RAPID COMMUNICATION

Patients with rheumatoid arthritis exposed to COVID-19: A family cluster report

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Introduction

Novel Coronavirus disease 2019 (COVID-19), emerged in Wuhan at the end of 2019, has progressed rapidly into a worldwide pandemic situation. As of August 16 of 2020, there have been over 21 million cases of confirmed infections and 761,779 deaths in over 200 countries and territories according to a COVID-19 situation report from World Health Organization. Under the current pandemic situation, therapeutic strategy for individuals with underlying immune-related disorders such as rheumatoid arthritis (RA) should be carefully considered.

Hydroxychloroquine has been suggested to have antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen for COVID-19 [1–3]. However, the results from several clinical trials assessing the efficacy of hydroxychloroquine in COVID-19 failed to reach a consistent conclusion [1,3–5]. The use of hydroxychloroquine in rheumatic disease was not exactly the same with its use in these trials in terms of duration, doses, and patient immune status. There have been no studies reporting the efficacy of hydroxychloroquine in COVID-19 in rheumatic patients. Here, we report a family cluster of SARS-CoV-2 infections that occurred in January 2020. In this family of five, three adult members successively developed respiratory symptoms and later tested positive for SARS-CoV-2, while the other two members, both of whom were taking hydroxychloroquine and leflunomide for the treatment of RA, showed no signs of infection during the observation period (February 1st to March 7th, 2020).

Case report

Figure 1(A) describes the disease status and the relationships among the five family members. Several days before Chinese New Year’s Eve (January 24th, 2020), symptoms of fatigue with unknown reason presented on a 59-year-old woman (P1) in a family with five adult members in Wuhan, China. One week after the family dinner for the celebration of this traditional Chinese festival, fatigue escalated in P1 and symptoms of cough, mild dyspnea, and low-grade fever appeared. Leukocytopenia was observed, and SARS-CoV-2 RNA was detected in throat swabs collected from P1 on February 13th, 2020 (Figure 1(B)). After admission to a mobile cabin hospital designated for the treatment of mild to moderate COVID-19 patients, multiple ground glass opacities (GGO) in both lower lobes were observed on her chest computed tomography (CT). By the end of January 2020, symptoms of viral pneumonia, including cough and low-grade fever, appeared in the son (P4) and daughter-in-law (P5) of P1. Subsequent laboratory tests of SARS-CoV-2 RNA and chest CT confirmed their infection with this dangerous virus (Figure 1(B)).

The other two family members (P2, 59-year-old man, husband of P1, and P3, 31-year-old women, daughter of P1), in close contact with P1 on a daily basis without protection until February 13th of 2020, did not present any symptoms of infection and multiple continuous SARS-CoV-2 RNA tests showed negative results (A total of 3 and 2 independent detections were made from February 21st to March 7th, 2020 for P2 and P3, respectively; Figure 1(B)). Interestingly, both P2 and P3 were suffering from RA and taking immunosuppressive anti-rheumatic agents. They both presented with pain, swelling, and tenderness in multiple symmetric pairs of joints at the time of diagnosis, along with significantly elevated blood C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) [6]. Serum anti-cyclic peptide containing citrulline antibody (ACPA) was also positive in both patients (Table 1). Leflunomide (10 mg po bid) and hydroxychloroquine (0.1 g po bid) were administered for both P2 and P3 since July 2018 and August 2019, respectively, with significant improvements in
symptoms and laboratory parameters observed after 3 months of treatment.

Discussion

SARS-CoV-2, the 7th human coronavirus identified recently [7], uses angiotensin-converting enzyme 2 (ACE2, the same receptor used by SARS-CoV) as a receptor to invade host cells. The binding affinity of SARS-CoV-2 to ACE2 is at least 10 times higher than SARS-CoV, indicating a strong infectivity [8,9]. Severe cases of COVID-19 displayed hyper-inflammation and tissue damage in multiple organs [10,11]. While proper anti-viral immunity is required for clearing the pathogen, hyperactive immune responses may be responsible for the lethal damage caused by COVID-19. Thus, during this pandemic, integration of strategies for the treatment of both COVID-19 and rheumatic situation is challenging for rheumatic disease sufferers, who always possess underlying dysregulated immune responsiveness and receive immunosuppressive agents.

RA affects 0.5–1% population in the world [12]. In addition to the anchor drug methotrexate (MTX), hydroxychloroquine and leflunomide is commonly used as important components of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD) in RA and other autoimmune disorders [13,14]. Hydroxychloroquine is a derivate of chloroquine and has similar mechanism of action with less toxicity. In addition to their

Table 1. Baseline information for the diagnosis of RA in P2 and P3.

| Joint involvement | P2 | P3 |
|-------------------|----|----|
| PIP: 4; Shoulder: 2; Wrist: 2; Knee: 1; Hip: 2 | PIP: 2; MCP: 2 |
| Acute-phase reactants | ACPA: ++; CRP: 15.7 mg/L | ACPA: ++; CRP: 19.5 mg/L |
| Duration of symptoms (≥6 weeks) | Yes | Yes |

ACPA: serum anti-cyclic peptide containing citrulline antibody; CRP: C-reactive protein; MCP: metacarpophalangeal joints; PIP: proximal interphalangeal joints. *Scores were evaluated based on ACR/EULAR 2010 rheumatoid arthritis classification criteria [2].
immunomodulatory effects, both hydroxychloroquine and leflunomide show potential in antiviral treatment. Chloroquine is able to interfere with terminal glycosylation of ACE2, the entry receptor of SARS-CoV-2 [9,15]. In addition, it increases endosomal pH required for virus/cell fusion. In in vitro cell culture system, both hydroxychloroquine and chloroquine have shown a potent anti-viral activity on SARS-CoV-2 [1,2]. Recently, in a randomized trial involving 22 COVID-19 patients, Gautret et al. reported that hydroxychloroquine accelerated the clearance of SARS-CoV-2 viral RNA [3]. It is noteworthy that hydroxychloroquine was administered as a treatment after the onset of COVID-19 in this study. Whether preventive use of hydroxychloroquine could provide protection on SARS-CoV-2 infection remains elusive. Leflunomide has shown anti-viral effects in patients infected with CMV [16] and transplant recipients with BK virus [17] and HPV virus [18]. However, leflunomide has been associated with increased interstitial lung disease, especially in those with prior methotrexate use and pre-existing interstitial lung disease [19]. Therefore, the potential benefits of leflunomide in COVID-19 pneumonia have not been reported and remain questionable.

Patients with rheumatic disease routinely take immunosuppressive anti-rheumatic agents to control the disease progression and thus usually are immunocompromised and susceptible to infection. Given the preliminary evidence shown in the in vitro and pilot trial [1-3], there were a number of randomized controlled clinical trials register to evaluate the safety and efficacy of hydroxychloroquine and chloroquine in the treatment of COVID-19. However, the results from the clinical trials currently available failed to reveal a definite answer to the efficacy of hydroxychloroquine in COVID-19 [1,3-5]. In these trials, hydroxychloroquine was given at doses of 400-1200 mg/day for 5-14 days. Unlike those trials assessing the efficacy of hydroxychloroquine in COVID-19, patients with rheumatic disease such as RA were taking hydroxychloroquine usually at a low dose for a long time. Higher doses of chloroquine or hydroxychloroquine have been shown to have cardiotoxicity in COVID-19 patients [20,21]. However, hydroxychloroquine, when used alone in patients with RA, was comparable in terms of safety to other DMARD drug such as sulfasalazine [22]. In this report, the two RA patients on regular anti-rheumatic medication were protected from infection of COVID-19 after daily close contact with P1 who transmitted the virus to all the other adults in the family. Given the same RA disease history and anti-rheumatic treatments, it is possible that one or some of the medications they were taking confer them protection in this family cluster of infection. This is consistent with our recent findings that patients with rheumatic diseases were at a higher risk of COVID-19 infection while preventive use of hydroxychloroquine may reduce this risk in these patients compared to other immunosuppressive DMARDs [23]. A study by Pablos et al. [24] also showed that patients with rheumatic disease on csDMARDs had a lower prevalence of COVID-19 compared to those on targeted synthetic DMARDs, which is possibly due to the frequent use of antimalarials. It is noteworthy that hydroxychloroquine may not alleviate the disease severity once infected with SARS-CoV2, although it may have beneficial effects on COVID-19 susceptibility. Several studies including a recent retrospective observation on 600 patients with rheumatic disease and COVID-19 showed no beneficial effect of antimalarial agents on improving COVID-19 severity once infected [25]. Other possibilities such as the awareness of personal protection against infections should also be considered. For example, patients on immunosuppressive medication may be more cautious about infections and may take extra protections against infections. Further studies on protection against infections in these patients are required to provide direct evidence.

Conflict of interest
None.

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