Managing Active Lupus Nephritis During COVID-19 Pandemic

Abstract
India is seeing a rapid rise in coronavirus disease-2019 (COVID-19). Immunosuppression is a possible risk factor for severe COVID-19, although their exact interaction is unclear. A total of 13 cases with active lupus nephritis (LN, with or without extra-renal manifestations) were managed with intense immunosuppression between January 2020 and June 2020 during the COVID-19 pandemic at our center. There were no other comorbidities in any patient. All patients received hydroxychloroquine as a part of standard of care. Vigorous precautionary measures were taken for preventing infection in all. One patient developed acute respiratory distress syndrome but was tested negative for COVID-19. None of the other 12 patients developed symptoms suggestive of COVID-19. We report safe management of patients with active LN with intense immunosuppression along with vigorous precautions amidst the COVID-19 pandemic. The role of hydroxychloroquine along with timely precautions needs to be further explored as protective measures against COVID-19 among systemic lupus erythematosus patients.

Keywords: COVID-19, flare, hydroxychloroquine, immunosuppression, lupus nephritis, systemic lupus erythematosus

Introduction
India is witnessing a rise in the number of cases of COVID-19 with 168,269 total active cases and 12,948 deaths as of 20th June 2020. The third phase of community spread has already been seen in some parts of the country. Among others, risk factors for severe COVID-19 include chronic kidney disease and cancer. Moreover, kidney transplant recipients are reported to have severe COVID-19 disease. The exact interaction of COVID-19 infection with immunosuppression is elusive. An early effective immune response is required to combat progression of COVID-19 infection to severe phase characterized by lung inflammation. In patients with active lupus nephritis (LN) on intense immunosuppression, an effective anti-viral immune response in case of exposure to COVID-19 may not develop and may predispose for the acquisition of the infection. This would make a case for withholding intense immunosuppression in such patients. However, the perils of not treating active LN patients seem to weigh over the risk of severe COVID-19 infection in them. European guideline has recommended continuing immunosuppressive drugs in patients with rheumatic diseases during the COVID-19 pandemic. However, the strategy to manage patients who present with flare or new onset of LN which would require intensification of immunosuppressive therapy during the peak of this pandemic is not clear. In this report, we describe the experience of treating patients with active LN during the COVID-19 pandemic.

Cases
There were 13 patients who were started on induction therapy for active LN during the last 6 months (from January 2020 to June 2020). The median age of the patients was 23 (19.5–25) years with 12 females and 1 male. While 3 patients had only renal manifestation of systemic lupus erythematosus (SLE), the other 10 had variable mucocutaneous, musculoskeletal, hematological, and pulmonary manifestations. Among 4 patients with known SLE, 3 had new onset LN and 1 patient with history of LN had severe nephritic flare. None of the patients had other comorbidities such as diabetes, coronary artery disease, chronic lung disease. Mycophenolate mofetil (2 g/day) or cyclophosphamide along with high-dose steroids (starting

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with 1 mg/kg/day prednisolone; 3 patients received additional intravenous methylprednisolone pulse 0.5–1 g per dose for first 3 days) were used as induction therapy in 10 and 3 patients, respectively. Cyclophosphamide at 0.5–0.75 g/m² every monthly was administered for 3 patients who presented with rapidly progressive glomerulonephritis (RPGN). All the 3 patients with RPGN were admitted at our hospital; 1 of these 3 patients had systemic thrombotic microangiopathy (TMA) and 1 had developed diffuse alveolar hemorrhage causing severe acute respiratory distress during hospital stay. The second patient was tested and found negative for COVID-19. None of the other 12 patients developed any symptoms suggestive of COVID-19 during this period. Two patients in addition were given plasma exchange (7 sessions, 40 mL/kg plasma volume replaced); one for diffuse alveolar hemorrhage and the other for systemic TMA. There was no history of travelling overseas or any obvious contact with persons who have travelled overseas in recent past in any patient. Thus, only one patient fulfilled the criteria for testing for SARS-CoV-2[1] and was tested. All patients received hydroxychloroquine (HCQ) (6.5 mg/kg/day) as a standard of care. In addition, 8 out of 13 patients were on renin-angiotensin-aldosterone system (RAAS) blocker. Nine (69.2%) of the 13 patients had recent onset of SLE (within last 3 months) and 4 (30.7%) were known cases of SLE with a median duration of 20.5 (7.2–70.5) months. The individual patient characteristics are shown in Table 1.

Vigorous precautionary measures were applied in all patients for preventing COVID-19 infection. This included the following measures: 1) hand hygiene, 2) avoiding touching face, 3) indications and proper handling of masks, 4) social distancing (which included stay at home and avoid meeting visitors even at home), and 5) avoiding going out and unnecessary visit to hospital. Teleconsults using phone calls and chat-based platform “WhatsApp” were used to provide regular updates on COVID-19 pandemic and circulation of health posters. Parenteral drug administration was being advised to be done locally at nearby centers. Patients were contacted for guidance and compliance with drugs and above measures regularly by calls. They were also notified about the local COVID-19 specific medical helpline number provided in each district.

**Discussion**

We report our experience of treating active LN patients with intense immunosuppressive therapy safely amidst the COVID-19 pandemic. None of the patients developed symptoms suggestive of COVID-19, except one who was tested and found negative for COVID-19. The reason could be three-pronged: 1) effective patient education on precautions and supportive patient management by using telemedicine, 2) absence of other comorbidities in our patients which are usual risk factors for severe COVID-19, and 3) concomitant prescription of HCQ for all patients as a standard of care for SLE.

Data concerning the risk and impact of SARS-CoV-2 infection in immunosuppressed patients is inconsistent. Inferring from the reports of COVID-19 in kidney transplant recipients and cancer patients, it is likely that immunosuppressed patients are at higher risk of severe COVID-19.[3,4] Data on COVID-19 in SLE patients is conflicting. In a series of 17 patients with clinically quiescent SLE and COVID-19, acute respiratory failure

**Table 1: Baseline patient characteristics**

| Age (years)/Sex | LN class | Induction agent (in addition to steroids) | Syndrome | Serum creatinine (mg/dL) | Serum albumin (g/dL) | 24-hour urine protein (g/day) | Duration (months) from start of therapy till last follow-up |
|-----------------|----------|------------------------------------------|----------|-------------------------|---------------------|----------------------------|---------------------------------------------------------|
| 38/F            | IV       | CYC<sup>a</sup>                          | RPGN<sup>c</sup> | 3.38                    | 2.12                | 3.34                      | 6                                                        |
| 35/F            | V        | MMF<sup>b</sup>                          | NS<sup>d</sup>   | 0.33                    | 2.4                 | 3.96                      | 5                                                        |
| 28/F            | IV+V     | MMF                                      | NS        | 0.77                    | 1.9                 | 1.886                     | 6                                                        |
| 17/F            | V        | MMF                                      | NS        | 0.6                     | 3.1                 | 0.656                     | 7                                                        |
| 28/F            | V        | MMF                                      | NS        | 0.5                     | 2.8                 | 3.5                       | 5                                                        |
| 23/F            | III      | MMF                                      | NS        | 1.2                     | 3.01                | 1.13                      | 5                                                        |
| 22/F            | V        | MMF                                      | Subnephrotic proteinuria | 0.6                | 3.8                | 0.678                     | 6                                                        |
| 24/F            | V        | MMF                                      | NS        | 0.58                    | 1.35                | 1.2                       | 7                                                        |
| 30/F            | II       | MMF                                      | NS        | 0.9                     | 2.19                | 5.216                     | 7                                                        |
| 15/F            | III      | MMF                                      | NS        | 0.77                    | 3.2                 | 4.2                       | 6                                                        |
| 19/M            | III      | MMF                                      | Asymptomatic proteinuria | 1.03               | 3.5                | 0.651                     | 4                                                        |
| 20/F            | Not done | CYC                                      | RPGN, Systemic TMA<sup>f</sup> | 4.2                | 2.1                 | 2.4                       | 4                                                        |
| 23/F            | IV       | CYC                                      | RPGN, DAH<sup>f</sup> | 6                    | 2.1                 | 1.8                       | 5                                                        |

<sup>a</sup>CYC - Cyclophosphamide, <sup>b</sup>MMF - Mycophenolate mofetil, <sup>c</sup>RPGN - Rapidly progressive glomerulonephritis, <sup>d</sup>NS - Nephrotic syndrome, <sup>e</sup>TMA - Thrombotic microangiopathy, <sup>f</sup>DAH - Diffuse alveolar hemorrhage
occurred in 65% and 14% died.[8] Of note, the studied population was older (mean age: 53.5 years) than usual SLE patients, and 60% and 50% had obesity and CKD as comorbidities, respectively.[8] Hence, it is likely that younger age and absence of comorbidities act as indirect protective factors for SLE patients at large, similar to our patients. Contrary to the findings by Mathian and colleagues,[5] two other studies from Hong Kong and Italy, respectively, found none of the SLE patients surveyed to be affected by COVID-19.[9,10] Moreover, SARS-CoV-2 infection was not observed to affect obviously immunosuppressed pediatric population in Italy.[11] Another report on 18 patients from the US found symptomatic COVID-19 infection in 4% among a cohort of 450 lupus patients with only 0.4% having severe COVID-19.[12] Previous intake of immunosuppressants was not observed to be associated with severity of COVID-19.[12]

Our patients were either not infected or were asymptomatic despite the community spread in some parts of India. Immunosuppression in SLE patients is often intense and prolonged. The reason for possible paradoxical protection of immunosuppressed SLE patients from severe COVID-19 could be explained based on the finding that immune tolerance in bats protects them from being affected by coronaviruses despite being their reservoir.[13] The absence of excessive inflammation in immunosuppressed SLE patients, which usually occurs in the second phase of COVID-19,[5] might be protective against severe COVID-19 in them. HCQ, an immunomodulatory drug used universally in lupus patients, is shown to reduce viral activity in vitro in SARS-CoV-2 infected Vero cells.[14] HCQ has also been shown to significantly reduce viral load in nasopharyngeal swabs in 20 French patients with COVID-19.[15] Hence, it has direct anti-viral effects in addition to anti-inflammatory effects. Although its role as a prophylaxis and treatment for COVID-19 is controversial,[8] HCQ is still being advocated by many nations including India.[16] Hence, HCQ, in terms of both prevention of acquisition of COVID-19 and progression of mild/asymptomatic infection to severe COVID-19, could be serving as a protective factor for lupus patients.

While it seems that SLE patients are at same, if not higher, risk of contracting COVID-19, the evidence for their risk for severe disease is conflicting, unlike cancer and kidney transplant patients.[3,4] The prophylactic role of HCQ needs further verification from larger database of SLE patients across various regions of the world. Notwithstanding the possible benefits of immunomodulation with therapy used for SLE, the use of intense immunosuppression like corticosteroids, cyclophosphamide, and mycophenolate mofetil is tricky during the COVID-19 pandemic. While moderate doses of corticosteroids for short-term are advocated in critically ill COVID-19 patients, rationale for using high-dose steroids is not straightforward.[17] The risk of progressive disease in case of undertreatment and the unsubstantiated pitfalls of immunosuppression in relation with COVID-19 infection would push clinicians to pursue intense immunosuppression. While it is possible that we could have missed some mild infections, criteria for testing was met in one patient only and none of them had any complications.

Although this is an early experience, we found it rational to start intensive immunosuppressive therapy, including high dose CYC, in patients with LN who presented with disease flare during the COVID-19 pandemic with the help of vigorous precautions. Immunosuppressed SLE patients may be different from cancer patients and kidney transplant recipients in terms of interaction with SARS-CoV-2 virus. A protective role of HCQ needs to be explored in larger studies of SLE patients.

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**Conflicts of interest**

There are no conflicts of interest.

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