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A Serious Discussion On: Tolvaptan

Srinithi S, Asifa shaz A, Aparna priya M, Ravina R V, Swathi Krishna K

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I. INTRODUCTION

Autosomal Dominant Polycystic Kidney Disease, abbreviated as ADPKD, is an inherited monogenic disorder which is quite prevalent and lethal. The disease is characterized by the progressive development of cysts in the kidneys and it is known to cause a number of abnormalities [(1)].Additionally, the proliferation and enlargement of the cysts in the kidneys eventually end up demolishing the renal parenchyma leading to renal failure [(2)]. ADPKD is considered to be the fourth major source of End-Stage Renal Disease (ESRD) in adults worldwide [1]. ADPKD typically presents with gross hematuria, acute and chronic pain of the kidneys associated with hypertension, kidney stones which ultimately result in defects in the urine concentration, and loss of renal function [(3,4)]. A few studies have been carried out to investigate the cause of this lethal disease. ADPKD occurs as a result of mutations caused in the PKD1 (polycystic kidney disease-1) or PKD2 (polycystic kidney disease-2) genes [(5)].

Management of the disease involves the treatment of hypertension and extra-renal complications along with lifestyle modifications and long-term monitoring of the disease condition [(6)]. It has been observed that in addition to the pharmacotherapy of symptoms and complications, pharmacotherapy with vasopressin-2-receptor antagonist (tolvaptan) has could be useful in the advanced stage of ADPKD [(7)]. The drug tolvaptan has been approved by US-FDA as the drug was observed to be able to slow down the decline of kidney functions thereby reducing the overall risk of ADPKD progression [(8)]. The mechanism of the drug in ADPKD patients is such that it acts by decreasing the cAMP at crucial sites of cyst expansions such as the distal nephrons and epithelial cells of collecting ducts [(9)]. The aim of the present review article is to provide detailed insights into the mechanism, pharmacokinetics, efficacy, and safety of tolvaptan essential for the treatment and management of ADPKD.

PATHOPHYSIOLOGY OF ADPKD:-

Diverse pathways are involved in the pathogenesis of ADPKD such as mitogen-activated protein activation, mammalian target of rapamycin kinase, intracellular dysregulation of calcium, accumulation of cyclic adenosine monophosphate (cAMP), and AVP instigated cAMP production of cyst in the kidney. Out of these pathways, one of the most significant pathways which result in ADPKD is the AVP induced cAMP production of cysts [(10)]. Argininevasopressin hormone or otherwise known as the anti-diuretic neuropeptide hormone (i.e arginine hormone) is produced in the hypothalamus and gets released into the systemic circulation from the posterior pituitary gland [(11,12)]. The three main vasopressin receptors namely V1A, V1B, and V2 involve a variety of activities such as platelet aggregation, adrenocorticotropic hormone release, glycogenolysis, vasoconstriction, osmoregulation, and body fluid regulation [(13,14)]. Vasopressin 2 receptors (expressed by renal collecting ducts) when bound to arginine vasopressin elevate the secondary messenger cAMP which eventually enhances aquaporin-2 channels and assists free water reabsorption [(15)]. Vasopressin 2 receptor agonists increase the renal cAMP production which in turn results in the promotion of cyst cell proliferation and cyst fluid secretion [(16)].

MECHANISM OF ACTION (tolvaptan):-

The vaptan drug family comprises agents that act by directly blocking the action of vasopressin at its receptors (V1AR, V1BR, and V2R)[(17)]. Tolvaptan is the first orally active vasopressin specific receptor antagonist that counteracts the actions of vasopressin by blocking the V2 receptor, thereby decreasing the expression of the aquaporin channels [(18,19)]. In ADPKD, Tolvaptan acts by decreasing the cAMP at the important sites of cyst expansion such as the distal nephrons and epithelial cells of collecting ducts [(20)]. This causes an increase in free water clearance, a decrease in urine osmolality, and an increase in the serum sodium concentration alongside a decline in the kidney functions [(15)].

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PHARMACOKINETIC PARAMETERS:-

The oral bioavailability of tolvaptan is 56% [21]. The maximum concentration of the drug (Cmax) is reached in 2 hours after the administration of the drug[22]. In healthy volunteers, tolvaptan increases the area under the plasma concentration-time curve. Some studies have found that tolvaptan found to be dose-proportional for single oral doses (60-480mg)[23]. Studies show that the plasma protein binding of tolvaptan is 99%[24]. The volume of distribution of tolvaptan takes place in 3 mL/kg[25]. The pharmacokinetic parameters of tolvaptan remain unaffected by certain factors like age, sex, and race [26]. Metabolism of Tolvaptan happens through cytochrome P450 (CYP)3A isoenzymes and its excretion takes place via non-renal routes (ie, < 1% of the dose is excreted unchanged in the urine) [27]. Till date, about fourteen metabolites of tolvaptan have been found in plasma, urine, and faeces; all of which have little or no contribution to the pharmacological effects of the drug [24]. It has been found that the terminal elimination half-life of tolvaptan is 8 hours and the apparent clearance value is 4 mL/min/kg[28].

EFFICACY

A clinical trial was conducted to study the '**T**olvaptan **E**fficacy and safety in the **M**anagement of Autosomal Dominant **P**olycystic Kidney Disease (ADPKD) and Its **O**utcomes (**TEMPO3:4** Trial)". This was a phase III, multicentric, randomized, double-blinded, placebo-controlled clinical trial involving 129 sites globally. The trial was conducted over a period of three years from 2007 to 2009. In this clinical trial, patients with a diagnosis of ADPKD in the age group of 18 to 50 years were enrolled through the central randomization method to either receive a tolvaptan or placebo (in the ratio of 2:1). Patients were put on tolvaptan with a starting dose of 45 mg in the morning and 15 mg in the afternoon. The doses were increased on a weekly basis with a maximum dose of 90 mg (Morning) and 30 mg (Afternoon) as per the patient's tolerability for over a period of three years. The patients' adherence to the medication was measured by self-reported and pill count method(s).

The assessment(s) were carried at baseline, during randomization, every week during the dose-escalation phase followed by every four months and after three years of completion of the treatment. The assessment(s) included general physical examination, ECG including vital recordings, blood (Serum creatinine) and urine examination (Microscopy), and MRI scans of kidneys (at baseline and then every year till the completion of treatment). The clinical trial endpoints were assessed using an annual rate of % change in the total kidney volume (Primary endpoint) and the time taken for the investigator-assessed clinical progression. The operational definition for the same was worsening of kidney function (with a one fourth reduction in the reciprocal of the creatinine levels from the value at the end of the dose-adjustment period) (Secondary endpoint).

In this clinical trial, a total of 1445 patients underwent randomization, of which, 961 were assigned to receive the experimental drug (Tolvaptan) and 483 were assigned the placebo. Among the experimental drug arm (tolvaptan), 221 were discontinued from the study [148 (15.4%) had an experience of AEs, 50 (5.2%) had withdrawn their consent, 15 (1.6%) failed to follow up, 4 (0.4%) met the withdrawal criteria, 3 (0.3%) were withdrawn by the investigator(s), and 1 (0.1%) violated the protocol]. In the placebo arm, a total of 67 were discontinued from the study [24 (5%) had an experience of AEs, 30 (6.2%) had withdrawn their consent, 8 (1.7%) lost to follow up, 4 (0.8%) were withdrawn by the investigator(s), and 1 (0.2%) violated the protocol]. Thus, a total of 740 patients (77%) in the tolvaptan arm and 417 (86.2%) in the placebo arm had successfully enrolled in the trial.

Moreover, in the tolvaptan arm, 842 (87.6%) were included for primary endpoint efficacy analysis and 961 (100%) for secondary endpoint analysis including 961 (100%) for safety analysis as well. Similarly, in the placebo arm, 465 (96.1%) were included for primary endpoint efficacy analysis with 484 (100%) for secondary endpoint analysis and 483 (99.8%) for safety analysis.

After the trials were carried out, in the tolvaptan arm, it was observed that the total kidney volume increased by 2.8% per year (95% CI, 2.5 - 3.1) while in the placebo it increased to 5.5% per year (95% CI, 5.1 -6) with a P value < 0.001. It was also seen in the composite endpoint with 44 events/100 follow up in the tolvaptan arm versus 50 events/100 follow up in the placebo arm (P =0.01). The rates of renal function worsening in the tolvaptan arm were found to be 2 events/100 person per year follow-up while in the placebo arm it was 5 events/100 person per year follow-up with a P value <0.001. Additionally, it was observed that painexperienced was more in the placebo arm when compared to the tolvaptan arm (5 events in

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tolvaptan arm and 7 events in placebo arm per 100 person-years follow-up with P =0.007).

The clinical trial also confirmed that the tolvaptan arm was associated with a slower decline in renal parameters and diseased related AEs when compared to the placebo arm. However, the aquaresis and hepatic related adverse events with discontinuation of therapy were observed to be more in the tolvaptan arm than in the placebo (23 vs. 14%).

ClinicalTrials.gov Number, **NCT02160145**

A phase III, multi-centric, randomized, double-blinded, and placebo-controlled clinical trial involving 213 sites spanning the entire globe. The study was conducted over a period of two years from 2014 to 2016. This clinical trial was mainly conducted to evaluate the efficacy of tolvaptan in the latter stages of ADPKD. The patients (n =1370), who fell between the age group of 18 to 55 years with an estimated GFR of 25 - 65 ml/min/1.73 m^2 of body surface area and patients between the age group of 56 to 65 years with an estimated GFR of 25 - 44 ml/min/1.73 m^2 of body surface area, were randomly assigned to either tolvaptan or placebo arms (in the ratio of 1:1). The primary endpoint of the clinical trial was to assess the change in the estimated GFR from the baseline values to the follow-up period for one year with safety assessments as the secondary endpoint(s).

It was observed in the primary endpoint in the tolvaptan arm that the change in the baseline estimated GFR was -2.34/ml/min/1.73 m^2. On the other hand, the change was found to be 3.61/ml/min/1.73 m^2 in the placebo arm and this change was significantly different from the experimental arm (P <0.001). The secondary endpoint(s) safety analysis showed that the occurrence of more than threefold increase in the alanine aminotransferase levels was 5.6% (38 events out of 681 patients) in tolvaptan arm and 1.2% (8 events in 685 patients) in the placebo arm. However, it was observed that these elevations in the tolvaptan arm were reversible upon stopping the experimental drug.

ClinicalTrials.gov Number, **NCT01280721 [TEMPO 4:4]**

This clinical trial (**TEMPO 4:4**) was an extension of the study '**T**olvaptan **E**fficacy and safety in the **M**anagement of Autosomal Dominant **P**olycystic Kidney Disease (ADPKD) and Its **O**utcomes (**TEMPO3:4** Trial)" to obtain an additional data for another two more years in order to establish the long-term efficacy and safety of tolvaptan in ADPKD.

This was a multi-centric, open-label clinical trial conducted to establish the effects of tolvaptan on total kidney volume and estimated GFR (Primary endpoint). In this trial, a total of 871 (60.3%) patients were enrolled from the TEMPO 3:4 trial. The results of the trial have shown that the slopes of total kidney volume growth were higher in the early (6.16%) vs delayed treatment (4.96%) per year. Similarly, the eGFR (secondary endpoint) was also favorable. Additionally, the effect of tolvaptan was sustained and established a non-inferiority in eGFR slopes.

SAFETY

Symptoms like thirst, dry mouth, loss of appetite, frequent urge to urinate, nocturia, fatigue, hematuria, kidney pain, and polyuria were observed in patients administered with tolvaptan. A greater percentage of patients who consumed tolvaptan showed increased levels of liver enzyme secretions, serum potassium, and uric acid levels. In these patients, the aminotransferase level was >2.5 times than the normal range [32]. Besides these symptoms, diarrhea, constipation, or weakness were some of the other suspected side effects [33]. Moreover, aquaretic effects were commonly reported in the slow down treatment groups who had no previous exposure to tolvaptan [34]. Apart from the aforementioned symptoms, several side effects have also been observed which include dehydration, a rapid increase in the heartbeat rate, and dizziness/lightheadedness. In addition to these, it has also been observed that tolvaptan may also increase the risk of liver damage [32].

In a double-blinded study, withdrawal regimen was observed due to adverse events in 65 participants out of a total of 681 participants (95%) in the tolvaptan group and15 participants experienced adverse events out of 685 (2.2%) in placebo group. Aquaresis related adverse effects were seen in 14 (2.2%) patients in the tolvaptan group in contrast to just 1 (0.1%) patient in the placebo group. On comparing the hepatic enzyme irregularities in the tolvaptan group and placebo group; it was found to be 11(1.6%) patients and (0.1%) patient respectively. Consequently, one patient was reported to have died during a dose adjustment in one of the on-going single-blind study [33].

CONTRA-INDICATION: The usage of tolvaptan is contra-indicated in pregnancy and lactation, due to the lack of safety data in this population.

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Additionally, it is also contraindicated in other conditions such as hypovolemia, uncorrected hypernatremia, urinary tract obstruction, and H/O hepatic damage which is not caused due to the polycystic liver disease.

Furthermore, the usage of tolvaptan is contra-indicated with the concomitant use of various other drugs such as strong CYP3A inhibitors (example; lopinavir, itraconazole, clarithromycin, and ketoconazole). Some studies show that Tolvaptan can elevate the OATP1B1/3 and OAT3 transporter substrates' level (example; furosemide, repaglinide, statins and methotrexate) as well as the BCRP transporter substrates' level (example; rosuvastatin)[6].

A case report had put forth that thiazide might increase the tolvaptan tolerability by decreasing the polyuria [(35)]. Nevertheless, the concomitant use of tolvaptan with diuretics is not recommended as it would further reduce the eGFR, increase the levels of circulating vasopressin, and might even elevate gout risk.

II. CONCLUSION:

Tolvaptan, a selective vasopressin V2 antagonist, is the first pharmacological treatment approved for ADPKD. Although the efficacy is marginal, the lack of alternative options has favored its position to obtain regulatory approval. While common side effects such as thirst, polyuria are to be expected with tolvaptan, one should avoid prescribing this drug in certain populations such as liver disease. It is hoped that in the coming days, we might see more advances in the pharmacotherapy of ADPKD that result in improving the mortality and morbidity associated with this illness.

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