A Prospective clinical trial of RENOCHLOR (Sodium Copper Chlorophyllin complex) formulations as an add-on therapy for the Management of Chronic Renal Failure (CRF)

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Research Article

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Abstract

Background: The study was performed to evaluate the efficacy of Renochlor tablet in comparison with Renochlor syrup for the Management of Chronic Renal Failure (CRF) / Chronic Kidney Disease. The primary objective of this study was to evaluate (Already proven) comparative performance of Tablet and Syrup dosage forms/Formulations and correlation of TGS-beta 1 as indicator of kidney function status in Chronic Renal failure

Hypothesis : to Access the efficacy of sodium copper chlorophyllin complies through Controlled randomized trial using primary end point as e GFR and secondary as decrease in fibrosis marker TGFb1 and albumin creatinine ratio.

Study design: It was a Prospective, Observational, Randomized, Open labelled, Multicentre, Parallel-Group, Two-arm, clinical trial to evaluate comparative performance of Tablet and Syrup dosage forms/Formulations

Method: It was a Prospective, Observational, Randomized, Open labelled, Multicentre, Parallel-Group, Two-arm, clinical trial to evaluate comparative performance of Tablet and Syrup dosage forms/Formulations and correlation of TGS-beta 1 as indicator of kidney function status as an add on to the standard of care (pl give standard care details) for the management of Chronic Renal Failure (CRF). In the study, patients were randomized in the ratio of 1:1. All the subjects were asked to take Renochlor Tablet (Sodium Copper Chlorophyllin) plus Standard Care of Treatment (1 tablet of 40 mg Sodium Copper Chlorophyllin Complex (active ingredient), TID) or Renochlor Syrup (Sodium Copper Chlorophyllin Complex) plus Standard Care of Treatment (10 ml TID, Each 10 ml contains 40 mg of Sodium Copper Chlorophyllin). The study medication was continued for 90±5 days with periodic follow-up of 30 days. On visit 2 visit 3visit 4 and visit 5 from start of treatment. This was CTRI registered trial (CTRI/2021/04/032987) with 5 clinical trial sites across India.

Results: The study showed the percentage increased eGFR from baseline to end of study treatment for Renochlor Tablet (n=22) and Renochlor Syrup (n=21). The eGFR increased by 12.45 %, 13.53 % and 27.33 % in respective visits in patients treated with Renochlor Syrup. The eGFR increased by 11.27 %, 23.64 % and 36.04 % in respective visits in patients treated with Renochlor Tablets. The mean percentage reduction in Serum Creatinine was by8.82%, 16.5%, 23.5% in Renochlor Tablet; whereas mean percentage reduction in Serum Creatinine was by 9.44%, 8.89%, 17.8% in Renochlor Syrup The mean percentage reduction in Albumin to Creatinine Ratio was by 20.08%, 26.09%, 29.91% in Renochlor Tablet whereas mean percentage reduction in Albuminn to Creatinine Ratio was by 22.48%, 26.27%, 30.76% in Renochlor Syrup (remove – sign). The mean percentage reduction in Serum Urea was by 11.64% in Renochlor Tabletwhereas mean percentage reduction in Serum Urea was by 9.76% in Renochlor Syrup (remove – sign).The mean percentage reduction in Blood Urea Nitrogen was by 10.38%, 21.27%, 22.40% in Renochlor Tablet whereas mean percentage reduction in Blood Urea Nitrogen was by 10.99%, 11.06%, 14.51% in Renochlor Syrup. The mean percentage reduction was observed in Serum Electrolytes in both Renochlor Syrup. The mean percentage reduction in TGF β-1 was by 14.56% in Renochlor Tablet whereas

in Renochlor Syrup was by 10.55% when compared with baseline to end of study visit.(Above differences in the clinical parameters of Tablet group and Syrup group are statistically significant.

There were 10 clinical adverse events (AEs) reported in 10 patients. Out of total 10 AES, 04 AEs were reported in Renochlor Tablet and 06 AEs were reported in Renochlor Syrup. There were no SAEs (Serious Adverse Events) reported in overall conduct of the clinical study.

Conclusion: Both dosage forms on RENOCHLOR,ie syrup and tablets (Sodium Copper Chlorophyllin Complex) is safe and efficacious . Reduction in TGF β-1 , S Creatinine, BUN , ACR ration. Increase in eGFR. Clinically and statistically significant in chronic renal failure, However tablets in Renochlor Tablet proved marginally superior in primary and secondary efficacy end points when compared with Renochlor Syrup

Introduction

Millions of people suffer from kidney disease around the world, and these patients eventually require renal replacement therapy. Haemodialysis, peritoneal dialysis, and kidney transplants save lives, but they come at a high price, which is becoming a big issue in western countries because they account for a large amount of healthcare spending.(Cockwell & Fisher, 2020). Additionally, they do not improve Quality of Life of patients. This also leads to devastation of the entire family of the patient psychologically as well as financially.

Chronic kidney disease (CKD) is linked to a rapid deterioration in renal function with age, which is intensified in persons with hypertension, diabetes, obesity, and primary renal diseases. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality and CKD is regarded as a risk factor for CVD events.(Virally et al., 2007) CVD risk and glomerular filtration rate (GFR) have a graded inverse association that is independent of age, sex, and other risk variables. Renal failure is linked to hospitalisation, cognitive impairment, and a poor quality of life. The healthcare impact is greatest in the early stages due to increased prevalence, which affects about 35% of individuals over the age of 70.(Al-Shdaifat & Manaf, 2013).

According to the World Health Organization Global Burden of Disease (GBD) 2004 Update Report, diseases of the genitourinary system (GUS) were responsible for 928,000 (1.6%) deaths out of the total number of global deaths of 58,772,000 and were listed as the 19th leading cause of global death in 2004. Also, diseases of the GUS accounted for 14,754,000deaths daily, which constituted 1% of the global 1,523,259,000.(Shahinian & Saran, 2010) However, these values are likely an underestimation of the contribution of CKD to GBD in view of several reasons. First, the articulation of diseases of the GUS in the GBD report in only 2 specific cause groups, namely, “nephrosis and nephritis” and “benign prostatic hypertrophy,” does not provide any significant insight into the contribution of specific kidney diseases to the GBD2 and, second, an unknown proportion of people whose death and disability are attributed to cardiovascular disease have CKD because patients with CKD are 5 to 11 times more likely to suffer premature death than to progress to ESKD (End Stage Kidney Disease) (Ayodele & Alebiosu, 2010). It can,

therefore, be argued that a proportion of the 12.9 million deaths attributable to ischemic heart disease and cerebrovascular disease, which were the leading causes of global death in 2004, were likely caused by underlying CKD.(Shrestha et al., 2019)CKD likely contributed to the 2.04 million and 1.14 million deaths attributed to human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and diabetes mellitus, respectively, because kidney involvement in these 2 conditions is common and adversely affects survival(Wu et al., 2022).

The high disease burden of CKD, its uneven distribution, the high cost of treatment, and the fact that preventive strategies, although available, are not yet fully in place in many countries and communities qualify CKD as a public health problem(Maciej Serda, 2013). The global increase in the prevalence of CKD and its disproportionate burden on economically developing countries is being driven by an increase in the prevalence of the main risk factors for CKD, namely, diabetes, hypertension, obesity, increasing and aging of the population. Diabetes remains the leading cause of CKD globally and is estimated to presently affect 285 million adults aged 20 to 79 years.(Wang et al., 2019) This number is expected to rise by 54% to 439 million by 2030 according to the International Diabetes Federation. The developing countries will account for 69%, whereas the expected increase in developed countries is 20%. The biggest percentage increase in the prevalence of diabetes is expected to occur in Africa, Eastern Mediterranean, and Middle East and South Asia. An increase in the prevalence of hypertension from 972 million to 1.56 billion by 2025 is also projected, with 80% of the increase (639 million to 1.15 billion) occurring in economically developing nations.(Siregar et al., 2020). Due to this growing risk of CKD there is unmet medical need.

Unmet Medical Need

The increased prevalence of diabetes, hypertension, and obesity and an aging population will only perpetuate the rise of CKD(Inker et al., 2014a). Patients have been, and continue to be, diagnosed with CKD later in the disease cycle, and therefore have to be prepared for life on dialysis or to undergo kidney transplant. However, with better screening, early management, and good life style and good dietary habits the disease progression may be delayed and patients with CKD may enjoy healthier and more productive lives(Yu, 2003).

The complex clinical nature of CKD is characterized and presented, including a description of the foundational interrelated factors of disease and progression that underlie the true burden and unmet medical needs of CKD.

PATHOPHYSIOLOGY CKD is term for many renal disease that results in the progressive loss of kidney function over time. The kidney possesses only a limited capacity for regeneration, and repeated or sustained injury to the kidney results in maladaptive responses including the deposition of excess extracellular matrix, particularly collagen, in the glomerulus and tubule-interstitium of the kidney.(Satoh, 2012)The pathological changes associated with CKD include glomerulosclerosis and tubule-interstitial fibrosis, which result in the loss of normal renal architecture, microvascular capillary rarefaction, hypoxia

and tubular atrophy. These changes lead to the loss of renal filtration capacity and ultimately to end-stage renal disease.(Mullins et al., 2016)

The sequence of events which lead to scarring and fibrosis are complex, overlapping, and are multistage phenomena.

- Infiltration of damaged kidneys with extrinsic inflammatory cells
- Activation, proliferation, and loss of intrinsic renal cells (through apoptosis, necrosis, mesangiolysis, and podocytopenia)
- Activation and proliferation of extracellular matrix (ECM) producing cells including myofibroblasts and fibroblasts
- Deposition of ECM replacing the normal architecture(Inker et al., 2014b; Yu, 2003)

Sodium Copper Chlorophyllin Complex (SCC)

Sodium Copper Chlorophyllin **(SCC)** is sodium copper derivative prepared from chlorophyll extracted from the plants. SCC is semi-synthetic derivative of natural green pigment chlorophyll. It is hydrophilic at one end and lipophy;lic at the other end in nature and more stable to light and acid as compared to natural chlorophyll.(Tumolo & Lanfer-Marquez, 2012). It is an approved colorant and food additive in various countries it is a bioactive compound with antioxidant, anti-mutagenic, anti-apoptotic, and immunomodulatory properties. (Lai et al., 1980; Suryavanshi et al., 2020). Patankar et al., 2019) in previous studies reported that when, sodium copper chlrophyllin syrup was administered to patients diagnosed for Chronic Kidney Disease (CKD), it resulted in statistically significant decrease in serum creatinine level over a two months period of administration when compared with serum creatinine level on the day of start of administration. The quality of life was improved. In view of the well-known nature of CKD as progressively degenerative disease wherein there are no known treatments for improvement of Quality of Life (QOL) this is a surprising invention. In some patients increase in haemoglobin was also noted.

TGF β

(TGF-β) Transforming growth factor beta (Tuan van Naguye & April Ky Dus Ngo21) has been recognized as an important mediator in the genesis of chronic kidney diseases (CKD), which are characterized by the accumulation of extracellular matrix (ECM) components in the glomeruli (glomerular fibrosis, glomerulosclerosis) and the tubular interstitium (tubule-interstitial fibrosis).(López-Hernández & López-Novoa, 2012)

TGF-β is a group of three ubiquitous cytokines (Ref to be written correctly). Most abundant in mammals is TGF β-1.(Schnaper et al., 2009)Activation of TGF-β receptors in the cell membrane induces intracellular signals that mediate many developmental, physiological and pathological processes, including CKD. It also regulates many endothelial functions including proliferation, migration and apoptosis.(Lebrin et al., 2005) .TGF-β1 may be involved in the progression of CRF,(Shuji Iida Clin Exp Nephrol (2006))

TGF-β also acts as a potent anti-inflammatory cytokine that negatively regulates renal inflammation. Thus, blockade of TGF-β inhibits renal fibrosis while promoting inflammation, revealing a diverse role for TGF-β in CKD(Gu et al., 2020)

Material And Methodology

Study Design

It was a Prospective, Observational, Randomized, Open labelled, Multi Centre, Parallel-Group, Two arm, Clinical trial Study to evaluate the comparative performance of Tablet and Syrup dosage forms/Formulations and correlation of TGS-beta 1 as indicator of kidney function status. (CTRI No.:- CTRI/2021/04/032987). All procedures followed the tenets of the Declaration of Helsinki, were in accordance with all regulatory standards, were approved by an Institutional Review Board and all subjects signed an informed consent form. Protocols, Informed consent and study related documents were approved by an Institutional Ethical Committee of the respective study sites.

Subjects

Total of 49 subjects were screened out of which 44 subjects were randomized in the study. 05 subjects were omitted in screening. One subject was lost to follow-up. Total 21 subjects were randomized in test arm of “Renochlor Tablet and 22 subjects were randomized in test arm of “Renochlor Syrup. All the subjects will be asked to take Renochlor Tablet + Standard Care of Treatment (1 tablet of 40 mg SCC (active ingredient), TID) AND in other arm Renochlor Syrup + Standard Care of Treatment (10 ml TID, Each 10 ml contains 40 mg of SCC).

The study medication continued for 90±5 days with periodic follow-up on day 1, day 30±5, day 60±5 and day 90±5 from the start of treatment. The end of study visit was conducted on day 90±5.

Study Eligibility Criteria

Chronic kidney disease (CKD) (an eGFR of 30 to 60 ml/min/1.73 m2 Subjects meeting all of the following criteria were recruited for the trial:

1. Male or female subjects aged between 18-75 years (both inclusive).
2. Subject diagnosed with chronic kidney disease (CKD) (an eGFR of 30 to 60 ml/min/1.73 m^2
3. Subject voluntarily provides written informed consent and willing to adhere to protocol requirements.

Treatment and compliance

The subjects (n =44) were randomly assigned to either of the arms in 1:1 proportion. Randomization was carried out using random number table. Prior to the randomization, site specific randomization list was generated by the statistician Each subject was instructed to take 1 Renochlor Tablet of 40 mg active SCC, 3 times in a day(TID)on empty stomach (i.e. one should not consume any food 30 minutes before and

half hour after taking the tablet.)+ Standard Care of Treatment Or Renochlor Syrup 10ml of 40 mg active SCC 3 times in a day(TID)on empty stomach (i.e. one should not consume any food 30 minutes before and half hour after taking the tablet.) + Standard Care of Treatment Do not exceed the stated dose. Shake the bottle well each time before use. Take this product with the enclosed Measuring cup for 90 ± 5 days, of Renochlor Tablet (SCC) + Standard Care of Treatment or Renochlor Syrup (SCC) + Standard Care of Treatment was for 90 ± 5 days/ end of treatment visit.

Time and events schedule

Total 5 visits were conducted during this entire study after baseline investigation (visit 1). Subjects were provided a drug dosing card toprovide guidance on the schedule of medication administration for 90±5 days. Subjects were asked to note down the details of the study medication administration in drug dosing card. The details of the study medication administration include date, time, dose, and frequency and missed dose information. During the treatment period of 90±5 days, the subject were asked to come for the follow-up visits on day 30 (±5), day 60 (±5) and day 90 (±5) (Final Visit) respectively to assess the primary endpoint i.e. change from baseline [Time Points: Day 1, Day 60 and 90]of following parameters: Serum Creatinine, eGFR. Albumin, Serum urea, electrolytes and TGF- β1 Change in Albumin-to-creatinine ratio (ACR) as compared to baseline, Albuminuria were measured using urinary albumin to creatinine ratio from first morning urine samples, Change in Serum Urea and electrolytes as compared to baseline and secondary endpoints i.e. Change in Transforming Growth Factor-β1 (TGF- β1) as compared to baseline, Incidence rates of AE(Adverse event)/ SAE(serious adverse event) including changes in vital signs and laboratory parameters, Kidney Disease Quality of Life (KDQOL-SFTM) Version 1.3 end of the study visit with used, unused or empty study medication vials and to evaluate the treatment compliance through drug dosing card. Drug dosing cards were be collected on visit5.

Study Period

The total treatment duration was of 90 ± 5 days. The first subject was screened on 07-Jun-2021 and randomized on 09-Jun-2021. The last subject was screened on 17-Jul-2021 and randomized on 19-July-2021. The first subject completed the study on 04-Sep-2021 and last subject completed the study on 21-Oct-2021. Therefore, the total duration of the study was 137 days.

Safety and efficacy parameters

The data was evaluated on efficacy and safety parameters. The efficacy parameters were evaluated based on Change in eGFRfrom baseline, Change in Albumin-to-creatinine ratio (ACR) as compared to baseline, Change in TGF-β1 from baseline visit to end of study visit; as compared within group and in-between the group. Also in combination of both groups are compare at the end of study with respect to change in Serum Creatinine, Change in BUN and electrolytes as compared to baseline. Incidence rates of AE/ SAE including changes in vital signs and laboratory parameters, Kidney Disease Quality of Life (KDQOL-SFTM) Version 1.3. All SAE and AE regardless of treatment group or suspected causal relationship to study drug were recorded on the adverse event page(s) of the Case Record Form.

Site team were in continuous contact with subjects over telephone for any side effects or new symptoms or worsening of any symptoms.

Primary Efficacy Parameter

1. The evaluations of Percentage change in eGFR from baseline to end of study treatment.

Secondary Efficacy Parameter

1. Change in Albumin-to-creatinine ratio (ACR) as compared to baseline.
2. Change in TGF-β1 from baseline visit to end of study visit (as compared within group and in-between the group; also in combination of both groups as compared at the end of study.
3. Change in Serum Creatinine
4. Change in BUN and electrolytes as compared to baseline.

Results

The study data was obtained from 44 Subjects. From enrolled subjects, 01 subject dropped out of the study, 43 subjects completed the study. Out of 44 subjects, 22 subjects were in Renochlor Tablet + Standard care of treatment and 22 subjects were in Renochlor Tablet + Standard care of treatment.

Efficacy of the investigational product was analysed on basis of mean change from baseline to end of study visit scores of eGFR, ACR, Blood Urea Nitrogen, TGF-β1, Serum Creatinine, Serum Urea, and Serum Electrolytes.

As per the statistical analysis plan, the efficacy data was analysed for effect on individual efficacy parameters.

Efficacy Results

Primary Efficacy Parameter-

1. Mean change in Estimated Glomerular Filtration Rate (mL/min/1.73m^2) from baseline to end of study

Secondary Efficacy Parameter-

2. Change in (mg/dL)
    1. Serum Creatinine , S Urea, Blood Urea Nitroen ,
    2. Albumin creatine ratio
    3. TGF-β

Observatory Parameter- For safety assessment

1. Hepatic parameters Day0 &Day 90
2. Serum electrolytes Day 0 &Day90

During the enrolment period, a total of 49 eligible participants were registered: 5 (10.20%) were excluded because they did not meet the study inclusion criteria. 44 (89.79%) enrolled patients were randomized, and finished their protocol of 90 days sessions. From 44 randomized patients 22 (50 %) were on Renochlor Tablet and 22(50 %) were on Renochlor syrup. No serious complications such as death or amputation occurred. On day 90, the increase in Percentage change in eGFR was significantly greater in the Renochlor tablet than in Renochlor syrup. The mean Percentage change in Serum Creatinine, Serum Urea, Blood Urea Nitrogen, ACR, Serum Electrolytes were significant in Renochlor tablet than in Renochlor syrup as compared with baseline

Safety Evaluation

There were 10 Adverse Events reported in 10 subjects. The adverse events mainly are dark green stool, supressed appetite, dry lips, headache, diarrhoea, GI cramping. All Adverse events were followed up until they were completely resolved. No adverse event led to serious adverse event.

Discussion

CKD is clinically diagnosed by analysis of biochemical and urine parameters like serum creatinine, albuminuria, proteinuria and haematuria; decrease in glomerular filtration rate (GFR); and finally renal failure. Biochemical parameters are significantly altered into chronic kidney disease due to remarkable kidney damage. Hence, we assessed eGFR, TGF β-1, ACR, Serum Urea, Serum Electrolytes, Serum Creatinine in the blood to determine the improvement in kidney function by sodium copper chlorophyllin treatment.

SCC is USFDA-approved GRAS listed edible food grade colour. Chlorophyll is its derivative. SCC is known for its antioxidant, anti-aging, and antibacterial activity. SCC shows TGF-β and COX-2 inhibitory activity (Thiyagarajan et al. 2014). Increased oxidative stress in the kidney induces inflammatory cascade .Also stimulates pro-inflammatory cytokines and chemokines like TNF-α, IL-6, COX-2, and TGF-β (Suryavanshi and Kulkarni 2017). Activation of these markers initiates the inflammatory and apoptotic process in the kidney leads renal damage (Garud and Kulkarni 2014, 2017a). The effect of sodium copper chlorophyllin treatment improved oxidative stress parameters and thereby inhibited kidney injury. (Suryavanshi and Kulkarni 2017).Renochlor Tablet has shown statistically significant improvements than Renochlor Syrup in primary and secondary efficacy parameters such as increase in eGFR, decrease in Serum Creatinine, Albumin to Creatinine ratio, Serum Urea, Blood Urea Nitrogen, Serum Phosphorus, TGF β-1 and Serum Potassium and increase in Serum Calcium and Serum Sodium from baseline to end of study.

Improvement in quality of life is one of the important outcome of CRF treatment that is rarely achieved in currently all known therapies.

Conclusion

Both dosage forms of RENOCHLOR, ie syrup and tablets (SCC) are safe and efficacious in management of Chronic Renal Failure. Showing reduction in TGF β-1, S Creatinine, S Urea, BUN, ACR ratio. Increase in eGFR and quality of life improves when given in 40 mg TID preferably on empty stomach for minimum 90 days. No change in hepatic parameters and serum electrolytes. All parameters clinically and statistically significant in chronic renal failure, However Renochlor tablet dosage form is marginally superior in primary and secondary efficacy clinical end points when compared with Syrup dosage form.

Declarations

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CREDIT AUTHOR STATEMENT

Dr. Milind Gharpure : Conceptualization Ideas, Methodology. **Nikhil Varma:** Review, Project administration. **Dr. Ravindra Mote:** Resources, Supervision. **Dr. Anurag Shukla , Dr Ramesh Rao , Dr Chaitanya Shukla :** Principal Investigators.

FINANCIAL STATEMENT

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DECLARATION OF INTEREST

 The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Authors MG,NV, they are associated with THINQ PHARMA CRO LTD which has funded the study.

Milind Gharpure – GM Natural Products

Nikhil Verma – GM Clinical Research

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Tables

Table 1 is in the supplementary files section.

Figures

Figure 1

Study Design

Supplementary Files

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