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Case Report

Decision to Use Rituximab as a Systemic Biological Treatment in Systemic Lupus Erythmatosus Among Sudanese Patients: Case Series Report

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Abstract

Systemic Lupus Erythematosus (SLE) is a disease with various manifestations. Its treatment aims to reduce the symptoms and to prevent the flairs. In this report, we are discussing three cases of SLE who required treatment with Rituximab. The first case was an 18 year old female who presented with urinary symptoms and subsequently she developed lupus nephritis. She was treated with prednisolone and hydroxychloroquine for two months without response. The Rituximab was introduced with a good initial response. The second case was a 20 year female, presented with nonspecific symptoms. She was treated with steroid but her condition was complicated by development of antiphospholipid antibodies, abortion and lupus nephritis. The last case also developed lupus nephritis despite the treatment with steroid and hydroxychloroquine. Rituximab was add but discontinued because the patient was financial unaffordable to provide the rest of the doses. Her condition deteriorated more and ultimately died.

Keywords: Biologic Treatment; Rituximab; Sudanese; Systemic Lupus Erythematosus

Abbreviations

SLE: Systemic Lupus Erythematosus; IL10: Interleukin 10; RFT: Renal Function Test; AKI Acute Kidney Injury; RBCs: Red Blood Cells; UTI: Urinary Tract Infection; CBC: Complete Blood Count; ESR: Erythrocyte Sedimentation Rate; CRP: C Reactive Protein; US: Ultra Sound; ANA: Anti-Nuclear Antibodies; MRI: Magnetic Resonance Imaging; PPI: Proton Pump Inhibitor; RF: Rheumatoid Factor; MMF: Mycophenolatemofitel; TB: Tuberculosis; BP: Blood Pressure.

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the production of antibodies that attack many body's organs. It affects women more than men (90% of new patients) [1,2]. Patients suffering from SLE present with constitutional symptoms; fever, fatigue and weight changes. Renal failure and sepsis are the leading causes of death [1]. Defect of T cell function and activation of B cell play a major role in the disease pathogenesis. Release of cytokines such as interleukin 10 (IL10) by T- helper cells results in increased production of antibodies by B cells [2]. Recently more studies describing apoptosis as a process that has a central role in the development of SLE, the presence of auto-antigen on the surface of apoptotic cells allow the production of more antibodies against self-antigens [3]. For all time, treatment of SLE has been aims at remission and prevention of flairs using Hydroxychloroquine, steroid and immunosuppressant drugs [4-6].

Biological agents that aim to deplete B cell by either general inhibition using direct monoclonal antibodies against B cell CD 20 (Rituximab) or selective inhibition of B cell survival factors BLyS (belimumab) has been one of the major ways to treat SLE patients. It used for patients presenting with life-threatening condition or refractory disease [7,8]. Other biologic modalities include the use of T cell, cytokines and complement inhibitors, however B cell targeted therapy is the most frequently used [9]. Clinically the most common scenario for using Rituximab is in the case of lupus nephritis resistant to cyclophosphamide and mycophenolate/azathioprine [7]. Two randomized controlled trials were conducted to evaluate the safety and efficacy of Rituximab therapy; one involved moderate to severe non-renal SLE and the other involved patients with proliferative nephritis [10]. Both studies failed to find a statistical difference between placebo and Rituximab in reducing disease activity [7]. Many data were published about the use of rituximab in SLE combined with other diseases such as antiphospholipid syndrome and Catastrophic antiphospholipid [11], but the efficacy of Rituximab alone in SLE without the concomitant use of high dose steroid as well as immunosuppressant medication were few. In this reports, we hope it will serve to increase knowledge and kindle awareness of the use of rituximab in SLE treatment in Sudan.

Case one

An 18 years old previously healthy lady presented in March 2017, with vomiting, fatigue, arthralgia and a puffy face to a secondary level hospital. She had been feeling unwell for the previous 3 months with recurrent urinary symptoms and she was diagnosed each time as a case of urinary tract infection (UTI) and discharged with antibiotics. In Hospital, her baseline renal function test (RFT) showed a picture of acute kidney injury (AKI) with urea of 71 mg/dl and a creatinine of 1.5 mg/dl. Her urine analysis showed uncountable red blood cells (RBCs), Pus cells and granular cast. Her 24 hour urine protein showed proteinuria of 0.53 g, she was normotensive and her vital signs were stable. Her complete blood count (CBC) revealed a thrombocytopenia (100,000/cm^3) and her hemoglobin was 4g/dl. She had normocytic normochromic anemia for which she was transfused. Her erythrocyte sedimentation rate (ESR) was 70 and her C reactive protein (CRP) within a normal range. She had a family history of SLE related to her grandmother and polycystic kidney disease in second degree relatives. On initial screening for the cause of acute kidney injury (AKI), her ultrasound (US) of kidneys showed normal sized kidneys and texture. Her antinuclear antibodies (ANA) profile showed a strongly positive antibodies against Ribo-nucleo-protein (RNP), Anti Sm antibody, anti sjogren syndrome antibody (SSA), anti Ro52 antibody, Ribosomal P protein and weakly positive antibodies against anti-double stranded DNA dsDNA, nucleosomes and histones. She was diagnosed as SLE with lupus nephritis and started on prednisolone 20 mg and referred to a Rheumatology on the same month of March. Further investigations were done to exclude other SLE manifestations, her chest X ray, echocardiography, magnetic resonance imaging (MRI) brain and X ray of hand and pelvic joints were normal. She was continued on prednisolone, hydroxychloroquine low dose of 200 mg a day initiated with the adjuvant medication of proton pump inhibitor (PPI), calcium and vitamin D tablets and haematinics. A decision to start on Rituximab was taken and the first dose of 500 mg infusion was administered by the end of the first week of May 2017, a total of 4 doses of 500 mg each 1 week apart, the last one on the 30th of May. There was good initial response following completion, clinically and biochemically with the disappearance of microscopic hematuria, casts and proteinuria in serial urine samples taken in July, October and December. RFT improved with urea ranged between 20 - 30 mg/dl and a creatinine between 0.5 - 0.9 mg/dl. Her CBC showed mild improved anemia in the range of 10 - 12g/dl, normal platelet count of above 150, 000 cm^3 but her C3 and C4 complements levels measured for the first time in 2018, were low at 40 and 9 respectively. Her ESR remained high between 70 - 80 mm/hr while CRP remained nonreactive. Repeat ANA profile on July 2017 tested negative for dsDNA and histone antibodies, the rest remained positive. A relapse was documented by positive urinary sediment of proteinuria (two crosses, roughly around 0.5g) in February 2018. The RFT remained stable, urea at 30 and creatinine at 0.9, with persistent proteinuria confirmed in May 2018 (proteinuria of 3 crosses roughly around 0.75g) and a concurrent drop of serum albumin from 3.5 to 3.2g/dl with no significant rise in urea and creatinine. Her CBC remained at her baseline. Another cycle of Rituximab 500 mg IV of two doses one week apart then monthly to a total of 4 infusions decided. The first given on 12th of February, 2018, the second on the 19th of February, the 3rd was withheld on 19 of March due to bacterial tonsillitis and again withheld on 8th of April due to unavailability of beds to monitor infusion. Now Patient is free of symptoms, renal function test and urine general are normal.

Case two

In January 2002 a female at the age of 20 years old developed a fever, generalized arthralgia and fatigue for one week, she was found to have leucopenia of 2800/cm^3 and was diagnosed as typhoid fever and treated with antibiotics. Also, she was simultaneously treated for falciparum malaria as Sudan is a country where it's highly endemic. There was not much improvement and upon testing her urine showed significant albuminuria of two crosses. With the persistence of the symptoms beyond two weeks the diagnosis was shifted towards pyrexia of unknown origin and more tests were undertaken, her ANA profile test and dsDNA were positive, and she was diagnosed as a case of SLE. Her complement levels C3 and C4 remained within normal limits throughout the course of her disease. Her other ANA profile, rheumatoid factor (RF) were all negative. She was started on a tapering prednisolone course with a starting dose of 15mg with significant improvement. In 2004 she got married and was got pregnant in the following year, she was tested for antiphospholipid antibodies which were positive. Her proteinuria worsened during the pregnancy. She was

restarted on prednisolone and aspirin was introduced as well, unfortunately she had aborted at 20 weeks of gestation. Her renal function deteriorated with a creatinine of 4 mg/dl and urea of 90. Renal Biopsy was done; it confirmed the diagnosis of stage four Lupus nephritis. She was given pulses of Methylprednisolone for 3 days and continued on high dose prednisolone of 60 mg daily, a tapering course to a daily maintenance dose of 10 mg. Azathioprine introduced with good recovery of renal function back to normal baseline but minimal regression of proteinuria. In 2007 Mycophenolatemofitel (MMF) was introduced to replace azathioprine with further regression of proteinuria to around 250 mg/day, i.e one cross. In the same year, she developed pain in the Right hip and was walking with a limp, a vascular necrosis of Right femoral head was confirmed by MRI and she was referred to the orthopedic surgeon for total hip replacement. In 2013 she was admitted to hospital with fever, chronic cough for three months and cervical lymphadenopathy, her chest X ray showed consolidation and so she was diagnosed clinically as tuberculosis (TB) with no microbiological or serological proof and was started on antituberculous medication. Her condition worsened on the second day and she became stuperose, she was then diagnosed as sepsis and pneumonia. MMF was ceased and she treated for sepsis and covered with broad spectrum antibiotics with good recovery. Since then MMF was replaced by Hydroxychloroquine. In 2016 she developed Left eye sudden loss of vision, fundal photography and optic angiography showed central retinal vein occlusion, the patient was treated with anticoagulation, warfarin with a target INR of 2 - 3. In 2017 she developed sudden Right side weakness and aphasia. Her Hemoglobin dropped to 9g/dl and ESR rose to 120. Brain CT scan showed a left side hemispheric infarct. Atorvastatin and clopidogrel were added to her medication. A decision to start Rituximab was taken and the patient was given four injections of 500 mg two weeks apart with improvement regarding her speech/language and her mobility. Her renal function remained stable but her white blood cells count remained low at 2000 cm^3. Her haematologic indices showed low platelet of 100,000/cm^3 and normocytic normochromic anemia. Now the patient is free of symptoms and CBC, RFT are all normal.

Case three

A Sudanese lady who had a mother with rheumatoid arthritis, had been suffering from polyarthritis for 2 years in Egypt before being diagnosed as a case of SLE in 2015, May with a positive ANA profile, dsDNA, and elevated inflammatory markers. She had severe anemia which was treated with multiple blood transfusions and haematinics, and was started on prednisolone and azathioprine. She developed a malar photosensitive rash during the course of her illness for which she received sun blocks. She also received hydroxychloroquine and NSAIDs for arthritis along with other adjuvant medication like calcium, vitamin D and PPI. In 2016 April, the patient was discovered to have high blood pressure (BP) for which she received methyldopa with moderate control on serial BP measurements in the range of 120 - 150 systolic and 85 - 5 diastolic and positive urinary sediments. Her renal function was impaired. Lupus nephritis confirmed by renal biopsy and she was started on intravenous cyclophosphamide monthly injections for 6 months in Egypt without any improvement in RFT but she remained stable in terms of hematological indices, her hemoglobin reflected a just mild anemia of normocytic normochromic type in the range between 8.5 and 10.6. Patient had recurrent admissions to hospital in the year that followed either due to flares of the disease reflected by a drop in hematological indices or recurrent infections i.e. abscess drainage, chest, gastrointestinal or urinary tract infections. A decision was made to try patient on Rituximab in 2017, April. Due to financial constraints and unavailability of the drug, the first dose was acquired and administered one month later, and only half the recommended dose, 500 mg of Rituximab infusion was given, with a decision to give the second dose of 500 mg one week later. There was no much improvement reflected clinically or biochemically in terms of RFT, urinary sediment, or inflammatory markers measured 1 week and 1 month later. The patient continued to have proteinuria and hypo proteinemia. Complement levels or CD19 and CD20 were not measured due to financial constraints. For the same reason the second dose was given in June 2017 without much improvement. In 14 September of 2017 she was admitted with abdominal pain and watery diarrhea, she had generalized edema, the cause of which was serum albumin of 1.1g/dl, a result of proteinuria which further worsened by enteric losses and a possible viscous cycle activation of the Angiotensin - Aldosterone system. Her RFT showed urea of 142 mg/dl and Creatinine of 2.9 mg/dl. She had no signs of cardiac failure and her liver function test was normal, She had a therapeutic tap for large Ascites causing respiratory discomfort and orthopnea, she received 5 infusions of HAS 20% for replacement without much improvement due to the ongoing losses, her renal function further deteriorated with enteric fluid and third space loss. Urea elevated to 236 and Creatinine to 4.9 mg/dl. She developed thrombocytopenia of 40 and a prolonged INR of 1.7. The patient was given vitamin K and units of platelets. She diagnosed as worsening SLE but was also treated as a case of sepsis and put on antibiotics according to hospital protocol. Her condition was further complicated by metabolic acidosis of PH of 6.9 and decision to dialyses was taken. On the 14th of October 2017 patient arrested during the hemodialysis session, CPR and advanced life support carried out successfully and she was intubated. Unfortunately, she had another cardiac arrest on the 19th but unsuccessful resuscitation and pronounced dead.

Discussion

The three cases are female patients in the childbearing age. The estimated incidents rate among men is 0.9 per 100 000 person years, for women it varies according to many studies in Europe and the United Kingdom from 1.9 – 5.5 per 100 000 person –years [12,13]. About 90% of the presented patients are females [1]. The

first case presented with nonspecific and urinary tract symptoms. On evaluation she had abnormal renal function test with high urea, creatinine, hematuria and proteinuria consistent with acute kidney injury. The kidney is the most commonly affected organ in SLE [1]. 50% of the patients had developed clinical manifestation of renal disease secondary to deposition of immune complexes. But proteinuria and some degree of kidney involvement had been noticed on biopsy in almost all patients [1]. In this case, the patient did not know about having SLE. Part of the disease process is the production of antibodies against blood cells leading to leukopenia, anemia and thrombocytopenia, it is common and some studies recorded more than 80% of patients presented initially with hematological manifestations [14], our case also had some hematological abnormalities manifested as anemia and low platelet count. With the wide range of presentation of SLE, the diagnosis depends on the clinical picture, exclusion of other differential diagnoses and serologic findings. Anti dsDNA and anti-smith antibodies are specific for SLE while ANA is more sensitive [15]. SSA and RNP present in 30% and 25% of patients respectively, anti-ribosomal P protein is highly specific but not sensitive [15]. In this case serology tests were positive for all above mentioned antibodies and she had a high ESR level supporting the diagnosis of SLE as the underlying cause of her kidney problem. She started on prednisolone 20 mg and hydroxychloroquine low dose of 200mg. according to 2019 EULAR guideline for SLE management, the steroid can gives a rapid symptomatic relief but it should be reduced to ≤7.5 mg/day prednisone equivalent or to be discontinued on the long term management. They also recommended that hydroxychloroquine to be used in all patients, the documented effective dose is 6.5 mg/kg/day [5]. Two months later her condition was not improved and a decision to start her on biological treatment was made. She received a cycle of 4 doses of 500 mg Rituximab one week apart. Rituximab is recommended for patients either presented with life threating organ involvement or fail to respond to the treatment [5]. it is usually used as induction therapy, either 4 doses of 375 mg/m2 one week apart or two fortnightly doses of 1000 mg [5,7]. Both indications applied to our patient. Fortunately, her condition both clinically and biochemically, CBC, RFT and urine analysis improved when checked 2 months after treatment. Moreover, anti dsDNA and histones became negative. Unfortunately she developed persistent proteinuria months later for which she received a second cycle of treatment with Rituximab.

The second patient was similar to the first one in term of her age, initial nonspecific constitutional symptoms and presence of significant proteinuria. But she had leucopenia ($2800/cm^3$). Leucopenia noted in 15.7% of newly diagnosed patients, however with hematological manifestation alone the diagnosis of SLE can be missed without high suspicious [14]. In this case she was wrongly diagnosed as having typhoid fever and pyrexia of unknown origin until her serology showed findings supporting the diagnosis of SLE upon searching for the causes. Her symptoms improved with tapering corticosteroid. Two years later proteinuria got worse during her pregnancy. In addition, she developed antiphospholipid antibodies for which she received prednisolone and aspirin; sadly she lost her pregnancy in the 20 week gestation. Presence of antiphospholipid antibodies in SLE patients found to be associated with more thrombotic events, obstetric complications and end organ damage. Many studies supported the use of low dose aspirin for prophylaxis and additional anticoagulant such as low molecular weight heparin when there is a high risk of thrombosis such as during pregnancy [5,16]. The patient also developed lupus nephritis confirmed by renal biopsy and was treated with pulses of Methylprednisolone for 3 days and then initially maintained on high dose oral steroid followed by tapering along with the introduction of azathioprine. Two years later MMF was started to replace azathioprine. The recommended treatment for lupus nephritis is divided into two phases; the first is induction phase using MMF or cyclophosphamide, the second is a maintenance phase using azathioprine or MMF. High dose intravenous Methylprednisolone for 3 days can also be used for acute renal involvement after exclusion of infections. Early addition of immunosuppressive drugs such as azathioprine is indicated to facilitate tapering and discontinuation of glucocorticoid. Reduction of proteinuria to ≤1 g/day at 6 months indicated a promising outcome [5]. A few years later the course of her illness complicated with avascular necrosis of the right femur head, TB, central retinal vein occlusion and left hemispheric infarct. For that, a decision to start her on Rituximab was made and she received 500 mg four injections 2 weeks apart.

The third case initial presentation was mainly a history of arthritis and anemia for almost two years. SLE had been diagnosed by a positive serological markers and she was treated accordingly with prednisolone, azathioprine and hydroxychloroquine. Later she developed lupus nephritis confirmed by biopsy and manifested as impaired renal function, hypertension and positive urinary sediments. There was no improvement on 6 months cyclophosphamide injections. Boumaps., *et al.* reported that Patients who received a short course of cyclophosphamide as monthly pulses for 6 months showed a sustained increase in creatinine and more exacerbations than those treated with long dose cyclophosphamide [17]. After this course, she had frequent hospitalizations due to infections and flare for which Rituximab was introduced. She received only half the recommended dose (500 mg) initially and the second recommended dose 2 month later instead of one week apart due to financial issues. The deterioration continued and she had ascites, low albumin, further deterioration of her renal function, sepsis and metabolic acidosis for which she needed dialysis but she had cardiac arrest during the session and return of spontaneous circulation after resuscitation. Unfortunately 5 days later she had a sec-

ond cardiac arrest, the resuscitation was unsuccessful. The most common causes of mortality in SLE are renal failure and sepsis [1]. In a multicenter study done among 164 SLE patients who were refractory to the standard therapy, 99% of them received Rituximab and corticosteroid, 124 received immunosuppressive treatment at 6 and 12 months. The results showed that 33% did not respond to the treatment. The role of Rituximab in the treatment of refractory cases was still not determined and 2 well designed studies failed to show additional benefits of Rituximab to the standard therapy [18]. But in this case, inadequate course of the treatment might be responsible for poor outcome.

Conclusion

The exact added effect of Rituximab to the treatment of refractory cases of SLE still needs more studies. In our report, three patients received Rituximab after failure to respond to the standard therapy. Two of them improved and unfortunately one died. The current usage of rituximab in SLE patients may be considered conservative, representing an appropriately used treatment and medication for those who with high medical need within larger patient population with immune diseases such as SLE (Figure 1).

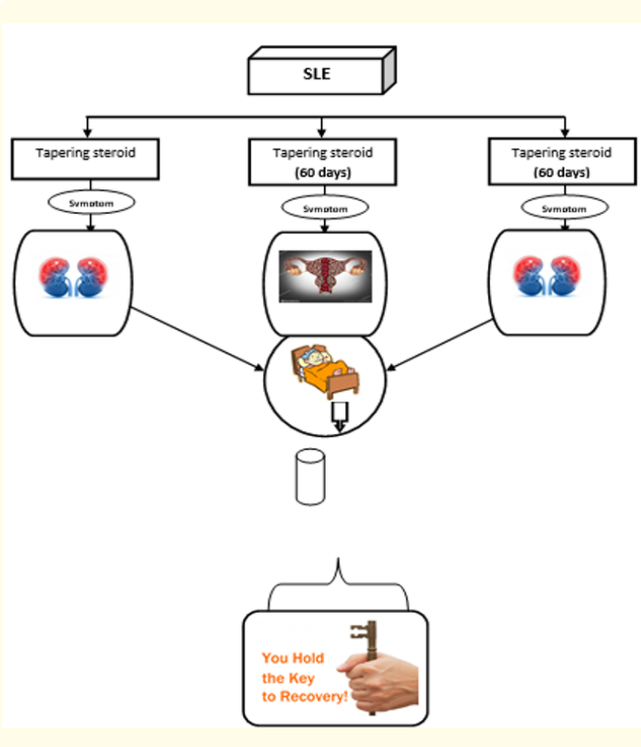

Figure 1: A graphical figure represents the high efficacy of Rituximab in the management of SLE after steroids resistant.

Ethical Approval

Obtained from federal ministry of health.

Disclosure of Conflict of Interest

None.

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