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Journal Watch

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Ustekinumab for the treatment of moderate-to-severe plaque psoriasis in paediatric patients (≥6 to <12 years of age): efficacy, safety, pharmacokinetic and biomarker results from the open-label CADMUS Jr study

Philipp S, Menter A, Nikkels AF, Barber K, Landells I, Eichenfield LF, et al.
Br J Dermatol 2020;183:664-72.

Ustekinumab is a human monoclonal antibody against interleukin 12, 23. It was approved for use for treatment of adolescents (age 12-18 years old) and adults (≥18 years) moderate-to-severe psoriasis. This was an open-label, single-arm, multicentre study for use of ustekinumab in paediatric moderate-to-severe plaque psoriasis. Weight-based dose of ustekinumab (<60 kg: 0.75 mg/kg, ≥60 kg to ≤100 kg: 45 mg, >100 kg: 90 mg) was injected subcutaneously at weeks 0 and 4, then every 12 weeks through week 40. Physician's Global Assessment score of cleared/minimal (PGA 0/1), Psoriasis Area and Severity Index (PASI 75/90), and change in Children's Dermatology Life Quality Index (CDLQI) was studied as primary or secondary endpoint at week 12.

A total of 44 patients were recruited (median age 9.5 years interquartile range IQR 7.5-10, range 6-11 years). PASI 75 & PASI 90 was achieved in 84% and 64% of cases respectively at week 12. PGA 0/1 was achieved by 77% of patients and mean improvement of CDLQI was 6.3 at week 12. Level of clinical response continue to improve or stablised up to week 52. Adverse events were reported in 77% of patients, the most common of which were nasopharyngitis, upper respiratory tract infection and pharyngitis.

It was concluded that ustekinumab was a safe and effective treatment for moderate-to-severe paediatric psoriasis cases.

Efficacy and safety of ixekizumab in a phase III, randomized, double-blind, placebo-controlled study in paediatric patients with moderate-to-severe plaque psoriasis (IXORA-PEDS)

Paller AS, Seyger MMB, Magarinos GA, J Bagel, Pinter A, Cather J, et al.
Br J Dermatol 2020;183:231-41.

Ixekizumab (IXE) is a monoclonal antibody selectively targets interleukin (IL)-17A, a cytokine responsible for development of psoriasis. It was recently approved by the US Food and Drug Administration for moderate-to-severe paediatric psoriasis. This was a randomised, multicentre, double-blind, placebo-controlled study of IXE (weight-based dosing every 4 weeks) on its efficacy and safety in patients aged 6-18 years old with moderate-to-severe plaque psoriasis. Endpoints were Psoriasis Area and Severity Index (PASI 75) and static Physician's Global Assessment score of 0 or 1 (sPGA 0,1) at week 12.

A total of 171 patients (mean+/-SD age: 13.5+/-3.04 years; range 6-17 years) were recruited. At 12 weeks, 89% patients in the IXE group achieved PASI 75 compared to 25% in the placebo group. More patients in the IXE group (78%) achieved the secondary endpoint of PASI 90 than

placebo group (5%). Similarly, more patients in the IXE group (81%) achieved sPGA (0,1) than placebo group (11%). The favourable response of IXE group maintained from week 12 through week 48. There was an improvement of scalp and genital psoriasis in significantly more patients in IXE group had than the placebo group at week 12. The rate of adverse events for IXE group and placebo group was 56% and 45% respectively. Most adverse event were mild or moderate in IXE group. No deaths were reported.

It was concluded that IXE was more effective than placebo in the treatment of moderate-to-severe paediatric psoriasis and that it has a similar safety profile as that in adult patients.

Peripheral inflammatory biomarkers as predictors of recurrence in surgically treated anogenital condylomata acuminata patients

Basim P, Yuksel M.
Int J STD & AIDS 2020;31:1380-8.

This study investigated the association of anogenital condylomata acuminata (CA) with recurrence and squamous intraepithelial neoplasia development, the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) in these patients. The descriptive data, disease characteristics, and pre-treatment peripheral inflammatory biomarkers (PIBs) in 95 patients who had undergone surgical treatment for CA were recorded retrospectively and compared between cases of recurrent and non-recurrent CA. Patients with a maximum genital wart size of >2 cm in the squamous intraepithelial lesion (SIL) group had significantly higher PIBs. There was a significant association between increased SII and high-risk human papillomavirus (HPV) types 16, 18, 31 and 33.

Recurrent disease was significantly associated with larger wart size, high-grade squamous intraepithelial lesion (HSIL), and higher PLR and SII values ($p=0.003$, 0.006, 0.005 and 0.000, respectively). HSIL and increased PLR and SII values were present in 34.1% of all recurrences. It was therefore concluded that PLR and SII can aid in risk analysis in certain patient groups.

Immunogenetics and human papillomavirus (HPV) in male genital lichen sclerosus (MGLSc)

Shim TN, Harwood CA, Marsh SGE, Gotch FM, Quint W, de Koning MN, et al.
Int J STD & AIDS 2020;31:1334-9.

As it has been suggested that human papillomavirus (HPV) and autoimmunity (e.g. Human Leukocyte Antigen [HLA]) are linked to the pathogenesis of male genital lichen sclerosus (MGLSc), a study to investigate these two factors in MGLSc was performed. Eighty-eight adult male cases with a clinical and histologically proven MGLSc from two specialised Male Genital Dermatoses Clinics between July 2011 and September 2012 were recruited. HLA and HPV typing from the blood and skin biopsy respectively. From the 88 cases, HPV DNA was detected as follows: genital types 30/8 (34.1%); beta types 6/88 (6.8%); cutaneous wart types 4/88 (4.5%). Of these, HPV16 was the most prevalent type: 181/88 (12.5%). When compared to the general Caucasian UK population, there was no statistically significant HLA associations, although there was an increased frequency of HLA-B*35, -DRB1*04, -C*15, -B*51, -DRB1*10 (predisposition) and a decreased frequency of -DQA1*01 (protection). There was no statistically significant association between HPV16-associated MGLSc cases and HLA genotype. It was therefore concluded that HPV is a passenger effect instead of being involved in the pathogenesis of MGLSc and that HLA is not associated with this condition.

The adverse effect profile of acitretin in a paediatric dermatology population — Longitudinal cohort study and recommendations for monitoring

Cave A, Plumptre I, Mellerio JE, Martinez AE, Kinsler VA.
J Am Acad Dermatol 2020;83:1779-81.

A retrospective case note review of the adverse effects of acitretin in paediatric patients was performed.

The records of 174 patients prescribed acitretin between 1993 and 2015 were reviewed. The mean age at starting acitretin was 8.1±0.4 years old (0.0-18.78). The mean duration of treatment was 3.5±0.3 years (0.02-17.58). The mean starting dose of acitretin was 0.42±0.01 mg/kg (0.15-0.68). The mean maximum dose was 0.45±0.02 mg/kg (0.14-1.24). Acitretin was prescribed for congenital ichthyosis (54.7%), psoriasis (29.1%), palmoplantar keratoderma (2.9%), eczema (2.3%).

Clinical adverse effects occurred in 24% which resulted in permanent cessation of acitretin in 10% of cases. On the other hand, laboratory adverse effects occurred in 22%, resulting in permanent cessation in 4% of cases. If treatment was tolerated at two years, laboratory adverse effects were then very uncommon.

All clinical adverse effects were reversible. These included skin irritation, fragility, or rash (10.3%), dry lips (9.2%), nausea (1.7%), tiredness or malaise (1.1%), mood swings (0.6%), hair thinning (0.6%). On the other hand, laboratory adverse effects were all reversible, that included abnormal triglyceride level (10%), abnormal alkaline phosphatase level (5.9%), abnormal alanine transaminase level (2.4%).

Reasons for stopping acitretin temporarily or permanently during study period included limited/no clinical improvement (19.2%), clinical adverse effects (12.2%), sustained clinical improvement (9.9%), worsening of skin disease (5.8%), and laboratory adverse effects (4.1%).

It was therefore concluded that, at the dose used in this study, with clinical and laboratory monitoring, acitretin is a safe drug.

Hand hygiene during COVID-19: Recommendations from the American Contact Dermatitis Society

Rundle CW, Presley CL, Militello M, Barber C, Powell DL, Jacob SE, et al.
J Am Acad Dermatol 2020;83:1730-7.

The recent COVID-19 pandemic has raised worldwide awareness of hand hygiene. Proper hand hygiene is crucial in the prevention of disease transmission and frequent hand washing with soap and water for 20 seconds is recommended by the CDC to prevent virus transmission. Hand sanitisers containing at least 60% alcohol may be used if soap and water are not available. However, it has been noted that during the COVID-19 outbreak in China, that only 22.1% of the 66.1% of healthcare workers who washed their hands more than 10 times per day, applied moisturisers afterwards, leading to an increased risk of hand dermatitis.

Several forms of hand hygiene products are available including antiseptic handwashes, liquid or bar soaps, alcohol-based hand sanitisers (ABHSs) and synthetic detergents. These inactivate viruses by disruption of the lipid membrane and intracellular lipids but may also alter skin barrier integrity and function, eventually leading to hand dermatitis. Alcohols in AHBS and bleach induce lysis of the viral particle by penetrating the viral membrane to denaturation and coagulation of viral proteins, disruption of cellular metabolism, and are the most effective agents against viruses.

The hands were the most commonly affected sites in a study of occupational dermatitis in health care workers. Likely causes included

irritation from gloves, detergents and disinfectants as well as frequent hand washing. Antimicrobial soaps (chlorhexidine, chloroxylenol, triclosan), detergents, iodophors, alcohol-based products, and other additives in hand cleansing products have also been reported to cause irritation.

The following are some recommendations for glove allergic contact dermatitis by the American Contact Dermatitis Society: rubber accelerator-free gloves (e.g. nitrile or rubber-free neoprene gloves); application of moisturiser after handwashing and before wearing gloves; cotton glove liners or loose plastic gloves (eg, plastic clear, disposable food gloves); and patch testing for patients with suspected hand ACD.

Regarding moisturisers, an application of a minimum of two fingertip units (FTU) of moisturiser to each hand is recommended after handwashing, with re-application of moisturisers every 3 to 4 hours and/or after each hand washing. Fragrance-free moisturisers with petrolatum or mineral oil have been recommended by the American Academy of Dermatology as they are the least allergenic.

Association between drug use and subsequent diagnosis of lupus erythematosus

Haugaard JH, Kofoed K, Gislason G, Dreyer L, Egeberg A.
JAMA Dermatol 2020;156:1199-207.

In this nationwide case-control study on the onset of drug-induced LE, medications in the Anatomical Therapeutic Chemical classification system from Denmark were systematically screened. Controls were matched for age and sex with patients with CLE or SLE (1:10) and the odds ratios (ORs) of the association of between drug exposure and diagnosis of CLE or SLE were calculated.

The study recruited a total of 3148 patients (CLE: n=1298; 1022 (78.7%) women), (SLE: n=1850; 1537 (83.1%) women) and 31 480 controls (25 590 (81.3%) women). Although there were many significant associations between drug exposure and onset of CLE and SLE, protopathic bias was likely in many cases. However, there were also new associations between CLE/SLE and certain medications which were unaltered by the sensitivity analyses as follows: metronidazole hydrochloride (SLE: OR, 1.57; 95%CI, 1.09-2.27; CLE: OR, 1.93; 95%CI, 1.25-2.97), fexofenadine hydrochloride (SLE: OR, 2.61 [95%CI, 1.80-3.80]; CLE: OR: 5.05 [95%CI, 3.51-7.26]), metoclopramide hydrochloride (SLE: OR, 3.38 [95%CI, 2.47-4.64]; CLE: OR, 1.47; 95%CI, 0.85-2.54), and levothyroxine sodium (SLE: OR, 2.46; 95%CI, 1.97-3.07, CLE: OR, 1.30; 95%CI, 0.96-1.75).

It was concluded that physicians should be aware of a possible drug aetiology in new cases of CLE or SLE. On the other hand, they should be wary of protopathic and publication bias.

Association between early severe cardiovascular events and the initiation of treatment with the anti-interleukin 12/23p40 antibody ustekinumab

Poizeau F, Nowak E, Kerbrat S, Le Nautout B, Droitcourt C, Drici MD, et al.
JAMA Dermatol 2020;156:1208-15.

As there has been clinical evidence of potentially severe cardiovascular events (SCEs) after the initiation of anti-IL-12/23p40 antibodies, this study was performed to assess the association of ustekinumab with SCEs (defined as acute coronary syndrome or stroke), within the 6-month period from initiation of treatment.

Data from 9290 patients from the French national health insurance database from 2010 to 2016 were analysed in this case-time-control analysis. Patients were stratified according to their cardiovascular risk (high-risk vs low risk). The risk period was defined

as the six months preceding the SCE, and the reference period was the six months before the risk period. The odds ratios (OR) for SCE after starting ustekinumab treatment were evaluated.

Of the 9290 patients exposed to ustekinumab, 4847 (52%) were men (mean age: 43 years; SD: 14 years), and SCEs occurred in 179 cases (46 cases of stroke, 65 cases of acute coronary syndrome, 68 cases of unstable angina). There was a statistically significant association between initiation of ustekinumab treatment and SCE in patients with a high cardiovascular risk (OR: 4.17; 95%CI: 1.19-14.59). On the other hand, there was no significant association between ustekinumab and SCEs in patients with a low cardiovascular risk (OR: 0.30; 95%CI: 0.03-3.13).

It was concluded that ustekinumab may induce SCEs among patients with high cardiovascular risk and that caution is required if ustekinumab is given in these patients.