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Sulfasalazine: a risk factor for severe COVID-19?

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Sulfasalazine, a disease-modifying antirheumatic drug (DMARD), has a well established role in the treatment of patients with rheumatoid arthritis, spondyloarthritis, and inflammatory bowel disease—diseases in which therapeutic benefit may primarily derive from the drug's inhibitory effect on tumour necrosis factor (TNF) and prostaglandin synthesis. In view of this mechanism, it is of note that several independent studies identified baseline treatment with sulfasalazine or mesalamine as a major risk factor (second only to rituximab and other B cell-depleting therapies) for severe COVID-19 in patients with autoimmune and rheumatic diseases. In the physician-reported case registry of the COVID-19 Global Rheumatology Alliance, use of sulfasalazine was associated with a significantly higher risk of death in patients with COVID-19 (odds ratio [OR] 3·6), which contrasted with that of TNF inhibitors (OR 0·85).[1] Similarly, data from the SECURE-IBD registry showed an increased risk of severe COVID-19 among patients treated with sulfasalazine (adjusted OR 3·1), but not with TNF inhibitors (OR 0·9).[2] In a post-hoc analysis of data from Swedish patients with rheumatoid arthritis, spondyloarthropathies, psoriatic arthritis, or juvenile idiopathic arthritis (n=110 567), increased point estimates for COVID-19-related hospitalisation and intensive care unit admission were seen for patients on sulfasalazine monotherapy (n=4675) compared with patients on any other conventional synthetic DMARD therapy (n=28 621).[3] These findings could not be explained by the known mechanisms of action of sulfasalazine; however, recent findings suggest that the association of clinical use of sulfasalazine with poor COVID-19 outcomes could be related to a previously unappreciated ability of the drug to inhibit type I interferon (IFN) production by plasmacytoid dendritic cells.[4]

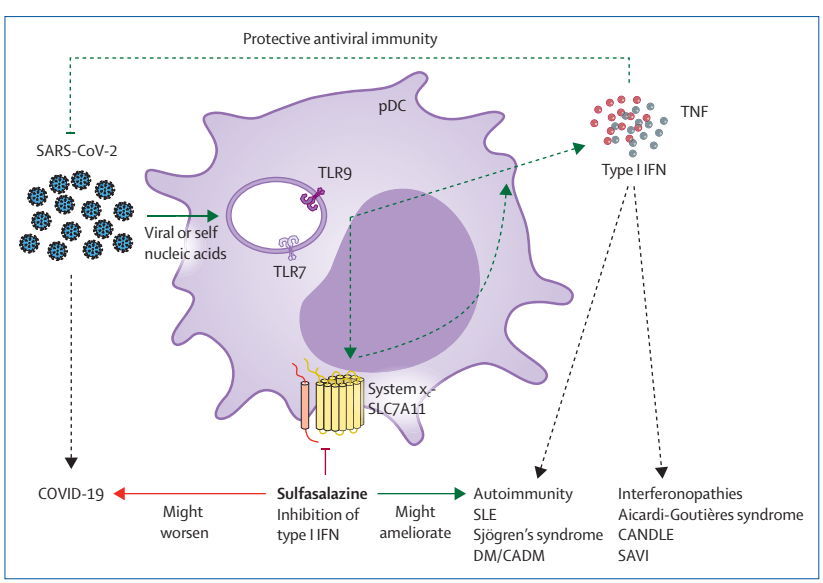

Figure: **Risk and opportunity associated with sulfasalazine being a potent inhibitor of type I IFN production by plasmacytoid dendritic cells**
Through Toll-like receptors 7 and 9, plasmacytoid dendritic cells are able to respond to SARS-CoV-2 single-stranded RNA or other pathogen-derived or self-derived nucleic acids by making large amounts of type I IFNs, along with other cytokines, such as TNF. Type I IFNs are necessary for immunity to SARS-CoV-2 and other viruses, but are also involved in the pathogenesis of interferonopathies and a subset of important autoimmune diseases. Sulfasalazine inhibits the production of type I IFNs and TNF by plasmacytoid dendritic cells due to its ability to inhibit x_c^-, a cystine importer required for plasmacytoid dendritic cell activation. We suggest that this drug be reassessed for the treatment of SLE, Sjögren's syndrome, DM/CADM, and for interferonopathies (eg, SAVI, CANDLE, and Aicardi-Goutières syndrome). CANDLE=chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature. IFN=interferon. DM/CADM=dermatomyositis or clinically amypopathic dermatomyositis. pDC=plasmacytoid dendritic cell. SAVI=stimulator of interferon genes-associated vasculopathy with onset in infancy. SLE=systemic lupus erythematosus. TLR=Toll-like receptor. TNF=tumour necrosis factor.

Plasmacytoid dendritic cells sense DNA and single-stranded RNA via toll-like receptors and produce type I IFNs in response. These cells play an important role in immunity to viruses, including SARS-CoV-2, where they have been implicated in protective type I IFN-mediated immune responses in individuals who are infected but remain asymptomatic.[5] However, plasmacytoid dendritic cells are also implicated in autoimmune diseases, such as systemic lupus erythematosus (SLE) and dermatomyositis—diseases in which type I IFN production plays a role in immunopathogenesis. Recent work revealed a pivotal role for interleukin (IL)-3-driven JAK2-STAT5 signalling for subsequent toll-like receptor-induced plasmacytoid dendritic cell activation and showed that activated plasmacytoid dendritic cells express SLC7A11 (cystine/glutamate transporter), a subunit of the x_c^- amino acid transporter that imports cystine for the production of the crucial anti-oxidant glutathione.[4] SLC7A11 is important in part because it is a negative regulator of iron-dependent programmed cell death (ferroptosis).[6]

To address the unmet need for diseases such as SLE, we explored new treatment possibilities that target plasmacytoid dendritic cells and tested combinations of inhibitors with known selectivity for targets within the plasmacytoid dendritic cell activation pathway, including JAK2 (eg, baricitinib) and x_c^- (eg, sulfasalazine[6]). Sulfasalazine strongly inhibited the production of type I IFN at clinically relevant concentrations, and

the combination of sulfasalazine and a JAK2 inhibitor had a synergistic effect.[4] Although sulfasalazine affects additional pathways, we believe that it is the ability to inhibit x_c^- that confers its inhibitory effect on plasmacytoid dendritic cells (figure). This observation supports the possible repurposing of sulfasalazine, a relatively cheap oral drug, for the treatment of type I IFN-driven autoimmune and autoinflammatory diseases. At the same time, it might provide a mechanistic explanation for the as-yet unexplained epidemiological association between sulfasalazine and COVID-19 severity, since sulfasalazine-mediated impairment of type I IFN production by plasmacytoid dendritic cells would be expected to inhibit effective early immune responses during SARS-CoV-2 infection. Indeed, the reported increase in risk of herpes zoster in patients with rheumatoid arthritis taking sulfasalazine might indicate a broader effect of this drug on immunity to viral infections than previously appreciated.

The realisation, over the space of a few months, that sulfasalazine is an inhibitor of type I IFN production by plasmacytoid dendritic cells and also a risk factor for death due to SARS-CoV-2 infection;[1] that autoantibodies against type I IFNs are observed in about 20% of critical COVID-19 cases and deaths;[8] and that SLE risk alleles associated with high type I IFN production are associated with asymptomatic SARS-CoV-2 infection (ie, potentially less severe disease),[9] have helped crystalise understanding of autoimmunity as it relates to anti-viral immunity. The data strongly support a role for type I IFN in resistance to SARS-CoV-2 and highlight the possibility that autoimmune diseases related to increased type I IFN production might be a consequence of evolutionary pressure to maintain genetic alleles that ensure resistance to viral pathogens.

This view has consequences for the treatment of patients with autoimmune diseases during viral pandemics, including the therapeutic use of antibodies that inhibit the type I interferon receptor, as used in the treatment of patients with SLE. Further, the findings on sulfasalazine are surprising. Previously, little attention has been paid to the use of this drug for the treatment of autoimmune and rheumatic diseases in which type I IFNs are strongly implicated. To our knowledge, sulfasalazine has never been systematically explored for the treatment of SLE, possibly due to concerns about potential drug-induced autoimmunity and intolerance to sulfa drugs. However, three studies reported high rates of complete responses (including some lasting for years) in patients with refractory cutaneous lupus treated with sulfasalazine.[10] With a more detailed understanding of the mechanism of action of sulfasalazine, related to its ability to inhibit type I IFN production by modulating plasmacytoid dendritic cell function,[4] the possibility of repurposing this drug for diseases such as SLE, dermatomyositis, Sjögren's syndrome, and monogenic interferonopathies—for which there is an unmet need for affordable, effective therapeutics—should be considered.

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