

## Rituximab for granulomatosis with polyangiitis in the pandemic of covid-19: lessons from a case with severe pneumonia

In the pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease 2019 (covid-19),<sup>12</sup> the preliminary experience reported by Monti S and colleagues<sup>3</sup> suggests that patients with chronic arthritis (rheumatoid arthritis and spondyloarthritis) receiving bDMARDs (biologic disease-modifying anti-rheumatic drugs) or tsDMARDs (targeted synthetic DMARDs) may not exhibit an increased risk of severe covid-19. These data must be strengthened and confirmed at a larger scale, but remain positive in this drastic context. The authors rightly recommend a continuous surveillance of patients under immunosuppressants, especially since data are lacking in many systemic autoimmune/inflammatory diseases. Notably, anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a group of vasculitides that can involve the respiratory tract (upper and lower airways) and the recent outbreak of covid-19 raises many specific questions concerning the severity of viral infection in AAV patients as well as the therapy with rituximab. Indeed, rituximab, a monoclonal antibody targeting CD20, has become the cornerstone of treatment in the last decade, but is responsible for long-lasting B-cell depletion and potentially severe infectious events (IE) independently from covid-19.<sup>4</sup> A recent observation from our centre illustrates some specific issues with this drug.

A 52-year-old woman was followed for granulomatosis with polyangiitis since 1988 (ear, nose and throat (ENT), orbital, lung, joint and skin involvements, proteinase3 (PR3)-ANCA). She previously received cyclophosphamide (total cumulated dose=41 gr), anti-tumour-necrosis factor agents, mycophenolate mofetil, methotrexate, leflunomide, rituximab and glucocorticoids. Her main comorbidities were overweight (body mass index: 27.05 kg/m<sup>2</sup>) and hypertension treated with nebivolol. In September 2019, the vasculitis relapsed (arthralgias, ENT, intermittent haematuria and increased PR3-ANCA levels). Four infusions of rituximab (375 mg/m<sup>2</sup>) were weekly administered in October 2019. The patient improved, and a maintenance therapy with rituximab (500 mg) was administered on 5<sup>th</sup> March 2020, while she was still under prednisone 15 mg daily. On 6<sup>th</sup> March 2020 (Day #0), the patient had headaches and myalgias, followed by a 39°C fever and non-productive cough. She was admitted on Day #4 and covid-19 was diagnosed by reverse transcription (RT)-PCR from nasopharyngeal swab specimens. Typical bilateral interstitial pneumonia related to covid-19 was demonstrated on CT scan (figure 1). Other concomitant infections (including pneumocystosis) were excluded. While she remained highly febrile under broad-spectrum antibiotics, the oxygen requirement increased progressively and she presented sudden respiratory failure on Day #18, requiring endotracheal intubation and mechanical ventilation for acute respiratory distress syndrome. Several drugs were given for compassionate use: lopinavir/ritonavir for 3 days from Day #12 and then hydroxychloroquine (200 mg/8 hour) for 10 days from Day #19. The clinical condition improved rapidly, and the patient was extubated (Day #20) and oxygen support was withdrawn (Day #25). Nasopharyngeal RT-PCR were negative twice in the following days and the patient returned home on Day #29.

Until today, immunosuppressive drugs are supposed to be risk factors of severe forms of covid-19. Furthermore, although risk factors are not yet clearly established,<sup>5</sup> our patient had two potential additional ones (overweight and hypertension),



**Figure 1** CT scan disclosing ground glass opacities and condensations consistent with a mixed (central and subpleural) pattern of severe covid-19 pneumonia.

making her recovery unexpected. We report herein a severe and life-threatening form of covid-19 in a patient under immunosuppressant, though the worsening occurred more progressively than observed in most series. Both glucocorticoids and rituximab may have limited the cytokine storm and delayed the worsening and need for mechanical ventilation, as compared with previous reports.<sup>2</sup> However, as proposed by Monti and colleagues,<sup>3</sup> we should consider these drugs with caution during the covid-19 pandemic.

Independently from covid-19, infectious events (IE) (mainly pyogenic) may occur in the 3 months following rituximab infusion. Classically, risk factors for infection in patients receiving rituximab include glucocorticoids, other immunosuppressive drugs, diabetes mellitus and age. We previously reported that severe IE were observed in about 25% of patients with autoimmune diseases, and some individuals experienced life-threatening, polymicrobial and opportunistic infections.<sup>4</sup> This frequency was higher than in other studies,<sup>6,7</sup> but this suggests that rituximab may not be as safe as usually supposed, probably depending on the subgroups of treated patients. During covid-19, which may generate an immunocompromised status (as illustrated by lymphopenia and opportunistic infections), the impact of rituximab treatment on IE remains to be clarified. Additionally, the B-cell depletion induced by rituximab reduces the immunogenicity of several vaccines, which encourages to perform vaccination before starting rituximab.<sup>8</sup> Similarly, the immunological memory following SARS-CoV-2 infection will probably be impaired by this biologic, making patients sensitive to a reinfection.

Although we cannot draw any definitive conclusion from our observation, we agree with those who recommend avoiding withdrawal of drugs, because this may lead to relapses of inflammatory diseases. Nevertheless, the specific and long-lasting effects of rituximab make this issue even more delicate and warrant further studies concerning the impact of covid-19 in immunocompromised patients.

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