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RESEARCH SQUARE

Drug–drug interaction potential of darolutamide: In vitro and clinical studies

Darolutamide is a novel androgen receptor inhibitor approved for the treatment of nonmetastatic castration-resistant prostate cancer, or nmCRPC. In the phase 3 ARAMIS trial, darolutamide demonstrated significant anti-tumor activity and a favorable safety profile for men with nmCRPC. The current studies aim to show how darolutamide interacts with other drugs. Such information is crucial because patients with prostate cancer are typically older men with multiple comorbidities that require taking several medications at a time.

Researchers recently examined the drug–drug interaction potential of darolutamide through both clinical and nonclinical studies. The goal was to determine whether other drugs taken to treat comorbidities can modulate the blood levels of darolutamide and vice versa. Lower blood levels of drugs may lead to loss of efficacy, whereas increased blood levels may increase side effects.

In vitro studies suggested darolutamide is mainly affected by the metabolizing enzyme CYP3A4 and the drug transporters P-glycoprotein, or P-gp, and breast cancer resistance protein, or BCRP. This was tested in a phase I study where researchers looked at the effects of co-administering two drugs on the pharmacokinetics of darolutamide in healthy volunteers: rifampicin, an inducer of CYP3A4 and P-gp, which might decrease darolutamide blood levels, and itraconazole, an inhibitor of CYP3A4 and P-gp as well as of BCRP, which might increase darolutamide blood levels.

Data showed that darolutamide exposure indeed decreased by 72% when co-administered with rifampicin, suggesting co-administration with strong CYP3A4 and P-gp inducers should be avoided. However, few drugs are strong CYP3A4 inducers, and these are not often used in patients with nmCRPC.

Darolutamide’s exposure increased by a factor of 1.75 with itraconazole. This increase is relatively small, given that other drugs sensitive to itraconazole show over 5-fold increases in blood levels. Moreover, in ARAMIS, co-administration of similar inhibitors was not found to be linked to changes in darolutamide levels.

In two additional studies, the researchers assessed the impact of darolutamide on the pharmacokinetics of midazolam, a CYP3A4 substrate, and dabigatran, a P-gp substrate—and on the pharmacokinetics of rosuvastatin, a substrate for BCRP, and other drug transporters, including organic anion transporting peptide, or OATP.

Co-administration of darolutamide with midazolam and dabigatran revealed no effect or only minor effects, while rosuvastatin exposure increased by a factor of 5.2 with darolutamide, most likely because of BCRP and possibly OATP inhibition.

These findings in healthy volunteers confirmed observations previously made in preclinical experiments. The increased blood levels of rosuvastatin seen here did not seem to translate into additional adverse events for patients taking similar types of drugs with darolutamide in the ARAMIS study.

Altogether, the studies suggest that darolutamide has a low potential for clinically relevant interactions with drugs used to treat comorbidities common in older patient populations. This means that many drugs taken to treat comorbidities in patients with nmCRPC are not meaningfully influenced by darolutamide. This might be an advantage to treat patients with nmCRPC who are taking concomitant medications. Apalutamide and enzalutamide, other drugs approved for treating nmCRPC, have a potential to change the blood levels of important co-medications such as opioid analgesics and anticoagulant drugs used to treat cardiovascular disorders.

A low interaction potential is critical when treating patients with prostate cancer, as they generally receive several additional medications for other medical conditions.