International Urology and Nephrology (2019) 51:2015–2025
https://doi.org/10.1007/s11255-019-02292-1

NEPHROLOGY - ORIGINAL PAPER

Use of mammalian target of rapamycin inhibitors in patient with autosomal dominant polycystic kidney disease: an updated meta-analysis

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Received: 3 May 2019 / Accepted: 17 September 2019 / Published online: 1 October 2019

Abstract

Purpose Mammalian target of rapamycin (mTOR) inhibitors were previously considered a potential therapy for autosomal dominant polycystic kidney disease (ADPKD), but prior studies remained controversial about their efficacy. We performed an updated meta-analysis regarding the therapeutic and adverse effects of mTOR inhibitors in patients with ADPKD.

Methods We systematically searched Cochrane Library, PubMed, EMBASE, and Medline for randomized controlled trials (RCTs) comparing mTOR inhibitors to placebo in ADPKD patients up to August 2019. We calculated weighted mean differences (WMDs) for total kidney volume (TKV), estimated glomerular filtration rates (eGFRs), and weighted odds ratios (ORs) for treatment-related complications between the treatment and the placebo groups, using the random effects model.

Results We retrieved a total of 9 RCTs enrolling 784 ADPKD patients receiving rapamycin, sirolimus, or everolimus between 2009 and 2016. The WMDs of TKV and eGFR from baseline to the last measurement were − 31.54 mL (95% confidence interval [CI] − 76.79 to 13.71 mL) and 2.81 mL/min/1.73 m^2 (95% CI − 1.85 to 7.46 mL/min/1.73 m^2), respectively. Patients receiving mTOR inhibitors had a significantly increased risk of any adverse effects (OR 5.92, 95% CI 3.53–9.94), with the most common ones being aphthous stomatitis (OR 15.45, 95% CI 9.68–24.66) and peripheral edema (OR 3.49, 95% CI 1.31–9.27) compared to placebo users.

Conclusions mTOR inhibitors did not significantly influence renal progression in patients with ADPKD, but were associated with a higher risk of complications. Whether mTOR inhibitors can be an add-on option or second-line agents remain undetermined.

Keywords Autosomal dominant polycystic kidney disease · End-stage renal disease · Estimated glomerular filtration rate · Mammalian target of rapamycin · Total kidney volume

Chun-Hung Lin and Mei-Yi Wu contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11255-019-02292-1) contains supplementary material, which is available to authorized users.

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited kidney disease with an incidence rate up to 1 in every 400–1000 live births [1]. Mutations involving PKD1 and PKD2 genes are thought to be important etiologies of ADPKD [2], resulting in the alteration of intracellular polycystin levels and leading to cyst formation. The massive accumulation of renal cysts subsequently causes physical compression of the adjacent nephrons, the functional units within the kidneys, compromises renal function, and increases the risk of end-stage renal disease (ESRD). Although phenotypes vary in ADPKD patients depending upon mutation types, cyst features, and environmental factors, patients' renal function usually remain stable during the first three decades, followed by a progressive renal functional decline and reaching ESRD during their fifth to sixth decade of life [3]. The proportion of ADPKD patients receiving transplantation also increased successively over time; a prior registry study showed that the percentages of transplantation recipients among all ADPKD patients reaching ESRD rose from 43 to 59% between 1990s and 2010 [4]. Furthermore, more than 50% of ADPKD patients who receive renal transplantation undergo native kidney nephrectomy [5]. Apart from having adverse renal survival, ADPKD patients frequently develop other renal complications such as urinary tract infection, urine concentration defects, cyst bleeding with hematuria, and nephrolithiasis with acute or chronic flank pain, accompanied by extrarenal manifestations, including hypertension, intracranial aneurysms, infertility, and diverticular diseases [6].

The complete pathophysiologic landscape of ADPKD remains incompletely understood, and multiple studies have attempted to address this knowledge gap. Loss of heterozygosity in PKD genes has been found to contribute to changes in vital intracellular signaling pathways involved in cyst growth or transformation, leading to renal function deterioration; the most renowned examples are the mammalian target of rapamycin (mTOR) and cyclic adenosine monophosphate (cAMP)-driven pathway, both of which presumably play an important role in the pathogenesis of ADPKD. mTOR is a protein kinase complex that promotes anabolism in renal cells and is capable of phosphorylating tuberous sclerosis complex 2 (TSC2). TSC2 subsequently functions as a GTPase-activating protein and increases cAMP levels, thereby augmenting fluid and ion secretion to renal cysts [7]. Animal models suggest that mTOR inhibition slows the progression of ADPKD; however, clinical experiences of using mTOR inhibitors in patients with ADPKD have been admixed, with some yielding favorable results while insignificant changes in others [8, 9].

Clinical trials examining the therapeutic efficacy of pharmacological interventions in patients with ADPKD frequently use total kidney volume (TKV) as a surrogate end point, in addition to measuring the relatively slow speed of renal function decline [10]. Reducing the elevation of TKV and retarding the trajectories of rising serum creatinine and decreasing creatinine clearance or estimated glomerular filtration rate (eGFR) have been the mainstay of treatment in most studies. Prior meta-analyses focusing on mTOR inhibitors in patients with ADPKD suggested that mTOR inhibitors failed to reduce the elevation of TKV [11, 12]. However, several new trials investigating the efficacy of mTOR inhibitors in patients with ADPKD have been available since the publication of these meta-analyses [13–15]. Therefore, we aim to perform an updated meta-analysis to re-evaluate the efficacy, using different end points, and the safety of mTOR inhibitors in ADPKD patients.

Method

Eligibility criteria

Randomized controlled trials (RCTs) reporting the efficacy and safety of mTOR inhibitors in patients with ADPKD were comprehensively retrieved and included in our analysis. RCTs that reported renal function parameter or its surrogates, including TKV and eGFR as the end points, were included. We excluded pilot studies, and those that were retrospectively designed, observational in nature, or intervention studies which were non-controlled or non-randomized.

Search strategy

We systematically searched Cochrane Library, PubMed, EMBASE, and Medline up to August 2019 for eligible studies (C.H. Lin and T.C. Lin), using wide search terms. Search keywords were devised in an effort to answer the proposed questions as follows: TORC1 inhibitors, everolimus, Afinitor, rapamycin, sirolimus, Zortress, Evertor, Rapamune, Siropan, polycystic kidney disease, ADPKD, and autosomal dominant polycystic kidney disease. No limit was applied during the search process. There was no restriction on the date of publication, countries, or languages. Citations that included search terms in the title, abstract, article content, or medical subject heading (MeSH) terms were retained. In addition, we also cross checked the reference lists of the identified RCTs. We attempted to identify other studies by hand searching the reference sections of these papers and by contacting known experts in the field. Finally, unpublished trials were retrieved from the ClinicalTrials.gov registry (http://clinicaltrials.gov/). A detailed search strategy in

different databases has been presented in the supplementary material.

Study selection

We included randomized controlled trials (RCTs) with clear inclusion and exclusion criteria. From each publication, we identified and included patients with ADPKD, but without ESRD or co-existing diseases. Two reviewers (C.H. Lin and T.C. Lin) independently screened the titles and abstracts of retrieved studies for eligibility. Studies were excluded if they did not meet our inclusion criteria or having the following conditions: participants receiving other interventions or treatments concurrently; medical conference abstract or expert opinions; or the same trials published in different journals. Potentially relevant studies were then extracted from these reports. Disagreements were resolved by the third reviewer (M.Y. Wu). Results were based on TKV vs. controlled groups with placebo after randomization.

Data extraction and quality assessment

Two reviewers (C.H. Lin and M.Y. Wu) independently extracted information from the included RCTs using a standardized electronic form. Differences between the reviewers were discussed until agreement was achieved, and the senior author (M.Y. Wu) was consulted in the event of persistent disagreement. Data from intention-to-treat populations were used whenever possible. The authors of the studies were contacted for additional information when necessary.

Study quality was assessed by ROBINS risk of bias scale developed by the Cochrane group. The risk of bias in the included trials was assessed according to individual domains, reporting the following aspects: allocation generation, allocation concealment, blinding, length of follow-up, percentage of loss to follow-up, and the use of intention-to-treat (ITT) analysis.

Outcomes

The primary outcome was the effect of mTOR inhibitors on renal function parameters including TKV and eGFR. The safety outcomes were drug-related complications including aphthous stomatitis, peripheral edema, dermatitis, and diarrhea.

Data synthesis and analysis

We used the random effect meta-analysis (Rev. Manager 5) weighted by the Mantel–Haenszel method to estimate pooled risk ratios and 95% confidence intervals. χ^2 statistics tests (Q statistics) and I^2 test were used to assess heterogeneity. All data were combined with the Mantel–Haenszel random effects model. This model usually yields wider CIs and provides more conservative statistical results. The significance and confidence intervals were further tested by using the Hartung–Knapp–Sidik–Jonkman (HKSJ) method, which has been shown to yield more adequate error rates than the DerSimonian and Laird approach (DL) method, when the number of studies is small (less than 10 studies). Statistical significance of the outcome measures was set at a p value < 0.05.

Result

Study extraction algorithm and studies characteristics

We searched through the PubMed, Cochrane, Embase, and Medline databases and 494 studies were identified initially. After applying the exclusion criteria, 485 studies were subsequently excluded. Thus, nine RCTs with a total of 784 patients were included for analysis [13–21]. The details of study extraction and selection are shown in Fig. 1. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist is also attached (see supplementary material).

The included RCTs were published between 2009 and 2016, and the sample sizes of these trials ranged between 15 and 433. The mTOR inhibitors utilized in these trials included sirolimus, everolimus, and rapamycin. The therapeutic efficacy of mTOR inhibitors was compared with placebo in six trials [13, 15–17, 20, 21], anti-hypertensive drugs [angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs)] in two trials [18, 19], and octreotide in one trial [14]. The duration of treatment and the time points of outcome measurement ranged between 6 and 24 months, and the baseline TKV of enrolled ADPKD patients ranged between 907 and 3123.4 mL. Clinical features of the enrolled patients from each of the nine trials included in this meta-analysis are shown in Table 1.

Study quality

The methodological quality of the nine included studies is displayed in Table 2. All the included studies clearly documented the use of random allocation; however, only two described allocation concealment [14, 15]. Among the nine trials, one was double blinded [20], five were assessor blinded [15–18, 21], and the other three were open label [13, 14, 19]. The percentages of enrollees with loss to follow-up ranged between 0 and 25%. Eight trials utilized the intention-to-treat analysis, while one [13] used per-protocol analysis. Factors that might otherwise influence our results were listed separately (Table 2). Funnel plots for trials assessing

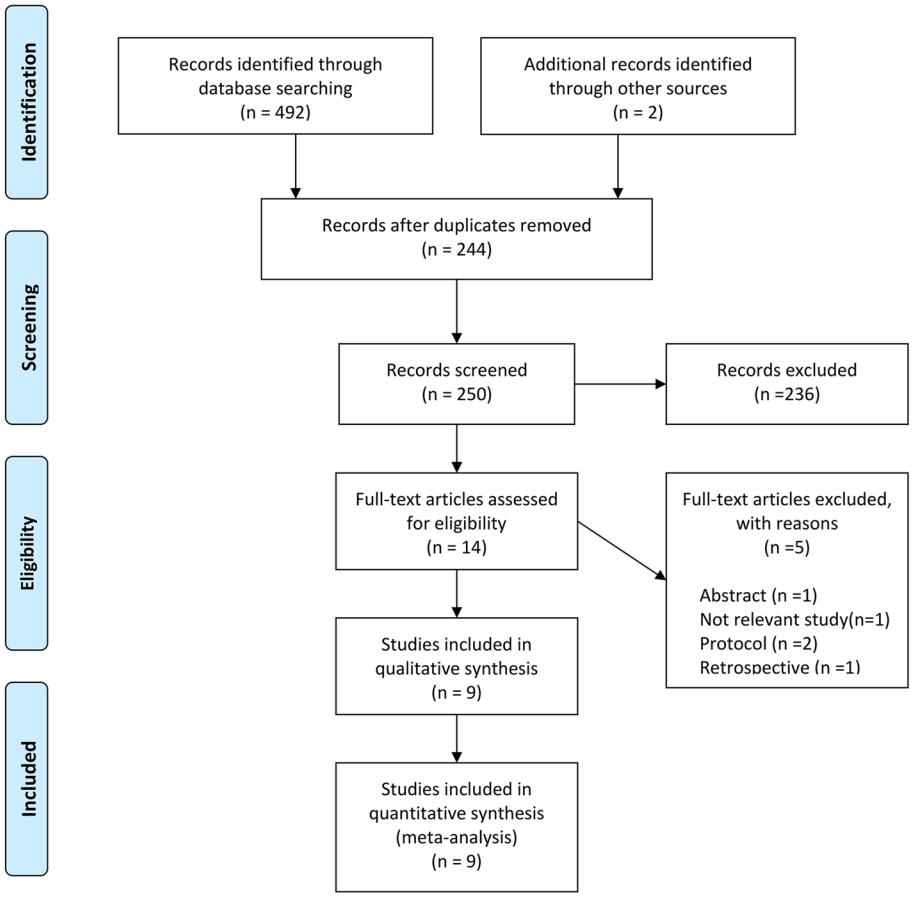

Fig. 1 The algorithm of study selection and retrieval from the existing databases

the outcomes of renal function and treatment-related complications are shown in Fig. 2.

Renal function assessment

TKV and eGFR were selected as indicators for renal function in our meta-analysis. The mean differences of TKV from their baseline to the last measurement was − 31.54 mL (95% confidence interval [CI] − 76.79 to 13.71 mL; $p = 0.17$ without significant difference observed) (Fig. 3a). In terms of changes in eGFR levels, five trials [13, 15–17, 20] were included, with a mean difference from the participants' baseline to their last measurement of 2.81 mL/min/1.73 m^2 (95% CI − 1.85 to 7.46 mL/min/1.73 m^2) (Fig. 3b).

Adverse effect profiles

Multiple types of adverse effects during the treatment with mTOR inhibitors were observed among the nine included trials. Aphthous stomatitis was the common adverse effects in those receiving mTOR inhibitors, with a summary odds ratio (OR) of 15.45 (95% CI 9.68–24.66) when using a random effects model (heterogeneity $I^2 = 0\%$, $p < 0.00001$) (Fig. 4). A significantly higher incidence of peripheral edema was also observed in those receiving mTOR inhibitors compared to the placebo group (summary OR 3.49, $p = 0.01$). Patients with ADPKD receiving mTOR inhibitors were more likely to develop gastrointestinal (diarrhea with a summary OR 3.27, $p = 0.0006$) and cutaneous side effects (for dermatitis, summary OR 3.04, $p = 0.006$) than those receiving placebos. Overall, mTOR inhibitor receivers had a significantly increased risk of any adverse effects during follow-up (OR 5.92, $p < 0.00001$) (Fig. 4).

Discussion

In the current meta-analysis, we showed that the use of mTOR inhibitors might exhibit a trend toward improving several renal function parameters among patients with ADPKD, although the differences did not reach statistical significance. In addition, adverse effects occurred more frequently among mTOR inhibitor users than those receiving placebo, especially cutaneous and gastrointestinal ones, with a nearly sixfold increase of risk for developing any complication. The use of mTOR inhibitors in patients with ADPKD thus should be very careful, since the efficacy was insignificant but the risk of side effects was obvious.

Table 1 Clinical features of the nine included trials

Study ID, year, trial design, and country	Number of patients	Mean age (years)	Intervention	Comparison	Baseline total kidney volumes	Baseline renal function	On antihypertensives (%)	Timing of outcome measure
Ruggenenti 2016, RCT Italy	N:41 I:21 C:20	I:49 C:47.6	Sirolimus (3 mg/day; serum target levels of 5–10 ng/mL)	Convention treatment	TKV (mL) (I) = 2857.7 ± 1447.3 (C) = 3123.4 ± 1695.3	CKD stage 3b or 4, and proteinuria < 0.5 g/24 h	95	CT 12 months
Braun 2014, RCT US	N:30 I1:10 I2:10 C:10	I1:44.9 I2:53.2 C:49.4	I1: low-dose (LD) rapamycin (blood level: 2–5 ng/mL) I2: standard-dose (STD) rapamycin (blood level: 5–8 ng/mL)	Placebo	TKV (mL) (I1) = 2479.3 ± 1965.7 (I2) = 1718.5 ± 932.7 (C) = 2072.7 ± 1184.4	eGFR (mL/min per 1.73 m^2) (I1) = 70.4 ± 33 (I2) = 65.1 ± 33.5 (C) = 69.9 ± 18.8	36.6	CT 6 and 12 months
Chrispijn 2013, RCT Netherlands	N:44 I:21 C:23	I:52.3 C:50.7	Everolimus 2.5 mg/day + octreotide 40 mg	Octreotide 40 mg	TKV (mL) (I) = 854 (543-1218) (C) = 798 (675-1960)	MDRD-GFR > 60 mL/min/1.73 m^2	Not stated	CT 12 months
Stallone 2012, RCT (three arm) Multicentre, Italy	N:55 I1:19 I2:18 C:18	I1:42.8 I2:42.3 C:45.3	I1= ramipril + high-dose sirolimus (trough levels: 6–8 ng/mL) I2 = ramipril + low-dose sirolimus (trough levels: 2–4 ng/mL)	C = ramipril alone	TKV (mL) (I1) = 1493 ± 672 (I2) = 1712 ± 634 (C) = 1869 ± 668	Serum creatinine < 0.2 mg/dL	100	MRI 24 months
Perico 2010, Crossover RCT Italy	N:15	N:39.1	Sirolimus 3.6 ± 0.7 mg/day (initial trough levels 10–15 ng/mL, reduced to 5–10 ng/mL due to poor tolerability)	Placebo	TKV (mL) (I) = 1960 ± 1095 (C) = 1977 ± 1133	Iohexol GFR (mL/min per 1.73 m^2) = 75.8 ± 23.4	67	CT 6 months
Serra 2010, RCT Switzerland	N:100 I:50 C:50	I:31 C:32	Sirolimus 2 mg/day (mean levels 4.1–4.9 ng/mL)	Conventional therapy	TKV (mL) (I) = 907 (577–1330) (C) = 1003 (574-1422)	Iohexol GFR (mL/min per 1.73 m^2) = 92 ± 20	50	MRI 18 months
Serra 2009, RCT Switzerland	N:50 I:25 C:25	I:29 C:29	Sirolimus 2 mg/day	Standard care	Not stated	Estimated creatinine clearance > 70 mL/min.	70	MRI 6 months
Walz 2010, RCT Germany, Austria and France	N:433 I:215 C:218	I:44.5 C:44.4	Everolimus 2.5 mg bid (trough levels: 3–8 ng/mL)	Placebo	TKV (mL) (I) = 2028 ± 1173 (C) = 1911 ± 1153	MDRD eGFR (mL/min per 1.73 m^2) = 75.8 ± 23.4	88	MRI 24 months

Table 1 (continued)

Study ID, year, trial design, and country	Number of patients	Mean age (years)	Intervention	Comparison	Baseline total kidney volumes	Baseline renal function	On antihypertensives (%)	Timing of outcome measure
Soliman 2009, RCT Egypt	N:16 I:8 C:8	I:40.4 C:41.1	Sirolimus 1 mg/day (mean levels 4.6; 3.3–7.5 ng/mL) telmisartan	Telmisartan	TKV (mL) (I) = 2845 ± 443 (C) = 2667 ± 399	MDRD GFR (mL/min per 1.73 m^2) = 32.5 ± 11.7	100	MRI 6 months

C comparison, *CKD* chronic kidney disease, *CT* computed tomography, *eGFR* estimated glomerular filtration rate, *I* intervention, *MRI* magnetic resonance imaging, *MDRD* modification of diet in renal disease, *N* number, *RCT* randomized control trial, *TKV* total kidney volume

Two mTOR inhibitors have been studied for their efficacy in ADPKD management in the retrieved literature, including sirolimus and everolimus. Sirolimus was first approved for preventing renal graft rejection in 1999; it exhibits a high rate of protein binding (92%) and a long half-life up to 63 h [22]. On the other hand, everolimus was approved one decade later for preventing kidney, heart, and liver graft rejection; everolimus has a relatively lower protein binding rate (74%) and a shorter half-life (30 h), but a substantially high oral bioavailability than sirolimus [22]. Despite these pharmacokinetic differences, sirolimus and everolimus share common features including protein interactions (CYP3A4 and P-glycoprotein) and > 90% bile excretion. Among the eight trials we included, there was no difference between the effect of sirolimus and that of everolimus among ADPKD patients; this suggests that pharmacokinetic issues do not play a role in modifying the therapeutic effects of mTOR inhibitors.

Prior meta-analyses have addressed similar issue 5 years ago. Xue et al. first performed an aggregate analysis of the influence of mTOR inhibitors on renal progression among patients with ADPKD [12]. They included five trials with 619 participants and found that TKV ($p = 0.23$) and parenchymal volume ($p = 0.99$) did not decrease after mTOR inhibitor treatment. However, they identified that cyst volumes decreased prominently after mTOR inhibitor use [weighted mean differences (WMD) − 15 mL, $p < 0.00001$], while eGFR had a trend toward improvement (WMD 4.94 mL/min/1.73 m^2, $p = 0.09$) [12]. Myint et al. conducted another meta-analysis 1 year later, included the same five trials, and examined their influences on renal function surrogates [11]. They similarly concluded mTOR inhibitor use was not associated with a significant decrease in TKV. A Cochrane Database review evaluating the efficacy of different medications against the progression of ADPKD concluded that the renal effects of mTOR inhibitors were uncertain [23], but this review only considered two trials. It should be noted that there are several limitations concerning Myint et al.'s analysis [11]. First of all, part of the data extracted from the included studies differed between their report and ours. For example, in one of their figures, the results of TKV changes from baseline to the end of treatment for Soliman et al.'s [18] and Stallone et al.'s [19] reports were not compatible with data we retrieved from the original ones. Similar discrepancies have been noted for eGFR despite our repetitive checking of the source studies. Second, we additionally included two recently published studies [13, 15], which were not considered in Xue et al.'s and Myint et al.'s analyses. We disclosed that the mean differences in TKV and eGFR were more conservative after further including the two reports (for mean changes in TKV, Xue vs. Myint vs. ours, − 90.01 vs. − 43.27 vs. − 31.54 mL; for mean changes in

Table 2 The potential sources of bias in the nine included trials

Studies	Allocation generation	Allocation concealment	Blinding	Loss of follow-up (%)	Data analysis	Other sources of bias
Ruggenenti (2016)	Computer-generated randomization	Telephone call	Assessors blind	19	ITT	
Braun (2014)	Randomly assigned	Unclear	Open-label	13.3	PP	Three groups: low-dose rapamycin, standard-dose rapamycin, standard care
Chrispijn (2013)	Computer-generated randomization	Permuted block design with a random block	Open-label	25	ITT	Every group had octreotide
Stallone (2012)	Random number tables	Unclear	Open label	3.6	ITT	Three groups: ramipril + high-dose sirolimus, ramipril + low-dose sirolimus, ramipril
Perico (2010)	Randomly assigned	Unclear	Assessors blind	0	ITT	Crossover study
Serra (2010)	Randomly assigned	Unclear	Assessors blind	4	ITT	
Serra (2009)	Randomization list	Permuted block design with a random block	Assessors blind	0	ITT	
Walz (2010)	Randomly assigned	Unclear	Double blind	23.7	ITT	Unblended interim analysis, multiple center data collection
Soliman (2009)	Randomly assigned	Unclear	Assessors blind	0	ITT	Every group had telmisartan

ITT intention-to-treat, *PP* per-protocol

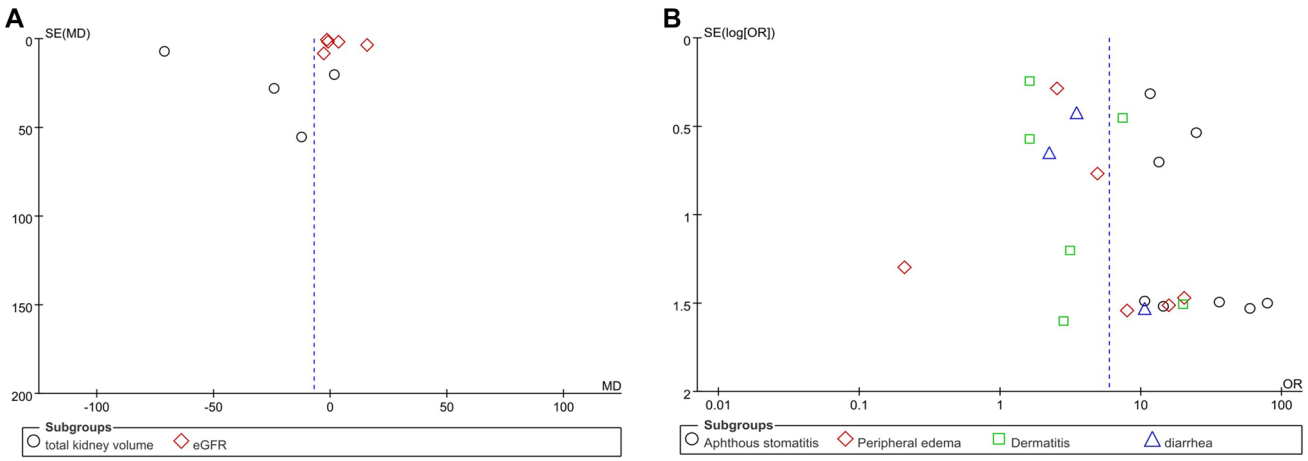

Fig. 2 The funnel plots of included trials in this meta-analysis regarding renal function assessment (**a**) and adverse events (**b**). *eGFR* estimated glomerular filtration rate, *MD* mean differences, *OR* odds ratio

eGFR, Xue vs. Myint vs. ours, 4.94 vs. − 1.00 vs. 2.81 mL/min/1.73 m^2). In light of these findings, we believe that at the present time, mTOR inhibitors cannot be considered a first-line choice for retarding renal progression among patients with ADPKD, although the approach using mTOR inhibitors as a second-line treatment or an add-on regimen remains a potential option. Indeed, pilot studies have shown that mTOR pathway inhibitions may have a synergistic effect with cAMP suppression [24], although animal studies are still awaited. Studies with ESRD as the ultimate end point are also needed for confirmation.

Tubular cell proliferation and apoptosis are typical renal features in patients with ADPKD and can propagate the enlargement of renal cysts, leading to ESRD [7, 25, 26]. The pathophysiological mechanisms of ADPKD have been uncovered gradually [25, 27–29]; Torres et al. suggested that mTOR signaling, as a vital pathway underlining tubular cell proliferation, played an important role in the progression

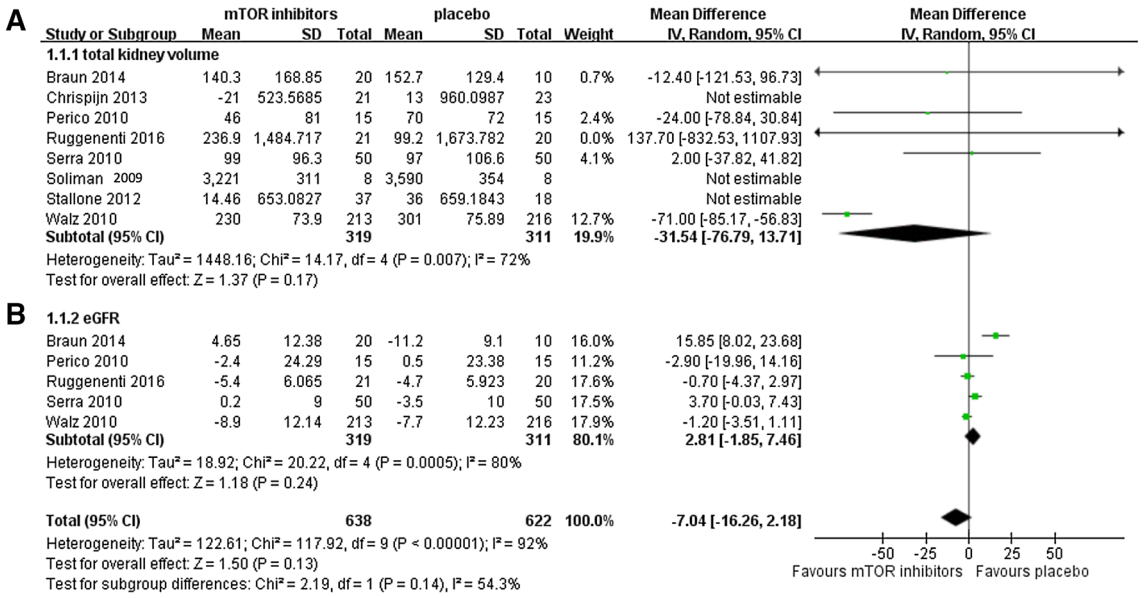

Fig. 3 The summary and the forest plots of the retrieved studies with regard to renal outcomes including total kidney volume (TKV) (**a**) and estimated glomerular filtration rate (eGFR) (**b**). *CI* confidence interval, *mTOR* mammalian target of rapamycin, *SD* standard deviation

of ADPKD [30]. mTOR inhibitors reportedly attenuate nephroangiosclerosis by down-regulating PI3K/Akt signaling, the activation of which suppresses platelet-derived growth factor receptor (PDGFR) expression [30, 31]. In animal studies, using high-dose rapamycin (50 mg/kg/day) could significantly lower renal cystic volume and increase the life span of mice with the ADPKD phenotype [32]. However, available clinical trials including those analyzed in our study used low to moderate doses of mTOR inhibitors in ADPKD patients (Table 1). Consequently, participants in these trials might not have adequate tissue concentrations of mTOR inhibitors for modifying the course of ADPKD. On the contrary, it is still of concern that mTOR inhibitors in high doses may cause a higher incidence of complication, precluding its applicability clinically. Finally, it is plausible that mTOR inhibitors may exhibit therapeutic efficacy against extrarenal manifestations of ADPKD patients. A retrospective small-scale study of ADPKD patients receiving renal transplantation with polycystic liver showed that those on a sirolimus-based immunosuppressive regimen exhibited a trend toward greater reduction of liver cyst volumes than those on tacrolimus-based regimen [33]. However, this phenomenon has not been tested in the trials included in this meta-analysis.

This meta-analysis has its strengths and limitations. The strengths lie in our comprehensive approach in study extraction from the literature and the thorough search strategy as we outlined above. The quality of all included studies has been carefully examined during study appraisal. However, several limitations need to be considered carefully before interpreting our results. First, the possibility of publication bias might still be present, as neutral findings were frequent among mTOR inhibitor studies in patients with ADPKD. Second, the sample sizes of most of the included studies were modest; from the nine studies we included, the patient numbers ranged between 15 and 433 per arm (Table 1). There were still multiple sources of biases inherent to the nine studies included (Table 2). This meta-analysis has not been registered in online registries beforehand. In addition, significant heterogeneity exists regarding the retrieved trials, including but not limited to patient numbers, the doses and durations of sirolimus/everolimus, participants' baseline renal function, TKV, the adjunct treatments (renin–angiotensin–aldosterone system blockers) assigned to treatment/control groups, and how the outcomes were defined in each trial (Table 1). Whether the results will alter according to anti-hypertensive medications use or not remains unclear. Furthermore, the severity of side effects examined in each trial was not described, rendering further sub-analysis difficult. Finally, we could not obtain more study detail data due to no response after contacting the source study authors, and therefore we had to calculate part of the results.

Conclusion

We systematically searched through the existing literature and retrieved nine studies with 784 patients with ADPKD receiving mTOR inhibitors or placebo. More than half of the included studies had multiple sources of bias. After

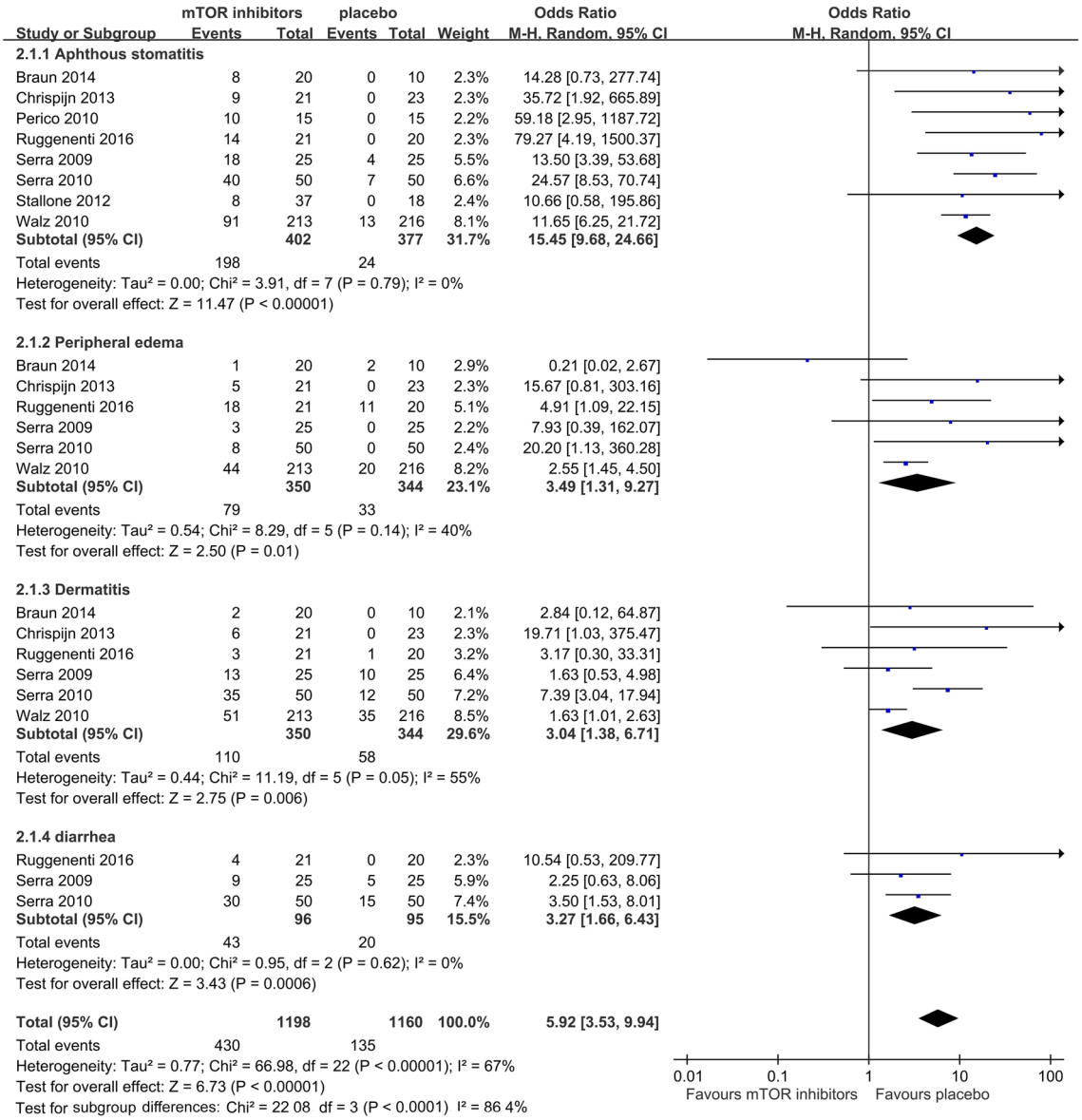

Fig. 4 The summary and the forest plots of the retrieved studies with regard to complications related to mTOR inhibitor treatment. *CI* confidence interval, *mTOR* mammalian target of rapamycin

meta-analysis, we found that renal function surrogates in patients with ADPKD, including TKV and eGFR, did not improve significantly after mTOR inhibitors treatment, while there was a significantly increased risk of developing any complication after treatment. mTOR inhibitors may therefore be of less utility in patients with ADPKD as a first-line therapeutic option.

Author contributions Study design: CHL, MYW, WCL; data analysis: CHL, WCL, TCL; article drafting: CHL, MYW, WCL, TCL, CTC; all authors approved the final version of the manuscript.

Funding The study was financially sponsored by Taipei Medical University Shuang-Ho Hospital. The sponsors have no role in the study design, data collection, analysis, and result interpretation of this study.

Data availability The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors have no relevant financial or non-financial competing interests to declare in relation to this manuscript.

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