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Tolvaptan vs. somatostatin in the treatment of ADPKD: A review of the literature

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Key words
autosomal dominant polycystic kidney disease – polycystic liver disease – tolvaptan – somatostatin analogues

Abstract. Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic disorder with an estimated prevalence between 1 : 1,000 and 1 : 2,500. Until a few decades ago, ADPKD was considered an untreatable disease, relentlessly progressing towards end-stage renal disease because of the lack of specific interventions. In the last decade, some aberrant molecular pathways involved in ADPKD development have been identified, and controlled clinical trials have been conducted to investigate the potential role of active drugs on these pathophysiological mechanisms such somatostatin and tolvaptan. Somatostatin analogues have been shown to be effective not only in ADPKD, but also in polycystic liver disease (PLD) with beneficial effect on cardiac function and a better cost/benefit profile; the only somatostatin analogue currently available for clinical use is octreotide long-acting release (octreotide-LAR), and it is approved only in Italy. On the contrary, tolvaptan is authorized worldwide and has received more attention in the last years, even if its clinical use is widely limited by aquaresis tolerability. The aim of this review is to investigate the advantages and drawbacks of somatostatin analogues and tolvaptan in the treatment of ADPKD.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic disorder with an estimated prevalence between 1 : 1,000 and 1 : 2,500 [1, 2]. It is characterized by the development of multiple renal cysts that lead to renal function loss, generally requiring dialysis in the sixth decade of life; extra-renal manifestations are liver, pancreas and seminal vesicles cysts, intracranial aneurisms, cardiac and vascular anomalies [3]. The condition is genetically heterogeneous and is caused by the mutation of two polycystin genes, PKD1 and PKD2, and much more rarely, by other recently identified genes as GANAB [4] and DNAJB11 [5]. Until a few decades ago, ADPKD was considered an untreatable disease, relentlessly progressing towards end-stage renal disease (ESRD) because of the lack of specific interventions. Analysis of data from the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry indicates that conventional treatments for chronic kidney disease (CKD) do not reduce the need for renal replacement therapy in ADPKD [6]. In the last decade some aberrant molecular pathways involved in ADPKD development have been identified and controlled clinical trials have been conducted to investigate the potential role of active drugs on these pathophysiological mechanisms such as mTOR inhibitors [7], somatostatin [8], metformin

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[9, 10, 11] and tolvaptan [12]. Tolvaptan received a market authorization valid throughout the European Union on May 27, 2015; it was specifically approved by the European Medicines Agency (EMA) to slow cysts and renal insufficiency progression in ADPKD patients aged 18 – 50 with stage 1 – 3 CKD and a rapid progression of the disease; its use was then extended in August 2018 to patients aged 18 – 55 and stage 4 CKD. In 2018 octreotide long-acting release (octreotide-LAR) was approved only in Italy by Italian Medicines Agency for the treatment of ADPKD adults with glomerular filtration rate (GFR) ranging from 30 to 15 mL/min/1.73m^2 at high risk of progression towards ESRD. Nowadays, nephrologists may choose between the treatment with tolvaptan and/or octreotide for ADPKD. The aim of this review is to investigate the most recent evidences on the currently available treatment of ADPKD and the patient-centred evaluation of advantages and drawbacks in the choice of the more adequate therapy.

Tolvaptan

Tolvaptan is a vasopressin V2 receptor antagonist whose action is limited to renal tubular cells in the distal nephron and collecting duct, where V2 receptors are expressed, less and less with advanced age. ADPKD is characterized by the high activity of the adenylyl cyclase (AC) in renal tubular cells, and consequently by high intracellular cyclic adenosine monophosphate (cAMP) levels that leads to an uncontrolled cell proliferation and chloride-driven fluid excretion in the kidney [13].

In 2012 Torres et al. [12] published the results of TEMPO 3:4 trial, conducted on 1,445 ADPKD patients, investigating tolvaptan versus placebo during a 36 months follow-up period. The patients enrolled aged 18 – 50 years and presented rapidly progressive ADPKD (total kidney volume (TKV) ≥ 750 mL) by magnetic resonance imaging, and an estimated creatinine clearance (Clcr) ≥ 60 mL/min. The initial dosage of tolvaptan was 45 mg in the morning and 15 mg in the afternoon, with weekly increases to 60 and 30 mg and then 90 and 30 mg, as tolerated. Over 3 years, tolvaptan significantly slowed the increase in TKV compared with placebo (2.80 vs. 5.51% per year, p < 0.001); of note, the treatment effect was more pronounced during the first year of treatment than during the second or third year.

In a post hoc analysis tolvaptan slowed the increase of TKV in stage 1 – 3 CKD. It significantly reduced the renal function decline in the tolvaptan group compared to placebo (estimated GFR (eGFR) decline –2.72 vs. –3.70 mL/min/1.73m^2, respectively); interestingly, the treatment was more effective in patients with higher albuminuria [14]. Tolvaptan group showed a lower incidence of kidney pain events compared to placebo, probably due to the reduced incidence of renal complications as urinary infections, kidney stones, and hematuria (1.1 vs. 16.8%, –36%; p < 0.001) [15]. Noteworthy, 10% of patients in tolvaptan group discontinued the treatment because of aquaretic symptoms (36% polyuria, pollakiuria 21%, nocturia 13%, thirst 8%, polydipsia 3%). Of these, 31% took the dosage 45/15 mg, 22% the dosage 60/30 mg, the 47% the dosage 90/30 mg. The subjects who discontinued the therapy were mostly young males with a better kidney function and a higher urine osmolarity [16]. However, at the end of the study, 75% stated that they would continue the therapy with tolvaptan for the rest of their lives. The most important adverse effect of the treatment with tolvaptan was hepatotoxicity in 3.7% of patients, an incidence that probably underestimates the impact of the hepatotoxicity because only the more advanced cases of alanine aminotransferase (ALT) elevation (i.e., more than three-fold the upper limit of normal range) were reported; in particular, in the first 18 months of treatment, 2 patients presented the so called "Hy's Law", i.e., the contemporary increase of ALT of more than 3-fold and total bilirubin more than 2-fold the upper limit of normal range. Liver parameters completely resolved upon the discontinuation of the treatment, and it seemed not dose-related, even if it occurred at the highest dosage [12].

In 2017, Torres et al. [17] published the results of TEMPO 4:4, a 2-year open-label extension of TEMPO 3:4; with 871 patients who successfully completed TEMPO 3:4, the "early treated" group, i.e., patients who continued tolvaptan in the next 2 years, showed a non-significant TKV change compared to the "delayed treated" patients, i.e., patients who received placebo in TEMPO 3:4 who experienced a similar beneficial effect of

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patients treated in the previous study; this finding suggested that tolvaptan exerts its maximum effect in the first 2 years of treatment and then TKV remains stable. In regards to the effects on eGFR in TEMPO 4:4, the significant difference between the two groups was maintained, particularly in those patients with more severe disease. In 2017, Torres et al. [18] showed the results of the REPRISE trial, conducted on 1,370 patients with later stages of ADPKD (eGFR 25 – 65 mL/min/1.73m^2, aged 18 – 55 or eGFR 25 – 45 mL/min/1.73m^2, aged 56 – 65) for a period of 12 months. Tolvaptan slowed eGFR decline compared to placebo at 1 year of follow-up (–2.34 vs. –3.61 mL/min/1.73m^2/year, respectively; p < 0,001), especially in 2 – 3a stage CKD, but no additional beneficial effect was recorded for patients older than 55.

Edwards et al. [19] performed a retrospective study on 97 patients enrolled in different tolvaptan trials conducted at the Mayo Clinic in the previous 7.6 years. They compared the eGFR data to those of the control groups of CRISP and HALT studies and they found that patients treated with tolvaptan showed a slower eGFR decline. It was estimated that there was a difference in renal function reduction of 1.09 mL/min/m^2/year between treatment and placebo groups similar to that observed in TEMPO 3:4 and REPRISE trials; these results suggested a sustained and cumulative effect of tolvaptan on eGFR decline over a longer period.

Recently, Nakatani et al. [20] reported 2 Japanese ADPKD patients (males, 36 and 29 years old) treated with tolvaptan (120 mg/day) for 9 years, during which time determinations of eGFR and TKV were performed. Their findings suggested that long-term administration of tolvaptan at a high dose is both safe and effective to preserve kidney function, though a gradual increase in TKV was seen in both of the 2 cases, particularly during the later phase. Of note, a meta-analysis conducted on 8 randomized controlled trials (RCTs) and 1 quasi RCT involving 1,536 patients showed that tolvaptan has a beneficial effect on ADPKD, with significant differences in the annual rate of change in TKV at any stages of CKD and GFR between the tolvaptan and the placebo group. Therefore, tolvaptan reduced the rate of serious hypertension and kidney pain events in ADPKD patients, but it is associated with an increase in adverse events at high doses when compared with the placebo; further RCTs on tolvaptan may be required to support this conclusion [21]. Interestingly, a recent retrospective study evaluated the relationship between genotype and the efficacy of tolvaptan in 18 patients with ADPKD; the group with no PKD1/2 mutation showed a more rapid annual eGFR decline compared with the group of patients with any PKD1/2 mutation (–0.7 vs. –0.6 mL/min/1.73m^2/year, respectively; p = 0.01) and in the annual rate of increase in TKV with tolvaptan (–1.1 vs. –6.7%, respectively; p = 0.02). Hence, detecting PKD1/2 mutations may be useful to predict the effectiveness of tolvaptan [22]. Finally, a post hoc analysis of the TEMPO 3:4 trial showed that tolvaptan slowed the increase in TKV in 29 patients aged 18 – 24 years with ADPKD compared to the 22 patients in the placebo group (3.9 vs. 6.5%, p = 0.0491), and none of them met the criteria for Hy's law of hepatotoxicity. These results suggest that tolvaptan, with appropriate patient selection and management, can be an effective and safe treatment in adolescent and young adults with ADPKD; additional studies with a larger population are needed, and RCTs are to be performed to investigate the potential benefit of tolvaptan in pediatric patients [23]. Table 1 summarizes the characteristics and outcomes of studies so far conducted on tolvaptan in the treatment of ADPKD.

Somatostatin analogues

Somatostatin is a cyclopeptide produced by central and peripheral nervous systems, the pancreas, and the gastrointestinal tract: in the kidney, it is especially secreted by mesangial cells and proximal tubular cells. Somatostatin interacts with G-protein coupled somatostatin receptors (SSTRs) 1, 2, and 5 expressed in the distal tubules, and here it inhibits the aldosterone and renin release. Therefore, somatostatin inhibits the secretion of the growth hormone (GH), insulin and glucagon, cholecystokinin, vasoactive intestinal peptide, secretin, thyroid stimulating hormone, adrenocorticotropic hormone, the vascular endothelial growth factors, and the insulin-like growth factor-1 (IGF-1). The latter mediates the GH effects on glomerular hypertrophy, but not the GH

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Table 1. Tolvaptan study characteristics and outcomes.

Study	Treatment	Inclusion criteria	Study design	Outcome GFR reduction	Outcome TKV increase
TEMPO 3:4 (2012) [12]	Tolvaptan	18 – 50 years TKV ≥ 750 mL eGFR ≥ 60 mL/min/1.73m^2	961/1,445 pts 3 years RCT	–2.72 vs. –3.70 p < 0.001	2.8 vs. 5.5% p < 0.001
TEMPO 4:4 (2017) [17]	Tolvaptan	– "early treated": 557 pts – "delayed treated": 314 pts	871 pts 2 years Open-label extension	3.15 mL/min/1.73m^2 p < 0.001 Slope of eGFR: –3.26 vs. –3.14 mL/min/1.73m^2 per year (early- and delayed-treatment groups); treatment difference 0.11 (95% CI 0.75, 0.52) p = 0.73	Changes in TKV from TEMPO 3:4 baseline to TEMPO 4:4 month 24: 29.9 vs. 31.6% (early-vs. delayed-treatment groups), p = 0.38 Slopes of TKV growth during TEMPO 4:4: 6.16 vs. 4.96% per year (early vs. delayed-treatment groups) p = 0.05
REPRISE (2017) [18]	Tolvaptan	–18 – 55 years, GFR 25 – 65 mL/min –56 – 65 years, GFR 25 – 44 mL/min	683/1,370 pts 1 years RCT	–2.34 vs. –3.61 p < 0.0001	None
Edwards (2018) [19]	Tolvaptan	Compared to control groups of CRISP and HALT studies	97 pts 4.6 ± 2.8 years retrospective	After 7.6 years of median follow-up the difference between observed and expected GFR: 1.09 mL/min/year	None
Xie (2020) [21]	Tolvaptan	ADPKD adults	1,536 pts Meta-analysis: 7 RCT + 1 quasi RCT	Mean difference between treatment and placebo 1.4% (95% CI 0.83, 1.97)	Mean difference between treatment and placebo –3.32% (95% CI-4.57, –2.07)
Sekine (2020) [22]	Tolvaptan	– PKD1 truncating: 4 pts – PKD 1 non-truncating: 7 pts – PKD2: 4 pts – no PKD1/2: 3 pts	18 pts retrospective	Annual eGFR difference between after and before treatment: – any PKD1/2 mutation vs. no PKD1/2 mutation 0.6 vs. –0.7 mL/min/1.73m^2 p = 0.01	Annual TKV difference between after and before treatment: – any PKD1/2 mutation vs. no PKD1/2 mutation –6.7 vs. –1.1% p = 0.02
Raina (2020) [23]	Tolvaptan	18 – 24 years 51 pts	29 pts Post hoc analysis of the TEMPO 3:4 trial	None	Annual TKV increase: 3.9 vs. 6.5% p = 0.0491

ADPKD = autosomal dominant polycystic kidney disease; eGFR = estimated glomerular filtration rate; HALT = halt progression of polycystic kidney disease trial; PKD1 = polycystin 1; PKD2 = polycystin 2; RCT = randomized controlled trial; TKV = total kidney volume.

effects on glomerular sclerosis. Somatostatin analogues (SAs) can inhibit the activity of AC, thus lowering cAMP levels in different tissues through the interaction with 5 receptor subtypes; SSTR1 and 2 are expressed in the thick ascending limb of Henle, distal tubule, and collecting duct, and SSTR3, 4, and 5 are expressed in the proximal tubules. Because it is rapidly metabolized, somatostatin plasma half-life is too short (1 – 3 minutes), so analogues with a longer half-life were synthesized; the most-used are octreotide, lanreotide, and pasireotide. Initially indicated for the treatment of neuroendocrine diseases, they were studied in ADPKD patients.

In 2005, Ruggenenti et al. [24] showed the safety and efficacy of SAs in ADPKD in which the assessment of renal volume was performed by abdominal computed tomography (CT); they found a stable TKV and eGFR in a 2-year follow-up.

Thereafter, octreotide was studied in two trials: ALADIN 1, conducted in 79 ADPKD patients in early disease phase (eGFR ≥ 40 mL/min/1.73m^2), and showed that the annual slope of TKV increase was significantly lower in the treatment group compared to place-

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Table 2. Somatostatin analogue study characteristics and outcomes.

Study	Drug	Inclusion criteria	Study design	Outcome GFR decline	Outcome TKV increase	Outcome TLV increase
Ruggenenti (2005) [24]	Octreotide 40 mg IM/28 d	> 18 years M Cr 1.2 – 3 F Cr 1.0 – 3.0	14 pts 6 months cross over	–5.5 vs. –0.2 NS	3.6 vs. 6.6% p < 0.05	–5 vs. +1% p < 0.05
Van Keimpema (2009) [30]	Lanreotide 120 mg SC/28 d	> 18 years	54 pts PLD/ADPKD 6 months RCT	Creatinine reduction more in treated group than control group. N.S.	1.5 vs. 3.5% p = 0.02	–2.9 vs. 1.6% p < 0.01
Hogan (2010) [32]	Octreotide 40 mg IM/28 d	> 35 years Cr ≤ 3.0	42 pts PLD/ADPKD 12 months RCT	–5.1 vs. +7.1% N.S.	0.3 vs. 8.6% p < 0.05	–5% vs. +1% p < 0.05
Hogan (2015) [33]	Octreotide 40 mg IM/28 d		25 pts PLD 2 years open-label extension			
ALADIN 1 (2013) [8]	Octreotide 40 mg IM/28 d	> 18 years ≥ 40 mL/min MDRD	79 pts ADPKD 3 years RCT	–3.9 vs. –5 mL/min N.S. 0 – 3rd year	220 vs. 454 mL N.S. 0 – 3rd year	
ALADIN 1 (2013) [8]				–2.3 vs. –4.3 mL/min p = 0.027 2nd – 3rd) years	77 vs. 152 mL/year p = 0.009 0 – 3rd year	–8 vs. +6% p < 0.05 PLD/ADPKD
ALADIN 2 (2019) [25]	Octreotide 40 mg IM/28 d	> 18 years eGFR: 15 – 40 mL/min/1.73m^2	100 pts 3 years RCT	▪ N.S. in total population ▪ in CKD 4 3/31 vs. 8/32 develop ESRD p = 0.036	29.9 vs. 37% p = 0.091	
Pisani (2016) [28]	Octreotide 40 mg IM/28 d	> 18 years eGFR ≥ 40 mL/min/1.73m^2	27 pts 3 years treatment +2 years after withdrawal RCT			▪ At 3 years: –7.8% ± 7.4% vs. + 6.1% ± 14.1% p = 0.003 ▪ at 2 years after treatment ended: –0.8% ± 9.7% vs. + 11.0% ± 14.4% p = 0.046
Griffiths (2020) [29]	Octreotide 40 mg IM/28 d Lanreotide 120 mg IM/28 d	ADPKD or PLD adults	Meta-analysis: 9 RCTs 592 pts	Difference between treatment and control 0.27 mL/min/1.73m^2, (95% CI −2.03 to 2.57) p = 0.82	Difference between treatment and control −190 mL (95% CI −0.50 to 0.12) p = 0.23	Difference between treatment and control −150 mL (95% CI −0.26 to −0.03) p = 0.01

ADPKD = autosomal dominant polycystic kidney disease; CKD = chronic kidney disease; ESRD = end-stage renal disease; F Cr = creatinine in females; GFR = glomerular filtration rate; M Cr = creatinine in males; MDRD = modification of diet in renal disease; N.S. = no significant; PLD = polycystic liver disease; RCT = randomized controlled trial; TKV = total kidney volume; TLV = total liver volume.

bo (76.6 vs. 152 mL, respectively; p < 0.009), but this finding was not confirmed by the difference in the TKV increase at the end of 3 years follow-up, which did not result in a statistical difference between somatostatin and placebo groups (220 vs. 454 mL, respectively; p = 0.25). The renal function decline was not significantly different between the two groups at the end of the study [8]. On the other hand, during the second and the third year of treatment, the renal function decline was almost 50% lower compared to placebo (–2.28 vs. –4.32 mL/min/1.73m^2/year, respectively), probably due to the nephroprotective effect of octreotide, which might inhibit cysts proliferation and consequently the compensatory hyperfiltration.

The ALADIN 2 study involved 100 patients in later stages of disease (eGFR between 15 and 40 mL/min/1.73m^2) treated with octreotide-LAR, which reduced median TKV growth at 1 and at 3 years of follow-up (p = 0.027), while the GFR variation was not significant. These results confirmed and ex-

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Table 3. Advantages and disadvantages of tolvaptan and somatostatin analogue treatments.

	Tolvaptan	Somatostatin
Advantages	– Large population analyzed	– Evidence of TKV reduction – Evidence of TKV reduction – Evidence of LV function improvement – Easy compliance – Absence of important side effects
	– Long observation period	
	– Evidence of TKV reduction	
	– Evidence of efficacy in reducing renal function decline	
	– Indication for worldwide treatment	
Disadvantages	– Absence of LV function improvement – Absence of TLV reduction efficacy – Difficult compliance – Important aquaretic effect and possible hepatotoxicity	– Evidence of efficacy in reducing renal function decline only in the early period – Indication for treatment only in Italy – Small population analyzed – Short observation period

LV = left ventricular; TKV = total kidney volume; TLV = total liver volume.

tended previous evidence showing that octreotide-LAR is safe in ADPKD adults, and it may have renoprotective effect on TKV and eGFR [25]. It is noteworthy that the treatment group presented lower renal volumes and better renal function compared to placebo. Furthermore, in the ALADIN 2 study, the measured GFR (mGFR) with iohexol was discrepant with creatinine data, thus raising some concerns on renal function outcomes [26].

The most numerically representative trial on SAs is the DIPAK-1 study, conducted on 309 patients with CKD 3a and 3b stages, and a follow-up of 2.5 years; lanreotide significantly reduced annual TKV compared to placebo but showed no significant difference in the slope of GFR reduction. For this reason, it was no indicated for the treatment of ADPKD in advanced stages [27]. Table 2 summarizes the available studies on SAs in the treatment of ADPKD and polycystic liver disease (PLD).

Effects of somatostatin analogues on extrarenal manifestations

Cholangiocytes, the cells responsible for the genesis of liver cysts, express all SSTRs but not V2 receptors; consequently, SAs are the only available drugs able to reduce the total liver volume (TLV) as demonstrated by our placebo-controlled study on 27 patients affected by PKD and PLD with a renal function of more than 40 mL/min/1.73m^2; 14 patients were treated with octreotide-LAR to evaluate the TLV change, measured by MRI at baseline, after 3 years of treatment and 2 years after treatment end. We showed that octreotide-LAR significantly reduced liver volume after 3 years of treatment compared to placebo, and these results were maintained for 2 years after the end of the treatment. Thus, 3 years of octreotide-LAR therapy delayed disease progression by at least 5 years [28]. Recently, Griffiths et al. [29] conducted a meta-analysis, including 592 patients, that demonstrated that SAs significantly reduced TLV, while there was no significant effect on TKV or eGFR and on progression to ESRD. Moreover, the treatment was safe and well tolerated, except some gastrointestinal adverse effect (i.e., diarrhea, abdominal pain, cholelithiasis, and cholecystitis) because of the expression of SSTRs at this level [28, 29, 30, 31, 32, 34].

Therefore, through the interaction with SSTR subtypes expressed on the surface of both myocytes and myocardial fibroblasts, octreotide-LAR can also improve or prevent left ventricular (LV) dysfunction as shown in our cross-sectional study, in which we evaluated LV function by speckle-tracking echocardiography in 34 ADPKD patients from one ALADIN trial center and in 34 age- and gender-matched healthy controls and 34 equally-matched renal controls with non-cystic CKD [35].

Inclusion criteria for the treatment

In order to start treatment with tolvaptan, patients have to be 18 – 50 years old, with a definite diagnosis of ADPKD on the ba-

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sis of either family history or genetics; 2 – 3 CKD (45 – 89 mL/min) by mGFR or eGFR according to chronic kidney disease-epidemiology collaboration (CKD-EPI) equation; TKV more than 750 mL or height adjusted-total kidney volume (ht-TKV) of more than 600 cc/m^2 at MRI or CT, or renal longitudinal diameter more than 16.7 cm, or more than 16.8 cm at ultrasound imaging. Tolvaptan use was then extended in August 2018 to stage 4 CKD. Moreover, patients have to present a rapidly progressive ADPKD defined as 1) a GFR (mGFR or eGFR) decline higher or equal to 5 mL/min/1.73m^2 in 1 year or higher or equal to 2.5 mL/min/1.73m^2 per year over a period of 5 years; 2) a TKV increase superior to 5% per year by repeated measurements (preferably 3 or more, each at least 6 months apart and by MRI); 3) Mayo image class 1C, 1D, or 1E; 4) a truncating PKD1 mutation in conjunction with early onset of clinical symptoms consistent with a predicting renal outcome in polycystic kidney disease (PROPKD) score of more than 6 [36]. Inclusion criteria for octreotide-LAR treatment in Italy are: patients older than 18 years, affected by ADPKD clinical and instrumental diagnosis, eGFR (according to modification of diet in renal disease (MDRD4)) ranging from 15 to 30 mL/min/1.73m^2. Exclusion criteria are pregnancy, breast-feeding, and inadequate contraception in women of childbearing potential [37].

Tolvaptan vs. somatostatin

Clinical trials, observational studies, and case reports data have provided evidence for the safety and efficacy of both tolvaptan and octreotide-LAR in ADPKD, however, we have only indirect comparisons of the two agents, from which no firm conclusion regarding their relative efficacy and safety is currently available, and neither is data on the effects of switching patients from one treatment to another. In the big match between the currently available studies on tolvaptan and octreotide-LAR use in ADPKD, many factors play a significant role. First, the clinical trials on both tolvaptan and octreotide are characterized by few years of follow-up, compared to the disease duration, which develops over decades; in particular, on the basis of the known biphasic effect of somatostatin analogues on renal function, which are well documented in tolvaptan, with an initial and reversible hemodynamic detrimental effect on GFR, followed by a slower decrease due to a structural beneficial effect, the observation period of somatostatin analogues is too short in order to notice the overall renoprotective effect. Tolvaptan studies have analyzed larger populations than somatostatin trials, and they are characterized by a longer observation period. Table 3 summarizes the advantages and disadvantages of both drugs. Tolvaptan reduces TKV and renal function decline, but its clinical use is widely limited by aquaresis tolerability; in fact, tolvaptan causes nephrogenic diabetes insipidus with polyuria of 6 – 8 L/d that make compliance difficult. In our experience, in 24 ADPKD "fast progressor" patients treated with tolvaptan, compliance, efficacy, and tolerability of the treatment were evaluated using questionnaires on the quality of sleep (Pittsburgh Sleep Quality Index), abdominal pain (Brief Pain Inventory), quality of life (Short Form 36) after 1-year follow-up. According to the available literature, the eGFR rate of change was not statistically different compared to the prior year; and the most important side effect was the aquaretic effect. Despite polyuria, sleep worsening, and constant need of drinking water, 90% of patients favorably accepted the treatment, and all patients continued tolvaptan at the highest tolerated dose. In fact, the compliance to the therapy was determined by many factors, especially those psychological effects concerning the awareness of ADPKD complications, already observed in blood relatives. Therefore, the adherence to the therapy was high and very similar to the available trials; up-tritation was not difficult; hepatotoxicity was infrequent and a manageable problem; most patients reported only a few problems related to urine volume (4 – 8 L/d in the majority of patients), which impacted quality of sleep [38]. These data were confirmed by a recent observational prospective study conducted in 98 patients (30 with and 68 without tolvaptan treatment); the impact of tolvaptan on health-related quality of life (HRQoL) was evaluated after 1 year follow-up using the standardized kidney disease quality of life short form (KDQOL-SF) questionnaire; HRQoL and kidney-specific health concerns were not influenced by tolvaptan treatment, whereas patients' satisfaction significantly

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increased [39]. Last but not least, tolvaptan is a very expensive therapy, with a great financial burden; in addition, concerns about tolvaptan use were raised as its efficacy to slow down renal function decline seems to be limited to the early period of treatment with no further improvement after ~ 2 years [17]. SAs, compared to tolvaptan, showed the advantage of reducing not only TKV but also TLV increase, and they can effectively improve LV function. Furthermore, after a 3-year treatment, their use is characterized by high compliance and absence of important side effects. In particular, in DIPAK 1, the most frequent side effects of lanreotide vs. placebo were diarrhea (91 vs. 6.6%), abdominal discomfort (79 vs. 20%), hepatic cyst infection (5.2 vs. 0%), poor glycemic control (5.2 vs. 0.7%); of note, these adverse effects appeared in the first month of treatment and spontaneously resolved [27]. In ALADIN trials, diarrhea and cholelithiasis were the most important side effects in the octreotide group [8, 25].

Conclusion

The current clinical trials are characterized by few years of follow-up, compared to a disease which lasts decades. Consequently, long-term effects of these therapies along with tolerability and side effects will have to be evaluated through clinical practice and post-marketing data. Nevertheless, octreotide-LAR was demonstrated to be effective not only on ADPKD, but also on PLD with beneficial effect on cardiac function and a better cost/benefit profile, tolvaptan has received more attention in the last years. It is noteworthy that studies investigating SAs trials have been conducted on smaller sample sizes. On the other hand, RCTs on tolvaptan showed that the potential benefit and harms of the treatment are strictly dependent on many patient characteristics such as age, eGFR, and ability to tolerate the medication. Interestingly, a new therapeutic approach in the treatment of ADPKD is under consideration; in fact, bardoxolone, a Nrf2 activator, already showed to increase eGFR in diabetic patients but its use was limited by cardiovascular complications [40, 41]. The Falcon study is a phase 3 RCT that will study safety, tolerability, and efficacy of bardoxolone methyl in ADPKD patients with eGFR 30 – 90 mL/min/1.73m^2 (18 – 55 years) or 30 – 44 mL/min/1.73m^2 (56 – 70 years); it started recruiting in June 2019, and ~ 300 patients will be enrolled and randomized 1 : 1 to either bardoxolone methyl or placebo, and primary and secondary outcomes will be eGFR change from baseline to 52 weeks and 104 weeks, respectively, (www.clinicaltrial.gov: NCT03918447). Thus, in the future, ongoing trials on more specific treatments (i.e., bardoxolone, but also venglustat, deoxy glucose, pioglitazone, and tyrosine kinase inhibitors) will make physicians able to tailor ADPKD therapy to patient needs [26].

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Conflict of interest

The authors have declared that no conflict of interest exists.

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