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UGT genotyping in belinostat dosing

Andrew K.L. Goey¹ and William D. Figg¹

¹Clinical Pharmacology Program, National Cancer Institute, National Institutes of Health, Bethesda MD, USA

Abstract

Certain genetic polymorphisms of UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) can reduce gene expression (*28, *60, *93) or activity (*6), thereby altering the pharmacokinetics, pharmacodynamics, and the risk of toxicities of UGT1A1 substrates, of which irinotecan is a widely-described example. This review presents an overview of the clinical effects of *UGT1A1* polymorphisms on the pharmacology of UGT1A1 substrates, with a special focus on the novel histone deacetylase inhibitor belinostat. Belinostat, approved for the treatment of peripheral T-cell lymphoma, is primarily glucuronidated by UGT1A1. Recent preclinical and clinical data showed that *UGT1A1**28 was associated with reduced glucuronidation in human liver microsomes, while in a retrospective analysis of a Phase I trial with patients receiving belinostat *UGT1A1**60 was predominantly associated with increased belinostat plasma concentrations. Furthermore, both *UGT1A1**28 and *60 variants were associated with increased incidence of thrombocytopenia and neutropenia. Using population pharmacokinetic analysis a 33% dose reduction has been proposed for patients carrying *UGT1A1* variant alleles. Clinical effects of this genotype-based dosing recommendation is currently prospectively being investigated. Overall, the data suggest that UGT1A1 genotyping is useful for improving belinostat therapy.

Graphical abstract

Corresponding author: William Douglas Figg, Sr., Pharm.D., Clinical Pharmacology Program, CCR, NCI, NIH, 9000 Rockville Pike, Building 10, Room 5A01, Bethesda, Maryland 20892. Tel: +1 301-402-3623. Fax: +1 301-402-8606. figgw@helix.nih.gov..

Conflict of interest

No potential conflicts of interest were disclosed.

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Keywords

belinostat; UGT1A1; polymorphisms; pharmacogenomics; pharmacokinetics; pharmacodynamics

1. Introduction

In the present era of precision medicine the role of pharmacogenomics has become increasingly important in regards to various aspects of cancer treatment. Pharmacogenomic analyses can be used to predict drug responsiveness in the presence of certain mutations in tumor cells. For example, in the treatment of ovarian cancer progression-free survival is significantly longer in olaparib-treated patients with BRCA mutations than in patients without these mutations [1]. Similarly, patients with non-small cell lung cancer carrying driver mutations in the epidermal growth factor (EGFR) gene benefit more from treatment with EGFR tyrosine kinase inhibitors (e.g. erlotinib [2, 3], gefitinib [4], afatinib [5]) than patients with wild type (WT) EGFR. Another example includes the EGFR monoclonal antibodies panitumumab and cetuximab, which appear to be less effective in tumors with KRAS mutations and are therefore recommended only in KRAS WT tumors [6].

Besides having value in predicting drug responsiveness, pharmacogenomics can also be useful in decreasing the incidence of adverse drug reactions. For example, the risk of neutropenia in irinotecan-treated patients is higher among patients homozygous for a genetic variant of UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1*28) [7], which is the main metabolizing enzyme of irinotecan's active metabolite SN-38. Furthermore, patients who are deficient in dihydropyrimidine dehydrogenase, the rate limiting enzyme in 5-fluorouracil (5-FU) metabolism, should not undergo treatment with the 5-FU prodrugs fluorouracil [8], capecitabine [9], and tegafur [10] to decrease the risk of drug-related toxicities.

Recent studies suggest that the histone deacetylase (HDAC) inhibitor belinostat (Beleodaq) is another drug for which genotype-directed dosing could be useful to improve drug safety [11-13]. In 2014 belinostat was approved for the treatment of peripheral T-cell lymphoma. Belinostat inhibits the process of histone deacetylation by HDAC, which is one of the

epigenetic mechanisms that regulate gene expression. HDAC inhibition leads to accumulation of acetylated histones resulting in a more relaxed chromatin structure which enhances the transcription of genes responsible for cell growth arrest, differentiation, and apoptosis of tumor cells [14].

Since belinostat is mainly metabolized by the highly polymorphic enzyme UGT1A1, patients carrying UGT1A1 variants associated with reduced enzyme function or expression could be exposed to higher belinostat plasma concentrations possibly leading to an increased incidence of belinostat-related toxicities. In this review we therefore evaluate the importance of UGT1A1 genotyping for belinostat dosing with regards to pharmacokinetics, pharmacodynamics, and toxicities. In addition, clinical effects of UGT1A1 polymorphisms on the pharmacology of other UGT1A1 substrates (and inhibitors) will be covered.

2. UGT1A1 polymorphisms

The UGT superfamily consists of four families: UGT1A, UGT2, UGT3, and UGT8 [15]. UGT enzymes are responsible for glucuronidation of endogenous (e.g. bilirubin) or drug substrates thereby increasing water solubility and biliary or renal clearance of these compounds.

UGT1A1, located on chromosome 2q37, is expressed in the stomach [16], liver, colon, and intestine [17]. The main function of hepatic UGT1A1 is glucuronidation of bilirubin [18]. Consequently, UGT1A1-deficiencies lead to hyperbilirubinemia as observed in patients with Crigler-Najjar syndrome [19] and Gilbert's syndrome [20]. Thus far, 113 *UGT1A1* genetic variants have been described [21], of which *UGT1A1**6 (rs4148323), *UGT1A1**28 (rs8175347), *UGT1A1**60 (rs4124874), and *UGT1A1**93 (rs10929302) are commonly reported variants associated with reduced enzyme expression or activity (Table 1).

*UGT1A1**6, a glycine-to-arginine substitution at position 71, has an allele frequency of 0.13 - 0.23 in Asians [22]. Individuals homozygous for *UGT1A1**6 have their UGT1A1 activity reduced by ~70%, which may contribute to the development of Gilbert's syndrome [23] and nonphysiologic neonatal hyperbilirubinemia [24].

*UGT1A1**28 is characterized by an extra TA repeat (A(TA)₇TAA) in the *UGT1A1* promoter region [20]. This genetic variant reduces UGT1A1 expression by approximately 70% compared to WT A(TA)₆TAA and is associated with Gilbert's syndrome [20]. Reported allele frequencies are 0.26 - 0.39 in Caucasians, 0.30 - 0.56 in Africans and African Americans, and 0.09 - 0.20 in Asian populations [25, 26].

Besides the polymorphic (TA)_n repeat, the phenobarbital-responsive enhance module (PBREM) also regulates UGT1A1 transcription and harvests genetic variation [27]. For example, *UGT1A1**60, caused by a T-to-G substitution at position 3279, decreases the transcriptional activity of the *UGT1A1* gene [28]. Allele frequencies of *UGT1A1**60 in Caucasians and African Americans are 0.47 and 0.85, respectively [29]. This variant is in linkage disequilibrium with *UGT1A1**28 [29].

*UGT1A1**93 is a G-to-A substitution at position 3156 in the PBREM and also in linkage disequilibrium with *UGT1A1**28 [29]. Individuals homozygous for *UGT1A1**93 had higher total bilirubin concentrations than WT *UGT1A1**93 [30]. Frequency of the variant allele is approximately 0.30 in Caucasians and African Americans [29].

3. Effects of *UGT1A1* polymorphisms on belinostat pharmacokinetics, pharmacodynamics, and toxicities

3.1 Clinical pharmacology of belinostat

The recommended dosage of belinostat is 1,000 mg/m² administered intravenously (IV) over 30 minutes once daily on days 1-5 of a 21-day cycle [32]. Nausea, fatigue, pyrexia, anemia, and vomiting are the most common toxicities [32]. After administration belinostat is limitedly distributed to tissue (as indicated by a mean volume of distribution approaching total body water) and shows extensive protein binding of 93%-96%.

Using a panel of human UGT supersomes, each specifically expressing *UGT1A1*, *UGT1A3*, *UGT1A4*, *UGT1A6*, *UGT1A7*, *UGT1A8*, *UGT1A9*, *UGT1A10*, *UGT2B4*, *UGT2B7*, *UGT2B15* or *UGT2B17*, Wang and colleagues have shown that belinostat was metabolized only by *UGT1A1* [11]. The vast majority (98%) of belinostat undergoes hepatic metabolism, primarily by *UGT1A1* and to a lesser extent by *CYP2A6*, *CYP2C9*, and *CYP3A4*. Less than 2% of belinostat is excreted unchanged in urine. Elimination of belinostat is rapid with an elimination half-life of only 1.1 hours [32].

3.2 Effects of *UGT1A1* genotyping on the clinical pharmacology of belinostat

Studies of *UGT1A1*-mediated metabolism of belinostat identified five metabolites in plasma samples of patients treated with belinostat [11]. Of these metabolites, belinostat glucuronide (belinostat-G) was found to be the most abundant one, suggesting that glucuronidation is the main metabolic pathway of belinostat. In HepG2 cells belinostat was shown to be cytotoxic, while belinostat-G was inactive. After the discovery that *UGT1A1* was mainly responsible for belinostat metabolism, the effect of *UGT1A1**28 genotype status on belinostat glucuronidation was determined in human liver microsomes. In this experiment belinostat glucuronidation was significantly decreased in microsomes homozygous for *UGT1A1**28 compared to WT microsomes.

Based on these preclinical findings only, the drug label of belinostat recommends a dose reduction to 750 mg/m² in patients who are homozygous for *UGT1A1**28 [32]. In order to provide a clinical rationale for this dose adjustment, Goey and colleagues carried out a retrospective analysis in 23 patients with solid tumors receiving belinostat as a 48 h continuous intravenous infusion (CIVI, 400 – 800 mg/m²/24 h) in combination with cisplatin and etoposide (BPE trial) [12]. In this analysis the effects of *UGT1A1* polymorphisms on belinostat pharmacokinetics, pharmacodynamics, and toxicities were investigated. The rationale of a 48 h infusion instead of the approved 30-minute infusion on days 1-5 of a 21-day cycle is based on preclinical data showing that 48 h exposure to belinostat substantially increased cytotoxicity [13, 33]. Using non-compartmental pharmacokinetic analysis, an increased number of *UGT1A1**28 and especially *UGT1A1**60

variant alleles was shown to be significantly associated with increased belinostat exposure and an increased risk of hematological toxicities, such as thrombocytopenia and neutropenia [12]. Interestingly, similar to what was shown for irinotecan [7], the gene-drug interaction was more profound at higher doses of belinostat. The findings of this pharmacogenomic analysis suggest that genotyping for *UGT1A1**60 status should also be included in the belinostat drug label. Furthermore, belinostat dose should be individualized based on *UGT1A1**28 and *60 genotype status to prevent toxic plasma concentrations of belinostat in patients carrying variants alleles.

In order to formulate belinostat dose-adjustments for patients carrying *UGT1A1**28 and *60 genetic variants, Peer and colleagues designed and validated a two compartment population pharmacokinetic model utilizing non-linear mixed effects modeling for the 48 h CIVI dosage regimen used in the BPE trial [13]. The primary objective of this analysis was to identify doses that would provide equivalent belinostat exposures in patients stratified by *UGT1A1* genotype. The following covariates significantly affected belinostat clearance and/or volume, and were incorporated in the final model: *UGT1A1* genotype status (*28 and *60), serum albumin concentration, creatinine clearance, and body weight. After exploring several stratification scenarios for *UGT1A1* status and dose simulations, the following dosing recommendation resulted from the model: patients who were WT for both *UGT1A1**28 and *60 or heterozygous for *28 should receive a dose of 600 mg/m²/24 h, while a reduced dose of 400 mg/m²/24 h should be given to patients homozygous for *UGT1A1**28 or patients heterozygous or homozygous for *UGT1A1**60 in order to reach equivalent AUCs. These recommended doses are currently being tested in a genotype-directed expansion of the BPE trial at the National Cancer Institute (NCI).

4. Effects of UGT1A1 polymorphisms on the pharmacology of other UGT1A1 substrates or inhibitors

Several clinical trials have studied the effect of *UGT1A1* genetic variants on the pharmacokinetics, pharmacodynamics and toxicities of other drugs (Table 2).

The importance of UGT1A1-genotype-based dose adjustments has extensively been shown for the topoisomerase I inhibitor irinotecan, which is used for the treatment of metastatic colorectal cancer. Irinotecan is a prodrug that requires metabolism to its active metabolite SN-38, which is predominantly glucuronidated by UGT1A1 [21]. Consequently, genetic UGT1A1 deficiencies lead to a build-up of SN-38 resulting in an increased risk of serious toxicities. For example, in 177 Japanese patients with cancer both *UGT1A1**6 and *UGT1A1**28 were associated with reduced SN-38 glucuronidation and severe irinotecan-induced neutropenia [31]. In line with these findings, another study with 66 patients showed that grade 4 neutropenia was significantly more common in patients homozygous for *UGT1A1**28 than in patients who were heterozygous for this variant or WT [30]. *UGT1A1**28 genotype status was also associated with the incidence of neutropenia [7, 35] and time to progression [36]. Due to the increased risk of neutropenia, the U.S. Food and Drug Administration approved drug label of irinotecan recommends a reduction in the starting dose by at least one level of irinotecan in patients homozygous for *UGT1A1**28 [52]. Several clinical trials have evaluated the concept of *UGT1A1* genotype-directed dosing

of irinotecan based on *UGT1A1**28 genotype and to a lesser extent on the *6 genotype in patients receiving irinotecan monotherapy [53, 54] or in combination therapy involving irinotecan with fluorouracil [55, 56], capecitabine [57], or capecitabine and oxaliplatin [58]. Overall, these studies supported the need for genotype-based dose adjustments by showing that patients homozygous for the *28/*28 allele are at the highest risk of irinotecan-related toxicity and require a dose reduction of up to 40%. Since the risk of neutropenia is greater at higher irinotecan doses [7], a dose-dependent dose recommendation would be more accurate. Therefore, the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy recommends an initial dose reduction of 30% for *28 homozygous patients receiving a dose greater than 250 mg/m² [59]. Consistently, the French joint workgroup comprising the Group of Clinical Onco-pharmacology and the National Pharmacogenetics Network recommends a dose reduction of 30% in patients homozygous for *28 who are receiving doses between 180 and 230 mg/m², while high irinotecan doses (240 mg/m²) should only be given to WT patients [60]. In addition to *UGT1A1**6 and *28 polymorphisms, *UGT1A1**60 is associated with increased bilirubin levels [37], decreased SN-38 glucuronidation [36], and with hematological toxicities [36] in patients treated with irinotecan. Patients heterozygous for *UGT1A1**93 also tended to have a greater risk of severe hematologic toxicity, while patients homozygous for *93 had a significantly increased tumor response rate compared with WT patients [36].

Several clinical studies have showed effects of *UGT1A1* polymorphisms on the pharmacokinetics and pharmacodynamics of other *UGT1A1* substrates, such as axitinib, etoposide, and raloxifene. The tyrosine kinase inhibitor (TKI) axitinib, used as second-line treatment of advanced renal cell carcinoma, is primarily metabolized by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and *UGT1A1* [61]. Probably due to the relatively small contribution of *UGT1A1* in the metabolism of axitinib, *UGT1A1**28 genotype status did not cause clinically relevant effects on axitinib clearance in healthy volunteers [38]. The topoisomerase II inhibitor etoposide is also partially glucuronidated by *UGT1A1* [62]. In children with acute lymphoblastic leukemia it was shown that etoposide clearance was higher in black children carrying *UGT1A1**28 WT alleles [39]. A lower area under the plasma concentration-time curve (AUC) of the etoposide catechol metabolite was also observed in both white and black patients who were WT for *UGT1A1* [39]. Nevertheless, the etoposide package insert does not recommend *UGT1A1* genotyping or genotype-based dose adjustments [63]. The pharmacokinetics of the estrogen agonist/antagonist raloxifene were also significantly affected by *UGT1A1**28 [40]. Raloxifene is used for treatment and prevention of osteoporosis and risk reduction of invasive breast cancer in menopausal women. Subjects with the *UGT1A1**28/*28 genotype exhibited twofold higher raloxifene glucuronide concentrations compared with individuals who were heterozygous or WT for *UGT1A1**28. According to the authors a possible explanation for this contradictory finding is that reduced *UGT1A1* activity also inhibited the excretion of the metabolites. Furthermore, unconjugated raloxifene was also suggested to be formed by cleavage of the glucuronide metabolites which leads to increased raloxifene exposure. In line with this hypothesis, bone mineral density was more increased in *28 homozygotes vs heterozygotes and WT patients.

No clinically relevant effects of *UGT1A1* genotype were observed on the pharmacokinetics of other UGT1A1 substrates, such as the human immunodeficiency virus-1 (HIV-1) integrase strand transfer inhibitor raltegravir [41] and the long-acting beta2-adrenergic agonists arformoterol [42] and indacaterol [64].

Certain drugs are (strong) inhibitors of UGT1A1 and could increase the risk of hyperbilirubinemia in patients with reduced UGT1A1 expression and pharmacokinetic interactions with concurrently administered UGT1A1 substrates. The TKI erlotinib should therefore be used with caution in patients with low UGT1A1 expression levels or genetic glucuronidation disorders [65]. The BCR-ABL1 kinase inhibitor nilotinib also inhibits UGT1A1 and causes an increased risk of hyperbilirubinemia in patients carrying *UGT1A1**6 and *28 variant alleles [44, 45]. However, these clinical observations did not lead to a recommendation of *UGT1A1* genotyping in the nilotinib drug label [66]. Similar to nilotinib, the multikinase inhibitor pazopanib inhibits UGT1A1 and significantly increased the incidence of hyperbilirubinemia in patients homozygous for *UGT1A1**28 relative to heterozygous and WT patients [46, 47]. The pazopanib package insert therefore recommends that pazopanib treatment should be interrupted in patients with mild indirect hyperbilirubinemia, known Gilbert's syndrome, and ALT elevation > 3 X ULN until ALT levels return to grade 1 values or baseline [47]. The pazopanib drug label also mentions the possibility of increased concentrations of co-administered UGT1A1 substrates, although no clinical pharmacokinetic interaction studies with pazopanib have been published to date. Regorafenib, another multikinase inhibitor, and its active metabolites M-2 and M-5 are also inhibitors of UGT1A1. Consequently, hyperbilirubinemia could occur in patients with Gilbert's syndrome [67]. Regorafenib can also impact the pharmacokinetics of co-administered UGT1A1 substrates. For example, in eleven patients given regorafenib in combination with irinotecan, the mean AUCs of both irinotecan and SN-38 increased by 28% and 44%, respectively [68]. Sorafenib, a TKI used for the treatment of hepatocellular, renal cell, and thyroid carcinoma, is associated with hyperbilirubinemia in patients carrying at least one *UGT1A1**28 variant allele [48]. Furthermore, sorafenib also increased exposure to concomitantly given irinotecan and SN-38 [69]. Tranilast [49], atazanavir [50], indinavir [51] are other examples of UGT1A1 inhibitors that are associated with an increased risk of hyperbilirubinemia in individuals carrying *UGT1A1* variant alleles such as *28 and *6.

5. Conclusions and future perspectives

Certain UGT1A1 polymorphisms (e.g. *6, *28, *60, *93) are known to decrease the expression or activity of this enzyme. Many clinical studies have investigated the effects of *UGT1A1* genetic variants (in particular *UGT1A1**28) on the pharmacokinetics and/or toxicities of drugs metabolized by UGT1A1. In the case of irinotecan, associations between *UGT1A1* genotype and irinotecan-induced neutropenia were clinically relevant resulting in genotype-based dosing recommendations for patients homozygous for *UGT1A1**28. For other UGT1A1 substrates, *UGT1A1* genotype status had no (clinically relevant) effects on their pharmacokinetics which was most likely due to the fact that UGT1A1 was not the main metabolizing enzyme of these drugs. In contrast to these drugs, the novel HDAC inhibitor belinostat is primarily metabolized by UGT1A1. Among 23 patients receiving belinostat by 48 h CIVI, the plasma concentrations of belinostat and the incidence of hematologic

toxicities were increased in patients carrying *UGT1A1**28 and *60 variant alleles suggesting that the belinostat dose should be lowered in those patients. In more detail, using population pharmacokinetic analysis a reduced dose of 400 mg/m²/24 h (instead of 600 mg/m²/24 h) has been proposed for patients homozygous for *UGT1A1**28 or patients heterozygous or homozygous for *UGT1A1**60. This genotype-based dosing recommendation is currently prospectively investigated at the NCI.

Given the dose-dependent nature of the effects of *UGT1A1**28 and *60 variants on the pharmacokinetics and pharmacodynamics of belinostat, it is expected that these polymorphisms would also cause clinically relevant affects in patients receiving standard belinostat therapy in which a higher dose is given over a shorter period of time (1000 mg/m², 30 minutes on days 1-5 of a 21-day cycle). In that case, the belinostat drug label should also recommend *UGT1A1**60 genotyping. However, these effects have yet to be confirmed by future clinical studies. Nevertheless, current preclinical and clinical data illustrates that, besides irinotecan, *UGT1A1* polymorphisms significantly affect the pharmacology of belinostat implying the desirability of upfront *UGT1A1* genotyping to optimize individualized belinostat therapy by minimizing the risk of toxicities and maximizing its therapeutic effect.

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Table 1

Common UGT1A1 variants associated with reduced activity or expression

UGT1A1 variant	RS number	Variant allele	Variant allele frequency	Effect on UGT1A1
*6	rs4148323	A	0.13-0.23 (Asians) [22] 0 (Caucasians, Africans) [31]	Reduced activity
*28	rs8175347	(TA) ⁷	0.26 – 0.39 (Caucasians) [25, 26] 0.30 – 0.56 (Africans, African Americans) [25, 26] 0.09 - 0.20 (Asians) [25, 26]	Reduced expression
*60	rs4124874	G	0.47 (Caucasians) [29] 0.85 (African Americans) [29]	Reduced expression
*93	rs10929302	A	0.31 (Caucasians) [29] 0.29 (African Americans) [29]	Reduced expression

Table 2

Clinical effects of UGT1A1 polymorphisms on pharmacokinetics and pharmacodynamics of UGT1A1 substrates and inhibitors

Drug	UGT1A1 variant	Clinical effects	Genotyping recommended in FDA approved drug label?
UGT1A1 substrates			
Irinotecan	*6, *28, *60, *93	- Increased incidence neutropenia: *6 [31, 34], *28 [7, 30, 31, 35], *60 [36, 37], *93 [36] - Decreased SN-38 glucuronidation: *6 [31], *28 [7, 31, 36], *60 [36] - Increased time to progression: *28 [36]	Yes
Axitinib	*28	No effect on CL [38]	No
Etoposide	*28	- Decreased CL etoposide in black *28/*28 patients [39] - Increased AUC etoposide catechol metabolite in homozygous *28 patients [39]	No
Raloxifene	*28	- Increased raloxifene glucuronide concentrations (*28/*28 vs *1/*1 + *1/*28) [40] - Greater increase in hip bone mineral density (*28/*28 vs *1/*1 + *1/*28) [40]	No
Raltegravir	*28	Increased (not clinically significant) AUC, C _{max} , C _{12h} in *28/*28 patients [41]	No
Arformoterol	Not specified	No effects on PK [42]	No
Indacaterol	*28	~20% increase of AUC and C _{max} (not clinically relevant) [43]	No
UGT1A1 inhibitors			
Nilotinib	*6, *28	Increased risk of hyperbilirubinemia [44, 45]	No
Pazopanib	*28	Increased risk of hyperbilirubinemia [46, 47]	No
Sorafenib	*28	Increased risk of hyperbilirubinemia [48]	No
Tranilast	*28	Increased risk of hyperbilirubinemia in *28/*28 patients [49]	Not FDA approved
Atazanavir	*28	Increased risk of hyperbilirubinemia in *28/*28 patients (also carrying other UGT1A variants) [50]	No
Indinavir	*6, *28	Increased risk of hyperbilirubinemia in patients carrying *6 and *28 variant alleles [51]	No

AUC: area under the concentration-time curve, C_{12h}: concentration at 12-h time point, CL: clearance, C_{max}: maximum plasma concentration, PK: pharmacokinetics.