Renal toxicity of targeted therapies for renal cell carcinoma in patients with normal and impaired kidney function

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Received: 13 December 2020 / Accepted: 13 March 2021 / Published online: 25 March 2021
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Abstract
The introduction of novel targeted therapies during the last 2 decades has led to a significant improvement in patients’ clinical outcomes with renal cell carcinoma. However, this improvement came at the price of a whole new spectrum of adverse events, including renal toxicity. Systemic treatment of patients with kidney neoplasms who often present with impairment of kidney function, even prior to treatment, poses an increasing diagnostic and therapeutic challenge for clinicians. Common lifestyle-related comorbidities, i.e., hypertension and diabetes, may contribute to further impairment of kidney function. The lack of official guidelines and the exclusion of patients with reduced kidney function from the clinical trials of recently approved drugs complicate the issue even further. Early detection and correct management of renal toxic effects are crucial to preserve kidney function and ensure the optimal administration of life-prolonging therapies. This review presents detailed information on the renal toxicities of three groups of drugs commonly used in renal cell carcinoma treatment: tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors, and immune checkpoint inhibitors. We outline the incidence and underlying mechanisms of renal adverse effects with a focus on patients on renal replacement therapy, as well as present suggestions for their management.

Keywords Renal cell cancer · TKI · MTORi · Immune checkpoint inhibitors · Renal insufficiency · Nephrotoxicity

Introduction
Renal cell carcinoma (RCC) is the 6th most common cancer type in men and the tenth most common in women, accounting for 5% and 3% of all cancer diagnoses, respectively. It remains one of the most lethal urological malignancies [1].

With growing incidence rates, mostly in high-income countries, RCC arises as an important diagnostic and therapeutic challenge. Common lifestyle-related diseases, i.e., hypertension and diabetes, are independent risk factors of RCC development, and, therefore, it is not surprising that hypertensive nephrosclerosis and diabetic nephropathy are common in RCC patients [2–4]. A history of kidney disease is an independent risk factor of RCC (HR 2.58, 95% CI 1.21–5.50) [2]. Approximately 26% of RCC patients have chronic kidney disease (CKD) even before RCC treatment [5]. Patients with end-stage renal disease (ESRD) requiring long-term dialysis or after renal transplantation are at a higher risk of developing RCC—0.3% and 0.7%, respectively [6, 7], compared to approximately 0.005% in the general population [8]. However, despite RCC’s higher incidence in ESRD patients, tumors in this population exhibit favorable clinical and pathological features [9, 10]. RCCs in native kidneys of ESRD patients are usually asymptomatic, small, low stage, low grade, and non-metastatic at diagnosis [9]. These differences may be attributed to increased surveillance and the distinct pathophysiology of these tumors, including unique
undergoing hemodialysis.

Despite improvements in renal tumors surgery, even patients without previously diagnosed CKD may develop renal insufficiency after RCC resection. New-onset CKD secondary to surgery develops more often in patients undergoing radical nephrectomy than partial nephrectomy, with various rates reported by studies (55.7–70% vs. 6.2–17.4%, respectively) [5, 12]. RCC’s surgical treatment may also result in acute kidney injury (AKI) in up to 5% of cases [13]. Patients presenting with sporadic bilateral and/or multifocal renal tumors represent a unique population, accounting for up to 5% of all RCC patients [14]. Despite the introduction of nephron-sparing surgery, a substantial group of patients in this population needs to be treated with bilateral nephrectomy and subsequently develops renal insufficiency that must be treated with dialyzes. Surgical resection is a curative procedure in most localized RCC cases, but 20–40% of the patients will ultimately develop distant metastases and require systemic treatment in the first 5 years after primary tumor surgery [15]. The last few decades brought tremendous changes to the therapeutic landscape of metastatic RCC, with the development of numerous tyrosine kinase inhibitors (TKIs), mammalian target of rapamycin inhibitors (mTORis), and immune checkpoint inhibitors (ICPIs). This progress has significantly improved RCC patients’ clinical outcomes, at the price of a whole new spectrum of adverse events (AEs), including renal toxicities. Because of the many links between cancer, kidneys, and drug metabolism, nephrologists should become aware of new anticancer drugs’ potential nephrotoxicity and be actively involved in certain aspects of cancer care. Emergence of a new subspecialty, onconephrology, underlines the need for a close collaboration between oncologists and nephrologists [16].

In this paper, we comprehensively review renal toxicities associated with the aforementioned classes of drugs used in the treatment of RCC from an epidemiological, pathophysiological, and clinical point of view. Additionally, we summarize recommendations and underline differences in systemic treatment between patients with CKD and ESRD undergoing hemodialysis.

Renal toxicities of tyrosine kinase inhibitors

Incidence

TKIs are one of the most commonly used groups of drugs in RCC treatment and include sunitinib, pazopanib, sorafenib, axitinib, and cabozantinib. All abovementioned drugs are multitargeted TKIs, which means that they interfere with the activity of more than one family of receptor tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and epidermal growth factor receptor (EGFR), and all share a similar structure. Additionally, sorafenib is a potent inhibitor of serine/threonine-protein RAF kinases. Their shared mechanism of action contributes to their similar side effects. The most common AEs involve gastrointestinal, skin, bone marrow, and cardiovascular system toxicities. Renal toxicities are also frequently reported; however, data regarding their exact rate are inconsistent (Table 1).

Most TKI-related renal AEs include mild renal injury, defined as a clinically insignificant serum creatinine elevation that develops in up to 70% of patients receiving sunitinib [17–20]. Clinically important renal insufficiency may develop in 7.7% to 33% of patients treated with sunitinib [21, 22]. In the AXIS trial, deterioration of kidney function (defined as creatinine clearance elevation) was observed in 41% of patients treated with axitinib and in 55% of patients treated with sorafenib during the first-line treatment; however, a clinically significant increase of creatinine clearance (grades 3 and 4 according to CTCAE version 3.0) was extremely rare in case of sorafenib (< 1%) and absent in patients receiving axitinib [23]. Pazopanib treatment is associated with a similar prevalence of kidney function deterioration, as observed in the COMPARTZ trial, where increased creatinine levels were present in 32% of patients [24]. Nevertheless, clinically significant kidney function impairment was extremely rare, with < 1% of acute kidney failure cases in this trial. In cabozantinib trials, i.e., CABOSUN and METEOR, 5% and 25% of patients demonstrated elevated creatinine levels, respectively (Table 1). In a retrospective analysis of Japanese patients treated with sunitinib, sorafenib, or axitinib in first, second, or third line, deterioration of kidney function was documented, however, with no significant differences between creatinine clearance at baseline and that at the end of therapy between patients receiving different lines of treatment [25].

Another side effect related to renal function, proteinuria, may develop in up to 63% of patients undergoing anti-VEGF therapy, depending on the type of drug (Table 1). According to a recent meta-analysis of newly approved VEGFR-TKIs (regorafenib, vandetanib, cabozantinib, lenvatinib, axitinib), the risk of developing high-grade proteinuria event was significant for patients with RCC [26]. In the course of nephrotic syndrome, heavy proteinuria may be seen in up to 6.5% of patients treated with anti-VEGF therapies [27].

Mechanisms of nephrotoxicity

Renal damage induced by TKIs can present with hypertension and proteinuria. In patients receiving anti-VEGF therapy, thrombotic microangiopathy (TMA) is the most common histopathological finding [28]. Cases of
### Table 1 Renal toxicities in major TKI trials

| Trial | Drug | Number of patients | Renal related toxicities | Overall, any grade (%) | Grades 3–4/SAE (%) | Refs. |
|-------|------|-------------------|--------------------------|------------------------|--------------------|-------|
| Renal EFFECT | NCT00267748 | 147 | Creatinine increase | 69 | 2 | [104] |
| Phase II, 2nd line | Sunitinib | 106 | Creatinine increase<sup>a</sup> | 8.49 | ND | [105] |
| Phase III, 1st line | Sunitinib | 375 | Creatinine increase<sup>a</sup> | 66 | ND | [17, 18] |
| Registration trial | NCT00083889 | 375 | Renal failure<sup>a</sup> | 1.07 | 1.07 | |
| Phase III, 1st line | Sunitinib | 553 | Creatinine increase<sup>a</sup> | 46 | 2 | [24] |
| Phase II, treatment-naive or post-cytokine | Pazopanib | 225 | Creatinine increase | 32 | <1 | [107] |
| Phase II, post-cytokine | Pazopanib | 55 | Proteinuria | 44 | 13 | [108] |
| Phase III, treatment-naive or post-cytokine | Pazopanib | 290 | Proteinuria | 10 | 2 | [109, 110] |
| Phase II, post-cytokine | Pazopanib | 52 | Hematuria<sup>a</sup> | 0.24 | 0.34 | |
| Phase II, post-cytokine | Axitinib | 64 | Proteinuria | 63 | 9 | [115] |
| Phase III, 2nd line | Axitinib | 361 | Creatinine increase | 55 | 0 | [23, 116] |
| INTORSECT | Sorafenib | 252 | Creatinine increase<sup>a</sup> | 12.85 | ND | [113] |
| Phase II, post-cytokine | Sorafenib | 52 | Renal failure | 1.61 | 1.61 | |
| Phase II, post-cytokine | Axitinib | 64 | Hematuria<sup>a</sup> | 9.62 | 1.92 | [114] |
| Phase II, post-cytokine | Axitinib | 361 | Proteinuria | 63 | 9 | |
| INTORSECT | Sorafenib | 252 | Creatinine increase | 12.85 | ND | [113] |
| Phase II, post-cytokine | Sorafenib | 52 | Renal failure | 1.61 | 1.61 | |
| Phase II, post-cytokine | Axitinib | 64 | Hematuria<sup>a</sup> | 9.62 | 1.92 | [114] |
| Phase II, post-cytokine | Axitinib | 361 | Proteinuria | 63 | 9 | |

<sup>a</sup> Numbers may not add up due to rounding.
mesangioproliferative glomerulonephritis, cryoglobulinemic glomerulonephritis, extracapillary proliferative glomerulonephritis [29], and immune complex-mediated focal glomerulonephritis [30] have also been reported. Patients receiving TKI’s may also experience nausea, vomiting, and diarrhea, which can cause dehydration and, in serious cases, contribute to prerenal kidney failure [31]. The mechanisms of renal toxicity on the molecular level are complex. TKIs activate the endothelin-1 system and modulate the renin–angiotensin system, resulting in hypertension and microvascular dysfunction [32].

Moreover, podocytes—cells forming the filtration barrier in renal glomeruli—are involved in proteinuria’s pathophysiology. Podocytes abundantly express VEGF and its receptors, maintaining these cells’ physiological function and glomerular filtration membrane integrity. TKIs, by interfering with VEGF receptors’ activity on the podocytes, impair the glomerular filtration barrier and, consequently, induce proteinuria and reduced glomerular filtration rate [33]. Some studies suggest that the TKI-mediated podocyte injury might be facilitated by tyrosine phosphorylation of nephrin, a protein expressed in podocytes critical for maintaining the integrity of the filtration barrier [34]. The loss of normal podocyte fenestration results in microvascular injury, capillary thrombosis, and renal glomeruli scleratization, which may cause TMA. Affected patients develop proteinuria, hypertension, anemia, thrombocytopenia, and eventually renal failure. Proteinuria as a side effect of TKIs is not only caused by increased glomerular permeability. Still, it is also secondary to increased intraglomerular pressure that is an effect of arterial hypertension, another TKI side effect. Even though hypertension and proteinuria often occur simultaneously, it is not clear whether both of these side effects occur independently as an effect of VEGF blockage, or one of them is secondary to the other. Moreover, TKIs may induce acute renal failure through toxic injury of renal tubules or tumor lysis syndrome [33, 34].

**Management**

TKI-induced hypertension has been well documented in several studies as a predictor of favorable prognosis in metastatic RCC (mRCC) patients [20, 35]. However, data regarding TKI-induced renal function impairment as a prognostic factor for RCC patients are limited. In a retrospective analysis of Korean patients receiving sunitinib, the incidence of renal AEs, namely proteinuria, was associated with longer progression-free survival (PFS) [21]. A pooled secondary analysis of patients with mRCC treated with pazopanib and sunitinib in phase III randomized clinical trials showed that proteinuria, particularly grades 3/4, was associated with improved overall survival (OS) (HR 0.53, 95% CI 0.30–0.92) [36]. In a previous analysis, the development of new-onset hypercreatinemia during TKI treatment was related to a more favorable prognosis in OS and PFS [20]. These results suggest that the presence of renal AEs during TKI treatment should not necessitate treatment discontinuation, especially when the side effects are moderate. There are no evidence-based recommendations on the treatment of TKI-associated renal AEs. Most patients with proteinuria are treated with renin–angiotensin system blockers (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers); however, no interventional studies have been conducted to confirm the recommendation of this treatment for TKI-induced proteinuria. Isolated proteinuria is not an indication for dose reduction unless nephrotic-range (3.5 g or more per day) or edema, hyperlipidemia, and hypoalbuminemia occur [37].

Acute kidney injury, nephrotic range proteinuria, and TMA

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**Table 1** (continued)

| Trial | Drug | Number of patients | Renal related toxicities |
|-------|------|--------------------|-------------------------|
|       |      |                    | Overall, any grade (%)  | Grades 3–4/SAE (%) | Refs. |
| Phase III, 1st or 2nd line | Axitinib | 192 (135 Asian pts) | Creatinine increase (data only for Asian pts) | 39.2 | 0.8 | [117–119] |
| NCT00920816 | | | Proteinuria (data only for Asian pts) | 20.7 | 5.2 | |
| CABOSUN | Cabozantinib | 79 | Creatinine increase | 25 | 3 | [120–122] |
| Phase II, 1st line | | | Hematuria | 2.56 | 2.56 | |
| NCT01835158 | | | Proteinuria | 7.69 | 1.28 | |
| METEOR | Cabozantinib | 330 | Proteinuria | 12 | 2 | [123, 124] |
| Phase III, post-cytokine | | | Creatinine increase | 5 | <1 | |
| NCT01865747 | |

*ND no data, SAE serious adverse events
a Data from clinicaltrials.gov registry
are generally considered reasons to discontinue therapy with TKIs [27, 38]. In TMA, anti-VEGF cessation halts further renal deterioration and enables at least partial recovery [39, 40]. Reintroduction of the drug allowing for continued anti-tumor treatment might be possible at lower doses; however, choosing an appropriate dose for reintroduction may be difficult. In an observational study, continued drug administration or reintroduction resulted in a more severe TMA recurrence in three of four patients requiring a maintenance dose of anti-VEGF agents [41]. Therefore, permanent drug discontinuation should be strongly considered in the case of TMA. It is important, that renal function parameters such as creatinine, blood urea nitrogen, baseline proteinuria, and estimated glomerular filtration rate (eGFR) are measured before initiating TKI treatment. Clinicians are also advised to check for proteinuria and renal function indices before each dose or therapy cycle.

**Patients with CKD or undergoing dialysis**

The tyrosine kinase inhibitors are primarily metabolized in the liver by the cytochrome CYP3A4, and their renal excretion does not exceed 23% (Table 2). In population pharmacokinetic analyses, no correlation between TKI exposure and renal function was observed in subjects with mild, moderate, or severe renal impairment who were not on dialysis. These data indicate no need for initial dose adjustment in patients with mild to severe CKD, although caution is advised if creatinine clearance is lower than 30 ml/min/1.73 m² (Table 2).

Patients treated with TKIs for an extended time may present with declining renal function. Age-related renal dysfunction interferes and prevents determining cause-effect relation between TKI therapy and renal function [42]. A study by Khan et al. [43] reports that in patients treated with sorafenib or sunitinib who developed renal insufficiency during treatment, median serum creatinine clearance declines from 61.5 mL/min to 39.2 mL/min with the median time to > 30% serum creatinine concentration buildup of 4.6 months. In patients who developed renal insufficiency before starting treatment, median creatinine clearance was rather stable (median fall from 38.4 mL/min to 36.2 mL/min) [43]. Renal insufficiency before the start of treatment does not necessarily increase the risk of kidney function deterioration. Still, in some studies, aggravation of pre-existing kidney impairment may comprise 66% of all renal insufficiencies [21]. Kidney injury that develops during treatment is a risk factor for progressive decline in renal function and increases the risk of dose reduction due to renal insufficiency [43].

The pharmacokinetics of sunitinib, sorafenib, and axitinib in patients with mild to severe CKD are similar to those observed in patients with normal renal function [44–46]. The pharmacokinetics of pazopanib in patients with impaired renal function has not been studied. In patients with mRCC, CKD present at baseline or developed during treatment with sunitinib or sorafenib was not associated with unexpected toxicities [43]. Importantly, patients with mRCC and impaired renal function treated with anti-VEGF drugs do not differ in response rate, time to treatment failure, and OS from patients with normal renal function [47]. A retrospective study of 229 patients with mRCC treated with pazopanib demonstrated that renal function at initiation of therapy did

| Drug | Main way of metabolism | Renal excretion of drug and metabolites | Dose reduction required |
|------|-------------------------|----------------------------------------|------------------------|
|      |                         |                                        | Patients with mild to moderate CKD | Patients with severe CKD | Patients on dialysis |
| Tyrosine kinase inhibitors | | | | | |
| Sunitinib [125] | Liver, CYP3A4 | 16% | No | No | No (ND) |
| Sorafenib [126] | Liver, CYP3A4 | 19% | No | No | No (ND) |
| Pazopanib [127] | Liver, CYP3A4 | <4% | No | No (ND) | No (ND) |
| Axitinib [128] | Liver, CYP3A4 | 23% | No | No | No (ND) |
| mTOR inhibitors | | | | | |
| Everolimus [129] | Liver, CYP3A4 | 5% | No (ND) | No (ND) | No (ND) |
| Temsirolimus [130] | Liver, CYP3A4 | 4.6% | No (ND) | No (ND) | No (ND) |
| Immune checkpoint inhibitors | | | | | |
| Ipilimumab [131] | Proteolytic degradation | No | No | No | No (ND) |
| Nivolumab [132] | Proteolytic degradation | No | No | No | No (ND) |
| Pembrolizumab [133] | Proteolytic degradation | No | No | No (ND) | No (ND) |
| Atezolizumab [134] | Proteolytic degradation | No | No | No (ND) | No (ND) |

CKD chronic kidney disease, ND no data

a 30–90 ml/min/1.73 m². b < 30 ml/min/1.73 m²
not adversely affect pazopanib’s safety and efficacy [48]. Therefore, impaired renal function should not prevent the initiation or continuation of anti-angiogenic therapies.

With the development and introduction of targeted therapies for RCC, TKIs were also studied in hemodialyzed (HD) patients. Studies in HD patients demonstrated no clearance of sunitinib, sorafenib, pazopanib, or axitinib from plasma by the dialyzer. The pharmacokinetics of these drugs is rarely influenced by dialysis [49–52]. Therefore, administration of these drugs may take place anytime, regardless of HD timing. Available data from larger studies of mRCC HD patients treated with TKIs are presented in Table 3. TKIs were generally well tolerated, with few reported AEs.

Nevertheless, a systematic review by Leonetti et al. [53] showed a higher incidence of sorafenib-related AEs in mRCC dialysis patients compared to the general mRCC population. Incidents of severe AEs such as subarachnoid hemorrhage resulting in the patient’s death were also noted (Table 3). The median PFS of 10.9 and 9 months and OS of 18.4 and 12.5 months presented in expanded-access trials of sunitinib and sorafenib, respectively [54, 55], are comparable to those reported in HD patients (Table 3). Evidence from a small number of cases also suggests a good efficacy and tolerability of pazopanib and axitinib treatment in mRCC patients undergoing dialysis [56, 57]. At this time, there are no established evidence-based guidelines on the management of such patients. Based on the available literature, the initial dose adjustment of TKIs seems unnecessary in patients receiving dialysis (Table 2). Long-term HD patients have a higher risk of cardiovascular comorbidities and should be monitored closely, as cardiovascular events are likely to be more frequent in this population [49]. Therapy administration should be performed with caution, followed by increased surveillance of AEs and appropriate dose reduction if AEs occur. Most importantly, dialysis should not be regarded as a contraindication to this type of treatment.

Renal toxicities of mTORis therapy

Incidence

Inhibitors of mammalian target of rapamycin (mTORis) such as temsirolimus and everolimus are well-established options for treating mRCC in further lines after TKI failure. Commonly reported side effects with mTORis include stomatitis, rash, fatigue, asthenia, diarrhea, metabolic complications, infections, and noninfectious pneumonitis [58]. Adverse renal effects, such as AKI, have also been reported. In a meta-analysis of nine randomized clinical trials assessing renal toxicity of mTORis, all-grade AKI and high-grade AKI occurred in 15.7% and 4.2% of patients, respectively. Interestingly, the AKI incidence rates did not differ significantly between mTORis and other drugs tested in RCC randomized clinical trials [59]. In another meta-analysis, AKI was the second most common cause of fatal AEs in patients receiving mTORis for cancer, representing 5.7% of all study deaths [60]. The incidence of proteinuria in mRCC patients treated with mTORis has not been reported in the literature; however, it has been described in renal transplant recipients receiving everolimus [61].

Mechanisms of nephrotoxicity

The mTOR complex plays an important role in the process of kidney regeneration and recovery. Although mTOR activity is low or absent in the healthy kidney, it increases markedly after ischemia–reperfusion injury [62]. Inhibition of mTOR by rapamycin delayed renal recovery and repair after AKI in animal models but, importantly, renal function fully recovered after several days, despite continued treatment [63]. Everolimus was also shown to have antiproliferative effects and, through induction of autophagy, to aggravate tubular dysfunction during recovery from kidney injury in a rat model [64]. Biopsy-proven acute tubular necrosis after starting mTORis therapy was reported in a case series of four patients [65]. The effect of everolimus on tubular cells can be reflected by an accumulation of the cellular protein LC3 A in the urine, which might in the future prove to be a useful marker of AKI induced by mTOR inhibition [64].

Moreover, everolimus induced renal function deterioration and proteinuria by inhibiting the proliferative activity associated with reduced VEGF expression in a remnant kidney model. This mechanism may be particularly important in patients with RCC after nephrectomy [66]. Another potential mechanism for mTORis nephrotoxicity is based on the fact that rapamycin inhibits mTORC2, a multiprotein complex containing mTOR, which activates the Akt/PKB kinase [67]. Thus, mTORis inhibit the Akt pathway, which is essential for maintaining cell survival and signaling. It is still unclear whether mTORis cause renal dysfunction directly or through impairment of kidney repair in response to stress caused by other nephrotoxic factors [65, 66].

Management

ACEIs and ARBs are indicated in the treatment of mTORi-associated proteinuria [68]. Caution should be taken while administering ACEIs in combination with temsirolimus, as sporadic cases of angioedema edema have been reported in the drug’s summary of product characteristics. If grade 3 renal toxic effects develop during mTORi therapy, treatment should be suspended and resumed upon renal function recovery. In AKI or grade 4 proteinuria, permanent discontinuation of treatment is generally recommended [38]. In a Korean retrospective study, the occurrence of AKI in RCC
| Reference                  | Number of patients | Cancer type                          | TKI      | Dose                                                                 | Dose reduction required | Response                  | PFS             | OS              | Duration of treatment | AEs (Grade ≥ 3)                                      |
|----------------------------|--------------------|--------------------------------------|----------|----------------------------------------------------------------------|-------------------------|----------------------------|------------------|-----------------|----------------------|----------------------------------------------------|
| Josephs et al. [135]       | 10                 | RCC                                  | Sunitinib| 50 mg/day (3), 37.5 mg/day (5), 25 mg/day (2)                        | Yes (3)                 | PR (3), SD (6), PD (1) | NA              | NA              | NA                   | Gr 4: HFSR (1); Gr 3: fatigue (3), diarrhea (1), HFSR (1), rash (1) |
| Kennoki et al. [49]        | 10                 | ccRCC (7), papillary RCC (2), unclassified (1) | Sorafenib| 200 mg/b.i.d. (1), 200 mg/day to 200 mg/b.i.d. (7)                   | No                      | CR (1), PR (3), SD (4), PD (2) | 6.3 mo (median) | 14.9 mo (median) | 11.3 mo (mean) | Gr 5: subarachnoid hemorrhage (1); Gr 4: cerebellar hemorrhage (1); Gr 3: HFSR (1), hypertension (5), diarrhea (4), deceased hemoglobin (6), pneumonitis (1), sepsis (1) |
| Casper et al. [136]        | 21                 | RCC                                  | Sunitinib| 25 mg/day (3), 37.5 mg/day (8), 50 mg/day (10)                      | Yes (5)                 | CR (1), PR (10), SD (5), PD (2) | 15 mo (median) | 29 mo (median) | NA                   | NA                                                |
| Masini et al. [137]        | 16                 | ccRCC (15), unclassified (1)          | Sunitinib| 50 mg/day (6), 37.5 mg/day (7), 25 mg (2), 12.5 mg (1)              | No                      | PR (7), SD (5)               | 10.3 mo (median)<sup>a</sup> | 22.6 mo (median)<sup>a</sup> | 12.7 mo (median)<sup>a</sup> | Gr 3: thrombocytopenia (1) |
|                            | 8                  | ccRCC (8)                            | Sorafenib| 400 mg/b.i.d. (4), 400 mg/day (3), 200 mg/day (1)                  | No                      | PR (1), SD (7)               | 10.3 mo (median)<sup>a</sup> | 22.6 mo (median)<sup>a</sup> | 13.9 mo (median)<sup>a</sup> | Gr 3: nausea (1), fatigue (1), diarrhea (1), symptomatic cardiac ischemia (1) |
| Shetty et al. [138]        | 8                  | ccRCC (5), papillary RCC (3)         | Sunitinib| 50 mg/day (3), 37.5 mg/day (4), 12.5 mg/day (1)                    | No                      | NA                         | 5.6 mo (median) | NA              | 6.2 mo (median) | None                                               |
|                            | 7                  | ccRCC (5), papillary RCC (2)         | Sorafenib| 400 mg/b.i.d. (2), 600 mg/day (3), 200 mg/b.i.d. (1), 200 mg/day (1) | Yes (2)                 | NA                         | 4.2 mo (median) | NA              | 5.3 mo (median) | Gr 3: fatigue (1), HFSR (1)                      |
|                            | 9                  | ccRCC (7), papillary RCC (2)         | Pazopanib| 800 mg/day (5), 600 mg/day (4)                                     | Yes (6)                 | NA                         | NA              | NA              | 11.6 mo (median) | Gr 3: fatigue (2), increased transaminases (1)     |
| Reference       | Number of patients | Cancer type          | TKI          | Dose                          | Dose reduction required | Response                  | PFS                     | OS                      | Duration of treatment | AEs (Grade ≥ 3)          |
|-----------------|--------------------|----------------------|--------------|-------------------------------|-------------------------|---------------------------|-------------------------|------------------------|------------------------|------------------------|
| Czarnecka et al. [139] | 5                  | ccRCC                | Sunitinib    | 50 mg/day (4), 37.5 mg/day (1) | Yes (2)                 | SD (4), PD (1)            | 8 mo (median)²         | NA                     | NA                     | None                   |
|                 | 3                  | ccRCC                | Sorafenib    | 400 mg/b.i.d                  | No                      | PR (1), SD (2)            | 8 mo (median)³         | NA                     | NA                     | Gr 4: hypertension (1) |
|                 | 1                  | ccRCC                | Pazopanib    | 400 mg/b.i.d                  | No                      | PD (1)                    | 8 mo (median)³         | NA                     | NA                     | None                   |
| Omae et al. [140] | 20                 | ccRCC (8), papillary RCC (8) | Sorafenib    | 200 mg/day (5), 400 mg/day (10), 600 mg/day (5) | No²                     | CR (1), PR (2), SD (1), PD (3) | 14.2 mo (median)       | 4.7 mo (median)        | Gr 5: LVDD (1), subarachnoid hemorrhage (1); Gr 4: cerebral hemorrhage (1); Gr 3: HSFR (1), hypertension (3), LVDD (1), fatigue (2), anorexia (2), diarrhea (3), syncope (1), pneumonitis (1), sepsis (1), anemia (5) |
| Ishihara et al. [57] | 8                  | ccRCC (4), papillary RCC (2), ACD–RCC (1), MiT family translocation RCC (1) | Axitinib     | 14 mg/day (2), 10 mg/day (4), 8 mg/day (2)³ | Yes (3)                 | PR (1), SD (5), PD (2)   | 8.1 mo (median)         | 13.3 mo (median)        | NA                     | None                   |

ACD–RCC acquired cystic disease-associated renal cell carcinoma, AEs adverse reactions, b.i.d. twice a day, ccRCC clear cell renal cell carcinoma, CR complete response, ESRD end-stage renal disease, Gr grade, HSFR hand-foot skin reaction, LVDD left ventricular diastolic dysfunction, mo months, NA not available, OS overall survival, PD progressive disease, PFS progression free survival, PR partial response, RCC renal cell carcinoma, SD stable disease, TKI tyrosine kinase inhibitor

²Estimated for the entire cohort of patients treated with sunitinib and sorafenib

³Estimated for the entire cohort of patients treated with sunitinib, sorafenib and pazopanib

⁴Four patients discontinued therapy because of serious AEs

⁵Maximum daily dose
patients did not require everolimus discontinuation in 9 of 14 cases. The authors suggested that the treatment decision should be made via a multidisciplinary approach, including the assessment of oncological benefits of everolimus and other therapeutic options [69].

**Patients with CKD or undergoing dialysis**

mTORis such as temsirolimus and everolimus are metabolized mostly by the liver. In population pharmacokinetic analyses, creatinine clearance was not affected by the clearance of everolimus in patients with mild to moderate CKD. No clinical studies were conducted with temsirolimus in patients with decreased renal function (Table 2). However, considering their very small renal excretion, no dosage adjustment of everolimus or temsirolimus is recommended in patients with renal impairment.

RCC patients with impaired renal function are at a higher risk of developing AKI with mTORis. In the previously mentioned Korean study [69], AKI incidence in patients receiving everolimus increased as the baseline eGFR decreased. Moreover, baseline eGFR was an independent risk factor for the development of everolimus-associated AKI [69]. In a retrospective analysis of 18 patients with non-dialysis dependent CKD and mRCC treated with mTORis, elevated creatinine level was noted in 77% of patients. The efficacy and safety of mTORis use were similar to patients with normal renal function [70].

mTORis do not require dose adjustment in hemodialyzed patients, as their blood concentration is not altered by dialysis [71, 72]. Table 4 summarizes available evidence of mTORis use in RCC patients on hemodialysis. Grade 3 AEs occurred in ten cases, and no grade 4 AEs were observed. The estimated median PFS and OS of 9.0 and 15.7 months, respectively, reported by Guida et al. in RCC patients on dialysis receiving everolimus [73], are in line with those reported in the phase III everolimus RECORD-1 study [74]. Therefore, mTORis seem to be an effective and safe treatment option for patients with mRCC and severe renal impairment requiring dialysis. Therefore, the use of mTORis should not be contraindicated in this subset of patients.

**Renal toxicities of immune checkpoint inhibitors**

**Incidence**

In the last years, ICPIs have become the standard first line of treatment in mRCC [75]. Among the drugs currently approved are cytotoxic T lymphocyte-associated protein 4 (CTLA-4) blocking antibodies (ipilimumab), programmed cell death protein 1 (PD-1) blocking antibodies (nivolumab, pembrolizumab), and PD-ligand 1 antibodies (atezolizumab). Several organ systems are affected by the use of ICPIs, including the central nervous system and cardiovascular, respiratory, musculoskeletal, and hematologic systems. However, the gastrointestinal tract, endocrine glands, skin, and liver seem to be the most commonly involved [76].

Adverse renal effects of ICPIs are rare but increasingly described. They include AKI, proteinuria, and electrolyte abnormalities. The frequency of immune checkpoint inhibitor-associated AKI (ICPI-AKI) does not seem to differ significantly between CTLA-4 and PD1 targeting drugs [77]. A recent review of 48 clinical trials involving 11,482 patients treated with PD-1 inhibitors reported a pooled relative risk for AKI of 4.19 (95% confidence interval, 1.57–11.18) when compared with non-nephrotoxic controls and an estimated incidence of 2.2% [78]. These numbers are likely underestimated, as they reflect data obtained in clinical trials, which might not be applicable in a standard clinical setting.

**Combination therapy**

In recent years, clinical investigations have focused on two types of combination regimens: combinations of ICPIs and combinations of ICPIs and TKIs. In April 2018, the FDA approved the combination therapy of ipilimumab and nivolumab to treat intermediate or poor-risk advanced RCC. In the CheckMate 214 study evaluating the combination of nivolumab plus ipilimumab as first-line treatment for advanced RCC, increased blood creatinine was present in 7.3% of patients. AKI occurred in 2.2% of patients treated with combination therapy [79]. In an analysis of data from phase II and III clinical trials, the incidence of ICPI-AKI was estimated to be higher in patients receiving combination ipilimumab/nivolumab therapy (4.9%) compared to monotherapy (pembrolizumab, 1.4%, nivolumab, 1.9%, ipilimumab, 2%) [80]. Recently, positive results of studies assessing outcomes of ICPIs and TKIs combinations led to FDA approvals of pembrolizumab plus axitinib and avelumab plus axitinib in first-line treatment of advanced RCC. In a phase III JAVELIN Renal 101 study investigating avelumab plus axitinib for advanced RCC, no renal AEs were reported with the data cutoff of ≥ 10% for any grade events and ≥ 5% for grade ≥ 3 events [81]. In an extended follow-up from a phase III study of pembrolizumab plus axitinib in RCC treatment (KEYNOTE-426), AKI was present in 5 of 429 patients (1.2%) and nephritis in 8 patients (1.9%) [82]. Importantly, in both studies, combination therapy was not associated with a higher incidence of AEs than sunitinib alone.

Additionally, in a phase I study of mRCC patients treated with nivolumab combined with sunitinib or pazopanib (CheckMate 016 study), treatment was associated with increased blood creatinine in 33.3% and 5%, respectively.
# Table 4 Summary of published cases of the use of mTORis in RCC patients with ESRD

| Reference | Number of patients | Cancer type | mTORi | Dose | Dose reduction required | Response | PFS | OS | Duration of treatment | AEs (Grade ≥ 3) |
|-----------|--------------------|-------------|-------|------|-------------------------|----------|-----|----|-----------------------|----------------|
| Thiery-Vuillemin et al. [72] | 2 | RCC | Everolimus | 5 mg p.o./day \(a\) | Yes (1) \(a\) | NA | NA | NA | NA | Gr 3: hyperglycemia (1), asthenia (1) |
| Syrios et al. [141] | 2 | ccRCC, chromophobe RCC | Everolimus | 10 mg p.o./day | No | NA | NA | NA | NA | None |
| Miyake et al. [142] | 10 | ccRCC (7), papillary RCC (3) | Temsirolimus | 25 mg i.v./week | Yes (4) | SD (9), PD (1) | NA | NA | 13 mo (median) | Gr 3: asthenia (1), anemia (1), thrombocytopenia (2) |
| Shetty et al. [138] | 3 | ccRCC (1), papillary RCC (2) | Temsirolimus | 25 mg i.v./week | No | NA | NA | NA | 1.9 mo (median) | None |
| Guida et al. [73] | 11 | ccRCC (11) | Everolimus | 10 mg p.o./day (10); 5 mg p.o./day (1) \(b\) | No | PR (1), SD (7) | 9 mo (median) | 15.7 mo (median) | 14.4 (mean) | Gr 3: cutaneous rash (1), anemia (1), thrombocytopenia (1), dyspnea (1) |
| Omae et al. [143] | 4 | ccRCC (2), papillary RCC (2) | Everolimus | 5 mg p.o./day (3); 10 mg p.o./day (1) \(c\) | No | SD (4) | NA | NA | 6.7mo (median) | None |
| | 2 | ccRCC (1), papillary RCC (1) | Temsirolimus | 25 mg i.v./week (1), 20 mg i.v./week (1) \(d\) | No | SD (2) | NA | NA | 9.5mo (median) | None |

\(a\)Everolimus starting dose was 5 mg/day with the possibility of escalation according to the tolerance after first pharmacokinetic assessment. One patient experienced escalation to 10 mg/day, but required dose reduction to 5 mg/day due to adverse events.

\(b\)Reduced dose was started in a patient receiving peritoneal dialysis due to individual physician’s choice.

\(c\)Therapy initiated at a low dose and titrated up to a maintenance dose based on tumor response and AEs.

**AEs** adverse reactions, **ccRCC** clear cell renal cell carcinoma, **ESRD** end-stage renal disease, **Gr** grade, **i.v.** intravenous, **mo** months, **NA** not available, **OS** overall survival, **PD** progressive disease, **PFS** progression free survival, **p.o.** per os, **PR** partial response, **RCC** renal cell carcinoma, **SD** stable disease, **mTORi** mammalian target of rapamycin inhibitor.
AKI leading to treatment discontinuation occurred in 9.1% of patients in the study’s nivolumab plus sunitinib arm [83]. Glomerulonephritis was also reported in a series of three patients treated with immunotherapy and TKIs [84]. Combinations of ICPIs and TKIs are currently tested in various clinical trials; they offer promising results regarding improved clinical outcomes while maintaining tolerable side effect profiles resulting in wider use in the nearest future. Currently available data do not suggest that combination therapy is associated with previously unknown toxicities. Considering these data and renal AEs observed in mono-therapy, special caution and close monitoring of renal function might be necessary to prevent and early detect possible toxicities from combination therapy.

**Mechanisms of nephrotoxicity**

Acute tubulointerstitial nephritis (ATIN), either alone or other kidney lesions such as acute tubular injury or glomerular disease, is the most common histopathologic finding ICPI–AKI on kidney biopsy [85]. In the largest study of patients with ICPI–AKI up to date, ATIN was the dominant lesion in 93% of the 60 patients biopsied [86]. In a study by Mamlouk et al., ATIN was present in 14 of 16 cases; however, nine of these cases were associated with glomerular disease, including pauci-immune glomerulonephritis, IgA nephropathy, and other pathologies [87].

The precise mechanisms of ICPI–AKI are not yet known, with two hypotheses suggested by most researchers [80, 88–90]. Through the inhibition of specific receptors (e.g., CTLA-4, PD-1) or their ligands (PD-L1), ICPIs “release the brakes” of the immune system, allowing T-cells to become activated and exert antitumor activity [91]. Mice with knockout CTLA-4 or PD-1 genes have been shown to develop autoimmunity against specific organs, including glomerulonephritis, driven by the emergence of antigen-specific T-cells targeting self-antigens [92, 93]. Blockade of PD-1 or CTLA-4 with ICPIs in humans may lead to a loss of tolerance against endogenous kidney antigens and cause cytotoxic injury to the kidney. The exact antigen has not yet been identified but is possibly expressed by tubular cells based on ATIN’s dominant finding on biopsy. Alternatively, it is also possible that ICPIs lead to activation of memory T-cells previously primed by other haptens causing ATIN, such as proton pump inhibitors (PPIs) or nonsteroidal anti-inflammatory drugs (NSAIDs). In support of this theory, in a recent large multicentre study, nearly 70% of patients with ICPI–AKI received a potential ATIN-causing medication, including PPIs in over 50% of cases. Concomitant use of PPIs was also an independent risk factor for the development of ICPI–AKI [86].

**Management**

The European Society for Medical Oncology (ESMO) guidelines recommend that serum sodium, potassium, creatinine, and urea should be measured before every infusion of ICPIs. Baseline urinalysis, with quantification of proteinuria or microalbuminuria if present, before initiation of ICPI therapy is also advised [94]. Baseline assessment and monitoring of the number of leukocytes in urinalysis could also be helpful, since sterile pyuria and/or leukocyte casts may suggest an inflammatory kidney lesion, although they are not specific for ATIN diagnosis [95]. If renal dysfunction develops during treatment, alternative AKI etiologies, such as hypovolemia, infection, contrast-enhanced nephropathy, and urinary tract obstruction, should be initially ruled out. Immunotherapy should be temporarily discontinued until further clarification of the cause of AKI. The role of kidney biopsy in patients who developed AKI while undergoing ICPI treatment is debated. American Society of Clinical Oncology (ASCO) and ESMO guidelines recommend proceeding directly with immunosuppressive therapy without a kidney biopsy unless an alternative cause of AKI is suspected [96, 97].

Once the diagnosis of ICPI–AKI is made, the discontinuation of ICPI therapy and glucocorticoid administration is generally recommended. Table 5 summarizes the published guidelines for the management of ICPI-related nephritis [96, 97]. In a multicenter study of 138 patients, this approach was associated with partial or complete kidney function recovery in 95% of cases [86]. Considering the potential influence of concomitant medications in the pathogenesis of ICPI–AKI, drugs that are known to induce ATIN, such as PPIs or NSAIDs, should be recognized and discontinued if possible [98]. Most authors also suggest that patients developing initial ICPI–AKI episode can be safely rechallenged with ICPIs once kidney function improves and corticosteroid administration is complete or nearly complete. Observational data support this statement. Out of 31 patients rechallenged with an ICPI after the initial episode of ICPI–AKI only 7 (23%) experienced recurrent AKI, 6 of whom had complete or partial renal recovery [86].

**Patients with CKD or undergoing dialysis**

Underlying kidney disease may cause significant difficulties in the treatment of RCC patients with ICPIs. Most clinical trials do not include patients with moderate to severe kidney failure. Thus, ICPIs have not been widely studied in patients with renal failure or end-stage renal disease on dialysis. Because ICPIs undergo proteolytic degradation and not renal excretion, the lower glomerular filtration rate is not expected to impact their pharmacokinetics. In fact, in the case of nivolumab, the pharmacokinetics is linear in
the dose range of 0.1 to 10 mg/kg. There is no relationship
between renal function status and pharmacokinetics [99]. In
the IMvigor210 phase II trial of atezolizumab for cisplatin-
eligible urothelial carcinoma, 70% of patients had eGFR
between 30 and 60 ml/min, a comparable response rate and
no loss in median eGFR was reported [100].

Considering the large molecular weights of ICPIs, drug
filtration through the renal glomeruli or dialysis pores is
unlikely. There are currently few published data on the use
of ICPIs in patients with ESRD on hemodialysis (Table 6).
Apart from nivolumab, other ICPIs have not been studied in
this group of patients. Of the 20 described cases, in 80% of
patients the treatment resulted in partial response or stable
disease. Four grade 3 immune-related adverse events (irAEs)
were observed, and no grade 4 irAEs have been reported
up to date. Despite the small sample size, Tachibana et al.
revealed no significant differences between the ESRD and
non-ESRD groups in terms of PFS and OS [101]. The pre-
sented evidence suggests that renal impairment or ESRD
may not be a contraindication for ICPI use in RCC patients.

Conclusions

Renal toxicity of targeted anticancer therapies represents an
increasingly recognized problem for clinicians involved in
treating patients with mRCC. As these AEs can lead to dose
reductions or interruption of treatment, which might have
a negative effect on the patient’s survival, correct recogni-
tion and management of specific toxic effects are especially
important.

There are several reasons why the relationships between
targeted agents and the kidneys remain largely unexplored.
Large randomized, controlled, phase III trials do not enroll
patients with reduced kidney function; renal AEs are often
not reported; the methodology and terminology differ across
oncological trials (for example, definitions of creatinine
elevation, CKD, or AKI); and most reports of patients on
hemodialysis involve only single cases or small case series.
Furthermore, direct comparison of PFS and OS is often not
possible since reported data include the usage of drugs in
various lines of therapy, differing starting doses, and subse-
quent dose escalation or reduction schemes.

Careful design of clinical trials focusing on renal toxic
effects should shed more light on a group of patients for
whom targeted therapies are a viable first- and second-line
option. Further studies are needed to establish treatment
guidelines for patients with impaired renal function and/or
treated with chronic dialysis.

Because of the complex relationship between cancer,
kidneys, and novel therapeutic agents, close collaboration
between clinical oncologists, urologists, and nephrologists
is crucial. The emergence of effective targeted therapies
for mRCC significantly improved patients’ prognoses, at

| Grade a | Management |
|---------|------------|
| G1: creatinine > ULN–1.5 × ULN | Continue ICPI, discontinue nephrotoxic drugs, monitor renal function and proteinuria, exclude alternative causes (dehydration, recent i.v. contrast, UTI, medications, obstruction, hypotension, hypertension) |
| G2: creatinine > 1.5–3.0 × baseline; > 1.5–3.0 × ULN | Withhold ICPI, discontinue nephrotoxic drugs, ensure hydration, monitor renal function and proteinuria, consult nephrologist, consider biopsy, exclude alternative causes (as above), initiate steroids (0.5–1 mg/kg/day oral prednisolone or equivalent) |
| G3: creatinine > 3.0 × baseline; > 3.0–6.0 × ULN | Admit patient for monitoring and fluid balance, withhold ICPI, consider permanent discontinuation, discontinue nephrotoxic drugs, monitor renal function and proteinuria, consult nephrologist, consider biopsy, evaluate alternative causes (as above), initiate steroids (1–2 mg/kg/day i.v. prednisolone or equivalent) |
| G4: creatinine > 6.0 × ULN | As grade 3, treat in a center where renal replacement therapy is available |

ICPI immune checkpoint inhibitor, i.v. intravenous, ULN upper limit of normal, UTI urinary tract infection

a According to CTCAE v 5.0

The dose range of 0.1 to 10 mg/kg. There is no relationship
between renal function status and pharmacokinetics [99]. In
the IMvigor210 phase II trial of atezolizumab for cisplatin-
eligible urothelial carcinoma, 70% of patients had eGFR
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kidneys, and novel therapeutic agents, close collaboration
between clinical oncologists, urologists, and nephrologists
is crucial. The emergence of effective targeted therapies
for mRCC significantly improved patients’ prognoses, at
Table 6  Summary of published cases of the use of immunotherapy in RCC patients with ESRD

| Reference | Number of patients | Cancer type | ICPI | Dose | Dose reduction required | Response | PFS | OS | Duration of treatment | irAEs (Grade ≥ 3) |
|-----------|-------------------|-------------|------|------|-------------------------|----------|-----|----|-----------------------|------------------|
| Carlo et al. [144] | 1 | ccRCC | Nivolumab | NA | No | PR | > 8 mo | NA | > 8 mo | None |
| Tabei et al. [145] | 1 | ccRCC | Nivolumab | 3 mg/kg every 2 wk | No | PR | > 6 mo | NA | > 6 mo | None |
| Ansari et al. [146] | 1 | ccRCC | Nivolumab | 3 mg/kg every 2 wk ➔ 240 mg every 2 wk | No | PR | > 22 mo | NA | > 22 mo | None |
| Cheun et al. [147] | 2 | RCC (1), ccRCC (1) | Nivolumab | 100 mg every 3 wk, 3 mg/kg every 3 wk | No | PR (1), SD (1) | 6.8 mo (1), > 9 mo (1) | 15 mo (1), > 9 mo (1) | NA | None |
| Tachibana et al. [101] | 7 | RCC (2), ccRCC (5) | Nivolumab | 3 mg/kg every 2 wk | No | PR (1), SD (4), PD (1), NA (1) | 5.9 mo (median), 11.9 mo (median) | 6 mo (median) | Gr 3: fatigue (1) |
| Vitale et al. [148] | 8 | ccRCC | Nivolumab | 3 mg/kg every 2 wk ➔ 240 mg every 2 wk or 480 mg every 4 wk | No | PR (1), SD (5), PD (2) | 16 mo (median), 26 mo (median) | 9 mo (median) | Gr 3: diarrhea (1), asthenia (1), anorexia (1) |

ccRCC clear cell renal cell carcinoma, Gr grade, ESRD end-stage renal disease, ICPI immune checkpoint inhibitor, irAEs immune-related adverse reactions, mo months, NA not available, OS overall survival, PD progressive disease, PFS progression free survival, PR partial response, RCC renal cell carcinoma, SD stable disease, wk weeks
the cost of a whole new spectrum of renal adverse events that differ from those observed with conventional cytotoxic chemotherapy. Therefore, nephrologists should become acquainted with various aspects of cancer care, including the biology of RCC and molecular mechanisms of action of novel anticancer drugs. Onconephrology is an evolving and expanding subspecialty that relies on a multidisciplinary approach necessary to provide cutting-edge care for RCC patients with kidney impairment [102, 103].

This analysis highlights that patients with mRCC, including those on hemodialysis, generally benefit from targeted treatment in PFS and OS. Renal toxicities of targeted therapies differ in incidence but are generally mild to moderate in severity and can be managed effectively. The occurrence of AEs should not necessarily result in treatment discontinuation, and even if that decision is made, treatment can be resumed in specific situations. That said, therapy selection, administration, and toxicity management in mRCC patients undergoing dialysis should be performed with caution and increased monitoring of AEs. Close cooperation between oncologists and nephrologists in managing renal toxic effects should be encouraged to improve patients’ outcome.

**Funding** This work was supported by subsidy from Ministry of Science and Higher Education of participating institutions.

**Declarations**

**Conflict of interest** AB has received a travel grant from Novartis and honoraria from Janssen. PS has received travel grants from MSD, Roche, and Pierre Fabre. AMC has received travel grants and honoraria from Janssen. PS has received travel grants from MSD, Roche, and Novartis. ŁM and ACJ declare no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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