Review

[Translated article] Influence of the *UGT1A1* gene polymorphism on treatment with sacituzumab govitecan. Narrative review

Eva María Legido Perdices[a,*], Fernando do Pazo Oubiña[b], Elena Prado Mel[c], Marta Miarons[d], Betel Del Rosario García[e] and Fernando Gutiérrez Nicolás[e]

[a] *Servicio de Farmacia Hospitalaria, Hospital Arnau de Vilanova-Llíria, Valencia, Spain*
[b] *Servicio de Farmacia Hospitalaria, Hospital Universitario Son Espases, Palma, Spain*
[c] *Servicio de Farmacia Hospitalaria, Hospital Universitario Virgen del Rocío, Sevilla, Spain*
[d] *Servicio de Farmacia Hospitalaria, Consorci Hospitalari de Vic, Barcelona, Spain*
[e] *Unidad de Investigación, Servicio de Farmacia Hospitalaria, Complejo Hospitalario Universitario de Canarias, San Cristóbal de La Laguna (Santa Cruz de Tenerife), Spain*

ARTICLE INFO

ABSTRACT

Objective: Sacituzumab govitecan is an antineoplastic therapy composed of a monoclonal antibody directed to the Trop2 antigen, conjugated to SN-38, an active metabolite of irinotecan that inhibits topoisomerase I. It is indicated for the treatment of metastatic triple-negative breast cancer in patients who have received at least two prior lines of treatment, with at least one in the metastatic context. SN-38 is eliminated by glucuronidation mediated by uridine diphosphate-glucuronosyltransferase-1A1 (UGT1A1) enzymes, present in the liver. Mutations in the *UGT1A1* gene decrease the expression of these enzymes, which increases the concentration of SN-38 and, consequently, increases the toxicity of the drug, especially in the form of neutropenia and diarrhea. This study aims to analyze the relationship between *UGT1A1* gene polymorphisms and toxicity associated with treatment with sacituzumab govitecan, in addition to reviewing the usefulness of genetic screening prior to starting therapy.

Methods: A non-systematic literature review was conducted on the impact of *UGT1A1* gene polymorphisms on the safety of sacituzumab govitecan treatment in patients with triple-negative breast cancer. The search included primary and secondary literature sources and communications from oncology conferences.

Results: Patients treated with sacituzumab govitecan with the *UGT1A1*28/*28* mutated genotype are more likely to experience grade more than 3 hematologic adverse events: neutropenia (approximate incidence of 60% compared to 40% for 1/*1 and 1/*28 genotypes), febrile neutropenia (18% homozygotes vs. 5% heterozygotes and 3% wild-type), grade more than 3 anemia (15% vs. 6% and 4%, respectively); as well as grade more than 3 diarrhea (24% vs. 13% and 6%, respectively). Additionally, treatment discontinuation rates are higher in *28/*28 individuals (6% compared to 1% heterozygotes and 2% wild-type).

Conclusions: Patients homozygous for the *UGT1A1*28* allele are at significantly increased risk of developing serious adverse events. Despite the clear relationship between *UGT1A1* polymorphisms and sacituzumab-govitecan toxicity, the review suggests that there is insufficient consensus on the need for systematic genetic screening. However, the findings indicate that such screening could be useful for identifying patients at risk and personalizing sacituzumab govitecan therapy.

Influencia de los polimorfismos del gen *UGT1A1* en el tratamiento con sacituzumab govitecan. Revisión narrativa

RESUMEN

Objetivo: Sacituzumab govitecan es una terapia antineoplásica compuesta por un anticuerpo monoclonal dirigido al antígeno Trop2, conjugado con SN-38, un metabolito activo de irinotecán que inhibe la topoisomerasa I. Está indicado para el tratamiento del cáncer de mama triple negativo metastásico en pacientes que han recibido al menos dos líneas de tratamiento previas, con al menos una en contexto metastásico. El SN-38 se elimina mediante glucuronización mediada por las enzimas uridindifosfato-glucuronosiltransferasas-1A1 (UGT1A1),

E.M. Legido Perdices, F. do Pazo Oubiña, E. Prado Mel et al.

presentes en el hígado. Mutaciones en el gen *UGT1A1* disminuyen la expresión de estas enzimas, lo que eleva la concentración de SN-38 y, en consecuencia, se incrementa la toxicidad del fármaco, especialmente en forma de neutropenia y diarrea. Este estudio tiene como objetivo analizar la relación entre los polimorfismos del gen *UGT1A1* y la toxicidad asociada al tratamiento con sacituzumab govitecan, además de revisar la utilidad del cribado genético previo al inicio de la terapia.

Métodos: Se realizó una revisión bibliográfica no sistemática sobre el impacto de los polimorfismos del gen *UGT1A1* en la seguridad del tratamiento con sacituzumab govitecan en pacientes con cáncer de mama triple negativo. La búsqueda incluyó fuentes bibliográficas primarias, secundarias y comunicaciones a congresos de oncología.

Resultados: Las pacientes tratadas con sacituzumab govitecan con el genotipo mutado *UGT1A1*28/*28* tienen una mayor probabilidad de padecer efectos adversos hematológicos de grado ≥ 3: neutropenia (incidencia aproximada del 60% respecto al 40% de los genotipos 1/*1 y 1/*28), neutropenia febril (18% homocigotos vs. 5% heterocigotos y 3% *wild-type*), anemia grado ≥ 3 (15% vs. 6% y 4%, respectivamente); así como diarrea grado ≥ 3 (24% vs. 13% y 6%, respectivamente). Además, las tasas de discontinuación de tratamiento son mayores en individuos *28/*28 (6% respecto al 1% heterocigotos y 2% *wild-type*).

Conclusiones: Las pacientes homocigotas para el alelo *UGT1A1*28* presentan un riesgo significativamente mayor de desarrollar efectos adversos graves. A pesar de la relación evidente entre los polimorfismos *UGT1A1* y la toxicidad de sacituzumab govitecan, la revisión sugiere que no hay consenso suficiente sobre la necesidad de realizar un cribado genético sistemático. Sin embargo, los hallazgos indican que este tipo de cribado podría ser útil para la identificación de pacientes en riesgo y personalizar la terapia con sacituzumab govitecan.

Introduction

Breast cancer (BC) accounts for nearly 30% of all new female cancer cases, representing the most common cancer in women[1]. BC encompasses a group of neoplastic diseases with differing molecular characteristics. Triple-negative breast cancer (TNBC) constitutes 15 to 20% of BC cases[2]. This subtype is associated with a poorer diagnosis, as compared to other breast neoplasms. Its distinctive molecular profile is characterized by the absence of expression of estrogen receptors (ERs), progestogen receptors (PRs), and epidermal growth factor 2 (HER2) in tumor cells, which limits therapeutic options[2].

To date, the treatments of choice for TNBC include standard chemotherapy schemes (CTX), with low response rates and poor disease control. The first targeted therapies were based on poly-adenosine diphosphate (ADP)-ribose-polymerase (PARP) inhibitors in patients harboring germline mutations in RCA1/2 (olaparib), with promising results. Subsequently, immunotherapy based on blockers of PD-L1 binding to the programmed death-receptor 1 (PD-1), atezolizumab and pembrolizumab, used in combination with CTX in advanced PD-L1-positive tumors, became the treatment of choice. However, the use of these two therapies is restricted to carriers of germline BCRA mutations or PD-L1-positive tumors. For this reason, research efforts are ongoing in pursuit of therapies that are effective in most TNBC patients[3].

The FDA (U.S. Food and Drug Administration) in 2020 and the EMA (European Medicines Agency) in 2021 approved the indication of sacituzumab govitecan (SG) for the treatment of metastatic TNBC (mTNBC) in patients having received at least two previous lines of treatment, one of them for metastatic disease[4]. This indication is based on the results of the ASCENT study[5], a randomized, open-label, multicentric, phase 3 clinical trial assessing the efficacy and safety of SG in patients with unresectable/metastatic TNBC with ≥2 previous systemic treatments. In this study, SG was compared to CTX alone at the investigator's discretion (eribulin, vinorelbine, capecitabine or gemcitabine), with a median progression-free survival (PFS) of 5.6 months for the SG arm versus 1.7 months for the CTX arm (HR 0.41; 95%CI 0.32–0.52; $p < 0.001$). Overall survival rates were 12.1 and 6.7 months, respectively (HR 0.48; 95%CI 0.38–0.59; $p < 0.001$).

Additionally, SG was recently granted EMA approval for metastatic hormone receptor-positive (RH +) breast cancer, HER2-negative BC previously treated with endocrine therapy and ≥2 previous additional systemic therapies for advanced disease. However, this indication has not yet been approved for coverage by the Spanish National Health System[4].

SG is an antibody-drug conjugate (ADC) of a humanized anti-Trop2 monoclonal antibody linked to SN-38 (the active metabolite of irinotecan), with the latter having antineoplastic activity. Its mechanism of action mimics that of other marketed conjugates: when SG binds to Trop-2, the conjugate internalizes into cancer cells and releases SN-38. This agent inhibits topoisomerase 1, thereby causing DNA damage and inducing apoptosis and cell death[6].

Its active metabolite, SN-38, is cleared from the body through glucuronidation mediated by hepatic uridine diphosphate (UDP) glucuronosyltransferase 1A1 (UGT1A1). Mutations in the *UGT1A1, UGT1A7* and *UGT1A9* genes may reduce the expression of these enzymes, leading to the elevation of SN-38 concentrations, which increases toxicity in the form of neutropenia and diarrhea[6,7]. The expression of this protein is reduced in homozygous and heterozygous carriers of the *UGT1A1*28* and *UGT1A1*6* alleles. As a result, glucuronidation is impaired, leading to a higher risk of toxicity, as compared to homozygous carriers of the *UGT1A1*1* allele. In the Spanish population, the incidence of this homozygous mutated genotype is 9% versus 51% for the heterozygous genotype. Some *UGT1A* polymorphisms also modify SN-38 metabolism, although with a lower clinical relevance[8].

A summary of allelic *UGT1A1* variants and a description of their phenotypic activity are provided in Table 1. *UGT1A1* diplotypes and their phenotypes[6,9] are shown in Table 2.

It is worth noting that the FDA contraindicates the concomitant use of this drug with *UGT1A1* inhibitors owing to the risk of SN-38 accumulation, which could increase toxicity. Likewise, the AEMPS recommends a cautious use of this agent. However, in general, *UGT1A1* screening prior to treatment initiation is not recommended by any regulatory agency. In contrast, the guidelines of the FDA and other agencies provide specific recommendations for irinotecan. Thus, the authorities recommend adjusting dosage according to the *UGT1A1* phenotype, especially when administered at doses >180 mg/m^2 for the treatment of metasta-

Table 1
Variants and phenotypic activity of the *UGT1A1* gene.

UGT1A1 variants	Phenotypic activity
UGT1A1*1 (WT)	Normal activity
UGT1A1*36	Increased activity
UGT1A1*28	Reduced activity
UGT1A1*6	Reduced activity
UGT1A1*37	Reduced activity

Table 2
Main *UGT1A* gene diplotypes and their phenotypes.

UGT1A1 variants	Phenotypic activity
1/*1	Normal metabolizer
1/*28, 1/*6	Intermediate metabolizer
28/*28, 6/*6, 6/*28	Poor metabolizer

tic colorectal cancer[10–13]. This difference is relevant, as a SG dose generates a SN-38 concentration of 90 ng/ml, whereas irinotecan 350 mg/m^2 (significantly higher than the dose administered in colorectal cancer) only induces a concentration of 56 ng/ml[14,15].

A review was conducted to assess SG toxicity based on an analysis of the evidence available on the influence of *UGT1A* polymorphisms on SG exposure and toxicity in patients with mTNBC. The results of this review will contribute to determining the need for genotyping prior to treatment initiation.

Methods

A non-systematic literature review was performed to assess the toxicity of SG and assess the impact of *UGT1A* mutations on treatment exposure and safety. Additionally, a review was conducted for evidence available on the need for screening for genetic polymorphisms prior to initiation of SG therapy.

A systematic review could not be conducted, since the articles selected used descriptive statistics for comparative analysis of AEs across different genotypes. Moreover, heterogeneous results were provided.

A literature search was performed on PubMed, Embase, Scopus, Web of Science, Cochrane and Epistemonikos without any time limit as of 2024, including primary and secondary literature sources. The search also included communications to the main medical oncology conferences, such as the *American Society of Clinical Oncology* (ASCO) and *European Society for Clinical Oncology* (ESMO) providing relevant results that had not yet been published in the literature.

Search terms included «*UGT1A1* polymorphism AND Sacituzumab Govitecan», «Glucuronosyltransferase pharmacogenomics AND Sacituzumab govitecan», «security AND Sacituzumab govitecan», «Sacituzumab govitecan AND toxicity AND *UGT1A1*»

Results

A total of 38 articles were retrieved from the databases mentioned above. Following preliminary screening, duplicates and articles not meeting inclusion criteria were excluded. Finally, five studies were selected. Fig. 1 shows the flow chart of article selection.
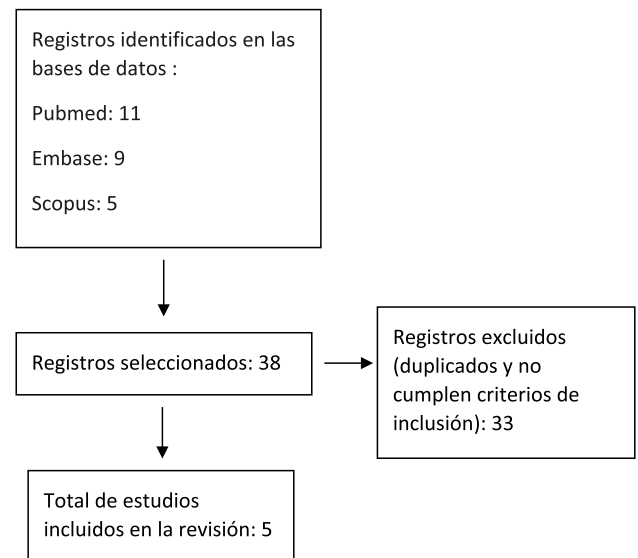
A review was performed of the evidence available on the influence of *UGT1A* polymorphisms in SG safety[16].

Influence of *UGT1A1* polymorphisms in the toxicity of sacituzumab govitecan

SG-related toxicity is the same as that associated with irinotecan, which has been examined in a variety of drug development studies.

The most frequent adverse events (AEs) reported in the IMMU-132-01 study[17] in TNBC patients who received SG included nausea (67%); neutropenia (64%); diarrhea (62%); fatigue (55%); and anemia (50%). Ten percent of study participants developed grade ≥3 AEs, with anemia and neutropenia being the most common. As many as 32% of patients with severe AEs required hospitalization, 7% due to febrile neutropenia; 6% for vomiting; 4% for diarrhea, and 3% for dyspnea. Treatment was discontinued permanently due to toxicity in three patients (2.8%)[8].

The main AEs reported in the ASCENT study[5] included neutropenia (64% in the SG group vs. 43% in the standard CTX group); diarrhea (59% vs. 12%, respectively); nausea (57% vs. 26%); alopecia (46% vs. 16%); and fatigue (45% vs. 30%) by that order. In total, 51% of patients treated with SG developed Grade ≥3 neutropenia vs. 33% in the CTX

Registros identificados en las bases de datos:

Pubmed: 11

Embase: 9

Scopus: 5

Registros seleccionados: 38

Registros excluidos (duplicados y no cumplen criterios de inclusión): 33

Total de estudios incluidos en la revisión: 5

Figure 1. Flow chart of article selection.

group. A higher proportion of patients in the SG group received granulocyte colony-stimulating factors (G-CSF) as compared to the CTX group (49% vs. 23%). Dose was interrupted in 61% of cases in the SG group, vs. 33% in the CTX group.

The TROPiCS-02 phase-3 clinical trial[13] included 543 patients with metastatic RH+ and HER2- breast cancer. Of them, 268 received SG and 271 received standard CTX alone (eribulin, vinorelbine, capecitabine or gemcitabine). The most common AEs in the SG arm, as compared to the CTX arm included neutropenia (70% vs. 54%); diarrhea (57% vs. 17%); and nausea (55% vs. 31%). In total, 74% of patients treated with SG developed grade ≥3 toxicity vs. 60% of the CTX arm, including grade ≥3 neutropenia (51% vs. 38%). During treatment, G-CSF was administered to 54% of SG patients vs. 34% of CTX patients.

An evaluation was conducted of the safety data obtained in the phase-3 TROPHY-U-01 study[14]. However, this study involved patients with metastatic urothelial cancer (mUC) at progression following platin-based chemotherapy in combination with checkpoint inhibitors. The TROPHY-U-01 study is a single-cohort clinical trial assessing SG treatment that included a total of 113 patients with mUC who received a SG dose of 10 mg/kg at days 1 and 8 of the 21-day cycle (the same as for TNBC). The most common AEs reported included diarrhea (65%); nausea (60%); fatigue (52%); alopecia (47%); neutropenia (46%) and anemia (33%). Grade ≥3 AEs included neutropenia (35%); anemia (14%); diarrhea (10%) and febrile neutropenia (10%). Neutropenia was treated with dose reductions or interruptions. Thirty percent of patients received G-CSF as support treatment (18% from Cycle 1, and the remainder in subsequent cycles).

In the pivotal studies mentioned above, *UGT1A1* genotyping was performed and safety was assessed for each variant.

Table 3 classifies the patients included in drug development studies by genotype prevalence.

In the IMMU-132 study, homozygous carriers of the *UGT1A1*28* allele were at a higher risk of developing neutropenia, with incidence rates of 33, 38.3 and 60.9% for patients with genotypes 1/*1, 1/*28 and 28/*28, respectively. The same was observed in relation to grade ≥3 neutropenias, occurring in 28% (1/*1), 39% (1/*28) and 58% (28/*28) of patients retrospectively analyzed.

The results of the ASCENT study regarding SG safety were similar to those of the IMMU-132 study for carriers of *UGT1A1*28* mutations. AEs led to dose reductions in 18, 19 and 35% of *wild type* heterozygous and homozygous carriers, respectively[18].

Table 3
Genotype-based patient classification in each study and common adverse events.

Author (study)	Type of study	Study population	Patients undergoing genotyping (n)[a]	UGT1A1 genotype			Grade ≥3 neutropenia			p	Grade ≥3 diarrhea			p	Dose reductions			p
				1/*1	1/*28	28/*28	1/*1	1/*28	28/*28		1/*1	1/*28	28/*28		1/*1	1/*28	28/*28	
				n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	
Bardia et al. (IMMU-132)[17]	Phase 2/3 CT	Patients with epithelial cancer	146	63 (43)	64 (44)	46 (9,3)	24 (28)	35 (39)	11 (58)	0,073	5 (8)	3 (5)	2 (16)	0,024	n.d.			n.d.
Rugo et al. (ASCENT)[5,18]	Phase 3 CT	Recurrent/refractory mTNBC	250	113 (44)	96 (37)	34 (13)	60 (53)	45 (47)	20 (59)	n.d.	11 (10)	9 (9)	5 (15)	n.d.	20 (18)	18 (19)	12 (35)	n.a.v.a.
Rugo et al. (TROPiCS-02)[19]	Phase 3 CT	Previously treated metastatic HER2-/RH + BC	268	103 (38)	119 (44)	25 (9)	46 (45)	68 (57)	16 (64)	n.d.	6 (6)	15 (13)	6 (24)	n.d.	26 (25)	49 (41)	10 (40)	n.a.v.a.
Tagawa et al. (TROPHY-U-01)[20]	Phase 3 CT	Locally advanced unresectable mUC	105	45 (39,8)	47 (41,6)	14 (13)	14 (31)	17 (36)	7 (50)	n.d.	24 (53)	34 (72)	10 (71)	n.d.	17 (38)	16 (34)	6 (43)	n.a.v.a.

mTNBC: metastatic triple-negative breast cancer; mUC: metastatic urothelial cancer; a.n.a.: abbreviation not available.
^a Drop-outs may have occurred and other genotypes may have not been included.

Grade ≥3 AEs were more common in homozygous 28/*28 carriers, including grade ≥3 febrile neutropenia (3% *wild-type*, 5% heterozygous and 18% homozygous carriers), grade ≥3 anemia (4, 6 and 15%, respectively), or grade ≥3 diarrhea (10, 9 and 15%, respectively). In this study, treatment was interrupted in 61% of SG patients vs. 33% for CTX patients. Dose was reduced in 22 and 26% of patients, respectively. In relation to SG efficacy, PFS was longer in patients subjected to dose reductions or treatment interruptions, as compared to those who received the full dose. The median PFS for the SG group was 8.3 months vs. 2.9 months for the CTX group with dose reduction; and 4.6 vs. 1.5 months, respectively, without dose reductions. The median PFS was 5.7 months for the SG group vs. 2.7 months for the CTX group with treatment interruption. PFS was 4.2 vs. 1.6 months, respectively, when treatment had not been discontinued.

These results are consistent with the TROPiCS-02[19] study, which reported a similar safety profile in patients undergoing genotyping. Rates of treatment discontinuation due to grade ≥3 AEs were more common in homozygous carriers of the *28 allele, as compared to heterozygous *wild-type* carriers (92, 75 and 67%, respectively). Grade ≥3 diarrhea was reported for 24, 13 and 6% of patients, respectively.

Similar results were obtained in patients with mUC (TROPHY-U-01 study)[20]. Grade ≥3 AEs such as neutropenia occurred in 31% of *wild-type* carriers; 36% of heterozygous carriers; and 50% of homozygous carriers. Grade ≥3 anemia was reported for 13, 19 and 29% of patients, respectively. Treatment was interrupted in 42, 43 and 71% of patients, and suspended in 7, 6 and 14% of patients. The study conducted by Wong et al. within routine clinical practice included 68 patients, of whom 25% were homozygous and 35% were heterozygous carriers. Treatment was suspended due to toxicity in a significantly higher proportion of *28/*28 allele carriers (HR 5.52, 95%CI 1.15–6.49, p = 0.039)[21].

Recommendations for genotyping prior to treatment initiation

All pivotal trials revealed an association between *UGT1A1* polymorphisms and SG safety. However, all authors highlight the need for further clinical trials to assess the safety of the treatment more thoroughly. As a result, genotyping prior to initiation of treatment is not currently recommended.

The Summary of Product Characteristics of SG (Trodelvy®) does not establish any dose adjustments according to the *UGT1A1* genotype but only recommends close monitoring of carriers of *UGT1A1* variants, including the *UGT1A1*28 allele due to impaired enzymatic activity[4]. Despite this, *UGT1A1* genotyping prior to initiation of SG treatment is not considered. In contrast, dose adjustments are recommended in the presence of grade 4 neutropenia for 7 or more days; grade 3–4 febrile neutropenia; or grade 3–4 neutropenia causing delayed dose administration. In these settings, secondary prophylaxis with G-CSF is recommended. In the event of a second episode of toxicity, it is recommended to reduce the SG dose by 25% and administer G-CSF. In case of a third episode of toxicity, the dose must be reduced by 50% and G-CSF must be administered. Finally, if a fourth episode of toxicity occurs, the treatment must be suspended. Non-hematological toxicities are managed with similar dose reductions.
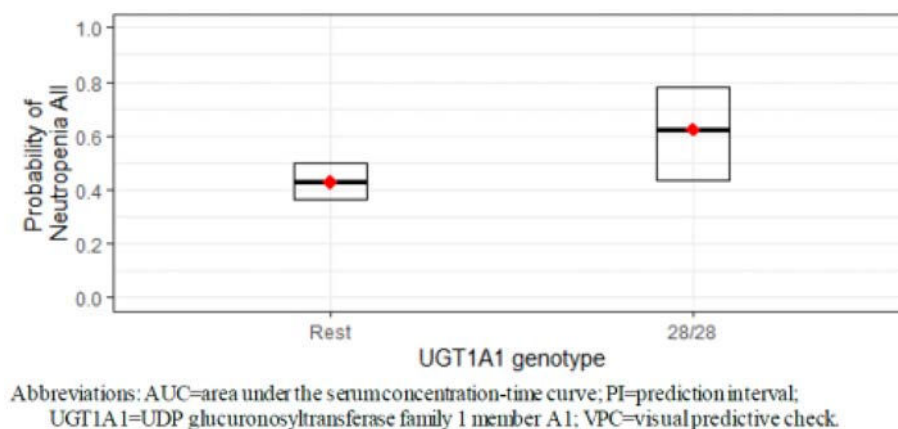
Influence of *UGT1A1* polymorphisms in sacituzumab govitecan exposure

Based on the non-compartmental pharmacokinetic (PK) analysis of SG included in the IMMU-132-01 and IMMU-132-05 (ASCENT) studies, the volume of distribution of SG is 2.96 L, with a SG and unbound SN-38 half-life of 15.3 and 19.7 h, respectively.

Population-based pharmacokinetic models have been developed for SG based on data from 529 patients of the IMMU-132-01 and ASCENT studies, both for SG and unbound SN-38. The results reveal two-compartmental kynetics with first-order elimination for this drug[22,23]. No association was observed with any of the covariates included (age, sex, moderate–severe kidney failure, moderate–severe liver failure, albumin, ECOG status, type of tumor, Trop2 expression or *UGT1A1* genotype). A study performed by the marketing laboratory to estimate exposure to SG and unbound SN-38 developed a PK model based on data from 237 patients from the IMMU-132-01, ASCENT and IMMU-132-06 studies. *UGT1A1* genotype data were also included (31.5% *1/*1; 13.6% *1/*28 and 12.4% *28/*28)[18]. The estimated areas under the curve (AUC) for SG were 9.790, 9.481 and 9.370 mg.h/ml for *wild-type*, heterozygous and homozygous carriers, respectively. The estimated AUC for unbound SN-38 were 5.39; 5.25 and 4.82 mg.h/ml, respectively, for each variant. No significant differences were observed in exposure to SG and unbound SN-38 by the type of polymorphism. Therefore, the authors concluded that no dose adjustment was necessary for carriers of *UGT1A1* polymorphisms[10].

However, the ASCENT study revealed a higher risk for developing neutropenia as the AUC and maximum SG concentration (Cmax) increased in carriers of the *UGT1A1 28/*28* genotype (OR > 1)[5] (Fig. 2).

E.M. Legido Perdices, F. do Pazo Oubiña, E. Prado Mel et al.

Abbreviations: AUC=area under the serum concentration-time curve; PI=prediction interval;
UGT1A1=UDP glucuronosyltransferase family 1 member A1; VPC=visual predictive check.

Figure 2. *Visual Predictive Check (VPC) for the final logistic regression model. Modified from the Trodelvy® EPAR report of the European Medicines Agency (EMA).*

Exposure-safety correlation was assessed for patients with metastatic TNBC and RH +, HER2 — breast cancer from the ASCENT, IMMU-132-01 and IMMU-132-09 studies, including a total of 569 patients with safety and pharmacokinetic estimates available. Mean SG concentration, (CAVGSG), Cmax and AUC were estimated during the first cycle of treatment for SG, unbound SN-39 and total antibodies. Then, the potential correlation between these parameters and the most common AEs was assessed. A statistically significant correlation was observed between elevated levels of CAVGSG and a higher probability of developing any-grade neutropenia (OR 1.39 HF 95%CI 1.33–1.45). The patients with the UGT1A1*28/*28 genotype were more likely to develop any-grade neutropenia and grade 3–4 neutropenia, as compared to patients without the UGT1A1*28/*28 genotype[10] (Fig. 3).

Discussion

The main limitation of this review is the low number of publications assessing the presence of UGT1A1 polymorphisms in patients treated with SG. Although the most relevant clinical trials provide some data,

the information available is primarily descriptive and lacks statistically significant values.

SG for the treatment of mTNBC is an alternative targeted therapy to standard chemotherapy, having shown improved overall survival rates in TNBC (12.1 months vs. 6.7 months, HR 0.48, 95%CI 0.38–0.59), with modest results in metastatic RH + HER2- breast cancer (14.5 vs. 11.2 months, HR 0.79; 95%CI 0.65–0.96). However, SG therapy is not exempt from AEs, the ones reported for irinotecan, including hematological toxicity (neutropenia and anemia) and gastrointestinal toxicity (nausea, vomiting and diarrhea). These AEs not only affect the quality of life of patients but also compromise treatment efficacy, as they result in delayed dose administration, as shown in the TROPiCS-02 study; dose reductions (24% of cases); or treatment suspension (7%)[13]. SG toxicity is directly related to SN-38, which is eliminated through glucuronidation by the UDP-glucuronosyltransferase enzyme (UGT1A1). In patients with impaired glucuronidation, such as carriers of the UGT1A1 gene, exposure to SN-38 increases, resulting in a significantly higher hematological and gastroenterological toxicity.
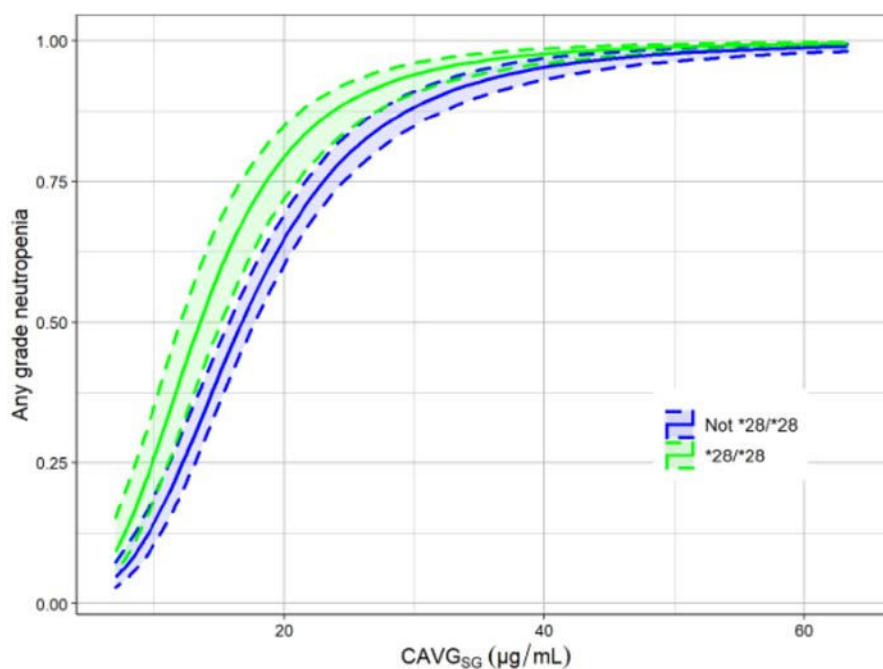
Figure 3. Predictive model for the probability of developing any-grade neutropenia by *UGT1A1* genotype. Modified from the Trodelvy® EPAR report of the European Medicines Agency (EMA).

The most relevant scientific societies and clinical pharmacogenetics working groups have established recommendations for *UGT1A1* genotyping prior to initiation of irinotecan therapy, due to the toxicity of the active metabolite SN-38[24,25]. The Dutch Pharmacogenetics Working Group-DPWG determined that *UGT1A1* genotyping was essential to ensuring safety in patients who are initiating irinotecan therapy[26]. According to the DPWG, genotyping should be performed prior to treatment initiation, irrespectively of the dose. Hence, homozygous *28 carriers must initiate irinotecan at 70% of the standard dose; then, the dose can be uptitrated according to the neutrophil count and clinical tolerance.

The French National Network of Pharmacogenetics-RNPGx establishes that all patients initiating treatment with irinotecan at doses >240 mg/m^2 must undergo genotyping[2] but contraindicates the administration of such high doses to *28/*28 carriers[27]. For the latter, the RNPGx recommends reducing the dose by 25–30%. Finally, the RNPGx considers it advisable to perform genotyping in patients receiving doses of 180–230 mg/m^2.

The *National Comprehensive Cancer Network Guidelines* (NCCN) do not recommend *UGT1A1* genotyping prior to initiation of irinotecan, as they consider that patients will require a dose reduction regardless of the result[28]. The Consensus ESMO guidelines[10] establish that screening for *UGT1A1* polymorphisms is an option for patients who are initiating irinotecan at a dose of ≥180 mg/m^2.

In relation to SG, regulatory agencies (FDA, EMEA, HS-Canada) do not recommend *UGT1A1* genotyping prior to treatment initiation, as they consider that AEs will be managed the same in all patients. When genotyping is performed, carriers of the *28 allele will require close monitoring for the occurrence of potential AEs.

Our results indicate that carriers of the *UGT1A1*28/*28* diplotype receiving SG therapy may be at a higher risk of experiencing grade ≥3 AEs, such as neutropenia (with an incidence of near 60%, vs. 40% in patients with other diplotypes); febrile neutropenia (18% in homozygous vs. 5% in heterozygous carriers; and 3% in *wild-type*) patients, grade ≥3 anemia (15% vs 6 vs 4%, respectively) and grade diarrhea ≥3 (24% vs. 13 vs. 6%). Accordingly, these patients may be at a higher risk for hospitalization and require support treatments such as G-CSF. Apart from influencing patient safety, these AEs may interfere with treatment efficacy due to treatment interruptions, delays, and suspensions[29].

In conclusion, considering the evidence available, screening for *UGT1A1* polymorphisms is recommended for all patients with BC prior to initiation of SG treatment. Systematic reduction of the dose should be considered prior to treatment initiation in homozygous carriers of the *28 allele. Additionally, these patients should be subjected to close monitoring to prevent the occurrence of severe AEs. Future studies, probably promoted by independent scientific societies, will support our recommendations as they will improve the efficacy of SG and the quality of life of patients with mTNBC.

CRediT authorship contribution statement

Eva María Legido Perdices: Writing – original draft, Validation, Methodology, Formal analysis. **Fernando do Pazo Oubiña:** Validation, Investigation, Data curation. **Elena Prado Mel:** Validation, Formal analysis, Data curation. **Marta Miarons Font:** Validation, Formal analysis, Data curation. **Betel Del Rosario García:** Writing – original draft, Validation, Formal analysis, Conceptualization. **Fernando Gutiérrez Nicolás:** Writing – original draft, Validation, Formal analysis, Conceptualization.

Authorship

All authors contributed to the literature search. Eva Legido, Fernando do Pazo, Elena Prado and Marta Miarons contributed to peer reading, analysis and data extraction. Eva Legido, Fernando Gutiérrez and Betel del Rosario contributed to the drafting of the manuscript. All authors were involved in successive reviews until the final review.

References

1. Ayala de la Peña F, Andrés R, Garcia-Sáenz JA, Manso L, Margelí M, Dalmau E, et al. SEOM clinical guidelines in early stage breast cancer (2018). Clin Transl Oncol. 2019;21(1):18–30. https://doi.org/10.1007/s12094-018-1973-6.
2. Garcia-Saenz JA, Blancas I, Echavarria I, Hinojo C, Margeli M, Moreno F, et al. SEOM–GEICAM–SOLTI clinical guidelines in advanced breast cancer (2022). Clin Transl Oncol. 2023;25(9):2665–78. https://doi.org/10.1007/s12094-023-03203-8.
3. Fu Z, Li S, Han S, Shi C, Zhang Y. Antibody drug conjugate: the "biological missile" for targeted cancer therapy, Signal Transduct Target. Ther. 2022;7(1):93. https://doi.org/10.1038/s41392-022-00947-7.
4. Agencia Española de Medicamentos y Productos Sanitarios. Trodelvy®. Ficha técnica. Madrid: Agencia Española de Medicamentos y Productos Sanitarios; 2021. [Consultado 25 Feb 2023]. Disponible en: http://www.aemps.gob.es.
5. Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. N Engl J Med. 2021;384(16):1529–41. https://doi.org/10.1056/nejmoa2028485.
6. Spring LM, Nakajima E, Hutchinson J, Viscosi E, Blouin G, Weekes C, et al. Sacituzumab govitecan for metastatic triple-negative breast cancer: clinical overview and management of potential toxicities. Oncologist. 2021;26(10):827–34. https://doi.org/10.1002/onco.13878.
7. Weiss J, Glode A, Messersmith WA, Diamond J. Sacituzumab govitecan: breakthrough targeted therapy for triple-negative breast cancer. Expert Rev Anticancer Ther. 2019;19(8):673–9. https://doi.org/10.1080/14737140.2019.1654378.
8. Fernández Salazar JM, Remacha Sevilla Á, del Río Conde E, Baiget Bastús M. Distribución del genotipo A(TA)7TAA asociado al síndrome de Gilbert en la población española. Med Clin (Barc). 2000;115(14):540–1. https://doi.org/10.1016/s0025-7753(00)71617-4.
9. Bosma PJ, Chowdhury JR, Bakker C, Gantla S, De Boer A, Oostra BA, et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med. 1995;333(18):1171–5.
10. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27(8):1386–422. https://doi.org/10.1093/annonc/mdw235.
11. Nelson RS, Seligson ND, Bottiglieri S, Carballido E, Cueto AD, Imanirad I, et al. UGT1A1 guided cancer therapy: review of the evidence and considerations for clinical implementation. Cancers (Basel). 2021;13(7):1566. https://doi.org/10.3390/cancers13071566.
12. Ando Y, Saka H, Ando M, Sawa T, Muro K, Ueoka H, et al. Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res. 2000;60(24):6921–6.
13. Karas S, Innocenti F. All you need to know about UGT1A1 genetic testing for patients treated with irinotecan: a practitioner-friendly guide. JCO Oncol Pract. 2022;18(4):270–7. https://doi.org/10.1200/op.21.00624.
14. Sharkey RM, McBride WJ, Cardillo TM, Govindan SV, Wang Y, Rossi EA, et al. Enhanced delivery of SN-38 to human tumor xenografts with an anti-Trop-2–SN-38 antibody conjugate (sacituzumab govitecan). Clin Cancer Res. 2015;21(22):5131–8. https://doi.org/10.1158/1078-0432.ccr-15-0670.
15. Trodelvy Assessment Report; 2021. [Consultado 27 Feb 2023]. Disponible en: https://www.ema.europa.eu/en/documents/assessment-report/trodelvy-epar-public-assessment-report_en.pdf.
16. Common Terminology Criteria for Adverse Events (CTCAE) version 5. Published: November 27, 2017. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute; [Consultado 25 Feb 2023]. Disponible en: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.
17. Bardia A, Messersmith WA, Kio EA, Berlin JD, Vahdat L, Masters GA, et al. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. Ann Oncol. 2021;32(6):746–56. https://doi.org/10.1016/j.annonc.2021.03.005.

18. Rugo H.S., Tolaney S.M., Loirat D., Punie K., Bardia A., Hurvitz S.A., et al., Safety analyses from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer, *NPJ Breast Cancer*, 2022;8(1):98. doi:10.1038/s41523-022-00467-1.

19. Rugo HS, Bardia A, Marmé F, Cortés J, Schmid P, Loirat D, et al. Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2023;402(10411):1423–33. https://doi.org/10.1016/s0140-6736(23)01245-x.

20. Tagawa ST, Balar AV, Petrylak DP, Kalebasty AR, Loriot Y, Fléchon A, et al. TROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors. J Clin Oncol. 2021;39(22):2474–85. https://doi.org/10.1200/JCO.20.03489.

21. Megan W, Wai, Kim, Yu LD, Sayeh Moazami Lavasani N, Patel MS, et al. UGT1A1 *28/*28 genotype and risk of toxicity and disease progression in breast cancer patients treated with sacituzumab govitecan-hziy, J Clin Oncol, 2023;41(16 suppl):1033. doi:10.1200/JCO.2023.41.16_suppl.103.

22. Sathe AG, Singh I, Singh P, Diderichsen P, Wang X, Chang P, et al. Pharmacokinetics (PK) of sacituzumab govitecan (SG) in patients (Pts) with metastatic triple-negative breast cancer (mTNBC) and other solid tumors. Ann Oncol. 2022;33(Suppl 3):S214. https://doi.org/10.1016/j.annonc.2022.03.208.

23. Sathe IAG, Singh I, Singh P, Boakye-Agyeman F, Goswamy T, Girish S, et al. Impact of UDP-glucuronosil transferase 1A1 polymorphisms on the pharmacokinetics of sacituzumab govitecan. En: Poster no. 2022;151. [Consultado 25 Feb 2023].

Disponible en: https://www.askgileadmedical.com/docs/trodelvy/trodelvy-pharmacokinetics.

24. García Gil S, Ramos Díaz R, Nazco Casariego GJ, Llanos Muñoz M, Viña Romero MM, Martín Calero B, et al. Efecto de los polimorfismos en UGT, SLCO, ABCB y ABCC en la toxicidad del tratamiento con irinotecán. Med Clin (Barc). 2018;151(11):425–30. doi:10.1016/j.medcli.2018.01.016.

25. Miarons M, Riera P, García-Gil S, Gutiérrez-Nicolás F. Efficacy and safety of high doses of irinotecan in patients with metastatic colorectal cancer treated with the FOLFIRI regimen based on the UGT1A1 genotype: a systematic review. Farm Hosp. 2022;46(4):224–33. https://doi.org/10.7399/fh.11736.

26. Hulshof EC, Deenen MJ, Nijenhuis M, Soree B, de Boer-Veger NJ, Buunk A-M, et al. Dutch pharmacogenetics working group (DPWG) guideline for the gene–drug interaction between UGT1A1 and irinotecan. Eur J Hum Genet. 2023;31(9):982–7. https://doi.org/10.1038/s41431-022-01243-2.

27. Quaranta S, Thomas F. Pharmacogenetics of anti-cancer drugs: state of the art and implementation – recommendations of the French National Network of Pharmacogenetics. Therapie. 2017;72(2):205–15. https://doi.org/10.1016/j.therap.2017.01.005.

28. NCCN guidelines version 3.2023 colon cancer. National Comprehensive Cancer Network; 2023. [Consultado 9-2024]. Disponible en: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.

29. Baek G, Jung L, Duong A, Gralow J. Case report of sacituzumab govitecan-hziy-induced neutropenia in a patient with metastatic triple-negative breast cancer and a uridine diphosphate glucuronosyltransferase family 1 member A1 poor metabolizer genotype. J Oncol Pharm Pract. 2022;28(3):710–6. https://doi.org/10.1177/10781552211057486.