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Short Communication

Type 1 interferons as a potential treatment against COVID-19

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**A R T I C L E   I N F O**

**Keywords:**
Interferon
COVID-19
SARS-CoV-2

**A B S T R A C T**

Type 1 interferons have a broad antiviral activity \textit{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.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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-I 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 \textit{in vitro} and \textit{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,
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 (Omran 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 (Zhang 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 more 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 Orf2b protein of SARS-CoV inhibits the phosphorylation of IRFs (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 interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive interferonopathy: it may suggest that SARS-CoV-2 induces an excessive

Declaration of competing interest

None.
Acknowledgments

The DiCoVeRy French Trial Management Committee includes the following members: Principal Investigator: Florence Adre. Scientific coordinator: Yuzdan Yazdanpanah. Chief methodologist: France Mentre. Infectious diseases specialists: François-Xavier Lesure, Nadine Peiffer-Smaja. Intensivists: Lila Bouadma, Julien Poissy, Jean-François Timsit. Virologists: Bruno Lina, Florence Morisset. Infectious diseases specialists: François-Xavier Lescure, Nathan Loutfy, Marine Mancebo, Jean-François Salette, Juliette Saillard, Caroline Semaille.

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