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EDITORIAL

Azithromycin for COVID-19: More Than Just an Antimicrobial?

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The COVID-19 infection due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a major public health issue worldwide, as no vaccines or drugs for prevention and treatment have been approved so far, except remdesivir that has been recently authorized for use in the USA and Japan [1]. Many clinical studies are ongoing. Most of them evaluate established antiviral drugs such as lopinavir/ritonavir, and chloroquine (CQ) or its derivative hydroxychloroquine (HCQ), which have shown in vitro antiviral activity against SARS-CoV-2 [2]. Because SARS coronavirus infections are known to induce inflammation and subsequent tissue damage in the lungs in moderate-to-severe cases [3], using immunomodulating drugs could provide a benefit in the treatment of COVID-19. Drugs with the most relevant immunomodulatory profile remain to be found. We believe the antibacterial macrolide azithromycin (AZM) has a special and interesting profile in this search for drug therapy for COVID-19. We discuss below the arguments for this claim.

It has been shown that AZM has significant antiviral properties. In contrast with CQ or HCQ, its antiviral activity has been shown in vitro and/or in vivo on a large panel of viruses: Ebola, Zika, respiratory syncytial virus, influenzae H1N1 virus, enterovirus, and rhinovirus [4–13]. Its activity against respiratory syncytial virus has been demonstrated in a randomized study in infants [10]. Azithromycin exhibited a synergistic antiviral effect against SARS-CoV-2 when combined with HCQ both in vitro [11] and in a clinical setting [13]. Of note, the pre-print version of the article from Andreani et al. [14] also reported a significant antiviral effect of AZM alone on SARS-CoV-2. The mechanisms of the antiviral effect of AZM support a large-spectrum antiviral activity. Azithromycin appears to decrease the virus entry into cells [2, 8]. In addition, it can enhance the immune response against viruses by several actions. Azithromycin up-regulates the production of type I and III interferons (especially interferon-β and interferon-λ), and genes involved in virus recognition such as MDA5 and RIG-I [7, 12, 13, 15, 16]. These mechanisms are universally involved in the innate response against infectious agents, and potentially against SARS-CoV-2.

The immunomodulation properties of AZM are the rationale of its use against inflammatory manifestations leading to interstitial lung disease [17, 18]. SARS-CoV-2 has been shown to exacerbate the inflammatory response of its host, leading to serious damage of lung interstitial tissue [19]. Patients with severe COVID-19-associated pneumonia may exhibit a syndrome of systemic hyper-inflammation designated as a cytokine storm [20]. Cytokine profiles of patients with severe COVID-19 have been compared to those of patients with moderate forms and have shown a notable increase in some pro-inflammatory cytokines such as interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10, IL-17, and tumor necrosis factor-α [19–21]. Therapeutic approaches targeting only IL-6 have been proposed but may be double-edged because the timing of its administration might adversely affect viral clearance [21]. By contrast, AZM shows an interesting immunomodulatory profile by inhibiting several cytokines involved in COVID-19 severe respiratory syndrome. Indeed, AZM regulates and/or decreases the production of IL-1β, IL-6, IL-8, IL-10, IL-12, and IFN-α [10, 22, 23]. Hydroxychloroquine also has immunomodulatory effects, and has been reported to decrease IL-1, IL-2, IL-6, IL-17, IL-22, IFN-α, and tumor necrosis factor [24, 25]. Azithromycin and HCQ both decrease the production of major inflammatory cytokines such as IL-1 and IL-6. However, the different profiles of immunomodulation between the two drugs may be crucial for selecting one of them for the treatment of COVID-19, in relation to the pathogenicity of the virus. Indeed, HCQ may decrease IL-2 levels but not AZM, while AZM may decrease IL-8 levels but not HCQ.

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Interleukin-2 is a key cytokine involved in the host innate immune response to bacterial or viral pathogens by inducing T-lymphocyte proliferation and differentiation [26]. Despite elevated IL-2 soluble receptor levels reported by Huang et al. in patients with COVID-19 [19], lymphocyte counts were at the lower limit and subsets were deeply modified [27]. Qin et al. showed that B cells, T-helper cells, T-regulatory cells, and natural killer counts were significantly decreased in patients with COVID-19, with a more pronounced decline in the severe cases [27]. A lower count of memory T cells was also observed in patients with COVID-19, which raises concerns about limited immunization against the virus [27]. Interleukin-2 production, enhanced by a native immune response in patients with COVID-19, should be maintained to favor an adaptive antiviral immune response and allow a sufficient production of adequate memory T and natural killer cells, but also induce T-regulatory cells to control inflammation. Chloroquine (and possibly HCQ) has been shown to inhibit IL-2 production [27, 28], while AZM showed an opposite action [29]. Hence, AZM could allow a sufficient memory T-cell count to be maintained and a better immunization. Otherwise, IL-8 is involved in neutrophil chemotaxis facilitating the lung infiltration and macrophage activation-like syndrome observed in patients with severe disease [20, 30]. Therefore, the inhibitory effect of AZM on IL-8 may also be of interest for COVID-19 therapy.

Another property of AZM is its antibacterial effect, which may be most interesting to prevent or treat co-infection by bacteria and SARS-CoV-2. Recent data suggested that anaerobic bacteria of lung microbiota may be involved in the SARS-CoV-2 pathogenesis. *Prevotella* cells, which have been found in abnormal quantities in patients with severe disease, could internalize SARS-Cov2 and enhance its pathogenicity [31–33]. *Prevotella* spp. are commensal anaerobic bacteria in the lungs [33]. They are involved in idiopathic inflammatory lung diseases, notably by facilitating IL-6 and IL-8 production [34–36]. Azithromycin is a possible treatment for *Prevotella* infections and decreases *Prevotella*-induced inflammation [37, 38].

Azithromycin has other attractive pharmacological and therapeutic properties in the search for COVID-19 drug therapy. It is extensively distributed into tissue, especially in lungs where average concentrations in both extracellular fluids and within cells are much higher than in plasma [39].

Azithromycin is approved in both adults and children aged ≥ 6 months. First approved in the USA in 1991, it has been administered to numerous patients and its tolerance is well known. The most frequent adverse drug reactions are related to the gastrointestinal tract (e.g., nausea, vomiting, diarrhea, or abdominal pain). Those are mild to moderate in severity and reversible. Like CQ and HCQ, AZM may prolong the QT interval but clinical consequences such as arrhythmias are rare. The arrhythmogenic potential of AZM appears to be lower than that of other macrolides [40]. Therefore, the risk of interactions with other drugs that prolong the QT interval is arguably lower as well.

Unlike other macrolide antibiotics such as erythromycin and clarithromycin, AZM is only a weak cytochrome P450 inhibitor [41]. Clinically relevant drug–drug interactions with AZM as the perpetrator drug appear to be rare. Interestingly, a study investigated the effect of AZM on CQ pharmacokinetics and reported no significant drug interaction [42].

A retrospective study has evaluated the effect of various macrolides including AZM in critically ill patients with MESR-CoV and reported no significant benefits [43]. However, AZM alone was used in a limited number of patients in this study, and late in the course of MERS-CoV infection. This uncontrolled study has many confounders, including co-treatment and is of low evidence. The optimal time for the introduction of drug therapy in COVID-19 including AZM is uncertain and needs to be investigated as well. A recent observational study reported data on AZM used alone in patients with COVID-19 [44]. Patients were treated immediately after diagnosis and received HCQ plus AZM or HCQ alone, or AZM alone. The mortality rates adjusted for comorbidities and demographics at 21 days were 22.5% (95% confidence interval 19.7–25.1) in patients with HCQ plus AZM, 18.9% (95% confidence interval 14.3–23.2) in patients with HCQ alone, and 10.9% (95% confidence interval 5.8–15.6) in patients with AZM alone [43]. These encouraging results need to be confirmed by further randomized studies. Considering the uncertain efficacy of most agents currently in use in patients with COVID-19 and the greater risk of adverse drug reactions associated with drug combinations [45], we believe that each drug candidate for treating COVID-19 should be first evaluated alone in randomized controlled trials.

To conclude, there are several arguments supporting a potential effectiveness of AZM in SARS-CoV-2 infection, including its antiviral activity and immunomodulatory effects. We believe AZM should be clinically investigated as a monotherapy in patients with SARS-CoV-2 infection.

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Compliance with Ethical Standards

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