Role of immunosuppressive therapy in rheumatic diseases concurrent with COVID-19

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The COVID-19 has been declared a pandemic by WHO since 11 March 2020. 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. As of 10 April 2020, COVID-19 has been confirmed in 1521252 people worldwide, carrying a mortality of approximately 6.1%. 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 log2 (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, Auronfin, dexamethasone, diclofenac (an NSAID), GW 627368X (an EP4 receptor antagonist), IL6 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 (log2): 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

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mechanisms of action</th>
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<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Inhibit NF-κB; suppress immune cell function; decrease cytokine production; increase apoptosis of immune cells.</td>
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<tr>
<td>Hydroxychloroquine</td>
<td>Interfere with tyrosine activity, autophagy and membrane stability; alter signalling and transcriptional activity; inhibit cytokine production; modulate costimulatory molecules.</td>
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<tr>
<td>Methotrexate</td>
<td>Pyrimidine and purine metabolism inhibitor via inhibition of dihydrofolate reductase; stimulation of adenosine signalling; downregulation of cytokines, eicosanoids and matrix metalloproteinases.</td>
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<tr>
<td>Leflunomide</td>
<td>Pyrimidine synthesis inhibitor via inhibition of dihydroorotate dehydrogenase.</td>
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<tr>
<td>Azathioprine</td>
<td>Purine synthesis inhibitor; inhibits lymphocyte proliferation.</td>
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<tr>
<td>Cyclosporine</td>
<td>Calcineurin inhibitor; binds cyclophilin; blocks T cell activation and inhibits cytokine transcription.</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Calcineurin inhibitor; binds FK506 binding protein; blocks T cell activation and inhibits cytokine transcription.</td>
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<tr>
<td>Mycophenolate mofetil</td>
<td>Purine synthesis inhibitor by inhibiting IMP dehydrogenase.</td>
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<tr>
<td>Anakinra</td>
<td>IL-1 antagonist.</td>
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<tr>
<td>Tocilizumab</td>
<td>IL-6 receptor antagonist.</td>
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<tr>
<td>Infliximab, adalimumab, certolizumab pegol and others</td>
<td>TNF-α inhibitor.</td>
</tr>
<tr>
<td>Tofacitinib, baricitinib and others</td>
<td>Inhibitor of JAK, which transmit extracellular data to the cell nucleus influencing DNA transcription.</td>
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IL, interleukin; JAK, Janus kinase; TNF-α, tumour necrosis factor-α.

Although it is not routinely recommended and might exacerbate COVID-19-associated lung injury, treatment with methylprednisolone may be beneficial for patients who develop ARDS. Chloroquine, an antimalarial medicine, was highly effective in reducing viral replication in vitro, and chloroquine phosphate has demonstrated marked efficacy and acceptable safety in treating COVID-19 associated pneumonia in multicentre clinical trials (not completed) in China. 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, followed by guidelines documented by Dutch Centers for Disease Control and Italian Society of Infectious and Tropical disease. A French open-label non-randomised clinical trial showed that hydroxychloroquine treatment reduces viral load in patients with COVID-19 and azithromycin reinforced it. 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.

Data on the susceptibility, disease severity and prognosis of COVID-19 in patients with RD on immunosuppressants still lack. Zhu et al 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.

As hyperinflammation underlies the mechanism of severe COVID-19, anti-inflammatory therapies may benefit these 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, azathoprine 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 in human cell lines (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.
Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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