7; 95%CI, 1.05-30.8) ($P<0.001$) and a higher dose of scalp radiation (odds ratio [OR], 1.15; 95%CI, 1.04-1.28). The main trichoscopic features were white patches (57%), milky red areas (32%) and arborising vessels (36%). A response to 5% minoxidil was seen in 28 of 34 patients (82%) at a median follow-up of 61 weeks (95%CI: 41-97; IQR: 21-105) with a complete response in four (16%) cases. Three patients were treated with procedural interventions for alopecia in which a partial or complete response was achieved.

It was concluded that pRIA in patients with head and neck sarcomas and primary CNS tumours is dependent on the radiation given. Topical minoxidil and procedural interventions may be efficacious in the treatment of this condition.