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Archives of Nephrology and Renal Studies Short Communication

Safety of Using Rituximab Therapy During COVID-19 Pandemic

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Key Messages

- Rituximab is an important therapeutic agent in various diseases including kidney transplantation field.
- Treatment with Rituximab could be continued during COVID-19 pandemic with special precautions and shielding.

Abstract

Introduction: Our modern world is facing extraordinary circumstances while passing through a serious pandemic caused by the novel coronavirus (COVID-19) which may lead to multi-organ system failure & death. Bcell depletion could compromise antiviral immunity, which makes the safety of rituximab use in the COVID19 era unclear.

Methods: All patients who had renal transplant from the 1st of March 2020 till 30th of July 2020 and registered in the OPTN were retrospectively reviewed. Patients were followed up to September 2020. We included patients who received rituximab induction therapy during this period. Exclusion criteria were patients who did not receive rituximab induction therapy, and patients with missing data about rituximab induction therapy. Measured outcome centered on patient survival until the end of the follow-up period.

Results: During the first wave of COVID-19 pandemic from the 1st of March 2020 till 31st of July 2020, 9,095 patients had renal transplant and were registered in OPTN database. 8,770 patients had single organ transplant (kidney transplant) and 325 patients had dual organ transplant (kidney and pancreas). Out of this cohort, 114 patients received rituximab induction therapy.

The total number of deaths was 127 patients (1.39%). Among those who received rituximab induction agent, only one patient died during the follow-up period. The cause of death for this patient was unknown.

Conclusion: Our study showed that it is safe to use Rituximab as an important therapeutic agent during COVID-19 pandemic. However, special precautions and shielding are needed.

Keywords: Rituximab, Kidney Transplantation, Safety, COVID-19

Introduction

Rituximab is a chimeric (20% rodent and 80% human) monoclonal antibody that binds to the CD20 antigen present on the cell surface and leads to depletion of mature B-cells [1,2]. It is the first approved monoclonal antibody to be used in the therapy of indolent B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia

[3]. However, the role of Rituximab exceeded the clinical use in cancer patients to include various immunological disorders [4].

Numerous systemic diseases characterized by Antibody production may lead to serious kidney effects [5]. Rituximab has an emerging role in treating various antibody-producing disorders affecting the kidneys specifically in resistant cases that are not responding to conventional therapy. It has been used as a treatment for systemic lupus erythematous [6], antineutrophil cytoplasmic antibody-associated vasculitis [7], hemolytic uremic syndrome [8], mixed essential cryoglobulinemia [9], membranous nephropathy [10], and focal segmental glomerulosclerosis [11]. The vital role of Rituximab expanded to include the kidney transplantation field either as induction/desensitization therapy or as a treatment of antibody-associated rejection [12].

Our modern world is facing extraordinary circumstances while passing through a serious pandemic caused by the novel coronavirus (COVID-19) which may lead to multi-organ system failure & death [13,14]. Bcell depletion could compromise antiviral immunity, which makes the safety of rituximab use in the COVID19 era unclear. Nevertheless, the clinical decision to avoid Rituximab may lead to serious deleterious side effects in many patients including those with severe, refractory rheumatic diseases [15]. In kidney transplantation, the lack of safety information regarding the use of Rituximab may limit the use of this vital treatment option in various transplant-related disorders [16]. Our study aims to examine the safety of using Rituximab in the kidney transplant population during the Covid-19 pandemic.

Methodology

All patients who had renal transplant during the first wave of COVID-19 pandemic from the 1st of March 2020 till 30th of July 2020 and registered in the organ procurement and transplantation network (OPTN) were retrospectively reviewed. The authors declared that no approval was necessary for this study. Patients were followed up until the first of September 2020. We included patients who received rituximab induction therapy during this period. Exclusion criteria were patients who did not receive rituximab induction therapy, and patients with missing data about rituximab induction therapy. Measured outcome was patient survival until the end of follow-up. Data collected were patient age, sex, ethnicity, type of induction therapy, dialysis before transplant, delayed graft function, donor age, type of donor (living or cadaveric), maintenance immunosuppressive therapy at time of discharge, time of death and cause of death at follow-up.

Statistical analysis

STATA package-15 was used to perform the analysis. We collected the data from the STARFILES available in OPTN database. The files used were: KIDPAN_DATA and KIDPAN_IMMUNO_DISCHARGE_DATA. Each of these files was deduplicated separately. The deduplicated files were merged into one file using m:1 merge command. Continuous variables were reported as means and standard deviation while categorical variables were reported as percentages or frequencies. We described the baseline characteristics of the patients who received rituximab induction therapy, the cause of deaths and the characteristics of the deceased patients.

Results

During the 1st wave of COVID-19 pandemic from the 1st of March 2020 till 31st of July 2020, 9,095 patients had renal transplant and were registered n OPTN database. 8,770 patients had single organ transplant (kidney transplant) and 325 patients had dual organ transplant (kidney and pancreas). Out of this cohort, 114 patients received rituximab induction therapy. The baseline characteristics of patients who received rituximab induction therapy are shown in table 1.

The total number of deaths in our cohort was 127 patients (1.39%). Among those who received rituximab induction agent, only one patient died during the follow-up period (0.87%). The cause of death for this patient was unknown. The number of deaths among patients who did not receive rituximab was 126/8,968 (1.40%). The causes of deaths are shown in table 2. Cause of death was missing for six patients.

Discussion

Our study concluded that Rituximab is safe to use in the COVID-19 era. During the first wave of COVID-19 from March 2020 until the end of July 2020, we found no significant effect in mortality rate due to COVID-19 disease among kidney transplant patients who received Rituximab. These results may be crucial for the patients that depend on Rituximab as a pivotal therapeutic agent.

Clinical trials demonstrated the association of using Rituximab in patients with low immunoglobulin levels, particularly IgM and to a lesser extent IgG [17]. Both IgM and IgG are the neutralizing antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Studies investigating the serum of patients with COVID-19 reported the detection of IgM and/or IgG antibodies to the spike protein of the SARS-CoV-2 envelope about two weeks after the onset of symptoms [18,19]. These findings raised questions about the safety of Rituximab use during the COVID-19 pandemic.

Table 1: Baseline characteristics for patients who received rituximab induction therapy.

Variable:	
AGE: mean (standard deviation)	48.66 (14.58)
Gender: male (%)	58 (50.88%)
Dialysis before transplant (yes) : number (%)	93 (81.58%)
Ethnicity: White : number (%) Black : number (%) Hispanic : number (%) Asian : number (%) Multiracial : number (%)	 38 (33.33%) 39 (34.21%) 31 (27.19%) 5(4.39%) 1 (0.88%)
Education: None : number (%) GRADE SCHOOL (0-8) : number (%) HIGH SCHOOL (9-12) or GED : number (%) ATTENDED COLLEGE/TECHNICAL SCHOOL : number (%) ASSOCIATE/BACHELOR DEGREE : number (%) POST-COLLEGE GRADUATE DEGREE : number (%) Unknown : number (%)	 2 (1.77%) 4 (3.54%) 43 (38.05%) 33 (29.20%) 18 (15.93%) 10 (8.85%) 3 (2.65%)
Diabetes: No : number (%) Type I : number (%) Type II : number (%) Type unknown : number (%)	 81 (71.05%) 3 (2.63%) 29 (25.44%) 1 (0.88%)
Body mass index : mean (standard deviation)	28.40 (5.27)

Table 2: Cause of deaths.

Cause of death	Frequency	Percent
Unknown	18	14.88
other	24	19.83
INFECTION: BACTERIAL PNEUMONIA	1	0.83
INFECTION: BACTERIAL SEPTICEMIA	6	4.96
INFECTION: FUNGAL	2	1.65
INFECTION: MIXED OTHER	1	0.83
INFECTION: URINARY TRACT	1	0.83
INFECTION: OTHER	2	1.65
CARDIOVASCULAR: MYOCARDIAL INFARCTION	5	4.13
CARDIOVASCULAR - PULMONARY EMBOLISM	1	0.83
CARDIOVASCULAR: OTHER	13	10.74
CEREBROVASCULAR: OTHER	1	0.83
HEMORRHAGE: GASTROINTESTINAL	1	0.83
HEMORRHAGE: INTRAOPERATIVE	1	0.83
HEMORRHAGE: OTHER	4	3.31
MISCELLANEOUS: RESPIRATORY FAILURE	4	3.31
MISC - LIVER FAILURE	3	2.48

MISC - MULTIPLE SYSTEM ORGAN FAILURE (MSOF)	9	7.44
PRIMARY NON-FUNCTION (GRAFT NEVER FUNCTIONED POST-TRANSPLANT)	1	0.83
INFECTION: VIRAL- COVID-19	19	15.70
INFECTION: BACTERIAL SEPTICEMIA	1	0.83
INFECTION: MIXED OTHER SPECIFY	1	0.83
INFECTION: OTHER SPECIFY	1	0.83
HEMORRHAGE: OTHER SPECIFY	1	0.83

Clinical decision making of using Rituximab is further complicated by a few observational studies. Schulze-Koops et al. reported losing two patients with rheumatoid arthritis after being diagnosed with COVID-19 disease. They suggested that their previous treatment with Rituximab was a leading cause of their fatal outcome [20]. Moreover, Loarce-Martos et al. conducted a descriptive study on 76 patients with systemic rheumatic disease who were treated with Rituximab and had a confirmed COVID-19 disease. They reported frequent hospitalization among those patients with a mortality rate as high as 23% [21]. Nonetheless, this study was limited by its small sample size, limitation to a single-center, and lack of reporting other comorbidities that may worsen the prognosis.

In contrast to the aforementioned studies, Guilpain et al. discussed a case of a patient with granulomatosis and polyangiitis who received four doses of Rituximab in her treatment course and was diagnosed with COVID-19 disease. Despite the initial deterioration in her condition that required mechanical ventilation support, her clinical condition improved rapidly. Extubation and oxygen support was withdrawn [22]. Their results support the conclusion of Monti et al., who suggested the absence of a significantly increased risk of severe COVID-19 in patients with chronic arthritis receiving biologic or targeted synthetic disease-modifying anti-rheumatic drugs [23]. Another study added more confusion when Mehta et al. spoke about the possible benefits of using Rituximab as a potential therapeutic agent in the management of specific complications of COVID-19 [15].

We believe that our results will support those who recommend avoiding withdrawal of Rituximab. After the interruption of this important therapeutic agent, a recommencement of therapy may not reverse the clinical decline from its initial discontinuation. In kidney transplantation, the value of Rituximab is well established in treating various conditions [24]. Rituximab is widely used in ABO blood group incompatible kidney transplantation [25], HLA antibody incompatibility [26], and even as a treatment for acute renal allograft rejection [27]. Moreover, Rituximab has been demonstrated to be effective in the management of lymphoproliferative disorders that may occur after transplantation [28]. Decision to withdraw Rituximab should be built on a definitive conclusion from solid evidence.

Our study has limitations. Being a retrospective observational study limits the ability to produce any causal interpretation. The available data was limited to the mortality causes without any comments on the infection rates, disease severity, or comorbid conditions. However, our study concluded important alarming results that trigger the conduction of more studies to address the short and long-term complications and outcomes for Rituximab use in the COVID-19 era.

In conclusion, our study showed that it is safe to use Rituximab as an important therapeutic agent during COVID-19 pandemic. However, special precautions and shielding are needed.

Conflict of Interest

The authors declare no conflict of interest.

Financial Disclosure

The authors declare no funding was received for this study.

Authors Contributions

Hatem Ali: Data analysis, Methodology, Acquisition, Final approval

Mahmoud Mohamed: Acquisition, Draft writing, Data collection, Final approval

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