

# Dose Adjustment of Poly (ADP-Ribose) Polymerase Inhibitors in Patients with Hepatic or Renal Impairment

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**Abstract:** Poly (ADP-ribose) polymerase (PARP) inhibitors are small-molecule inhibitors of PARP enzymes (including PARP1, PARP2, and PARP3) that exhibit activity against tumor cells with defects in DNA repair. In recent years, five PARP inhibitors, olaparib, niraparib, rucaparib, talazoparib and veliparib, have been developed for the treatment of solid tumors, particularly in patients with breast-related cancer antigen (BRCA) 1/2 mutations, or those without a functional homologous recombination repair pathway. These novel treatments exhibit improved efficacy and toxicity when compared to conventional chemotherapy agents. The five PARP inhibitors are eliminated primarily via the liver and kidneys, hepatic or renal impairment may significantly affect their pharmacokinetics (PK). Therefore, it is important to know the effects of hepatic or renal impairment on the PK and safety of PARP inhibitors. In this review, we characterize and summarize the effects of hepatic and renal function on the PK of PARP inhibitors and provide specific recommendations for clinicians when prescribing PARP inhibitors in patients with hepatic or renal impairment.

**Keywords:** PARP inhibitors, cancer, hepatic impairment, renal impairment, PK

## Introduction

DNA damage and its repair are critical to induce gene mutations, which can lead to the development of cancers. Through an inter-related series of molecular pathways, such as the DNA damage response, cells can protect themselves against the harmful effects of DNA damage.<sup>1</sup> DNA damage response can recognize DNA damage, stall the cell cycle and mediate DNA repair. Poly (ADP-ribose) Polymerase (PARP) enzymes play a key role in the DNA damage response, and cells with homologous recombination (HR) deficiency show a greater reliance on PARP activity to maintain cell survival.<sup>2</sup> Thus, PARP enzymes are critical for cancer cells to respond to DNA damage. PARP inhibitors are broadly based on the genetic concept of synthetic lethality, whereby inhibition of PARP enzymes in HR deficient cells, particularly cells with breast-related cancer antigen (BRCA) 1/2 mutations, results in cell death.<sup>3</sup> At present, five PARP inhibitors have been developed for the treatment of cancer patients with or without BRCA mutations and showed superior safety and efficacy compared to chemotherapy agents.<sup>4,5</sup> Among the five PARP inhibitors, olaparib, niraparib, rucaparib, and talazoparib have been approved by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA). Veliparib is still under clinical investigation, but numerous studies have shown that veliparib was effective and safe in the treatment of epithelial ovarian cancer and human epidermal growth factor receptor type 2 (HER 2)-negative locally advanced or metastatic breast cancer.<sup>6,7</sup>

Hepatic or renal impairment is common in cancer patients, because of the disease metastasis and treatment-related adverse effects. Earlier studies showed that approximately 55% of cancer patients had abnormal renal function.<sup>8</sup> However, specific prevalence data of hepatic impairment in cancer patients are currently absent. The prevalence of hepatic or renal impairment varied between cancer types. For instance, the prevalence of renal impairment in breast cancer and ovarian cancer is 51.8% and 75.2%, respectively.<sup>8</sup> In patients with hepatic or renal impairment, drug exposure can either be increased or decreased, which may require dose adjustment to ensure optimal efficacy and minimize the unwanted toxicities.<sup>9,10</sup> PARP inhibitors are small molecule targeted agents, they

are eliminated primarily via the hepatic and renal routes, thereby hepatic or renal function may significantly affect their pharmacokinetics (PK). Therefore, it is essential to know the drug PK and safety in patients with hepatic or renal impairment. In this review, we characterize and summarize the effects of hepatic and renal function on the PK of PARP inhibitors and provide dose recommendations for the five PARP inhibitors in patients with varying degrees of hepatic or renal impairment.

## Molecular Mechanisms of PARP Inhibitors

Many factors can cause DNA damage, and DNA damage is a frequent event during cell life. DNA damage activates a complex range of processes, including DNA damage response signaling, DNA repair, and cell cycle regulation, and these processes can result in single-strand DNA breaks (SSBs) or double-strand DNA breaks (DSBs) and then cause cell death, if DNA damage is not correctly been repaired.<sup>11</sup> There are six main pathways of DNA repair have been identified: mismatch repair (MMR), nucleotide excision repair (NER), base excision repair (BER), and trans-lesional synthesis are responsible for repairing SSBs, while non-homologous end joining (NHEJ) and homologous recombination (HR) are responsible for repairing DSBs.<sup>12,13</sup>

HR is a high fidelity repair pathway, whereas NHEJ is faster but error prone. If HR pathway is altered, the cells rely above all on NHEJ, with a less preserved genomic integrity and a higher risk to develop cancers.<sup>14</sup> BRCA 1 and BRCA 2 are the first HR proteins that have been studied, both of them are critical to the repair of DSBs. Cells with BRCA 1/2 mutations may exhibit HR deficiency, and NHEJ becomes the main DNA repair pathway, which can result in a higher risk to develop cancers.<sup>15</sup>

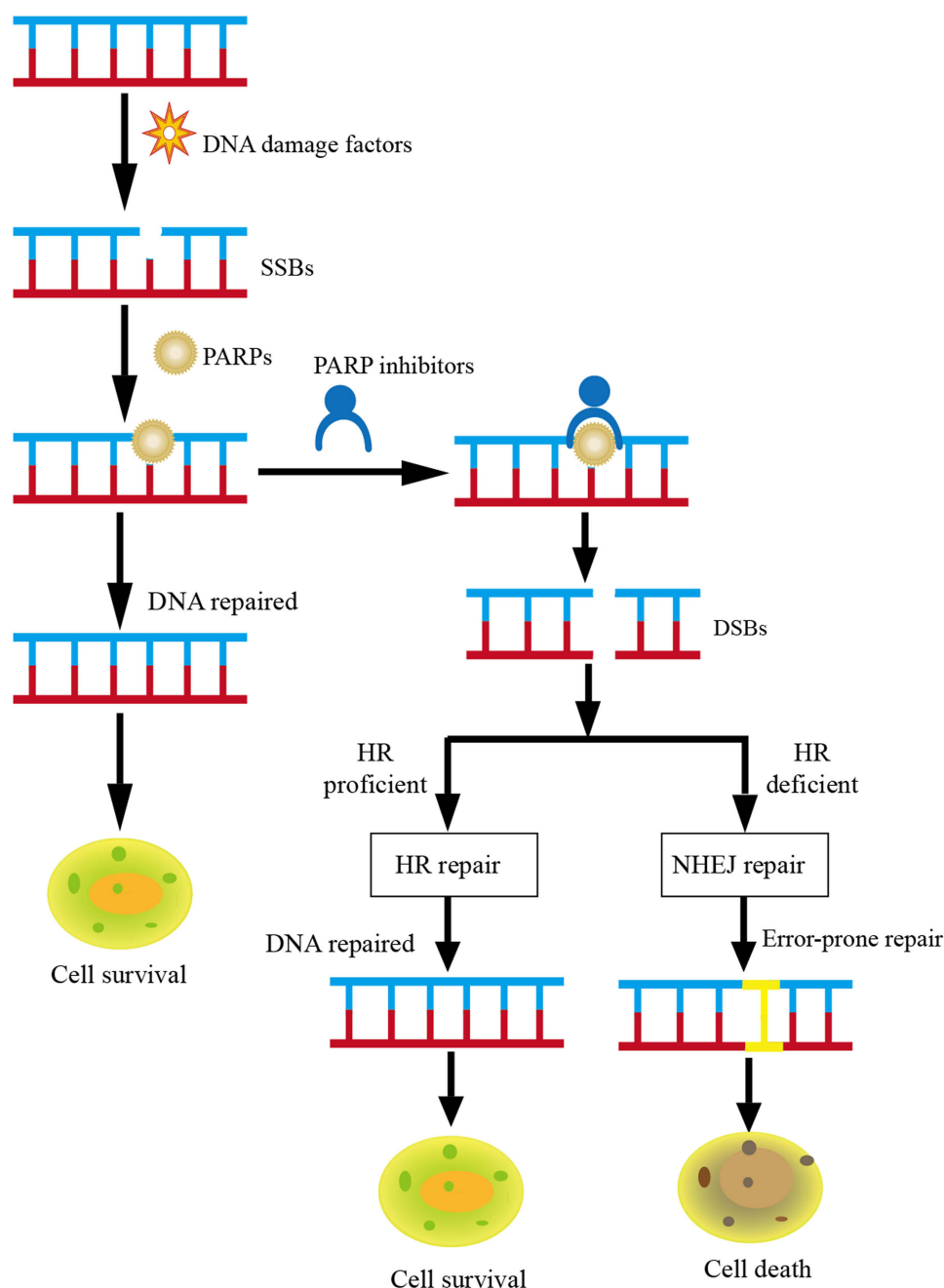
PARP enzymes play an important role in the DNA repair, they are involved in different pathways of DNA repair, including SSBs repair and DSBs repair.<sup>16</sup> Among the PARP family, PARP-1, 2 and 3 are the most extensively studied, and PARP-1 plays a major role in the total activity.<sup>17</sup> PARP inhibitors trap the PARP-1 and PARP-2 in DNA damage sites and prevent the recruitment of additional DNA repair proteins. For HR deficient cells (ie, those with BRCA mutation), without the complete set of DNA repair proteins at the damage site, the cell is unable to properly repair its DNA during replication, which can cause cell death.<sup>18</sup> The molecular mechanisms of PARP inhibitors are illustrated in [Figure 1](#).

## PK Parameters of PARP Inhibitors

PARP inhibitors are administered orally, and the median time to the peak plasma concentration ( $C_{max}$ ) is 0.5 to 3 h.<sup>5,19–31</sup> The apparent volume of distribution ( $V_d$ ) of PARP inhibitors shows a huge variability. In white patients with cancer, the  $V_d$  at steady-state ( $V_{ss}$ ) of olaparib, rucaparib, and talazoparib is 158–167, 113–262, and 420 liters, respectively,<sup>19,21,22,24,28,30</sup> the  $V_d$  of niraparib and veliparib is  $1220 \pm 1114$  and 173 liters, respectively.<sup>20,23,26</sup> The five PARP inhibitors have a moderate plasma protein binding rate (from 51% to 83%).<sup>19–31</sup> In terms of the metabolism pathway, olaparib, rucaparib and veliparib are primarily metabolized by the cytochrome P450 (CYP) enzymes,<sup>19,21,23,24,28</sup> talazoparib undergoes minimal hepatic metabolism,<sup>22,30</sup> while niraparib is predominantly metabolized by carboxylesterases (CEs).<sup>20,26</sup> The elimination half-life ( $T_{1/2}$ ) is long for talazoparib and niraparib,<sup>20,22</sup> and is short for veliparib.<sup>23</sup> Finally, talazoparib and veliparib are predominantly excreted in the urine,<sup>22,23</sup> whereas rucaparib is excreted primarily in the feces.<sup>21,28</sup> For olaparib and niraparib, both renal and pathways are involved in the elimination.<sup>19,20,24,26</sup> PK parameters for PARP inhibitors are demonstrated in [Table 1](#).

## Dose Adjustment for Patients with Hepatic or Renal Impairment

The liver is involved in the elimination of many agents through hepatic metabolism and biliary excretion. Hepatic impairment may affect the PK of a drug through multiple mechanisms, including alterations in drug absorption, plasma protein binding, first-pass elimination, hepatic metabolism, biliary secretion and renal clearance.<sup>32</sup> Alterations of these PK parameters by hepatic impairment can lead to drug accumulation or failure to form an active metabolite. The degree of effect is associated with the severity of hepatic impairment. Most clinical studies and guidelines used the National Cancer Institute–Organ Dysfunction Working Group (NCIOWG) criteria and Child–Pugh criteria to evaluate the hepatic function. The NCIOWG criteria are based on total bilirubin and AST levels. Per these criteria, patients with mild, moderate or severe hepatic impairment correspond to the Child–Pugh A, B and C. The classification of hepatic



**Figure 1** Molecular mechanisms of PARP inhibitors. PARPs bind to the DNA damage sites and induce a DNA damage response. PARP inhibitors trap the PARPs in DNA damage sites and prevent the recruitment of additional DNA repair proteins, which resulting in DSBs accumulation. HR proficient cells have the ability to repair the DSBs and restart; maintaining survival. But for HR deficient cells, NHEJ is the only pathway to use to repair DSBs, which can lead to accumulation of genome instability and results in cell death.

impairment by Child–Pugh criteria and NCIODWG criteria are listed in Table 2. To maximize the efficacy and minimize the toxicity, dose adjustment should be considered when drug PK is significantly altered in patients with hepatic impairment.

Renal clearance is an important elimination route for PARP inhibitors, thereby impaired renal function can reduce the drug clearance, leading to an increased drug exposure.<sup>33</sup> In addition, renal impairment can affect hepatic and intestinal metabolism and has also been associated with other alterations, such as alterations in absorption, plasma protein binding, and tissue distribution.<sup>34</sup> These alterations may be particularly prominent in patients with severe hepatic impairment. The degree of effect on drug PK is associated with the severity of renal impairment. In practice, estimated glomerular

**Table 1** PK Parameters for PARP Inhibitors

PK	Molecular Weight (Dalton)	T <sub>max</sub> (h)	V <sub>d</sub> /V <sub>ss</sub> (Liters)	Plasma Protein Binding (%)	Metabolism Enzymes	T <sub>1/2</sub> (h)	Clearance (L/h)	Excretion		References
								Urine (%)	Feces (%)	
Olaparib (tablet)	434.46	1.5	158 ±136 <sup>ss</sup>	82	CYP3A4/5 (major), CYP2A6, CYP1A1, UGTs, SULTs	14.9 ±8.2	7.4±3.9	44	42	[19, 24, 25]
Olaparib (capsules)	434.46	1–3	167 ±196 <sup>ss</sup>	82	CYP3A4/5 (major), CYP2A6, CYP1A1, UGTs, SULTs	11.9 ±4.8	8.6±7.1	44	42	[19, 24, 25]
Niraparib	510.61	3	1220 ±1114	83	CEs (major), CYP1A2, CYP3A4/5, CYP2D6, UGTs	36	16.2	47.5	38.8	[20, 26, 27]
Rucaparib	555.67	1.9	113–262 <sup>ss</sup>	70	CYP2D6 (major), CYP1A2, CYP3A4, UGTs, SULTs	17–19	15.3–79.2	17.4	71.9	[21, 28, 29]
Talazoparib	552.56	1–2	420 <sup>ss</sup>	74	Minimal hepatic metabolism (<10%)	90 ±58	6.45	68.7	19.7	[22, 30, 31]
Veliparib	244.29	0.5–1.5	173	51	CYP2D6 (major), CYP1A2, CYP2C19, CYP3A4, UGTs	5.2	20.9	79.4	5	[23]

**Abbreviations:** T<sub>max</sub>, time to achieve; C<sub>max</sub>, T<sub>1/2</sub>, elimination half-life; V<sub>d</sub>, apparent volume of distribution; V<sub>ss</sub>, apparent volume of distribution at steady-state; ss, at steady-state; UGTs, uridine-5'-diphospho-glucuronosyltransferases; SULTs, sulfotransferases; CEs, carboxylesterases.

**Table 2** Classification of Hepatic Impairment by Child-Pugh Criteria and NCIODWG Criteria

Degree	Child-Pugh Criteria (Points)	NCIODWG Criteria
Mild	A (5–6)	TBil ≤ULN and AST >ULN, or TBil >1–1.5 × ULN and any AST
Moderate	B (7–9)	TBil >1.5–3×ULN and any AST
Severe	C (10–15)	TBil >3 × ULN and any AST

**Abbreviations:** TBil, total bilirubin; AST, aspartate aminotransferase; ULN, upper limit of normal.

filtration rate (eGFR) is most commonly used to assess the renal function. The eGFR is based on serum creatinine concentration, age, weight, and sex. Dose adjustment may be necessary for patients with renal impairment when renal impairment is likely to significantly alter the PK of the drug or its active metabolites. The dose adjustment recommendations for PARP inhibitors in patients with hepatic or renal impairment are summarized in Table 3.

**Olaparib:** Olaparib is primarily metabolized by CYP3A4/5 and is cleared by both liver and kidneys. Following oral administration of a single oral dose of olaparib, 44% (15% unchanged) of the radioactive dose is recovered in urine and 42% (6% unchanged) in feces.<sup>24,25</sup> Theoretically, both hepatic and renal impairment are therefore can affect the PK of olaparib. In a Phase I open-label study, patients with mild or moderate hepatic impairment had no clinically significant changes in the olaparib exposure compared with subjects with normal hepatic function (NHF).<sup>35</sup> The safety profile of olaparib did not differ to a clinically relevant extent between cohorts.<sup>35</sup> Thereby, no dose adjustment is needed in patients with mild or moderate hepatic impairment. No clinical study has been conducted in patients with severe hepatic impairment. From the physiologically based PK (PBPK) data, the olaparib AUC increased by 120% in patients with severe hepatic impairment.<sup>36</sup> Therefore, olaparib is not recommended in patients with severe hepatic impairment.<sup>24,25</sup>

**Table 3** Dose Adjustment Recommendations for PARP Inhibitors in Patients with Hepatic or Renal Impairment

Hepatic/ Renal Impairment	Dose Adjustment is Not Required	Dose Adjustment is Required	Not Recommended for Use	Not Known or Use with Caution	References
Mild hepatic impairment	Olaparib, Niraparib, Rucaparib, Talazoparib, Veliparib				[26, 27, 35, 39, 42, 44]
Moderate hepatic impairment	Olaparib, Rucaparib, Talazoparib, Veliparib	Niraparib (200 mg once daily)			[35, 38, 40, 42, 44]
Severe hepatic impairment	Talazoparib, Veliparib		Olaparib, Rucaparib	Niraparib	[27, 29, 36, 42, 44]
Mild renal impairment (60–89 mL/min)	Olaparib, Niraparib, Rucaparib, Talazoparib	Veliparib			[26, 27, 37, 39, 43, 44]
Moderate renal impairment (30–59 mL/min)	Niraparib, Rucaparib,	Olaparib (200 mg twice daily for tablets; 300 mg twice daily for capsules), Talazoparib (0.75 mg once daily), Veliparib			[26, 27, 37, 39, 43, 44]
Severe renal impairment (15–29 mL/min)		Talazoparib (0.5 mg once daily), Veliparib	Olaparib, Rucaparib	Niraparib	[25, 27, 29, 36, 43, 44]
ESRD not on dialysis ( $<15$ mL/min)			Olaparib, Rucaparib	Niraparib, Talazoparib, Veliparib	[23, 25, 27, 29, 31, 36]
ESRD on dialysis ( $<15$ mL/min)		Rucaparib (200 mg twice daily)	Olaparib	Niraparib, Talazoparib, Veliparib	[25, 41]

**Abbreviation:** ESRD, end stage renal disease.

Based on a phase I open-label study, a small increased exposure was found in patients with mild renal impairment, which was not considered clinically relevant,<sup>37</sup> whereas the exposure of olaparib was increased by 44% in patients with moderate renal impairment.<sup>37</sup> Therefore, dose adjustment is not required in patients with mild renal impairment, but the dose should be reduced to 200 mg twice daily for tablets and 300 mg twice daily for capsules in patients with moderate renal impairment.<sup>24,25,37</sup> Clinical study of olaparib in patients with severe renal impairment or end-stage renal disease (ESRD) has not been conducted. From the PBPK simulations, the olaparib AUC increased by 127% in patients with severe renal impairment and ESRD.<sup>36</sup> Thus, olaparib is not recommended in patients with severe renal impairment or ESRD.

**Niraparib:** Niraparib is predominantly metabolized by CEs. Niraparib undergoes hepatic and renal elimination, with 47.5% (11% unchanged) and 38.8% (19% unchanged) of the administered dose recovered in urine and feces, respectively.<sup>26,27</sup> Thus, similar to olaparib, both hepatic and renal impairment may have significant impacts on the PK of niraparib. In the population PK analysis, mild hepatic impairment did not influence the PK of niraparib.<sup>26,27</sup> According to a PK study, the niraparib AUC was increased by 56% in patients with moderate hepatic impairment, compared with subjects with NHE.<sup>38</sup> Therefore, niraparib can be administered in patients with mild hepatic impairment with no dose adjustment, but the dose should be adjusted to 200 mg once daily in patients with moderate hepatic impairment.<sup>26,27,38</sup> The PK and safety of niraparib in patients with severe hepatic impairment are lacking, thus niraparib should be used with caution in these patients.<sup>26,27</sup>

In the population PK analysis, patients with mild-to-moderate renal impairment had mildly altered the niraparib exposure compared to subjects with normal renal function (NRF), and the alterations in exposure were not considered to warrant dose adjustment.<sup>26,27</sup> No patients with severe renal impairment or ESRD have been studied, thus niraparib should be used with caution in these populations.<sup>27</sup>

**Rucaparib:** Rucaparib is metabolized extensively by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4. Rucaparib is primarily cleared by the liver and intestines, with 17.4% (7.6% unchanged) and 71.9% (63.9% unchanged) of the administered dose recovered in urine and feces, respectively.<sup>28,29</sup> Therefore, hepatic impairment is more likely to affect the PK of rucaparib as compared to renal impairment. Based on the population PK data, no statistically significant difference was observed for rucaparib exposure between patients with mild hepatic impairment and patients with NHF.<sup>39</sup> Thus, dose adjustment is not necessary for patients with mild hepatic impairment.<sup>39</sup> In a trial of patients with moderate hepatic impairment, the rucaparib AUC was mildly increased, which was not considered clinically significant and did not necessitate dose adjustment.<sup>40</sup> There are no clinical data in patients with severe hepatic impairment, therefore rucaparib is not recommended for use in these patients.<sup>28,29</sup>

A population PK analysis showed that mild-to-moderate renal impairment had no clinically significant effect on the PK of rucaparib, indicating that dose adjustment is not required for these populations.<sup>39</sup> There are limited data available for rucaparib in patients with severe renal impairment, therefore rucaparib is not recommended for use in these patients.<sup>28,29</sup> For patients with ESRD undergoing dialysis, a case report demonstrated that treatment with rucaparib at a dose of 200 mg twice daily was well tolerated and effective in a patient with ESRD undergoing dialysis.<sup>41</sup>

**Talazoparib:** Talazoparib undergoes minimal hepatic metabolism.<sup>30,31</sup> The major route of elimination for talazoparib is renal excretion, with 68.7% (54.6% unchanged) and 19.7% (13.6% unchanged) of the total administered dose recovered in urine and feces, respectively.<sup>30,31</sup> Thus, hepatic impairment seems to have little impact on the PK of talazoparib, whereas renal impairment may significantly impact the PK of talazoparib. Based on the results of the population PK analysis and clinical studies, mild, moderate and severe hepatic impairment had no significant impact on the clearance of talazoparib.<sup>42</sup> Therefore, no dose adjustment is recommended for patients with various degrees of hepatic impairment.<sup>30,31,42</sup>

Based on the PK study, patients with mild, moderate, and severe renal impairment had a 12.2%, 43.0%, and 163.3% increase in talazoparib AUC, and an 11.1%, 31.6%, and 89.3% increase in talazoparib  $C_{max}$ , respectively.<sup>43</sup> Therefore, no dose adjustment is required for patients with mild renal impairment, but the recommended dose of talazoparib is 0.75 mg once daily for patients with moderate renal impairment, and 0.5 mg once daily for patients with severe renal impairment.<sup>30,31,43</sup>

**Veliparib:** Veliparib is metabolized by multiple CYP enzymes, including CYP1A2, CYP2D6, CYP2C19 and CYP3A4, with CYP2D6 playing a key role in the biotransformation.<sup>23</sup> Veliparib is primarily cleared by the kidneys, with 79.4% (70% unchanged) and 5% of the total administered dose recovered in urine and feces, respectively.<sup>23</sup> Thereby, hepatic impairment is less likely to affect the PK of veliparib, whereas renal impairment may have a clinical impact on the PK of veliparib. The PBPK simulations predicted that hepatic function had no clinically meaningful influence on the exposure of veliparib; therefore, dose adjustment is not required for patients with various degrees of hepatic impairment.<sup>44</sup>

The PBPK simulations showed that veliparib exposure was increased by 27.3%, 65.4%, and 130% in patients with mild, moderate and severe renal impairment, respectively, compared with those in subjects with NRF.<sup>44</sup> Based on these results, patients with mild to severe renal impairment may need dose adjustment.

## Discussion

Hepatic and renal elimination are the major route for most drugs; therefore, impaired hepatic or renal function may significantly alter the PK of most drugs, and patients with hepatic or renal impairment may need dose adjustment.<sup>45</sup> As the metabolism and excretion are quite different between the five PARP inhibitors, hence the effect of hepatic and renal impairment on drug PK differs among the different PARP inhibitors.



Olaparib and niraparib are cleared via both liver and kidneys,<sup>24,26</sup> thus both hepatic and renal function may alter the drug PK. Based on the results of clinical studies, population PK analysis and PBPK simulations, moderate hepatic impairment could significantly change the niraparib PK but did not significantly change the olaparib PK.<sup>35,38</sup> The possible reason is that hepatic impairment may decrease gastrointestinal absorption due to the portal hypertension and decreased blood flow in intestinal mucosa.<sup>45</sup> The decreased absorption could counteract the theoretical effect of decreased metabolism, resulting in little alteration in the exposure of olaparib in patients with moderate hepatic impairment compared with those with NHF.<sup>35</sup> Regarding the renal impairment, moderate renal impairment could significantly alter the olaparib PK<sup>37</sup> but did not significantly change the niraparib PK.<sup>26</sup> The mechanism that moderate renal impairment has little impact on the PK of niraparib is unclear, and further studies are therefore needed to explore the potential mechanism. Rucaparib is mainly cleared by the liver and intestines, thereby hepatic impairment may have clinically impacts on the PK of rucaparib. However, based on the population PK and clinical studies, mild-to-moderate hepatic impairment did not significantly influence the PK of rucaparib.<sup>39</sup> The reason may be similar to olaparib that hepatic impairment can decrease the oral absorption. Consistent with the minor role of renal excretion in the clearance of rucaparib, mild-to-moderate renal impairment had no clinically significant effect on the PK of rucaparib.<sup>39</sup> Based on the PK data, dose adjustment is not required for talazoparib and veliparib in patients with varying degrees of hepatic impairment, but the dose should be modified in patients with moderate or severe renal impairment.<sup>42–44</sup> These results are consistent with the major role of renal excretion in the clearance of talazoparib and veliparib.<sup>23,30</sup>

In practice, it is difficult to conduct a clinical study to evaluate the drug efficacy and safety in patients with severe hepatic or renal impairment. Therefore, population PK studies and PBPK models are commonly used to predict the drug PK in patients with severe hepatic or renal impairment.<sup>36,39,44</sup> However, the prediction cannot be made with a high level of granularity and precision, since the mechanisms of PK alteration in patients with hepatic or renal impairment are complicated, and the PK of a drug may display high interindividual variability.<sup>46</sup> To make an appropriate dosage, therapeutic drug monitoring may be a good option for patients with severe hepatic or renal impairment.<sup>47</sup> In addition, close monitoring of potential toxicities is also important for patients with severe hepatic or renal impairment.

PARP inhibitors can induce hepatic and renal toxicities, it is important to monitor hepatic and renal function in patients receiving PARP inhibitors.<sup>48</sup> When patients do not exhibit hepatic or renal impairment prior to PARP inhibitor treatment but develop PARP inhibitor-related hepatic or renal toxicities, the dose adjustment is based on the grade of the adverse reactions.<sup>30,31</sup> For example, if patients experience grade 3 or grade 4 hepatic or renal impairment during talazoparib treatment, it is recommended to withhold talazoparib until levels resolve to grade 0 or grade 1, then resume talazoparib with a reduced dose.<sup>30,31</sup>

## Conclusion

For certain PARP inhibitors, hepatic and renal impairment can significantly alter the drug PK, and dose adjustment is required in patients with hepatic or renal impairment for ensuring the efficacy and avoiding unwanted toxicities. There are few clinical trials to assess the drug efficacy and safety in patients with severe hepatic or renal impairment, and most of the PK data in patients with severe hepatic or renal impairment are predicted by using population PK studies and PBPK models. However, the prediction cannot be made with a high level of granularity and precision. Therapeutic drug monitoring may be a favorable option to make an appropriate PARP inhibitor dosage in patients with severe hepatic or renal impairment. In addition to the use of therapeutic drug monitoring, close monitoring of potential toxicities is also essential for these patients.

## Disclosure

The authors declare that they have no competing interests in this work.

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