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Journal Watch

Reviewed by CW Chow 周志榮, CC Koh 許招財, AHW Wong 王慶榮, CK Wong 黃之鍵

Mosaic structure of the penA gene in the oropharynx of men who have sex with men negative for gonorrhea

Marangoni A, Marziali G, Salvo M, D'Antuono A, Gaspari V, Foschi C, et al.
Int J STD AIDS 2020;31:230-5.

The mosaic penA alleles which are associated with decreased susceptibility to cephalosporins, have been found in commensal pharyngeal *Neisseria* species. The risk of multi-drug resistance in *Neisseria gonorrhoeae* of the oropharynx is therefore higher. This study investigated the prevalence of the mosaic structure of the penA gene in the oropharynx of 351 men who have sex with men (MSM) (mean age 33.5+/-10.3 years) who tested negative for pharyngeal gonorrhea. Real-time polymerase chain reaction (PCR) was performed on pharyngeal swabs underwent a real-time PCR to detect the mosaic penA gene. The PCR products of samples that tested positive were analysed for *Neisseria* strain sequences. The mosaic penA gene was found in 31 patients (8.8%) and was significantly associated with recent exposure to beta-lactams (RR: 4.29, 95% confidence interval 2.20-8.38) and with previous pharyngeal gonorrhoea (relative risk [RR]: 3.56, 95% confidence interval 1.44-8.80). There was no association with penA positivity and age. All penA-positive samples showed a high association (90-99%) with mosaic positive *Neisseria* strains. It was concluded that commensal *Neisseria* species of the oropharynx may be an important source of transferring genetic material associated with antimicrobial resistance in *N. gonorrhoeae* and that education on condom use during oral intercourse is therefore important.

Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension

Cork MJ, Thaçi D, Eichenfield LF, Arkwright PD, Hultsch T, Davis JD, et al.
Br J Dermatol 2020;182:12-3.

Dupilumab is a fully human VelocImmune-derived monoclonal antibody that inhibits interleukin (IL)-4 and IL-13. It is used to treat moderate-to-severe atopic dermatitis (AD) for patients ≥12 years old. This was a multicentre, open-label cohort study of the pharmacokinetic profile, safety and efficacy of dupilumab in paediatric patients (age ≥6 to <18 years old). Patients were given a single subcutaneous dose of 2 mg/kg or 4 mg/kg dupilumab (maximum 300 mg). Patients then had four weekly doses of dupilumab and followed up regularly for up to 52 weeks for safety and efficacy assessment.

Dupilumab was found to have nonlinear, target-mediated pharmacokinetics. At 48 week, mean±standard deviation trough dupilumab serum concentrations for 2 mg/kg and 4 mg/kg dupilumab were 74±19 mg/L and 161±60 mg/L respectively. Eczema Area and Severity Index at 52 week after 2 mg/kg and 4 mg/kg dupilumab dose

showed a reduction of 85%±12% and 84%±20% respectively. Dupilumab was well-tolerated over 52 weeks. Most common side effects for 2 mg/kg and 4 mg/kg dose were nasopharyngitis (41%, 47% respectively) and atopic dermatitis exacerbation (29%, 42% respectively) when dupilumab was not given. There was a low incidence of skin infections and injection site reactions were mild and uncommon. There were no cases of conjunctivitis reported.

It was concluded that the pharmacokinetic profile of dupilumab in adolescents was similar to that seen in adults and that dupilumab is an effective and safe treatment for adolescent atopic dermatitis patients.

Continued treatment with secukinumab is associated with high retention or regain of response

Augustin M, Thaçi D, Eyerich K, Pinter A, Radtke M, Lauffer F, et al.
Br J Dermatol 2020;182:67-75.

Secukinumab is a human monoclonal antibody against interleukin (IL)-17A, a cytokine responsible for development of psoriasis. It is safe and effective in the management of psoriasis. However, secondary loss of response over time for biologic therapy in psoriasis has been reported. This was a post hoc analysis of two randomised controlled trials ('CLEAR' and 'FIXTURE') to investigate the long term stability of response of secukinumab in management of psoriasis e.g. changes in efficacy, secondary loss of response, regain of efficacy with continued treatment. Efficacy of secukinumab 300 mg, etanercept 50 mg, ustekinumab 45 or 90 mg in management of psoriasis over 52 weeks was analysed. Response categories to biologic treatment were defined by Psoriasis Area and Severity Index (PASI) as follows: excellent response(PASI ≥90), good response (PASI ≥75-PASI <90) and insufficient response (PASI <75). A downward shift of response categories between two consecutive visits (maintained for a third consecutive visit) was classified as reductions in efficacy. A reduction of efficacy to 'insufficient' category was classified as loss of efficacy.

Around 90.2% (303/336) of secukinumab patients vs 77.7% (261/336) of ustekinumab patients achieved stable efficacy without loss of efficacy at 52 weeks in CLEAR study. Around 74.3% (252/339) of secukinumab patients vs 59.9% (203/339) of ustekinumab patients achieved stable efficacy without reduction of response at 52 weeks in CLEAR study. Around 83.5% (273/327) and 64.4% (217/327) of secukinumab patients vs 58.3% (190/326) and 42.6% (139/326) of etanercept patients achieved stable efficacy without loss or reduction of response at 52 weeks in FIXTURE study respectively. First reductions of response was found in 'CLEAR' secukinumab patients at week 12 and ustekinumab patients at week 8. The median number of weeks to regain response in 'CLEAR' study was 21.29 weeks for secukinumab patients and 32.14 weeks for ustekinumab patients.

The median number of weeks to regain response in 'FIXTURE' study was 27.86 weeks for secukinumab patients and 20.43 weeks for etanercept patients.

The median time to regain efficacy with secukinumab by Dermatological Life Quality Index response categories was 40.1 weeks in 'CLEAR' and 30.1 weeks in 'FIXTURE' study. About 50% of secukinumab patients in 'CLEAR' study and 26% of secukinumab patients regained response in 'FIXTURE' study. It was concluded that secukinumab treatment had stable efficacy over 52 weeks in most cases. Efficacy was regained after continued treatment in some patients with initial loss of efficacy and it was uncommon to have a persistent loss of response.

Mycoplasma genitalium and antimicrobial resistance in Europe: a comprehensive review

Fernandez-Huerta M, Barbera MJ, Serra-Pladevall J, Esperalba J, Martlınez-Gomez X, Centeno C, et al.
Int J STD AIDS 2020;31:190-7.

A comprehensive review of the literature on antimicrobial resistance data in *Mycoplasma genitalium* (MG) in Europe between 2012 and 2018 was performed. Twenty-five studies were finally selected which showed the rapid appearance of macrolide resistance is rapid in Europe, especially in Nordic countries except Sweden where estimates are exceeding 50%. Despite an increasing trend in the prevalence of macrolide resistance in Sweden, the estimates are relatively low compared with other European countries. This due to the difference in drug of choice for treatment (doxycycline in Sweden, azithromycin in other European countries) of non-gonococcal urethritis and *Chlamydia trachomatis* infection may account for this observation. In addition, fluoroquinolone resistance is emerging in Europe with estimated prevalence of 5% (interquartile range, 5-6%) despite limited data. Overall, the study findings illustrate the importance of surveillance on MG antimicrobial resistance. Further research on new treatments for MG is required.

Frequency and Clinical Presentation of Mucocutaneous Disease Due to Mycoplasma pneumoniae Infection in Children With Community-Acquired Pneumonia

Meyer Sauteur PM, Theiler M, Buettcher M, Seiler M, Weibel L, Berger C, et al.
JAMA Dermatol. Published online, December 18, 2019. doi:10.1001/jamadermatol. 2019.3602.

This prospective, longitudinal cohort study investigated the frequency and clinical presentation of *Mycoplasma pneumoniae*-induced mucocutaneous disease in children with community-acquired pneumonia (CAP). The study included 152 children aged 3 to 18 years with CAP. Mucocutaneous disease was defined as any eruptive lesion that involved skin and/or mucous membranes occurring during the CAP episode.

Of the 152 enrolled children with CAP (median [interquartile range] age, 5.7 [4.3-8.9] years; 84 [55.3%] male), 44 (28.9%) tested positive for *Mycoplasma pneumoniae* by PCR. Ten of the 44 children (22.7%) tested positive for *Mycoplasma pneumoniae* children developed mucocutaneous lesions. On the other hand, skin manifestations were found in three cases (2.8%) of *Mycoplasma pneumoniae* PCR-negative CAP ($P<0.001$). The spectrum of *Mycoplasma pneumoniae* -induced mucocutaneous disease included *Mycoplasma pneumoniae*-induced rash and mucositis (3 cases [6.8%]), urticaria (2 cases [4.5%]), and maculopapular skin eruptions (5 cases [11.4%]).

In addition, when compared with patients with CAP due to *Mycoplasma pneumoniae* without mucocutaneous manifestations, patients with *Mycoplasma pneumoniae*-induced mucocutaneous disease had longer duration of prodromal fever (median, 10.5 days; interquartile range, 8.3-11.8 days; $P=0.02$), higher C-reactive protein levels (median, 31 mg/L; interquartile range, 22-59mg/L; $P=0.04$), were more likely to require oxygen (odds ratio, 17.6; 95% CI, 1.5-984.1; $P=0.007$). Besides, patients with *Mycoplasma pneumoniae*-induced mucocutaneous disease were more likely require hospitalisation (odds ratio, 9.0; 95% CI, 1.4-81.4; $P=0.01$) and long-term sequelae (3 [30%] vs 0; $P=0.03$) such as exertional dyspnea, bronchiolitis obliterans, and postinflammatory pigmentary changes.

The author concluded mucocutaneous disease occurred significantly more frequently in children with CAP due to *Mycoplasma pneumoniae* than in children with CAP of other origins. Evidence from this study showed *Mycoplasma pneumoniae*-induced mucocutaneous disease was associated with a higher risk of long-term sequelae, increased systemic inflammation, and morbidity.

Incidence of Myocardial Infarction and Cerebrovascular Accident in Patients With Hidradenitis Suppurativa

Reddy S, Strunk A, Jemec GBE, Garg A.
JAMA Dermatol. Published online, November 13, 2019. doi:10.1001/jamadermatol. 2019.3412

The aim of this retrospective cohort study was to compare risk of myocardial infarction (MI), cerebrovascular accident (CVA), and composite disease (MI or CVA) in patients with hidradenitis suppurativa (HS) with controls without HS.

Among the 49862 patients with HS, 29711 were white (59.6%), and 37981 were women (76.2%). The mean (SD) age was 38.3 (13.3) years. The crude incidence of composite MI or CVA was 6.6 (95% CI, 6.3-7.0) per 1000 person-years in patients with HS, compared with 6.8 (95% CI, 6.7-6.8) per 1000 person-years among control patients. Moreover, in patients with HS vs control patients, crude incidence rates of MI alone were 2.9 (95% CI, 2.6-3.1) vs 3.2 (95% CI, 3.18-3.25) per 1000 person-years. In patients with HS vs control patients, crude incidence rates of CVA alone were 4.1 (95% CI, 3.9-4.4) vs 4.1 (95% CI, 4.0-4.1).

In addition, patients with HS had a 23% (hazard ratio [HR], 1.23; 95% CI, 1.17-1.30; P<0.001) increased risk of incident MI or CVA, a 21% (hazard ratio [HR], 1.21; 95% CI, 1.12-1.32; P<0.001) increased risk of incident MI alone, and a 22% (hazard ration [HR], 1.22; 95% CI, 1.14-1.31; P<0.001) increase in risk of incident CVA alone, after taking relevant cardiovascular risk factors into consideration. However, the association between HS and CVA or composite MI decreased with older age groups.

The author concluded hidradenitis suppurativa appears to be an independent risk factor for cardiovascular events, including myocardial infarction and cerebrovascular accident. The author suggested that periodic assessment of cardiovascular risk with the appropriate early adjustment of risk factors may be indicated for patients with HS.

Crisaborole 2% ointment for the treatment of intertriginous, anogenital, and facial psoriasis: A double-blind, randomized, vehicle-controlled trial

Hashim PW, Chima M, Kim HJ, Bares J, Yao CJ, Singer G, et al.
J Am Acad Dermatol 2020;82:360-5.

Crisaborole is a phosphodiesterase 4 (PDE-4) inhibitor that increases levels of intracellular cyclic adenosine monophosphate and decreases the production of proinflammatory cytokines. It was approved in 2016 for the treatment of mild-to-moderate atopic dermatitis.

This was a randomised, double-blinded, vehicle-controlled study comparing the efficacy of crisaborole in 21 cases with facial, anogenital, or intertriginous psoriasis. In phase 1 of the study, participants were randomised to receiving either crisaborole 2% ointment twice daily (n=14) or vehicle ointment twice daily (n=7). On day 29, all participants received open-label crisaborole 2% ointment twice daily until day 57 (phase 2). The primary efficacy endpoint was the percentage change in lesion severity between baseline and day 29 which was measured using the Target Lesion Severity Scale (TLSS).

Of the 21 patients enrolled, only one patient in the vehicle group opted out at day 8. There was a 66% improvement in TLSS score at day 29 in the crisaborole group versus 9% in the vehicle group (P=0.0011). This improvement persisted throughout the open-label period in the crisaborole group. At day 57, there was a 81% reduction in TLSS score in the crisaborole group with 71% of

participants reaching clinical clearance (TLSS score <=1). There were no application site reactions nor signs of atrophy or telangiectasias.

The limitations of this study included small sample size and the recruitment of cases from a single tertiary care centre. It was concluded that crisaborole 2% ointment improved intertriginous, anogenital, and facial psoriasis. Future prospective studies of larger sample size are needed.

A randomized phase 3b/4 study to evaluate concomitant use of topical ivermectin 1% cream and doxycycline 40-mg modified-release capsules, versus topical ivermectin 1% cream and placebo in the treatment of severe rosacea

Schaller M, Kemeny L, Havlickova B, Jackson JM, Ambroziak M, Lynde C, et al.
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The efficacy of ivermectin 1% cream (IVM) combined with doxycycline (DMR) versus that of ivermectin cream (IVM) and placebo (PBO) in the treatment of severe rosacea was evaluated in this 12-week multicentre, randomised, investigator-blinded, parallel-group study. Subjects were randomised (1:1) to 12 weeks of combination therapy (IVM and DMR) or monotherapy (IVM and PBO). Inclusion criteria included severe rosacea (Investigator's Global Assessment [IGA] score of 4), at least 18 years of age with 20 to 70 inflammatory lesions (papules and pustules) and under two facial nodules. The percentage change from baseline in inflammatory lesion count at week 12 was the primary endpoint.

At week 12, 251 of 273 enrolled subjects (91.9%) completed the study. At baseline, both groups were similar with all subjects having severe rosacea (IGA score, 4). There was a reduction of inflammatory lesions from baseline with both treatments. Combination therapy resulted in a significantly greater reduction as compared to those receiving monotherapy starting from week 4 (P=0.007). A higher proportion of subjects achieved 100% lesion clearance with combination therapy at week 12 (17.8% vs 7.2% for monotherapy [P=0.006]). The DLQI score was much improved with mean change of -4.4±5.1 with combination therapy and -4.3±5.8 with monotherapy [P<0.001 with both treatments]. There was a low incidence of treatment-related adverse events (4.4% for combination therapy vs 7.2% for monotherapy) of which most were dermatological. Discontinuation due to treatment-related AEs were reported only in subjects receiving monotherapy (2.2%).

In conclusion, the study findings suggest that combination therapy with topical ivermectin cream and oral doxycycline modified release capsule improves treatment efficacy regime for severe rosacea.