

# Role of immunosuppressive therapy in rheumatic diseases concurrent with covid-19

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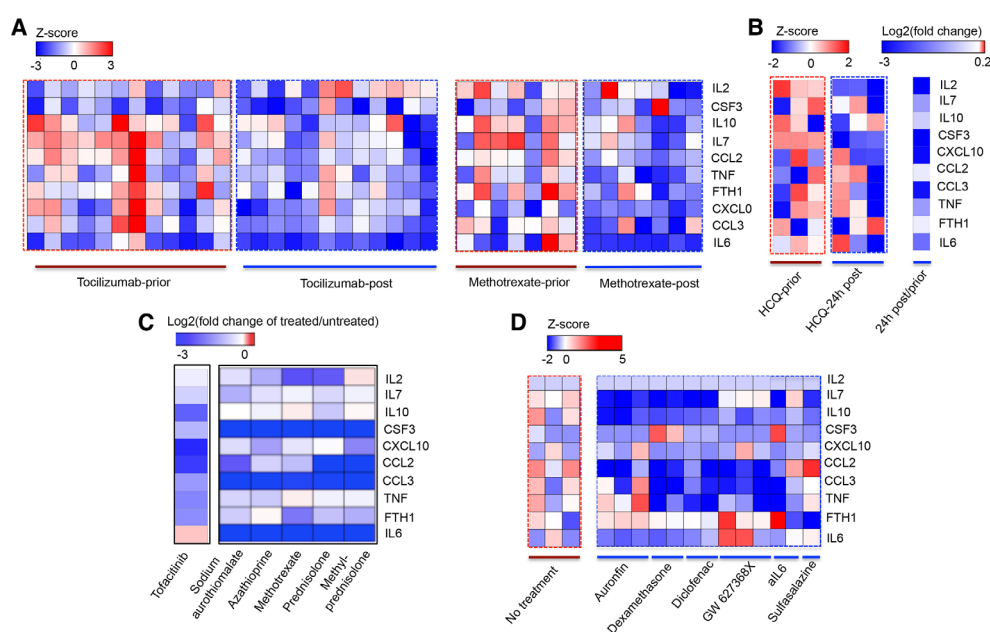
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The covid-19 has been declared a pandemic by WHO since 11 March 2020.<sup>1</sup> The cumulative incidence of covid-19 cases is showing similar trends in European Union and USA, and the UK confirmed that, while at a different stage depending on the country, the covid-19 pandemic is progressing rapidly in all countries.<sup>2</sup> As of 10 April 2020, covid-19 has been confirmed in 1521252 people worldwide, carrying a mortality of approximately 6.1%.<sup>3</sup> With

tens of millions of individuals suffering rheumatic diseases (RDs) around the world who routinely receive glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs) (table 1), RD patients with compromised immune systems make up a large population of susceptible patients in which novel coronavirus infection may cause devastating consequences.



**Figure 1** Expression profiling of glucocorticoids and some DMARDs on the cytokine profile represented in severe covid-19 in patients, mouse models and human cells. (A) Heatmap showing both tocilizumab and methotrexate induced a significant downregulation of genes including IL-2, CSF3, IL-10, IL-7, CCL2, TNF, FTH1, CXCL10, CCL3 and IL-6 (GSE45867). Each column is a patient; data were represented by z-score. The expression level of paired synovial biopsy samples obtained from the affected knees of patients with early RA before and 12 weeks after initiation of tocilizumab (n=12) or methotrexate (n=7) therapy were measured using GeneChip human genome U133 plus 2.0 arrays; (B) heatmap showing that HCQ downregulated the expression of targeted cytokines in PBMC of three healthy participants induced by rheumatogenic, heat-killed group A Streptococcus (GSE74235); each column is a PBMC sample (before or 24 hours after HCQ treatment); the expression level of each gene was measured by RNA-seq of Illumina HiSeq 2000; data were represented by z-score and the log<sub>2</sub> (fold change). (C) Tofacitinib (GSE69300), sodium aurothiomalate, azathioprine, methotrexate, prednisolone, methylprednisolone (GSE12860) downregulated genes of targeted cytokines; left: whole skin from C57/B6 female mice after 4 days of treatment of vehicle (n=2) or tofacitinib (n=3) were used to calculate the fold change; expression was measured by Affymetrix mouse genome 430 2.0 array; right: human chondrocytes were stimulated with supernatant of rheumatoid arthritis synovial fibroblast (RASf), which have been treated with steroids, DMARDs or nothing; expression level of cytokines in RASf supernatant-stimulated chondrocytes were measured by Affymetrix human genome U133A array and fold change was represented; (D) compared with no treatment, Aurofinin, dexamethasone, diclofenac (an NSAID), GW 627368X (an EP4 receptor antagonist), aIL6 and sulfasalazine treated cells showed lower expression of these genes (GSE95588); expression level of samples from TNF treated CD14+ MCSF-differentiated macrophages with or without drug treatment were measured by Illumina HiSeq; each column is a replicate. Z-score: relative expression level of a gene in all samples, fold change (log<sub>2</sub>): drug treated versus untreated. blue cells: downregulated; red cells: upregulated. DMARDs, disease-modifying anti-rheumatic drugs; HCQ, hydroxychloroquine; IL, interleukin; MCSF, macrophage colony-stimulating factor; NSAID, non-steroidal anti-inflammatory drugs; PBMC, peripheral blood mononuclear cells; RA, rheumatoid arthritis; SF, synovial fibroblasts; TNF, tumour necrosis factor.



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**Table 1** Summary of drugs commonly used in rheumatic diseases and their mechanisms of action

Drugs	Mechanisms of action
Glucocorticoids	Inhibit NF- $\kappa$ B; suppress immune cell function; decrease cytokine production; increase apoptosis of immune cells. <sup>24</sup>
Hydroxychloroquine	Interfere with lysosomal activity, autophagy and membrane stability; alter signalling and transcriptional activity; inhibit cytokine production; modulate costimulatory molecules. <sup>25</sup>
Methotrexate	Pyrimidine and purine metabolism inhibitor via inhibition of dihydrofolate reductase; stimulation of adenosine signalling; downregulation of cytokines, eicosanoids and matrix metalloproteinases. <sup>26</sup>
Leflunomide	Pyrimidine synthesis inhibitor via inhibition of dihydroorotate dehydrogenase.
Azathioprine	Purine synthesis inhibitor; inhibits lymphocyte proliferation. <sup>27</sup>
Cyclosporine	Calcineurin inhibitor; binds cyclophilin; blocks T cell activation and inhibits cytokine transcription. <sup>28</sup>
Tacrolimus	Calcineurin inhibitor; binds FK506 binding protein; blocks T cell activation and inhibits cytokine transcription. <sup>27</sup>
Mycophenolate mofetil	Purine synthesis inhibitor by inhibiting IMP dehydrogenase. <sup>27</sup>
Anakinra	IL-1 antagonist.
Tocilizumab	IL-6 receptor antagonist.
Infliximab, adalimumab, certolizumab pegol and others	TNF- $\alpha$ inhibitor.
Tofacitinib, baricitinib and others	Inhibitor of JAK, which transmit extracellular data to the cell nucleus influencing DNA transcription.

IL, interleukin; JAK, Janus kinase; TNF- $\alpha$ , tumour necrosis factor- $\alpha$ .

Accumulating evidence suggests that a subgroup of patients with severe covid-19 might have a cytokine storm syndrome represented by acute respiratory distress syndrome (ARDS) and secondary haemophagocytic lymphohistiocytosis, which are two of main causes of mortality.<sup>4</sup> Disease severity of covid-19 was correlated with hypercytokinaemia, characterised by increased serum interleukin (IL)-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), IP10/CXCL10, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1- $\alpha$  (MIP-1), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), ferritin and IL-6.<sup>5-8</sup> In addition, decreased monocyte count was found in patients with covid-19,<sup>9</sup> low levels of CD4<sup>+</sup> T and CD8<sup>+</sup> T cells were more common in severe cases,<sup>7</sup> while numbers of leucocytes, B cells and NK cells were similar between patients and healthy controls.<sup>9</sup> On the novel coronavirus infection, CD4<sup>+</sup> T cells were activated to become pathogenic Th1 cells and generate granulocyte-macrophage colony-stimulating factor, augmenting the expression of IL-6 in CD14<sup>+</sup>CD16<sup>+</sup> monocytes.<sup>9</sup>

As hyperinflammation underlies the mechanism of severe covid-19, anti-inflammatory therapies may benefit those patients. The immunocompromised situation may prevent them from the virus-induced cytokine storm syndrome. Available transcriptome data including RNA-seq and GeneChip human genome arrays show that glucocorticoids (prednisone, methylprednisolone and dexamethasone) and some DMARDs (tocilizumab, methotrexate, hydroxychloroquine, tofacitinib, azathioprine and so on) could suppress the cytokine profile represented in severe covid-19 (IL-2, 7, 10 and 6, G-CSF/CSF3, IP10/CXCL10, MCP-1/CCL2, MIP-1/CCL3, TNF and FTH1) in patients with rheumatoid arthritis (figure 1A), in mouse models (figure 1C left) as well as in human cells in vitro (figure 1B,C (right) and figure 1D) (detailed in figure legends and online supplementary materials). Therefore, these immunosuppressive agents could likely reduce hyperinflammation in concurrent Covid-19 of patients with RD by inhibiting gene expression of the cytokine profile.

Although it is not routinely recommended and might exacerbate covid-19-associated lung injury,<sup>10</sup> treatment with methylprednisolone may be beneficial for patients who develop ARDS.<sup>11</sup> Chloroquine, an antimalarial medicine, was highly effective in reducing viral replication in vitro,<sup>12</sup> and chloroquine phosphate has demonstrated marked efficacy and acceptable safety in treating covid-19 associated pneumonia in multicentre clinical trials (not completed) in China.<sup>13</sup> Chloroquine phosphate was then recommended in the new version of the Guideline for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by covid-19 issued by the National Health Commission of the People's Republic of China,<sup>14</sup> followed by guidelines documented by Dutch Centers for Disease Control<sup>15</sup> and Italian Society of Infectious and Tropical disease.<sup>16</sup> A French open-label non-randomised clinical trial showed that hydroxychloroquine treatment reduces viral load in patients with covid-19 and azithromycin reinforced it.<sup>17</sup> However, the sample size is small, and dropout rate is relatively high. Another clinical trial in China did not find significant difference in rates of viral load disappearance in patients with covid-19 taking hydroxychloroquine or not.<sup>18</sup> Therefore, the use of chloroquine or hydroxychloroquine in covid-19 is still under debate. Some other DMARDs also were promising therapies in covid-19, such as cytokine-targeting biologicals and signalling molecules inhibitors. The IL-6 receptor antagonist tocilizumab has been approved in patients with covid-19 pneumonia and elevated IL-6 in China.<sup>19</sup> Furthermore, Janus kinase inhibition could affect both inflammation and cellular viral entry in covid-19.<sup>20</sup> By targeting IL-1, anakinra, showed significant survival benefit in patients with sepsis, which is a hyperinflammation situation, without increased adverse events in a phase III randomised controlled trial.<sup>21</sup> There is also an ongoing clinical trial comparing the efficacy and safety of emapalumab, an anti-interferon- $\gamma$  monoclonal antibody, with anakinra in covid-19.<sup>22</sup>

Data on the susceptibility, disease severity and prognosis of covid-19 in patients with RD on immunosuppressants still lack. Zhu *et al*<sup>23</sup> reported a case of covid-19-associated pneumonia following kidney transplantation who is receiving immunosuppressive therapy of prednisone, tacrolimus and mycophenolate mofetil, recovered with reduction of immunosuppressants and a low dose of methylprednisolone.<sup>23</sup> In this case, the patient only had mild symptoms and recovered quickly with antiviral and anti-inflammation therapies. It is still too early to forecast the risk of infection and disease severity of covid-19 in patients with RD, especially those who are on immunosuppressive therapies, but it is likely to follow the deleterious course previously reported by other community-acquired respiratory viruses. When treating opportunistic virus infection following DMARDs treatment in patients with RD, a reduction or even temporary discontinuation of those immunosuppressants is a common strategy and allows them to reacquire anti-infection immunity within a short period, which is conducive to eliminating the virus. Clinical manifestations of covid-19 infection in this population may be distinctive, and treatment requires careful consideration. More observation data about the prevalence and severity of covid-19 in patients with RD and experience of management are urgently needed.

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