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Short Communication

Type 1 interferons as a potential treatment against COVID-19

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ABSTRACT

Type 1 interferons have a broad antiviral activity *in vitro* and are currently evaluated in a clinical trial to treat MERS-CoV. In this review, we discuss preliminary data concerning the potential activity of type 1 interferons on SARS-CoV-2, and the relevance of evaluating these molecules in clinical trials for the treatment of COVID-19.

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1. Main text

SARS-CoV-2 is a human coronavirus causing the COVID-19 disease. It emerged in China in December 2019 and rapidly propagated in numerous countries, having contaminated more than one million people and killing more than 55,000 up to April 3, 2020. Antiviral treatments are warranted to contain the epidemics. Several candidates are already being investigated, including type 1 interferon (IFN–I) (Martinez, 2020; Belhadi et al., 2020). Indeed, in the context of emerging viral infections, IFN-I are often evaluated (usually in combination with other drugs) before specific treatments are developed, due to their unspecific antiviral effects (Gao et al., 2010; Loutfy et al., 2003; Omrani et al., 2014). We aimed to review the evidence supporting the evaluation of IFN-1 in the treatment of coronaviruses and to discuss its potential in SARS-CoV-2.

Type 1 interferons (IFN–I) designate a group of cytokines comprising the ubiquitous α and β subtypes (themselves subdivided in several isoforms), as well as the ε, ω and κ subtypes (Samuel, 2001). They are secreted by various cell types, notably plasmacytoid dendritic cells, upon recognition of viral components by pattern recognition receptors (PRR) (Liu, 2005). IFN-I are thus among the first cytokines produced during a viral infection. They are recognized by the IFNAR receptor present at the plasma membrane in most cell types. Interferon fixation on IFNAR induces the phosphorylation of transcriptional factors such as STAT1 and their relocalization to the nucleus, where they activate interferon-stimulated genes (ISG). Most ISGs are involved in inflammation, signaling and immunomodulation. They interfere with viral replication and spread by several mechanisms such as a slowdown of cell metabolism or secretion of cytokines which promote the activation of the adaptive immunity. ISGs include PRRs, which further sensitize the cell to pathogens, proteins which decrease membrane fluidity, preventing viral egress or membrane fusion, and antivirals that specifically inhibit one step of the viral cycle (Schneider et al., 2014; Totura and Baric, 2012). IFN-I thus play a major role in antiviral immunity. Because of their immunomodulatory properties, IFN-I are used in the treatment of numerous diseases: for example, subcutaneous injections of IFNβ have been used for more than 20 years for the treatment of patients with multiple sclerosis. The role of IFNβ in the treatment of multiple sclerosis is still debated and likely results partly from the down-regulation of the major histocompatibility complex (MHC) class II expression in antigen-presenting cells, the induction of IL-10 secretion and the inhibition of T-cell migration (Jakimovski et al., 2018).

MERS-CoV and SARS-CoV are coronaviruses closely linked with SARS-CoV-2 and presenting similar properties, despite differences in their epidemiology, pathology and in several of their proteins (Lai et al., 2020). IFN-I treatment has been studied against MERS-CoV and SARS-CoV (reviewed in Stockman et al., 2006), in numerous experiments, both *in vitro* and *in vivo*, and in combination or not with lopinavir/ritonavir (Chan et al., 2015; Sheahan et al., 2020), ribavirin (Chen et al., 2004; Morgenstern et al., 2005; Omrani et al., 2014), remdesivir,

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corticosteroids (Loutfy et al., 2003), or IFNγ (Sainz et al., 2004; Scagnolari et al., 2004). IFNα and β were systematically relatively efficient *in vitro* and succeeded in certain animal models (Chan et al., 2015), but generally failed to significantly improve the disease in humans (Stockman et al., 2006). For example, a combination of IFNβ with lopinavir/ritonavir against MERS-CoV improved pulmonary function but did not significantly reduce virus replication or lung pathology severity (Sheahan et al., 2020), while a combination of IFNα2a with ribavirin delayed mortality without decreasing it on the long run (Omrani et al., 2014). Similarly, the combination of IFNα2b with ribavirin gave excellent results in the rhesus macaque (Falzarano et al., 2013), but was inconclusive in human (Arabi et al., 2017). The lack of significant disease improvement with IFN-I treatment in numerous studies can be explained by the mechanisms of inhibition of the IFN signaling pathway used by MERS-CoV and SARS-CoV, by the limited number of patients or animals used in the studies, or by the difficulty to decipher whether disease improvements were caused by IFN-I or the drugs used in combination with it. In addition, results often differ substantially between studies because of inconsistencies in the experimental settings or the clinical conditions (Stockman et al., 2006): for example, a study on SARS-CoV revealed a positive effect of IFN-I treatment (Loutfy et al., 2003), while another study with a larger cohort did not detect any significant effect (Zhao et al., 2003). It has also been proposed that interferon was efficient in patients only if they lacked comorbidities (Al-Tawfiq et al., 2014; Shalhoub et al., 2015). Subtype diversity could be another explanation of inconsistencies between studies. It was repeatedly shown that IFNβ is a more potent inhibitor of coronaviruses than IFNα (Scagnolari et al., 2004; Stockman et al., 2006): depending on the studies, IFNβ1b or IFNβ1a were the most potent IFN-I subtype in the inhibition of SARS-CoV (Hensley et al., 2004) and MERS-CoV (Chan et al., 2013; Dong et al., 2020; Hart et al., 2014). Consequently, IFNβ1 appears to be most relevant interferon to treat coronavirus infections. This fact can be related to the protective activity of IFNβ1 in the lung: it up-regulates cluster of differentiation 73 (CD73) in pulmonary endothelial cells, resulting in the secretion of anti-inflammatory adenosine and the maintenance of endothelial barrier function. This process explains why clinical data indicate a reduction of vascular leakage in acute respiratory distress syndrome (ARDS) with IFNβ1a treatment (Bellingan et al., 2014). However, this effect is insufficient to decrease ARDS mortality (Ranieri et al., 2020). It has been suggested from *in vivo* studies in mice that the timing of IFN-I administration plays a crucial role: positive effects were observed if IFN-I was administered shortly after infection, but IFN-I failed to inhibit viral replication and had side-effects when administered later (Channappanavar et al., 2019). Following a study showing that IFNβ1b was as efficient as lopinavir/ritonavir against MERS-CoV in marmosets (Chan et al., 2015), the combination of IFNβ1b (injected intravenously) and lopinavir/ritonavir is currently investigated in a clinical trial in Saudi Arabia (Arabi et al., 2018). This is to our knowledge the only clinical trial against MERS-CoV.

The knowledge gained from experiments of IFN-I treatment against SARS-CoV and MERS-CoV is valuable in the selection of potential treatments against SARS-CoV-2. SARS-CoV and MERS-CoV are able to disrupt the interferon signaling pathway. For example, the Orf6 protein of SARS-CoV disrupts karyopherin transport (Frieman et al., 2007; Kopecky-Bromberg et al., 2007) and consequently inhibits the import in the nucleus of transcriptional factors such as STAT1, resulting in the interferon response. Similarly, the Orf3b protein of SARS-CoV inhibits the phosphorylation of IRF3 (Kopecky-Bromberg et al., 2007), a protein involved in the activation of IFN expression. However, the Orf6 and Orf3b proteins of SARS-CoV-2 are truncated (Lokugamage et al., 2020) and may have lost their anti-interferon functions. It could explain why SARS-CoV-2 displays *in vitro* a substantial sensitivity to IFNα (Lokugamage et al., 2020): although SARS-CoV-2 replication is not entirely suppressed by interferons, viral titers are decreased by several orders of magnitude. SARS-CoV2 is substantially more sensitive to IFN-I than SARS-CoV, which suggests that IFN-I treatment should be at least as effective for the former than for the latter. Supporting this hypothesis, it was shown that IFNα2b sprays can reduce the infection rate of SARS-CoV-2 (Shen and Yang, 2020). This study shows that IFN-I can be used as a prophylaxis against SARS-CoV-2, which is confirmed by the *in vitro* efficacy of interferon pretreatment against the virus (Lokugamage et al., 2020), while the replication of MERS-CoV (Sheahan et al., 2020) and SARS-CoV (Menachery et al., 2014; Thiel and Weber, 2008), was reported to be indifferent to IFN-I prophylaxis.

From the data presented above, IFN-I might be a safe and efficient treatment against SARS-CoV-2. Knowledge acquired during studies on MERS-CoV or SARS-CoV would be critical assets in that perspective: for example, they indicate that IFNβ should be the most relevant interferon subtype, and that IFN-I should be administered as early as possible to optimize antiviral therapy and avoid adverse events (Channappanavar et al., 2019). Furthermore, COVID-19 pathology, mainly consisting in pulmonary lesions, presents similar characteristics with interferonopathies: it may suggest that SARS-CoV-2 induces an excessive IFN-I mediated antiviral response, leading to tissue damage. IFN-I treatment should be limited to the early phases of the infection if this hypothesis is confirmed, as suggested in (Siddiqi and Mehra, 2020) and by early clinical data showing that inflammatory biomarkers are associated with increased mortality (Zhou et al., 2020). In the late phases, it is even possible that anti-interferon drugs should be used to mitigate the pathology (Zhang et al., 2020).

In China, the guidelines for the treatment of COVID-19 recommend to administer 5 million U of IFNα by vapor inhalation twice a day to the patients, in combination with ribavirin (Dong et al., 2020; Lu, 2020). Clinical trials have been recently registered to evaluate a combination of lopinavir/ritonavir and IFNα2b (ChiCTR2000029387) or a combination of lopinavir/ritonavir with ribavirin and IFNβ1b administered subcutanously (NCT04276688) for the treatment of COVID-19. The administration by vapor inhalation currently performed in China offers the advantage of targeting specifically the respiratory tract; however, to the best of our knowledge, the pharmacodynamics and pharmacokinetics of this mode of administration have never been assessed. On the contrary, the intravenous and subcutaneous modes of administration are well-described, have already proven safe in several clinical trials, and have similar pharmacodynamics and pharmacokinetics (Mager and Jusko, 2002). The combination of IFN-I with lopinavir/ritonavir, ribavirin or remdesivir could improve its efficacy, because of the efficiency of such combinations observed *in vitro* in other coronaviruses (Sheahan et al., 2020). It might also be relevant to evaluate type III IFN for the treatment of COVID-19 (Lokugamage et al., 2020), because of the protective effects of this interferon type in the respiratory tract. Subcutaneous IFNβ1a in combination with lopinavir/ritonavir is compared to lopinavir/ritonavir alone, hydroxychloroquine, and remdesivir in the DisCoVeRy trial (NCT04315948), which is the first clinical trial of the WHO Solidarity consortium of clinical trials.

In conclusion, IFNβ1 may account for a safe and easy to upscale treatment against COVID-19 in the early stages of infection. Similar treatments had a mixed efficiency against MERS-CoV and SARS-CoV viruses, but *in vitro* studies suggest that SARS-CoV-2 could be substantially more sensitive to IFN-I than other coronaviruses. The current lack of animal model for COVID-19 should not prevent the clinical evaluation of IFN-I treatment, since its safety has already been assessed in numerous independent clinical trials. Publications of data about IFN-based COVID-19 treatment performed in China in early 2020, expected in a near future, should give more accurate information on the relevance of this therapy.

Declaration of competing interest

None.

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