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Assessment of cytochrome P450 3A inhibition and induction of abrocitinib: Midazolam drug-drug interaction (DDI) study and oral contraceptive DDI study

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Background: According to in vitro assessments, abrocitinib was identified as a weak time-dependent inhibitor with NADPH for CYP3A, 2C8, 2C19, 2D6, and a potential inducer for CYP3A4 and 2B6.

Design: Two phase 1, randomized, open-label, 2-way crossover studies in healthy participants

Methods: Two drug-drug interactionstudies were conducted to investigate the effects of abrocitinib on the pharmacokinetics (PK) of midazolam (MDZ) or oral hormonal contraceptives (OC; ethynyl estradiol [EE] and levonorgestrel [LN]). Maximum observed plasma concentration (Cmax) and area under the concentration-time curve (AUC) were calculated for, MDZ, EE, and LN.

Results: When MDZ was coadministered with abrocitinib 200 mg qd on day 2, the ratios of the adjusted geometric means (aGMRs) (90% CIs) relative to administration of, MDZ alone for AUC and Cmax were 84.28% (78.95%-89.97%) and 86.29 (77.27%-96.36%), respectively, with upper bounds of the 90% CIs 80%.

Conclusions: There was a lack of clinically relevant inhibition or induction effect of abrocitinib on CYP3A system. There was absence of induction effect of abrocitinib on the metabolism of OC.

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Ability of mathematical models to predict human percutaneous penetration

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Background: Human skin is a common route for organic chemicals and drugs to enter the body. To aid with risk management of environmental chemical exposure, the US Environmental Protection Agency estimates percutaneous penetration using mathematical models.

Research Question: How accurate are mathematical models in estimating percutaneous penetration/absorption?

Methods: In this study, the accuracy of predicted flux (penetration/absorption) by the widely used Potts and Guy model based on in vitro data is compared with actual human in vivo data of percutaneous absorption of organic compounds and pesticides.

Results: For most chemicals the flux was over- or underestimated by a factor 10-100. The Potts and Guy model significantly correlated to experimental human in vivo data (Pearson correlation = 0.37, $P = .03$), however the correlation was not strong. Furthermore, the physiochemical parameters used in the Potts and Guy equation, namely Kp, Koctanol, and molecular weight, did not correlate significantly with in vivo flux.

Discussion and Conclusions: Current mathematical models used in estimating percutaneous penetration/absorption did not accurately predict in vivo flux. Why? Proposed limitations to mathematical models currently used include: not accounting for volatility, lipid solubility, hydrogen bond effects, as well as protein binding. Further research is needed into increasing the predictive nature of such models for in vivo flux.

Commercial disclosure: None identified.

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Integrating complement into the molecular pathogenesis of hidradenitis suppurativa

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Complement inhibition has been identified as a potential therapeutic target for multiple inflammatory disorders including hidradenitis suppurativa (HS). It is currently unclear how complement integrates into our current model of molecular pathogenesis in HS. Levels of C5a in serum and tissue correlate with disease activity and degree of neutrophilic infiltrates in HS. C5a has been associated with T_H17 immune axis activation in psoriasis, rheumatoid arthritis and Crohn disease with strong similarities to T_H17 activation in HS. Porphyromonas species (identified in the HS microbiome) are able to cleave inactive C5 into C5a implicating the cutaneous microbiome as an activator of complement. C3a and C5a are associated with activation of the NLRP3 inflammasome, implicated in the inflammatory drive in HS. Complement receptors are present upon dendritic cells, monocytes, fibroblasts and adipocytes which may broaden the potential contribution of complement to multiple aspects of HS pathogenesis. Dysregulation of complement receptor pathways have been documented in obesity, insulin resistance and polycystic ovarian syndrome leading to the possibility that complement may explain the epidemiologic associations between these conditions and HS. The therapeutic potential of complement inhibitors in HS may be related to the therapeutic target (complement receptor or complement subunit), and the presence of alternate receptors (such as C5L2) or ligands (including C3a, PAMPs and DAMPs). Integrating complement into the known pathogenesis of HS may aid in explaining the contradictory results between phase 2 studies of C5a antagonists. It also allows for the identification of existing knowledge gaps to target further clinical investigation and research.

Commercial disclosure: None identified.

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Cost-per-responder analysis of guselkumab versus secukinumab in obese patients using efficacy results from the ECLIPSE head-to-head clinical trial

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Background: Psoriasis patients have higher prevalence and incidence of obesity compared with the general population.

Objective: To estimate the cost per responder in the United States for guselkumab relative to secukinumab in obese patients in the first 48 weeks of treatment.

Methods: In the ECLIPSE study, patients were randomized to receive guselkumab 100 mg (n = 534), or secukinumab 300 mg (n = 514) through week 44. Dosing was based on the FDA label for the first year of treatment, and number of doses was based on 44 weeks of treatment (7 doses of guselkumab, 15 doses of secukinumab). Patients were considered obese if they had a body mass index $\geq$30 kg/m^2. Response was based on the percentage of obese patients achieving at least 90% improvement in their Psoriasis Area and Severity Index score (PASI90 response) at 48 weeks. Cost per responder was estimated by calculating (per unit drug cost in US) $\times$ (number of doses for 44 weeks of treatment) $\div$ (percentage of obese patients with a response at 48 weeks). All costs were based on wholesale acquisition cost as of June 2019.

Results: At week 48, 82.5% of obese guselkumab patients and 65.3% of obese secukinumab patients had a PASI90 response. The cost per PASI90 responder for obese patients through the first 48 weeks of treatment was \$92,140.87 for guselkumab (\$92,140.87 = \$76,016.22/82.5%) versus \$118,964.24 for secukinumab (\$118,964.24 = \$77,683.65/65.3%).

Conclusions: This model demonstrates that guselkumab has a lower cost per PASI90 responder in obese patients than secukinumab through the first 48 weeks of treatment.

Commercial disclosure: Janssen Scientific Affairs.