Hyperbilirubinemia in pazopanib- or sunitinib-treated patients in COMPARZ is associated with UGT1A1 polymorphisms†

Pazopanib and sunitinib are angiogenesis inhibitors approved for treatment of advanced renal cell carcinoma. Treatment-associated elevations in alanine aminotransferase (ALT) and bilirubin have been reported for both therapies [1]. UGT1A1 polymorphisms are known to cause reduced expression/ activity of UGT1A1 and predispose individuals to Gilbert’s syndrome, a benign form of episodic jaundice [2, 3]. Our analyses of previous pazopanib clinical trials found that UGT1A1 *28 was associated with on-treatment hyperbilirubinemia [4]. This study extended our previous analysis of UGT1A1*28 to additional alleles (*36, *37, and *6) and investigated their association with on-therapy serum total bilirubin in COMPARZ (NCT00720941 and NCT01147822), a phase III, randomized, clinical trial comparing pazopanib versus sunitinib for the treatment of advanced renal cell carcinoma [1].

Of 1110 randomized participants, on-therapy hyperbilirubinemia [total bilirubin ≥1.5 × upper limit of the normal range (ULN)] was observed in 16% (89/557) of pazopanib-arm patients and 9% (49/553) of sunitinib-arm patients. In the pharmacogenetic population (patients who received at least one dose of study treatment, consented, and were successfully genotyped, n = 719), the incidence of hyperbilirubinemia was 17% (62 of 369) for pazopanib and 10% (34 of 350) for sunitinib.

The incidence of hyperbilirubinemia varies by UGT1A1 genotypes for both therapies (Figure 1). Logistic regression adjusted for ancestry principal components was used to compare hyperbilirubinemia cases ( pazopanib n = 62; sunitinib n = 34) against controls ( pazopanib n = 211; sunitinib n = 212). Controls were defined as patients with all on-therapy bilirubin ≤1 × ULN and treatment exposure equal to or greater than median exposure until bilirubin elevation in cases (defined in the supplementary materials, available at Annals of Oncology online). Patients with predicted reduced UGT1A1 function (homzygous or inferred compound heterozygous for *28, *37, and *6) had higher baseline bilirubin and were more likely to experience hyperbilirubinemia when receiving either pazopanib (P = 7.7 × 10⁻⁸) or sunitinib (P = 1.7 × 10⁻⁶), with odds ratios (95% confidence interval) 9.97 (4.13–24.03) and 5.83 (2.04–16.68), respectively. After adjusting for baseline bilirubin, patients with predicted, reduced UGT1A1 function remained more likely to experience hyperbilirubinemia when receiving pazopanib (P = 0.012) or sunitinib (P = 0.024), with odds ratios (95% confidence interval) 3.65 (1.31–10.16) and 4.51 (1.26–16.11), respectively.

UGT1A1 genotypes were not significantly associated with ALT ≥3 × ULN in pazopanib-treated patients. A borderline significant association (P = 0.030) was seen between UGT1A1 genotypes with reduced function (predicted) and decreased incidence of ALT ≥3 × ULN in sunitinib-treated patients; additional studies are required to confirm this observation.

Pazopanib is a potent inhibitor of UGT1A1 in vitro [4]. Our data suggest that hyperbilirubinemia in pazopanib-treated patients may be the result of inhibition of UGT1A1 combined with effects of genetic variants in the UGT1A1 gene. We expect this would result in higher levels of unconjugated hyperbilirubinemia, usually associated with a benign clinical course. Sunitinib, however, does not inhibit UGT1A1 [5]. To our knowledge, this is the first study reporting the association between UGT1A1 genotype and hyperbilirubinemia in patients receiving sunitinib.

Our data suggest that some instances of hyperbilirubinemia in patients treated with pazopanib or sunitinib may be benign manifestations of Gilbert’s syndrome. Bilirubin fractionation or, if not available, UGT1A1 genotyping, would enable further characterization of liver safety risk and help in making treatment decisions.

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**disclosure**

TJ, KCD, ZX, LNP, CC and CFX are employees of GlaxoSmithKline and own company stock. TKC is on the advisory board for GlaxoSmithKline, Pfizer, Aveo and Novartis, and holds a research grant from Pfizer. RJM has received consulting fees or honoraria from Pfizer, Genentech and AVEO Oncology; travel support from GlaxoSmithKline; and institutional grants from Pfizer, Novartis, AVEO Oncology, Genentech and GlaxoSmithKline.

**references**


Figure 1. The cumulative incidence of total bilirubin ≥1.5 × ULN by predicted UGT1A1 function in pazopanib- or sunitinib-treated patients. Predicted UGT1A1 function was classified as homozygous Normal (N_N), heterozygous for reduced function allele (N_R) and homozygous/compound heterozygous for reduced function alleles (R_R). Pazopanib was administered orally at 800 mg once daily by continuous dosing schedule. Sunitinib was administered orally at 50 mg once daily in 6-week cycles (4 weeks on, 2 weeks off). The horizontal axis represents the cumulative number of days receiving treatment (not elapsed calendar days). Significant correlation between predicted UGT1A1 function (by genotype) and treatment discontinuation due to any safety events was not observed for either pazopanib or sunitinib. PGx, pharmacogenetic.

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Central venous catheter care for the patients with cancer: ultrasound-guided insertion should be strongly recommended for internal jugular vein catheterization

A central venous catheter (CVC) is essential in patients with cancer, and the need for an intravenous access device for the administration of cancer therapy has increased proportionally with the increasing number of patients diagnosed with cancer.

In a recent article, Schiffer et al. [1] reported the American Society of Clinical Oncology clinical practice guideline for central venous catheter care for the patients with cancer.

The authors confirmed in the recommendation 1.3 that image-guided insertion [e.g. ultrasound (US), fluoroscopy ....]