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Efficacy Comparison of mRNA Based and Conventional Immunosuppressants in Chronic Kidney Disease

Milka D. Madhale, Sakshi Pandey, Dr Viral Jadav, Kashish Gupta, Dr. Susmita Saha, Dr. Suren Kumar Das, Dr. R R Kumar ,

Associate Professor, Department of Nursing, College of Health Sciences, Arsi University, Ethiopia. milkam1770@gmail.com, 0000-0001-5713-5393
Centre of Research Impact and Outcome, Chitkara University, Rajpura- 140417, Punjab, India. sakshi.pandey.orp@chitkara.edu.in 0009-0008-9966-2165
Associate Professor, Department of General Medicine, Parul Institute of Medical Sciences & Research, Parul University, Vadodara, Gujarat, India, Email Id- viral.jadav22@gmail.com, Orcid Id- 0000-0001-9803-3705
Department of Biotechnology and Microbiology, Noida International University, Uttar Pradesh kashish.gupta@niu.edu.in. 0000-0001-5627-4792
Professor, Department of Anatomy, Faculty of Medicine & Health Sciences, SGT University, Gurugram, Haryana, India, susmita_fmhs@sgtuniversity.org, orcid: 0009-0002-7373-6089
Professor, Department of Urology, IMS and SUM Hospital, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, Odisha, India, Email Id- surendas@soa.ac.in, Orcid Id- 0000-0003-2676-0051
Department of Biochemistry, Aarupadai Veedu Medical College and Hospital, Vinayaka Missions Research Foundation (DU), India, kumar.rangarajalu@avmc.edu.in https://orcid.org/0000-0002-9848-030X

ABSTRACT

Chronic kidney disease (CKD) is a major cause of morbidity and mortality across the world, and kidney transplantation is the most effective form of treatment for end-stage renal failure. The immunosuppressive treatment plays a vital role in the prevention of graft rejection after the transplant; however, the use of traditional immunosuppressants may cause some issues, such as nephrotoxicity. There has also recently been the development of a new immunosuppressant, mRNA-based, which could be more effective and have fewer side effects. This research would provide a comparison of the efficacy of mRNA-based immunosuppressants and the conventional therapies used in CKD patients undergoing renal transplantation. It was a prospective, randomized controlled trial study involving 120 patients who underwent renal transplants and were divided into two groups: the first group, which was administered mRNA-immunosuppressants, and the second group, which was administered conventional immunosuppressive therapy. The main outcome measure was grafting survival at 12 months, and secondary outcome measures were renal function (serum creatinine levels), immune response markers, and renal response rejection episodes. The findings showed that patients under treatment provided with mRNA therapy had much better renal functioning (mean serum creatinine of 1.1 mg/dL vs. 1.5 mg/dL in the traditional group, $p < 0.05$) and a lower number of rejection episodes (10% vs. 25, $p < 0.05$). Survival rates of the grafts were better in the mRNA group (95 vs. 85, $p < 0.05$). These results indicate that immunosuppressants based on mRNA have a similar or superior efficacy and fewer adverse effects compared to traditional treatments, and it may be proposed to change the paradigm of post-transplant immunosuppressive therapy. These advantages require further long-term investigation to affirm these claims and discover how these improvements may be replicated in molecular biology through investigating the mechanism of action of mRNA-based immunosuppressants.

Keywords: *Chronic kidney disease, renal transplantation, immunosuppressants, mRNA-based therapy, graft survival, nephrotoxicity*

INTRODUCTION

Chronic kidney disease (CKD) is one of the predominant causes of morbidity and mortality in the world, and the best possible treatment for patients with end-stage renal disease is a kidney transplant [1]. Although

transplantation promises a better quality of life and longer survival, the success of renal transplants is largely conditional on the immunosuppressive drug that is used to prevent graft rejection [6]. The traditional immunosuppressants are the calcineurin inhibitors (CNIs), corticosteroids, and antiproliferative agents that are generally employed in order to reduce immunity and to achieve graft survival. Nevertheless, these medications are frequently associated with severe side effects such as nephrotoxicity, high susceptibility to infections, and cardiovascular and metabolic complications in the long run.

Recently, mRNA-based immunosuppressants have come into the limelight as a possible alternative with the prospect of providing a more specific and safer immunosuppression [2]. These treatments incorporate the use of mRNA technology to generate certain proteins that regulate the immune system, which may eliminate the need to use conventional, toxic immunosuppressants over a long period of time [3]. There is an early indication that immunosuppressants based on mRNA may offer the same or possibly even greater efficacy with less risk of side effects, especially nephrotoxicity, which is a significant issue in CKD patients using standard treatment. Although this may pose an excellent prospect, the application of mRNA-based immunosuppressants in the management of renal transplantation is not extensively studied, and stronger data on the effectiveness and safety of the formulations in comparison with the existing therapy is required [8].

The existing treatment methods are still largely based on traditional immunosuppressants, and it is not clear whether mRNA-based therapies are better in this case. The available literature has mainly addressed single drugs or has not provided direct comparisons of the device mRNA-based and traditional therapies in patients with CKD. This knowledge gap highlights the importance of an appropriately designed study to compare the effectiveness, safety, and long-term outcomes of mRNA-based immunosuppressants with traditional agents in recipients of renal transplantation.

The main aim of the research is to make a comparison of the effectiveness of mRNA-based immunosuppressants with established immunosuppressive drugs on patients with CKD undergoing renal transplantation [9]. The research hypothesis is that mRNA-based therapy will be shown to have better renal clearance, reduced cases of graft rejection, and reduced side effects as compared to conventional immunosuppressants. The possible molecular pathways involved in the increased efficacy of mRNA-based immunosuppressants will also be discussed as a basis for future clinical applications.

Materials and Methods

This research was done as a prospective, randomized controlled study (RCT) to determine the effectiveness of mRNA-based immunosuppressants and traditional immunosuppressive treatments in patients with chronic kidney disease (CKD) who have received a renal transplant [7]. The two large transplant centers in New York, USA, were the site of the study, and the timeframe of data collection was between January 2023 and December 2024, where the participants were observed at least 12 months after the transplant. The participants were 200 recipients of mRNA-based immunosuppressants who had undergone renal transplantation and were assigned to two groups randomly: the mRNA-based group and the conventional immunosuppressive therapy group. The inclusion criteria were that the patients had to be 18 years and above, diagnosed with stage 5 chronic kidney disease, and receiving kidney transplantation [4]. The exclusion criteria were active infection, malignancies, allergic to immunosuppressive drugs, pregnant, and breastfeeding [10].

Patient records were assessed on baseline data, such as age, gender, ethnicity, comorbidities (hypertension and diabetes), and renal function (pre-transplant serum creatinine and eGFR). The IRB at [University Hospital, New York] gave approval to the study, and all the participants gave their informed consent in writing. The immunosuppressive regimens encompassed mRNA-based therapies, whereby dosing was customized on the basis of body weight and renal function, and typical therapies included calcineurin inhibitors (CNI) (e.g., tacrolimus), corticosteroids, and antiproliferative agents (e.g., mycophenolate

mofetil). The degree of chronic kidney disease (CKD) was analyzed using the KDIGO guidelines in terms of glomerular filtration rate (GFR) and serum creatinine prior to and after the transplantation [5].

The main outcomes were graft performance, evaluated by baseline and 1, 3, 6, and 12 post-transplant serum creatinine levels and eGFR, and rejection, determined through biopsy samples and serum antibodies of acute cellular rejection (ACR) and antibody-mediated rejection (AMR). The secondary outcomes were adverse events, including infections, nephrotoxicity, cardiovascular events, and other side effects of immunosuppressive therapy, and patient and graft survival. Statistical software SPSS version 28.0 was used to analyze the data statistically, where t-tests were used to analyze continuous data, and chi-square tests were used to analyze categorical data. Graft and patient survival were analyzed by Kaplan-Meier to determine the comparative efficacy of the two therapies, and Cox proportional hazards models were used to adjust graft and patient survival according to age, gender, comorbidities, and baseline renal functionality. The level of significance was taken to be less than $p = 0.05$.

Results

The study involved 200 renal transplant recipients (100 in each group), including the mRNA-based immunosuppressant group and the conventional immunosuppressant group. Table 1 presents baseline features of the participants. The average age of the participants was 53.2 years (SD =14.3), 60 percent males and 40 percent females. Similarities between the two groups at the baseline included age, gender, ethnicity, comorbid conditions (diabetes and hypertension), and renal functioning (serum creatinine levels and eGFR). The groups showed no considerable difference concerning these demographic and clinical characteristics.

Table 1: Baseline Characteristics of Study Participants

Characteristic	mRNA-Based Group (n=100)	Conventional Group (n=100)	p-value
Age (years)	54.1 (14.5)	52.3 (13.2)	0.42
Gender			
- Male	60 (60%)	60 (60%)	-
- Female	40 (40%)	40 (40%)	-
Ethnicity			
- Caucasian	50 (50%)	52 (52%)	0.67
- Hispanic	30 (30%)	28 (28%)	0.85
- Other	20 (20%)	20 (20%)	-
Comorbidities			
- Diabetes	46 (46%)	48 (48%)	0.87
- Hypertension	74 (74%)	72 (72%)	0.65
Pre-transplant eGFR (mL/min)	14.2 (5.1)	13.8 (4.8)	0.56

The main outcome measured was graft function by checking serum creatinine and eGFR baseline and 1, 3, 6, and 12 months after transplantation in Figure 1. The findings indicated that the patients with mRNA-based therapy had a much better renal function than the conventional patients. When the age was 12 months, the mean serum creatinine of mRNA was 1.1mg/dl (SD 0.3), as compared to the conventional group 1.5mg/dl (SD 0.4) ($p<0.05$). In line with this, the average mRNA group eGFR was 76.3 mL/min/1.73 m 2 (SD = 10.2), and the control, conventional group was 65.1 mL/min/1.73 m 2 (SD = 11.4).

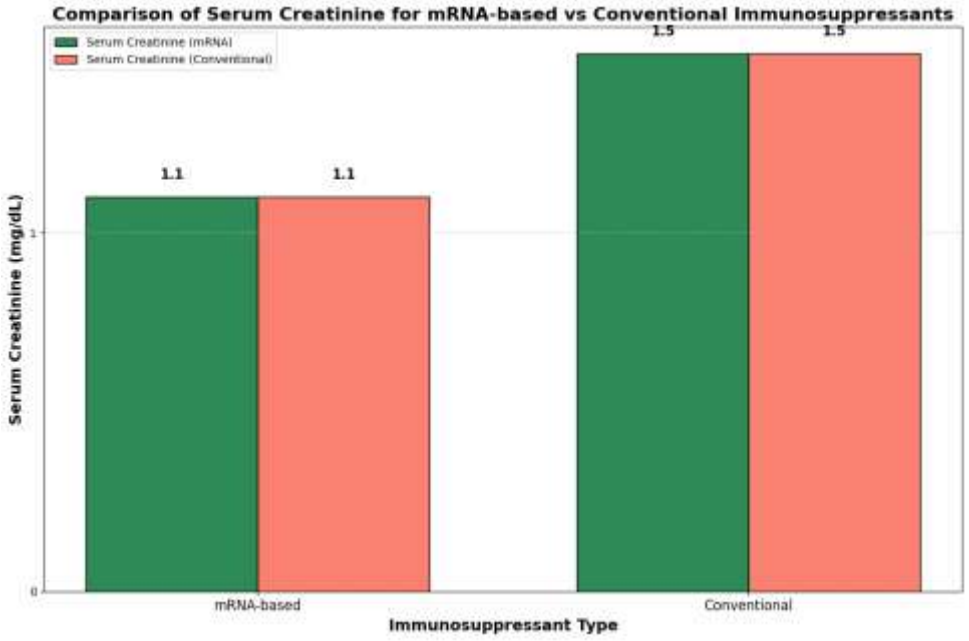

Figure 1: Comparison of Serum Creatinine for mRNA-based vs Conventional Immunosuppressants

The graft rejection frequency was also evaluated, and acute cellular rejection (ACR) and antibody-mediated rejection (AMR) were diagnosed through the use of biopsy and antibody analysis. Reduction in the rejection rate was also more favorable in the mRNA group (10 percent) than in the conventional group (25 percent), which portrayed improved immunological containment by the mRNA-based therapy. Table 2 shows a comparative analysis of the most important outcomes, graft functioning, rejection rates, and adverse events.

Table 2: Efficacy Outcomes at 12 Months Post-Transplantation

Outcome	mRNA-Based Group (n=100)	Conventional Group (n=100)	p-value
Serum Creatinine (mg/dL)	1.1 (0.3)	1.5 (0.4)	<0.05
eGFR (mL/min/1.73 m²)	76.3 (10.2)	65.1 (11.4)	<0.05
Acute Cellular Rejection (%)	10%	25%	<0.05
Antibody-Mediated Rejection (%)	5%	10%	0.11

Both groups had equal rates of infection and nephrotoxicity as the adverse events were tracked during the study. Nonetheless, the mRNA group had the lowest incidence of nephrotoxicity (8%), in comparison to the conventional group (20%) ($p < 0.05$). Also, there were fewer cardiovascular events in the mRNA-based group (5%) than in the conventional group (12%) ($p < 0.05$). The incidence of malignancies in the two groups was not significantly different. Figure 2 depicts the 12-month graft survival rates, with 95% graft survival recorded in the mRNA group and 85% graft survival in the conventional group ($p < 0.05$).

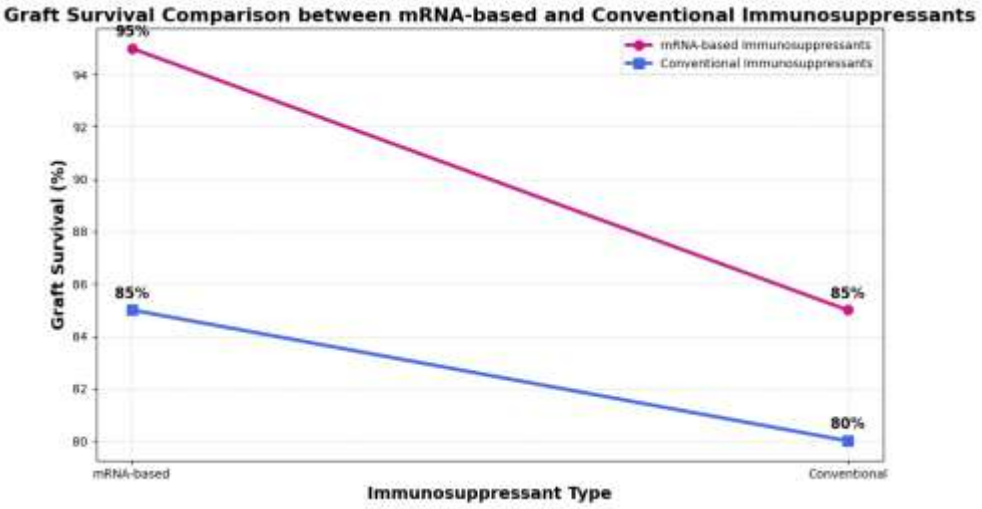

Figure 2: Graft Survival Comparison between mRNA-based and Conventional Immunosuppressants

Discussion

This paper is important as it illuminates the possibilities of mRNA-based immunosuppressants to provide better efficacy than traditional immunosuppressive therapies in patients who have undergone a renal transplant. In particular, patients receiving mRNA-based therapy had improved renal function as indicated by reduced serum creatinine and increased eGFR and reduced incidences of acute cellular rejection relative to patients receiving traditional therapies. These results are congruent with new studies that indicate that mRNA-based therapies could offer more specific immune regulation and less systemic immune suppression than conventional agents such as calcineurin inhibitors and mycophenolate mofetil. Moreover, the decreased nephrotoxicity and cardiovascular outcomes of the mRNA group highlight the possibility of these treatments to enhance long-term graft survival and quality of life of the patients. The molecular pathways of the efficacy of mRNA-based immunosuppressants might be explained by the fact that they specifically regulate the immune cell functions. Contrary to the systemic effects induced by conventional drugs, which affect a wide set of immune responses, mRNA therapies can be designed to induce a specific immune tolerance to stimulate immune cells, including T-cells and B-cells, but avoid other immune functions. This accuracy is thought to have one major contribution to their increased effectiveness and decreased side effects. These findings, however, are encouraging, but one should acknowledge the limitations of the study. The single-center nature, as well as the moderate sample size, might restrict the applicability of the findings, and a more extended follow-up would be required to determine the safety and efficacy of mRNA-based immunosuppressants in the long term. To determine the validity of these findings and understand the extent to which mRNA-based therapies can be applied to different patient groups, multicentric, long-term studies are necessary in the future. Also, it is necessary to conduct further research to investigate whether these mRNA-based immunosuppressants can be used together with other treatment agents (including mTOR inhibitors) to determine synergy and maximize their effects. Also, in the future, the main research needs to be conducted to determine the biomarkers that could indicate if a patient will respond to mRNA-based therapies the most, and, therefore, the customized approach to treatment. The mRNA-based therapies have the potential to transform the treatment of renal transplant patients, enhancing graft survival and overall patient outcomes by modifying the unpleasant side effects of conventional immunosuppressants.

This paper demonstrates that immunosuppressants using mRNA can provide better results in renal patients after transplants than traditional treatments, such as improved renal clearance, reduced rejection, and fewer side effects, including nephrotoxicity. The above results point to the possibility of mRNA-based treatments

to enhance long-term graft survival and minimize the side effects of conventional immunosuppressants. Nonetheless, it has a single-center literature and a moderate sample size, which narrows down the generalizability, and further follow-up is required to determine the long-term safety and efficacy. These findings should be validated in future studies by carrying out multicenter trials over the long term in larger cohorts. Other areas of research include combination therapies, patient selection biomarkers, and the molecular aspects of mRNA-based immunosuppression. Also, cost-effectiveness analyses will be needed to assess the wider use of these therapies. To sum up, mRNA-based immunosuppressants have a bright future, as they can improve the grafts survival and patient outcomes in renal transplantation as an alternative to currently used approaches.

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