NEUROLOGICAL RISKS AND BENEFITS OF CYTOKINE-BASED TREATMENTS IN COVID-19: A JOURNEY FROM PRECLINICAL TO CLINICAL EVIDENCE

Giuseppe Pignataro MD PhD[1*], Mauro Cataldi MD PhD[1*],
and Maurizio Taglialatela MD PhD[1#]

[1]Division of Pharmacology, Department of Neuroscience, University of Naples "Federico II", 80131 Naples, ITALY

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[*]These authors contributed equally

[#]Corresponding Author: Maurizio Taglialatela, MD PhD.
Department of Neuroscience, University of Naples "Federico II". Via Pansini 5, 80131, Naples (IT).
Tel. +39-081-7463310; Fax: +39-081-7463323. email: mtaglial@unina.it. ORCID ID: 0000-0002-8202-0560

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Abstract

Immunodeficiency and hyperinflammation characterize COVID-19 associated states; thus, repurposing of multiple cytokine and/or anti-cytokine drugs currently being used in other therapeutic areas has been suggested as a potential therapeutic strategy in COVID-19 patients. Clinical trials involving these drugs target the most frequent and life-threatening peripheral consequences of the disease, mainly focusing on lung, heart, and coagulation functions; however, a growing number of reports describe a wide range of COVID-associated neurological manifestations (altogether defined as neuro-COVID) including anosmia, seizures, confusion, stroke, encephalopathy, and paralysis. Notably, the underlying pathophysiological mechanisms for neuro-COVID may also include dysregulation of cytokines/chemokines, deficiencies in the innate immune response, and autoimmunity. This suggests that therapeutic attempts with drugs targeting cytokine-mediated inflammation in peripheral organs could also positively affect neuro-COVID manifestations. As a matter of fact, some of these drugs have also been scrutinized for their potential efficacy in treating neuroinflammatory diseases such as optic neuromyelitis, epilepsy, stroke, and traumatic brain injury, among others. On the other hand, anti-cytokine drugs, by impairing relevant physiological activities exerted by these mediators in the CNS, may also be endowed with significant neurological risk. Therefore, the primary aim of the present manuscript is to review the available preclinical and clinical data regarding the neurological effects of the drugs targeting cytokine-mediated inflammation, in order to raise awareness about their potentially beneficial or detrimental neurological consequences when used to treat COVID-19 patients.

INTRODUCTION

Although most Coronaviruses (CoVs) mainly cause animal diseases, few have been known for decades as responsible for self-limiting respiratory infections in humans (van der Hoek, 2007). This view of CoVs as relatively un-hostile viruses has dramatically changed in the last 20 years, when three outbreaks of human severe respiratory infections caused by highly pathogenic CoVs have occurred: the severe acute respiratory syndrome (SARS) by the SARS-CoV, the Middle East respiratory syndrome (MERS) by the MERS-CoV, and the currently-ongoing Coronavirus Disease 2019 (COVID-19) pandemic by the SARS-CoV-2.

In COVID-19 patients, the respiratory system complications of a multiorgan dysregulation are the most frequent and life-threatening; however, reports of neurological signs and symptoms due to central and peripheral nervous system involvement (neuro-COVID) are growing exponentially (Paterson et al., 2020), and it has been suggested that damage to the bulbar respiratory centers could contribute to respiratory failure and death of COVID-19 patients (Li et al., 2020). Neurological manifestations range from relatively mild symptoms such as anosmia and dysgeusia (Mao et al., 2020), often accompanied by dizziness and headache (Mao et al., 2020), to more severe neurological conditions. In a recent retrospective study performed in PCR-confirmed COVID-19 patients (Paterson et al., 2020), these more severe neurological disorders could be classified as: 1. encephalopathy with delirium/psychosis and seizures, and no distinct MRI or CSF abnormalities (Helms et al., 2020); 2. meningo-encephalitis most commonly referred to as acute disseminated encephalomyelitis, an inflammatory demyelinating disease of the central nervous system (CNS) (Moriguchi et al., 2020); 3. ischaemic stroke associated with a prothrombotic state and pulmonary thromboembolism (Beyrouti et al., 2020); 4. acute hemorrhagic necrotizing encephalopathy, a rare encephalopathy representing one of the remote complications of influenza and other viral infections (Poyiadji et al., 2020); and 5. peripheral neurological disorders, most often represented by the Guillain-Barré Syndrome (GBS), a paralytic demyelinating disorder with massive lymphocytic infiltration and damage to the myelin sheath of the peripheral nerves and neurological symptoms emerging few days after the first respiratory symptoms (Toscano et al., 2020), or by the Miller-Fisher syndrome, a GBS variant characterized by the triad of ataxia, areflexia, and ophthalmoplegia(Gutierrez-Ortiz et al., 2020). Notably, such neurological complications closely resemble those occurring in SARS- and MERS-affected patients (Kim et al., 2017; Tsai et al., 2005).

Current evidence supports the notion that, in COVID-19, most of the tissue damage, including that of the CNS, is likely due to the immune and inflammatory response triggered by SARS-CoV-2 rather than being a direct consequence of the cytopathic effect of the virus; this suggests that drugs targeting cytokine-mediated inflammation, which are currently being explored as potential therapeutic means in COVID-19, could also positively affect neuro-COVID manifestations. As a matter of fact, some of these drugs, although being mostly clinically used against rheumatic diseases, have also been investigated for the treatment of neuroinflammatory diseases. On the other hand, anti-cytokine drugs, by impairing relevant physiological

activities exerted by cytokines in the CNS, may be endowed with significant neurological risk mainly attributable to their immune-depressant effects. Therefore, the aim of the present manuscript is to review the available data regarding the neurological effects of the drugs targeting cytokine-mediated inflammation currently being investigated against COVID-19, in order to raise awareness about their potentially beneficial and/or detrimental neurological consequences.

To this aim, we interrogated the Pubmed citation database of the National Library of Medicine (PubMed; https://pubmed.ncbi.nlm.nih.gov/) for studies published in English in peer-reviewed International journals using the following keywords: SARS-CoV-2, COVID-19, neuroinflammation, cytokines, cytokine inhibitors, anti-cytokine drugs, neurological diseases, and immune-mediated neurological damage. The screening of titles and abstracts was performed by all authors, and those titles considered relevant for the purpose of the present review were retrieved, analyzed, and their main findings reported in the present manuscript. In addition, we searched the NIH database of clinical trials (https://clinicaltrials.gov/) for ongoing clinical trials in COVID-19 patients with the terms Coronavirus/SARS-CoV-2/COVID and one of the following: IL-1, IL-6, IL-7, TNFα, NF-kB, JAK/STAT, GM-CSF, and Complement system.

RATIONAL BASIS FOR TARGETING NEUROINFLAMMATORY MECHANISMS IN COVID-19

SARS-CoV-2 may enter the brain through multiple routes including the fibers of olfactory and vagus nerves or the blood by crossing the BBB directly or being vehiculated by leukocytes that have been infected elsewhere, for instance in the airways (Cataldi et al., 2020). Although no data is currently available for SARS-CoV-2, evidence gathered over the years for other neurotropic CoVs strains clearly suggest that, once in the CNS, these viruses may infect neuronal, glial and brain microvascular endothelial cells (Cataldi et al., 2020; Yamashita et al., 2005). However, cell killing is not the only consequence of the infection since the virus may, instead, establish persistent infection of their host cells. I*n vivo* evidence for CoV-induced cytopathic effect in neuronal or glial cells is limited, and direct virus-induced cell demise may only have a role in acute or hyperacute forms of CoV-induced CNS damage which occur with limited tissue inflammation (Morfopoulou et al., 2016). Instead, the CNS might be damaged by the unique association of immune deficiency and hyperinflammation, the latter being manifested mainly by a cytokine storm, characterizing COVID-19 pathogenesis (Jamilloux et al., 2020), with high levels of circulating TNF-α, IL-1β, IL-Ra, IL-6, IL-10, IL-17, IFN-γ, M-CSF, and G-CSF, among other soluble immune mediators (Huang et al., 2020). The triggering factor of this hyperinflammatory condition is probably the virus-induced activation of the innate immune system through the interaction of its RNA and structural proteins with cytosolic pattern recognition receptors (PRR) (Jensen *et al.*, 2012), inducing the expression of both type I and type III interferons and proinflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8. In addition, hyperactivated chemiotaxis driven by the enhanced expression of CXCL- or CCL-type chemokines and their receptors may

also participate in tissue recruitment of neutrophils, monocytes, and macrophages (Jamilloux *et al.*, 2020). Resident cells of the CNS including glia, neurons and neuro-endothelial cells all synthesize and release these molecules. Mononuclear cells entering the brain parenchyma, in addition to acting as Trojan horses carrying more virus particles in the brain, also facilitate the progression of CNS damage as they release mediators of inflammation such as free oxygen radicals, cytokines and chemokines such as IL-1β, IL-6, TNFα, GM-CSF, CXCL-8 and CCL-3. Strong activation of innate immunity can cause CNS damage either through direct cytopathic effects of cytokines, as demonstrated, for instance for TNFα (Venters et al., 2000) and IL-1β (Viviani *et al.*, 2003), or indirectly through the activation of inflammatory cells and the further release of free radicals. Therefore, it will be the fine adjustment of the immune response triggered by neuroinfection to determine whether the tissue will be cleared from the viruses and healing will occur or, instead, significant tissue damage will overcome the repairing capacity of the CNS. In this scenario, a crucial role is played by anti-inflammatory cytokines such as IL-10 and IL-Ra that are also released in response to neuroinfection and counteract the activity of proinflammatory cytokines.

On average 7-10 days after CoV infection, adaptive immune responses are activated and virus-specific $CD4^+$ and $CD8^+$ lymphocytes are recruited in the CNS by the chemoattractant activity of chemokines released by innate immunity effector cells. Recruitment of virus-specific T lymphocytes during the adaptive immune response results in a dramatic decrease in virus replication and inflammation but not always in the complete clearance of CoVs that may persist for a very long time in infected cells and trigger a chronic inflammatory status. Whether, as demonstrated in experimental animals for other CoVs (Libbey *et al.*, 2014), SARS-CoV-2 may induce chronic inflammation and facilitate the occurrence of chronic neurological disorders in humans is still unknown.

The immuno-inflammatory mechanisms triggered during SARS-COV-2 infection pose the theoretical basis for pharmacological strategies interfering with specific immune soluble mediators at different levels (e.g cytokines, their receptors or transductional mechanisms) in COVID-19 patients. Noteworthy, these same mechanisms, besides being critical determinant of peripheral tissue damage in COVID-19, also play a relevant role in the pathogenesis of a wide spectrum of neurological disorders such as epilepsy and stroke, whose neuroinflammatory basis has long been hypothesized and whose manifestations resemble those described in neuro-COVID. In all these conditions, immunomodulatory approaches with the same drugs have already been investigated, leading to clinical improvement, and established uses in some cases, at the same time also raising safety concerns. Therefore, immunomodulatory pharmacological strategies currently under investigation which target critical components of the immune system will be reviewed in the following paragraphs, in order to highlight and discuss their potentially beneficial or detrimental neurological impact when used in COVID-19-affected patients.

NEUROINFLAMMATION AND CYTOKINE-TARGETED INTERVENTIONS

a. Targeting IL-1β: anakinra, canakinumab

IL-1β is among the earliest cytokines whose levels increase in the plasma of CoV patients (Huang *et al.*, 2020). This 269 aminoacid protein is a key mediator of innate immune response that also participates in triggering adaptive immunity (Dinarello, 2018). IL-1β activity can be pharmacologically blocked with anakinra, a recombinant form of its natural antagonist IL-Ra, which has been approved for the treatment of rheumatoid arthritis and cryopyrin-associated periodic syndrome (CAPS) (Dinarello, 2018) or with canakinumab, a high-affinity human monoclonal antibody against IL-1β, also approved for CAPS (Lachmann *et al.*, 2009). A wealth of data suggests that IL-1β has a role in the genesis of CNS damage in neuroinflammation and that anakinra can be beneficial in neuroinflammatory diseases (Dinarello, 2018). In fact, IL-1β is generated by the proteolytic degradation of the precursor molecule Pro-IL-1β whose expression is induced via NF-KB by the activation of the PRRs activated not only by the so called *pathogen-associated molecular patterns* (PAMPs), which include signals related to viral diseases, but also by *danger-associated molecular patterns* (DAMPs), which, instead, are released upon tissue damage of infectious and non-infectious origin (Roh *et al.*, 2018). Therefore, IL-1β , together with other cytokines, may trigger the so-called "sterile" inflammation that accompanies non-infective neuroinflammatory diseases. By interacting with intracellular PRRs, both PAMPs and DAMPs trigger the assembly of inflammosomes which promote the conversion of procaspase 1 into caspase-1, and, ultimately, caspase-1 dependent mediated cleavage of Pro-IL-1β into the active form IL-1β (Voet *et al.*, 2019). IL-1β has both physiological and pathological roles in the CNS where it can be released by glial cells, mainly by microglia, and by neurons (Wang *et al.*, 2015). In physiological conditions this cytokine potentiates the glutamatergic neurotransmission and is required for long term potentiation (LTP), an elementary form of memory (Hewett *et al.*, 2012). An excessive IL-1β-dependent activation of the glutamatergic neurotransmission leads to glutamate-dependent neurotoxicity, as demonstrated in experimental models of MS (Mandolesi *et al.*, 2013); therefore, it has been proposed that IL-1β could bridge neuroinflammation to excitotoxicity (Hewett *et al.*, 2012). IL-1β-induced excitotoxicity, together with enhanced vascular permeability (Wong *et al.*, 2019), may account for the detrimental role played by this cytokine in several neurodegenerative conditions including stroke (Wong *et al.*, 2019), brain hemorrhage (Greenhalgh *et al.*, 2012), spinal cord injury (Hasturk *et al.*, 2015), demyelinating diseases (Badovinac *et al.*, 1998) and epilepsy (Vezzani *et al.*, 2000). In all these conditions, IL-1β antagonism with anakinra exerts protective effects in experimental animals. Remarkably, clinical evidence of anakinra efficacy in these conditions begins to be available (Everett *et al.*, 2020; DeSena *et al.*, 2018; Smith *et al.*, 2018; Kenney-Jung *et al.*, 2016). The pharmacological antagonism of IL-1β may be also effective in demyelinating diseases, as shown in rats with experimental allergic encephalomyelitis (Martin *et al.*, 1995) and in a patient who developed neuromyelitis optica (NMO) as a complication of Familial Mediterranean fever (FMF), a rare disease related to inflammosome hyperactivation (Ozdogan *et al.*, 2020).

The neurodetrimental effects of IL-1β are partially counterbalanced by the positive consequences of activating innate and adaptive immunity. For instance, it has been shown that IL-1β may help removing amyloid plaques in the the APPswe/PS1dE9 mouse model of Alzheimer Disease (AD) (Shaftel *et al.*, 2007). In addition, IL-1β promotes the release of NGF (Carlson *et al.*, 1999), hence facilitating neurorepair after TBI (DeKosky *et al.*, 1996). Therefore, as for other cytokines, the final effect of IL-1β released in the CNS will be the result of the balance between its favorable and detrimental effect. Viral CNS diseases well exemplify this principle since IL-1β is critically important to limit viral multiplication and CNS damage in the case of highly cytopathic viruses such as the herpes simplex 1 (Sergerie *et al.*, 2007) or the West Nile virus (Durrant *et al.*, 2013), whereas it mainly promotes neuroinflammation and tissue damage for less severely cytopathic and long persistent viruses such as HIV (Brabers *et al.*, 2006) and Sindbis virus (Prow *et al.*, 2008). Studies performed with the Theiler's virus, which remains latent in the CNS and induces a chronic demyelinating disease with similarities to human MS, showed that both an excessive and an insufficient release of IL-1β may be detrimental since the first directly damages the CNS, whereas the second promotes virus persistence and, ultimately, the reactivation of viral infection (Kim *et al.*, 2012). Given the current knowledge of CoVs neurobiology (Cataldi *et al.*, 2020), it may be speculated that CoV-induced CNS damage is mostly a consequence of neuroinflammation and, therefore, that IL-1β antagonism could be beneficial. In COVID-19, lung and multiorgan injury depend on systemic inflammation and high levels of IL-1β have been detected in the peripheral blood and broncho-alveolar fluid of patients with COVID-19 (Yang *et al.*, 2020); therefore, several clinical studies are ongoing to evaluate the effect of anakinra and canakinumab on the course of the disease (Table 1). Though these investigations were not specifically designed in patients with neuro-COVID and no neurological safety or efficacy objectives are listed among primary or secondary endpoints of these studies, it will be of interest to evaluate whether IL-1β blockade will induce neurological improvement in COVID-19 patients showing evidence of CNS involvement.

b. Targeting IL-6: tocilizumab, sarilumab and siltuximab

IL-6 is a pleiotropic class I cytokine that is released during the innate immunity response by multiple cell types including macrophages, T and B cells, fibroblasts and endothelial cells (Uciechowski *et al.*, 2020). As for IL-1, also IL-6 synthesis is induced by the activation of PRRs; in addition, IL-1 also promotes IL-6 synthesis, and, therefore, some of the biological consequences of the activation of IL-1 may be mediated by IL-6 (Smith *et al.*, 2018). IL-6 exerts both pro- and anti-inflammatory effects and has a crucial role in the activation of adaptive immunity (Smith *et al.*, 2018). In the CNS, IL-6 is produced not only by microglial cells and infiltrating immune cells such as lymphocytes and macrophages, but also by neurons and endothelial cells. IL-6 exerts its biological effects through the binding to its specific IL-6R which binds to and activates another receptor subunit, gp 130, ultimately leading to the activation of members of the signal transducer and activator of transcription family, STAT1 and STAT3 (Sanz-Moreno *et al.*, 2011). IL-6R exists in two

different forms: an integral plasmamembrane receptor protein (mIL-6R), and a soluble form (sIL-6R). In cells that express both these receptor types, IL-6 induces the so called "*classical*" IL-6 signalling: the same cells that express IL-6R also respond to IL-6. Conversely, in IL-6 "*trans-signalling*" sIL-6R binds IL-6 extracellularly and this ligand-receptor complex combines with gp130 in cells lacking IL-6R. Both in classical- and in trans-signalling, gp130 binding to both forms of IL-6R leads to the recruitment of JAK proteins and ultimately to the activation of STAT-dependent gene expression (Uciechowski *et al.*, 2020).

In physiological conditions, IL-6 is released at low concentrations in the CNS and has a role in neuroendocrine regulation, in the control of body temperature, food intake and energy metabolism and pain sensitivity; it is also involved in learning and memory, and in emotions (Erta *et al.*, 2012). CNS IL-6 concentrations dramatically increase in a variety of neurological disorders including TBI, stroke, AD, MS, or infective brain diseases (Rothaug *et al.*, 2016; Uciechowski *et al.*, 2020). High concentrations of IL-6 potentiate the activity of NMDA receptors, thus enhancing glutamate-dependent neurotoxicity (Qiu *et al.*, 1998). Transgenic mice overexpressing IL-6 in astrocytes (GFAP-IL-6 mice) showed ataxia, seizures and a progressive decrease in learning capabilities (Campbell *et al.*, 1993; Heyser *et al.*, 1997), with diffuse atrophy, neuronal degeneration and loss, reactive astrogliosis and angiogenesis (Campbell *et al.*, 1993). IL-6-mediated neurodegeneration depends on the activation of sIL-6R as demonstrated by its loss in double transgenic mice that not only overexpress IL-6 in the astrocytes but also a soluble gp130-Fc fusion protein that binds and inactivates sIL-6R in the extracellular space (Campbell *et al.*, 2014). In sharp contrast with these chronic neurodegenerative changes, GFAP-IL-6 mice were apparently protected against acute neurological damage such that induced by focal cryo-lesion or by the intraperitoneal injection of 6-aminonicotinamide (Penkowa *et al.*, 2003; Swartz *et al.*, 2001). Similarly, preclinical evidence for both pro- and anti-convulsant actions of IL-6 are available; in fact, a higher susceptibility to chemically-induced seizures was observed in both rats intranasally-treated with IL-6 (Kalueff *et al.*, 2004) and IL6-KO mice (De Sarro *et al.*, 2004). In addition, a dual role for IL-6 has also been postulated in stroke, given that CSF IL-6 concentrations positively correlated with larger stroke volume and less favorable prognosis in humans (Waje-Andreassen *et al.*, 2005), despite the fact that IL-6 is required for post-stroke angiogenesis in experimental animals (Gertz *et al.*, 2012). Finally, IL-6 uniformly contributes to tissue damage in experimental models of MS, as indicated by the protective effect of its immunoneutralization against Experimental Autoimmune Encephalomyelitis (EAE) in mice (Gijbels *et al.*, 1995) and by the milder disease course observed in IL-6 KO mice (Samoilova *et al.*, 1998).

The biological effects of IL-6 can be pharmacologically blocked with siltuximab, a neutralizing monoclonal antibody directed against IL-6 (Fajgenbaum *et al.*, 2016), or with tocilizumab (Sheppard *et al.*, 2017) and sarilumab (Scott, 2017), two anti-IL-6R monoclonal antibodies that neutralize both mIL-6R and sIL-6R, thus blocking IL-6 classical- and trans-signaling pathways. Given the prominent role of IL-6 in systemic inflammation during COVID-19, several controlled randomized trials are ongoing to evaluate the use of IL-6

modulators in these patients (Table 2). Given our aims, it is worth reminding that tocilizumab efficacy has been already demonstrated in several human neurological diseases. A first example is given by NMO (Araki, 2019), a demyelinating disease of the optic nerve in which the high concentrations of IL-6 observed in the CSF (Uzawa *et al.*, 2013) promote the production of pathogenetically-determinant AQP4 auto-antibodies (Chihara *et al.*, 2011). Tocilizumab seems also effective in autoimmune encephalitis, a neurological disease caused by autoantibodies directed against synaptic and neuronal cell surface proteins, particularly in patients refractory to rituximab (Lee *et al.*, 2016), and in new onset refractory status epilepticus (NORSE) (Jun *et al.*, 2018). A favorable clinical response to IL-6R blockade with tocilizumab has been also reported in severe acute necrotizing encephalopathy of childhood, a devastating parainfectious encephalopathy that occurs early during the course of viral infections and is presumed to be determined by massive release of cytokines including IL-6 (Koh *et al.*, 2019). Finally, tocilizumab was also shown to be effective in attenuating inflammation in patients affected by Takayasu's arteritis with associated stroke (Osman *et al.*, 2015) , multiple sclerosis (Hoshino *et al.*, 2020) and amyotrophic lateral sclerosis (ALS) (Fiala *et al.*, 2013; Mizwicki *et al.*, 2012). Notably, clinical trials in rheumatoid arthritis (RA) showed that sarilumab treatment, independently from its antirheumatoid effect, improved outcomes for pain, social functioning, and mood (Atzeni *et al.*, 2019). In addition, siltuximab ameliorated depressive symptoms in RA patients or multicentric Castleman's disease (MCD), again independently on its anti-rheumatic effects (Sun *et al.*, 2017).

Preclinical data mainly suggest that IL-6 facilitates tissue damage during viral CNS infections, such as encephalitis caused by the intracerebral inoculation of the human Enterovirus 71 (EV71) in mice (Luo *et al.*, 2019). In addition, in mice infected with the Theiler's murine encephalomyelitis virus (TMEV), high levels of IL-6 in the CNS promote virus persistence and chronic demyelination by preventing, in concert with IL-17, apoptotic cell death of virus- infected cells (Hou *et al.*, 2014) and by upregulating the expression of the coinhibitory protein PDL-1 in macrophages and in microglia (Jin *et al.*, 2013). Thus, on the basis of these results, anti-IL-6 strategies might be expected to reduce the risk of SARS-CoV-2 persistence in the CNS possibly associated to chronic forms of neuro-COVID; nevertheless, the ability of these drugs to mediate serious side effects , including recurrent meningitis (Richebè et al., 2018), HTLV1-associated conditions (Tereda et al., 2017), multifocal and limbic encephalitis (Yamagouchi et al., 2014), requires careful consideration.

h. Targeting TNF-α: infliximab and adalimumab

TNF-α plays a key role in almost all acute inflammatory reactions by promoting oxidative stress and inflammation. TNFα is mainly produced by macrophages, monocytes and B cells and, in the CNS, by microglia, neurons, and astrocytes. TNF-α, which is produced initially as a transmembrane molecule (tmTNF), is subsequently released from cells as a soluble cytokine (sTNF) via regulated cleavage by TNF-α converting enzyme (TACE). Both tmTNF and sTNF are biologically active and interact with two receptors

with different tissue expression: TNFR1 and TNFR2. TNFR1, which is expressed in all cell types and is preferentially activated by sTNF, contains a death domain, mediates apoptosis and triggers inflammation by inducing the production of other cytokines such as IL-1 and IL-6 (the so-called "TNF dependent cytokine cascade"). On the contrary, TNFR2 is expressed mainly in neurons, immune cells, and endothelial cells preferentially binds tmTNF, and promotes cell survival, resolution of inflammation, and even myelination. The opposite effects elicited by the stimulation of TNFR1 and TNFR2 may explain why TNF-α, which is essential in the acute phase of the inflammatory process, becomes immune-suppressive when produced at excessive levels for prolonged times. Several monoclonal and chimeric antibodies such as adalimumab and infliximab have been developed to block the effect of TNF-α in vivo. These drugs elicit major anti-inflammatory and immunosuppressive effects, and were granted approval in several autoimmune disorders including Crohn's disease (CD), ankylosing spondylitis (AS), and rheumatoid arthritis (RA) (Kalliolias *et al.*, 2016).

TNF-α, both peripherally released and centrally produced, has a role in neuroinflammation and the blockade of TNF-α in the periphery reduces the release of IL-1 and other cytokines in the CNS (Kalliolias *et al.*, 2016). Therefore, anti-TNF-α drugs have been investigated, with promising results in preclinical models of several neurodegenerative disorders including MS (Kemanetzoglou et al., 2017), stroke (Jayaraj *et al.*, 2019), and epilepsy (Vezzani *et al.*, 2016) although they did not receive approval for any of these conditions in humans. Nonetheless, adalimumab has been successfully used in Rasmussen encephalitis (Lagarde *et al.*, 2016).

An important reason of concern, when using anti-TNF-α antibodies, especially in neurological disorders, is that clinical experience with these drugs in rheumatology and dermatology showed that not only they cause a variety of immune-mediated adverse events, such as urticaria, psoriasis, lupus-like syndrome, and type I diabetes mellitus (Fischer *et al.*, 2020), but also immune-mediated CNS diseases in about 4% of patients (Kaltsonoudis et al., 2014) such as optic neuritis, chronic inflammatory demyelinating polyneuropathy, mononeuritis multiplex and Guillain-Barré syndrome (Zhu *et al.*, 2016; Kemanetzoglou *et al.*, 2017), vasculitis and amyloidosis (Theibich *et al.*, 2014). It is still debated whether In these cases treatment with TNF-α blockers triggered the development of these diseases or unmasked a preexisting still silent disease status (Kaltsonoudis *et al.*, 2014).

Anti-TNF-α drugs may exert dual effects in viral diseases: on the one side, by lowering TNF-α-dependent immune responses they increase the risk of developing viral infections including HIV, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, and human papillomavirus and frequently cause the reactivation of herpes zoster (Strangfeld *et al.*, 2009; Kim and Solomon, 2010; Shale et al., 2010), whereas, on the other, they attenuate tissue damage and ameliorate the course of specific viral diseases by decreasing inflammation as shown, for instance, for severe respiratory syncytial virus (RSV) and influenza infections in mice (Rosenberg *et al.*, 2012). A similar duality of effects has also been reported for CNS viral infections

since serious encephalitis (Bradford et al., 2009) and meningitis (Ma *et al.*, 2013), mainly of herpetic etiology, may occur in patients treated with anti-TNF-α antibodies for inflammatory bowel disease or for rheumatoid arthritis (Bradford et al., 2009); however, it shoud be pointed out that these drugs seem also to reduce disease severity in experimental murine models of herpes simplex (Boivin et al., 2013) and Japanese encephalitis (Ye *et al.*, 2014).

Studies performed with SARS-CoV suggested that excessive TNF-α-dependent inflammation could be crucial in the genesis of this disease. As a matter of fact, the binding of SARS-CoV spike proteins to plasma-membrane ACE-2 activates TACE and, consequently, increases TNF-α release and the activation of the TNF dependent cytokine cascade (Haga et al., 2008). By generating a transcriptomic network model through the bioinformatic analysis of published data on the transcriptional response elicited by SARS-CoV infection in mice, McDermott et al. (2016) predicted that TNFR2 could be crucial for the virulence of this pathogen; they also validated their prediction by showing that the severity of SARS-CoV infection is greatly attenuated in TNFR2-ko mice as compared to their wild type controls. Few data are available on the effect of anti-TNF-α drugs in SARS-CoV-2 infection, essentially limited to case reports. For instance, Bezzio et al. (2020) reported a favorable clinical response to infliximab in a patient with COVID-19 who was treated with infliximab because he also developed a recurrence of ulcerative colitis, whereas Okeke et al. (2020) described the unusually benign clinical course of a patient with rheumatoid arthritis who developed COVID-19 a few days after receiving adalimumab injection. Notably, data from the SECURE-IBD database showed that IBD patients treated with anti-TNF-α drugs do not do worse than those receiving sulfasalazine or mesalazine when they develop COVID-19 (Feldmann *et al.*, 2020). This evidence prompted Feldmann et al. to state that "trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed" (Feldmann *et al.*, 2020) and, at the time of writing, RCTs are ongoing with both infliximab and adalimumab in COVID-19 patients (Table 3). In a recent review paper Jamilloux et al. (2020) listed the theoretical reasons supporting TNF-α blockade as a strategy for COVID-19 treatment and they emphasized that these drugs are expected not only to reduce cytokine release and inflammation, but also to downregulate the production of VEGF and the expression of adhesion molecules in endothelial cells and, therefore, they could impede vascular permeabilization that is crucially important in the pathophysiology of cytokine storm. Whether beneficial effects of TNF-α blockade can be achieved also in neuro-COVID still remains to be addressed in experimental and clinical studies.

d. Targeting Interferon gamma: emapalumab

Interferon-gamma (IFN-γ) is a type II cytokine produced and released by natural killer (NK) and γ/δ T cells during innate immunity and by CD4 and CD8 T cells during adaptive immunity. IFN-γ promotes the activation of macrophages and NK cells enhancing their microbial killing activities, also inducing the differentiation of Th1 lymphocytes and the expression of class II MHC (Huang *et al.*, 1993). These biological

effects are exerted through activation of plasmamembrane IFN-γ receptors consisting of two subunits, IFNGR1 and IFNGR2 which, upon ligand binding, dimerize and activate JAK1 and JAK2 tyrosine kinases, and, ultimately, activate STAT1-dependent gene transcription (Stark *et al.*, 2018).

Preclinical evidence shows that IFN-γ may exert specific effects on neurons and glial cells, which express this cytokine and its receptors (Neumann *et al.*, 1997). IFN-γ has been implicated in the control of a variety of brain functions including sleeping behavior, learning and memory, and mood (Monteiro *et al.*, 2016) and these effects may be explained in part by the regulation of the serotoninergic neurotransmission through the activation of tryptophan-indoleamine-pyrrole 2,3-dioxygenase, an enzyme that degrades the serotonin precursor tryptophan (Oxenkrug, 2011). IFN-γ may also play a major role in neurodegenerative diseases because of its ability to interfere with neuronal survival, differentiation and regeneration. Neural precursor cells express the receptors for IFN-γ and this cytokine has long been shown to affect their differentiation and survival (Jonakait *et al.*, 1994). IFN-γ promotes neurogenesis in adult animals and improves memory and spatial learning in wild type mice and in a transgenic mouse model of AD (Baron *et al.*, 2008). In contrast to these neuroprotective and neuroregenerative properties, other studies reported that IFN-γ promotes cell death and potentiates the killing activities of other noxious agents such as β-amyloid 1-42 (Bate *et al.*, 2006). This duality of effects has also been observed in experimental models of MS; in fact, while IFN-γ potentiates the demyelinating effects of anti-myelin/oligodendrocyte antibodies injected into the subarachnoid space (Vass *et al.*, 1992) and, when directly injected in the striatum, it induces the appearance of lesions similar to those observed in EAE (Sethna *et al.*, 1991), this cytokine has been also shown to protect against cuprizone induced demyelination (Gao *et al.*, 2000) and its immune-neutralization worsens the course of EAE (Ottum *et al.*, 2015).

Opposing effects of IFN-γ have also been described in viral infections of the CNS. While antiviral activity is, in fact, one of the major physiological role of IFN-γ and this cytokine is crucial for the antiviral defense against many virus-induced encephalitis (Chesler *et al.*, 2002), there are also cases in which IFN-γ seems to significantly contribute to viral damage of the CNS. In fact, IFN-γ release in the brain strongly increases in HIV neuroinfection, and this cytokine may paradoxically facilitate HIV replication in astrocytes by inhibiting the β-catenin pathway, a physiological antiviral system (Li *et al.*, 2011). In addition, IFN-γ may contribute to viral damage of the CNS by enhancing the permeability of the blood brain barrier (Daniels *et al.*, 2015) as demonstrated, for instance, in rabies virus infection (Chai *et al.*, 2014). The potential benefits of inactivating IFN-γ in viral encephalitis have been demonstrated in mice receiving intracranial administration at neonatal age of an attenuated lymphocytic choriomeningitis virus which induces a chronic viral encephalitis characterized by an IFN-γ/STAT1-dependent dendrite and synapse loss (Kreutzfeldt *et al.*, 2013).

In humans, emapalumab, a monoclonal antibody directed against IFN-γ, has been approved as a second line treatment in haemophagocytic lymphohistiocytosis (HLH), a rare clinical condition which mainly consists in

severe tissue damage and multi-organ failure due to the hyperactivity of macrophages and T-lymphocytes and the excessive release of cytokines (Al-Salama, 2019). Notably, in ADA-SCID patients, treatment with emapalumab reduced the size of brain lesions occurring during disseminated tubercolosis (Tucci *et al.*, 2020).

Emapalumab is currently under investigation in combination with the IL-1 antagonist anakinra for the treatment of COVID-19 with the rationale of decreasing hyperinflammation and respiratory distress (Table 4). No data is yet available in humans on the effect of emapalumab in neuro-COVID or any other CNS disease.

e. Targeting JAK1-2: tofacitinib, baricitinib, ruxolitinib

The JAK-STAT transduction pathway is a signaling cascade that mediates the response to numerous cytokines (e.g. IL-1, IL-6, INF-γ…….) through the sequential activation of JAK proteins, which are phosphorylated by activated cytokine receptors, and STAT proteins, which, after being phosphorylated by JAK proteins, dimerize and migrate into the nucleus to regulate gene transcription (Schindler *et al.*, 1995). Four different JAK proteins (JAK1, 2, 3, and TYK) may activate seven different STAT proteins (STAT 1, 2, 3, 4, 5A, 5B, and 6) and the response to each cytokine is fingerprinted by the specific set of JAK/STAT proteins that they activate (Ishihara *et al.*, 2002). The JAK-STAT signaling cascade can be pharmacologically blocked, with the intent to treat rheumatological and hematological diseases, with selective JAK inhibitors such as tofacitinib, which has a higher affinity for JAK3 and JAK1 than for JAK2, and ruxolitinib and baricitinib, which preferentially block JAK1 and JAK 2 (Schwartz *et al.*, 2017).

Early studies on the JAK/STAT cascade demonstrated its critical role in immune response, inflammation and tumorigenesis. More recently, the expression in the brain of JAK and STAT proteins has been demonstrated and evidence has emerged for their involvement in neuronal and glial differentiation and in the regulation of LTP (Nicolas *et al.*, 2013). The JAK-STAT signaling cascade becomes activated in response to many different infectious and non-infectious conditions of the CNS that cause cytokine release as a consequence of tissue damage. For instance, a strong activation of STAT1 and STAT3, mainly occurring in reactive microglia and in macrophages, has been observed after cerebral ischemia in experimental animals (Planas et al., 1997; Planas et al., 1996). Nevertheless, there is no evidence that JAK-STAT inhibitors could be beneficial in human stroke and, on the contrary, these drugs could even be dangerous considering that they increases the risk of venous thromboembolism (Scott et al., 2018). The JAK-STAT pathway is also activated by a variety of epileptogenic conditions including TBI (Zhao *et al.*, 2011), exposure to proconvulsant drugs such as kainate and pilocarpine (Choi *et al.*, 2003), and brain ischemia (Planas *et al.*, 1996). Besides causing tissue damage, JAK-STAT activation also increases the excitability of the epileptic brain by lowering GABAergic neurotransmission hence contributing to seizure development (Brooks-Kayal *et al.*, 2009). Interestingly, JAK-STAT activation in this context is not triggered by inflammatory cytokines but by brain

derived neurotrophic factr (BDNF) (Lund *et al.*, 2008), a growth factor released upon CNS damage; BDNF also regulates, in a STAT-3-dependent manner, the expression of other receptors and ion channels implicated in epilepsy such as Dopamine receptor D5 (Drd5), Galanin receptor 1 (Galr1), Glutamate metabotropic receptor 1 (Grm1), and γ2 subunit of the GABAAR (Gabrg2) (Hixson et al., 2019).

Given their role in the immune response, the JAK/STAT proteins are also involved in the pathophysiology of autoimmune CNS diseases (Benveniste *et al.*, 2014). As a matter of fact, while STAT3 and STAT4 ko mice are protected against EAE (Chitnis *et al.*, 2001; Liu *et al.*, 2008), STAT1 ko mice are instead highly susceptible to EAE (Bettelli *et al.*, 2004). In addition, the pharmacological blockade of either JAK2 with tyrphostin B42 (Bright *et al.*, 1999) or both JAK1 and JAK2 with AZD1480 (Liu *et al.*, 2014) ameliorates the course of EAE; similar effects can be also obtained by the adoptive transfer of dendritic cells made tolerogenic *ex vivo* with tofacitinib (Zhou *et al.*, 2016). Up to date, the only evidence that JAK/STAT inhibitors could be effective in human neuroimmune diseases is the excellent clinical response to ruxolitinib reported in a patient with highly active NMO refractory to other immunosuppressive drugs (Hodecker *et al.*, 2017).

STAT1 is the downstream effector of all the members of the INF family (Schneider *et al.*, 2014) and, as such, it is crucial in protecting from viral infections, including those of the CNS. STAT1 ko mice are, in fact, highly susceptible to reovirus- (Goody *et al.*, 2007), enterovirus 71- (Liao *et al.*, 2014) and HSV1-induced (Pasieka *et al.*, 2011) encephalitis. In addition, a high risk of developing HSV1 encephalitis is also observed in subjects with rare inactivating mutations in STAT1 (Sancho-Shimizu *et al.*, 2007). The risk of opportunistic viral infection is also significantly increased by JAK/STAT inhibitors both in experimental animals and in patients taking these drugs for reumathological or hematological disorders. For instance, treatment with tofacitinib has been associated with the appearance of Herpes Zoster flares (Winthrop *et al.*, 2018) or even encephalitis (Hosking *et al.*, 2018). STAT1 is essential in protection from Polyomavirus Encephalopathy (Mockus *et al.*, 2020) and fatal cases of JC polyomavirus encephalopathy (Reoma *et al.*, 2019) and meningitis (Ballesta *et al.*, 2017) have occurred in patients on chronic immunosuppressive treatment with ruxolitinib.

Whilst, in most of the cases, JAK/STAT blockade increases the risk of severe viral neuroinfections, in other circumstances it may protect against these diseases by reducing cytokine-mediated tissue inflammation or decreasing virus replication; for example tofacitinib reduces viral replication and virus-induced expression of inflammatory cytokines in human astrocytes and microglial cells infected in vitro with the Venezuelan Equine Encephalitis Virus, a neurotropic arbovirus that may infect humans causing encephalitis in about 10-15% of cases (Risner *et al.*, 2019). In addition, JAK/STAT blockade is expected to exert beneficial effects in HIV-encephalitis (HIVE) and HIV-Associated Neurocognitive Disorder (HAND) since it may prevent the effect of cytokines (such as IL-6) released during HIV infection of the CNS and promoting viral replication and brain damage. As a matter of fact, ruxolitinib reduced HIV replication in an animal model of HIVE (Haile *et al.*, 2016), whereas baricitinib improved the neurobehavioral abnormalities that partially replicate the

symptoms of human HAND (Gavegnano *et al.*, 2019). Data are yet unavailable on the effects of JAK/STAT inhibitors on CNS infection with neurotropic CoVs and, more specifically on neuro-COVID. However, clinical trials are ongoing in patients with COVID-19 (although these are not specifically targeting neuro-COVID patients) with tofacitinib, baricitinib, and ruxolitinib (Table 5) with the rationale of reducing cytokine effects and systemic inflammation; however, the ability of these drugs to induce thromboembolic events and promote new viral infections or the reactivation of latent infection are matter of concern and will require careful monitoring (Scott *et al.*, 2018).

f. Targeting human granulocyte macrophage colony-stimulating factor (GM-CSF): **sargramostim; mavrilimumab, gimsilumab**

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a proinflammatory class I cytokine produced by many different cell types including fibroblasts, monocytes, macrophages and T-cells that induces the proliferation and maturation of myeloid precursors to granulocytes and monocytes (Shi *et al.*, 2006). Because of GM-CSF ability to promote myelogenesis, recombinant forms of this cytokine, such as sargramostim and molgramostim, have long been used in clinical conditions in which myelogenic support is needed, such as upon myelosuppression during cancer chemotherapy (Hume *et al.*, 2012). More recently, the benefits of counteracting GM-CSF proinflammatory effects in inflammatory diseases like RA have been highlighted and several neutralizing monoclonal antibodies directed against GM-CSF such as otilimab (MOR 103), gimsilumab and lenzilumab or against its receptor, such as namilumab and mavrilimumab are in clinical development for rheumatological conditions (Crotti *et al.*, 2019). A role has been suggested for the proinflammatory activity of GM-CSF also in SARS-COV2 infection, because high circulating levels of this cytokine are found in lung of COVID-19 affected patients (Bonaventura *et al.*, 2020). Therefore, blocking GM-CSF could be beneficial in COVID-19, an hypothesis that is currently being investigated in clinical trials with either gimsilumab or mavrilimumab (Table 6). On the other hand, it has also been observed that GM-CSF can help fighting serious infection and its use has been suggested in sepsis of bacterial origin (Chousterman *et al.*, 2018). Therefore, clinical trials are also ongoing to evaluate the effectiveness of sargramostim in COVID-19 patients (Table 6). Although this may seem counterintuitive, both apparently opposing strategies might be effective, possibly depending on the disease stage, as late stages of COVID-19 are thought to be driven by host overactive immunity rather than high viral load (Lang *et al.*, 2020).

A wealth of data suggests that GM-CSF exerts biological effect in the CNS not only because circulating GM-CSF may cross the BBB (McLay *et al.*, 1997) but also because this cytokine is synthetized and released by resident CNS cells, mainly astrocytes (Malipiero *et al.*, 1990). GM-CSF receptors are expressed in neurons, astrocytes, oligodendrocytes and microglia, which is considered the major target of this cytokine in the CNS (Aram *et al.*, 2019). GM-CSF can act both as a proinflammatory and as a regulatory cytokine and therefore, it may be both beneficial and detrimental in specific neurological disorders(Bhattacharya *et al.*, 2015).

The best example of the detrimental effects played by GM-CSF in neurological disorders is given by EAE, one of the best characterized experimental models of MS (Aram *et al.*, 2019), where GM-CSF, produced by infiltrating T17 lymphocytes, establishes tissue damage by promoting the margination and tissue penetration of inflammatory cells, although the induction of antigen presentation by microglial cells, and the enhanced expression of other proinflammatory cytokines such as TNFα, IL-1β, and IL-6 may also have a role (Bhattacharya *et al.*, 2015). GM-CSF ko mice are protected from EAE (McQualter *et al.*, 2001); in addition, disease severity is increased in mice receiving the infusion of lymphocytes infected with adenoviruses carrying a GM-CSF transgene (Spath *et al.*, 2017). Moreover, transgenic mice overexpressing GM-CSF in lymphocytes spontaneously developed a demyelinating disease (Marusic *et al.*, 2002). These data suggested that GM-CSF could represent a druggable target in demyelinating CNS diseases, an hypothesis confirmed by the positive effects obtained by the intraperitoneal injection of an anti- GM-CSF mAb to mice with EAE (McQualter *et al.*, 2001). Consistent with these preliminary data, a phase I tolerability study has been performed with the anti GM-CSF mAb otilimab in patients with MS (Schottelius, 2013) showed moderate beneficial effects on both symptoms and MRI lesion size(Constantinescu *et al.*, 2015). Interestingly, GM-CSF neutralization with lenzilumab reduces chimeric antigen receptor T (CAR-T) cell therapy-induced neurotoxicity (Sterner *et al.*, 2019) and phase 2 studies with lenzilumab in combination with CART cell therapy are planned.

While these results are encouraging, the potential toxicity of anti-GM-CSF drugs that includes an increased risk of opportunistic infection, the worsening of inflammatory bowel disorders and alveolar proteinosis will deserve the highest attention in further clinical development (Aram *et al.*, 2019).

The effects of GM-CSF are, instead, predominantly neuroprotective in other neurological disorders including, for instance, TBI, stroke, PD and AD. Different mechanisms may account for the neuroprotective effect of this cytokine in these diseases. First, as previously mentioned, besides promoting inflammation, GM-CSF may also exert a more subtle modulatory effect on immune responses by promoting a tolerogenic phenotype in antigen-presenting cells (Bhattacharya *et al.*, 2015) and by inducing Treg lymphocytes (Sheng *et al.*, 2011). Second, GM-CSF exerts direct antiapoptotic effects on neurons and glia by inducing JAK2-dependent STAT3 phosphorylation and by activating the PI3K-Akt pathway (Schabitz *et al.*, 2008) and, third, this cytokine may promote neuronal differentiation of adult neural precursor cells thus enhancing neuroregenerative responses to CNS damage (Kruger *et al.*, 2007). As a matter of fact, recombinant GM-CSF reduces infarct size and neurological deficits in rats with middle cerebral artery occlusion (MCAO) (Schabitz *et al.*, 2008) and ameliorates stab wound-induced brain injury in rats (Nishihara *et al.*, 2011); moreover, brain atrophy and behavioral deficits induced by lateral fluid percussion are significantly worsened in GM-CSF KO mice when compared to wild-type mice (Shultz *et al.*, 2014). GM-CSF also exerts a significant neuroprotection in primary neuronal midbrain cultures exposed to the parkinsonigenic toxin 1-methyl-4-phenylpyridinium (MPP+) (Meuer *et al.*, 2006) and decreases dopaminergic neuron death in the

substantia nigra and locomotor deficits in mice treated with this neurotoxic agent (Kim *et al.*, 2009). Encouraging results have been obtained in a small double-blind clinical trial in which recombinant GM-CSF has been given subcutaneously to PD patients for 8 weeks (Gendelman *et al.*, 2017). Neuroprotective effects have been observed after recombinant GM-CSF administration also in a mouse transgenic model of AD (the Tg2576 mice that overexpress the Swedish mutation of APP, the human amyloid precursor protein) (Kiyota *et al.*, 2018) and a clinical trial (NCT01409915) has been completed (data not available yet) to assess the efficacy of this drug in patients with AD. It is worth mentioning that part of the protective effects triggered by GM-CSF in AD could be exerted on the bone marrow and not directly in the brain since this cytokine could promote the release of monocyte that could, then, transmigrate in the CNS and phagocyte amyloid plaques (Heinzelman *et al.*, 2015).

The duality of GM-CSF effects, protective and detrimental, is also observed in viral infections of the CNS. GM-CSF production is increased upon intravitreal injection of HSV-1 in rats and the pretreatment with recombinant GM-CSF protects these animals from the ensuing HSV-1 encephalitis (Tsuboi *et al.*, 1998). Most of this protective effect is consequent to emergence hematopoiesis, a process that enhances the ability to fight against infection by producing more white cells that penetrate in the CNS and clear the virus. However, this mechanism must be finely tuned because its excessive activation may be lethal leading to a massive inflammatory CNS damage as observed in HSV-1 encephalitis. Evidence has been recently reported that IFN-γ is the major physiological downregulator of GM-CSF release in viral encephalitis and contributes to limiting brain damage in this condition (Ramakrishna *et al.*, 2018). Viruses that remain latent in the CNS use specific mechanism to overcome GM-CSF effects. This has been shown, for instance, in the case of HIV which, upon infecting microglia, decreases both GM-CSF synthesis and responsiveness in these cells (Cosenza-Nashat *et al.*, 2007). The role of GM-CSF in controlling CNS infection by CoVs is largely unknown; however, children with encephalitis complicating respiratory infection with human CoVs (presumably mainly HCoV-OC43) showed high GM-CSF concentrations in peripheral blood and in the CSF, whereas children with respiratory infection and no neurological symptom only had high GM-CSF in peripheral blood, a result suggestive of a local CNS production of this cytokine (Li *et al.*, 2016). No data has been yet reported on the effect of GM-CSF in CNS infection by the new human CoVs including SARS-CoV-2 and whether pharmacological strategies targeting this cytokine would improve or worsen CNS damage is presently unclear.

g. Targeting IL-7: CYT107

Interleukin 7 (IL-7) is a cytokine belonging to the IL-2/IL-15 subfamily that was originally identified as a factor secreted by stromal cells in the bone marrow acting as a major driver of B and T lymphopoiesis (Fry *et al.*, 2005). Because of this effect on lymphocytes, recombinant IL-7 (CYT107) has been experimented to boost immune response in immunocompromised patients, in patients with HIV, and in support of cancer

immunotherapy (Mackall *et al.*, 2011). Based on these premises, it has been suggested that IL-7 could enhance the ability to fight SARS-CoV-2 infection and CYT107 is currently being investigated in four clinical trials for the treatment of COVID-19 patients (Table 7), particularly those who develop severe lymphopenia, which represents a negative prognostic indicator in this disease (Tan *et al.*, 2020). Whether IL-7 could also be also effective in neuro-COVID is still to be investigated. IL-7 is produced in the mature and developing CNS where it also exerts biological functions unrelated to the immune response, such as promoting the differentiation of neuronal precursors and the survival of mature neurons (Moors *et al.*, 2010). IL-7 helps fighting viral infections not only by promoting the expansion of the T-lymphocyte pool but also by preventing virus-induced upregulation of the suppressor of cytokine signalling 3 (SOCS3), a common strategy used by viruses-to suppression cytokine release in the host (Bordon, 2011). IL-7 has been used successfully in treating progressive multifocal leukoencephalopathy in few patients with idiopathic CD4 lymphocytopenia with the rational of enhancing the immune response against the causative JC virus (Alstadhaug *et al.*, 2014).

Whilst the effects IL-7 we have discussed so far suggest that this cytokine could be beneficial in infections of the CNS, other data mitigate the enthusiasm for such a therapeutic strategy. More specifically, it has been demonstrated that IL-7 controls macrophage activation and exerts a proinflammatory activity by inducing the release of TNF-α, IL-1β and IL-6 (Ziegler *et al.*, 1991). In the CNS, such proinflammatory activity may contribute to the tissue damage occurring in spinal trauma (Bao *et al.*, 2018). Moreover, IL-7 induces Fas-mediated neuronal apoptosis by directly acting on IL-7 receptors (IL-7R) expressed in neurons (Nunnari *et al.*, 2005). Finally, IL-7 may promote the autoimmune aggression of the CNS and both the blockade of IL-7Rα with monoclonal antibodies (Lawson *et al.*, 2015) and gene knockout of this receptor (Walline *et al.*, 2011) may prevent or ameliorate EAE in mice. Interestingly, people with specific allelic variants of the α subunit of IL-7R have an increased risk of developing MS, further supporting the possible involvement of IL-7 in autoimmune demyelinating diseases (Gregory *et al.*, 2007).

h. Targeting the complement system: eculizumab

The complement system, a major mediator of innate immunity, consists of a group of about 30 small proteases that circulate in the blood in inactive forms and undergo cascade proteolytic activation in response to a heterogeneous group of pathogenic signals (Carroll, 2004). Specifically, three different routes of complement activation have been described: the *classical route*, in which the activating signal is represented by the interaction between the C1q complement protein and complement-fixing antibodies bound to their antigen targets, the *lectin system*, in which complement is activated through the binding of mannose-binding lectin, ficolins or collectins to mannose residues exposed on the surface of bacteria, and, finally, *the alternative route*, a proteolytic amplification loop, which in normal conditions is active at a very low level because of the spontaneous activation of the C3 complement protein but becomes

hyperactivated in the presence of pathogens. Complement activation ultimately leads to the formation of a multiprotein complex, the *complement membrane attack complex* (MAC) (made by C5b, C6, C7, C8 and C9), that binds to and permeabilizes the cell membrane, inducing cell death. In addition, complement activation promotes the chemotaxis of myeloid cells that express specific receptors for the anaphylatoxin C3a and C5a and the phagocytosis of cells on whose membranes the C3 complement protein has been bound (Ember *et al.*, 1997) and enhances B cell response to antigens, thus bridging adaptive and innate immunity (Fearon *et al.*, 1995). The complement cascade is tightly regulated by specific protein inhibitors since, besides destroying bacteria and other pathogens, it may also cause significant tissue damage if inappropriately activated as it occurs, for instance, in many viral infections and in immune-based diseases. In these conditions, pharmacological blockade of the complement cascade could be helpful and at least one approved drug, eculizumab, can be used to achieve this goal. Eculizumab is a humanized IgG2/4κ monoclonal antibody that binds to C5 and prevents its activation by C5 esterases; since C5 is located at a terminal stage of the complement cascade, its blockade with eculizumab impairs the formation of the protrombotic and proinflammatory anaphylotoxin C5a and of the *complement membrane attack complex*, while leaving the upstream steps of the complement cascade unaffected (Cataldi *et al.*, 2011). Eculizumab has been originally approved for two rare hematological disorders, atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria; more recently, its indications have been extended to include two immune-mediated and complement dependent neurological disorders, NMO and myasthenia gravis (Frampton, 2020). Eculizumab has been shown to be effective also in patients with a genetic demyelinating neuropathy caused by mutation in the glycosyl phosphatidylinositol (GPI)-anchored cell surface membrane glycoprotein, CD59, a protein able to inhibit the final step of MAC formation (Mevorach *et al.*, 2016).

Several considerations suggest that the complement system could have a role in disorders of the CNS. It is clear, in fact, that a full complement system does exist in the CNS and its components are produced and released not only by microglia and astrocytes but also by neurons, oligodendrocytes and neurendothelial cells (Carpanini *et al.*, 2019). The endogenous CNS complement system takes part to synapse pruning and maturation and is involved in CNS development (Morimoto *et al.*, 2019). Importantly, the CNS complement system is activated and contributes to tissue damage in several neurological disorders. This has been demonstrated in animal models of TBI, spinal trauma, ischemic stroke, AD, PD, MS and ALS, all conditions in which a significant protection is obtained by the genetic deletion of specific components of the complement cascade, mainly C3 or C5 (Carpanini *et al.*, 2019). Although few recent clinical trials have explored the efficacy of anti-complement drugs in CNS diseases associated with BBB impairment, and eculizumab has been shown to be effective in NMO, no human trials of anti-complement therapies for most CNS diseases have been carried out (Carpanini *et al.*, 2019) . While the reported data strongly suggest that blocking the complement cascade could improve the course of neuroinflammatory diseases, the loss of complement-mediated synapse pruning may have deleterious effects on the neuroreparative process and

this could explain, for instance, why the benefits of complement inhibition in experimental stroke are often only transitory (Alawieh *et al.*, 2015). In addition, complement activation may help clearing protein precipitates such as β-amyloid plaques and, therefore, its inhibition may also be paradoxically detrimental in AD and similar diseases (Wyss-Coray *et al.*, 2002).

The complement cascade protects the CNS from viral encephalitis caused, among others, by HSV-1, (Bibert *et al.*, 2019), West Nile virus (Mehlhop *et al.*, 2005), Sindbis Virus (Hirsch *et al.*, 1980), and Venezuelan equine encephalitis virus (Brooke *et al.*, 2012). Indeed, eculizumab, by blocking complement activation, may aggravate progressive multifocal leukoencephalopathy caused by JC polyomavirus (Gomez-Cibeira *et al.*, 2016). Different mechanisms may account for complement antiviral activity including viriolysis, through the permeabilization of the membrane of enveloped viruses, phagocytosis of opsonized virus particles, virus aggregation and, importantly, antibody-dependent neutralization through the co-ligation on B cells of the B-cell receptor and the complement receptor CD21 by viral antigens bound to C3d (Agrawal *et al.*, 2017). Many viruses, such as HIV, have developed strategies to overcome these complement-dependent antiviral mechanisms and to exploit them for their own benefit; these include the incorporation of complement inhibitors in their envelope, the synthesis of virus-encoded complement inhibitors or the ability to use complement receptors to penetrate into susceptible cells (Agrawal *et al.*, 2017). By the latter mechanism, several viruses including HIV, Epstein-Barr Virus, Measles virus, Newcastle disease virus and Borna disease virus infect neurons and glia using complement components as Trojan horses (Speth *et al.*, 2002). In addition, complement activation in response to viral infection may directly kill bystander cells and aggravate tissue damage (Morrison *et al.*, 2007). Interestingly, a correlation has been observed in viral encephalitis between complement expression by nervous cells and tissue damage, suggesting that that local synthesis of complement proteins may be critical for the establishment of the CNS lesions (Veerhuis *et al.*, 2011). Therefore, depending on the pathogen and on the clinical circumstances, complement may either limit or enhance viral pathogenicity.

Whilst no data is yet available on the effect in neuro-COVID, several considerations suggest that blocking the complement cascade could be beneficial in COVID-19. Favourable effects have been observed upon pharmacological blockade of C5a/C5aR axis in mice with experimental MERS infection (Jiang et al., 2018), and in baboons with cytokine storm during E. Coli-induced sepsis (Keshari et al., 2017). In addition, mannose-binding protein (MBL) contributes to the first-line host defense against SARS-CoV and its deficiency is a susceptibility factor for SARS-COV infection (Ip et al., 2005). Moreover, SARS-CoV infection causes a milder disease in mice lacking C3 (Gralinski et al., 2018), suggesting that complement activation may worsen the course of the disease. Based on these evidence it was suggested that blocking the complement system with eculizumab could be beneficial in COVID-19 patients and, this hypothesis is currently being investigated in several ongoing clinical trials (Table 8).

In conclusion, the complement system, similarly to all cytokines discussed in the previous paragraphs, should be added to the list of the double-edged swords in CNS disease since, depending on the clinical conditions considered and on the timing in their natural history in which treatment is initiated, it can either contribute to tissue damage or produce neuroprotection and neurorepair (Brennan *et al.*, 2012). This duality of effect, in addition to the increased risk of life- threatening meningococcal infection associated to its clinical use (McNamara et al., 2017), may be of concern when clinical efficacy of eculizumab is evaluated in COVID-19 patients.

CONCLUDING REMARKS

In the present review, we aimed to provide a general framework for the understanding of the potential neurological effects exerted by drugs affecting different cytokine pathways currently being under clinical investigation for COVID-19. This is relevant for at least two reasons: first, because COVID-19 may affect the CNS and it would be important to establish which of the drugs mentioned in this review could be more effective in treating neuro-COVID and, second, because early or late unwanted neurological effects may occur as a consequence of COVID-19 treatment with these drugs.

Several points remain to be clarified. Probably the most fundamental question is how important are endogenous, CNS-synthetized cytokines both for antiviral and toxic effects. Circulating levels of many cytokines dramatically increase in COVID-19 patients. If we assume that circulating cytokines could affect the brain, their pharmacological manipulation in the periphery should be sufficient to influence central functions. If, instead, most of the CNS effects are exerted by endogenous CNS cytokines, the ability of cytokine drugs to enter the CNS becomes a critical point for efficacy. Most of the anti-cytokine drugs are bulky monoclonal antibodies and, as such, they are not expected to significantly cross the BBB even though, in the presence of meningoencephalitis or of a cytokine storm, their CNS penetration through the damaged BBB may be enhanced. Under this pharmacokinetics respect, JAK/STAT inhibitors appear as the privileged drugs because of their small size and chemico-physical characteristics. As a matter of fact, the recent report of severe visual hallucinations in two COVID-19 patients at the beginning of baricitinib therapy has been interpreted as an indirect demonstration that this drug efficiently penetrates into the CNS to exert drug-related toxic effects (Richardson *et al.*, 2020). Another point deserving attention is that cytokines, and neuroinflammation as a whole, do not only exert detrimental effects during CNS disorders but can also be instrumental for beneficial processes such as neurorepair and neuroregeneration (DiSabato *et al.*, 2016). Therefore, the general scenario emerging from the data we discussed in the present review is that, even in the CNS, cytokine drugs are double-edge swords that can be either beneficial or detrimental depending on many factors related to the disease (natural history, timing, severity, …), the host (presence of risk factors for specific CNS manifestations, comorbidities, …), and the drug itself (molecular size, dosage, administration schedules, concomitant drugs,…). In fact, it has been proposed that COVID-19 progresses

through at least three consecutive phases: *stage I* (early infection), characterized by lymphopenia, which could benefit from immune response boosting strategies, whereas in *stage II* (pulmonary phase) and *stage III* (hyperinflammatory phase) inflammatory response is progressively (hyper-) activated and the use of anti-cytokine drugs could be more rational. A three-stage classification has also been proposed for neuro-COVID: in *stage 1* the virus is confined to gustatory and olfactory cells and the patient only experiences dysgeusia and hyposmia, in *stage 2* the virus invades the neuro-endothelium inducing a strong inflammatory response that can cause intracerebral thrombosis and stroke, and, finally, in *stage 3* viruses invades the brain parenchyma through the damaged BBB together with circulating cytokines and cause a massive encephalitis(Fotuhi *et al.*, 2020). According to this evolution, it would be essential to identify patients with neuro-COVID very early, when they are in stage 1 and could, presumably, benefit of treatments boosting their immune response against the virus. On the contrary, in neuro-COVID stage 2 and 3, a pharmacological intervention aiming to decrease neuroinflammation would likely be more effective.

In conclusion, drugs affecting the cytokine system, which are currently being explored for their efficacy in COVID-19 treatment, could also affect the CNS and be helpful against neuro-COVID manifestatios. However, clinicians must be aware that a precise risk/benefit assessment is needed given the fine line existing between the desired beneficial effect of an increased virus clearance, and unwanted effects such as the enhancement of the inflammatory response or the loss of reparative signals. Well-designed clinical trials and precise patient stratification will be necessary to establish which drug would be preferred at each neuro-COVID stage to maximize such risk/benefit ratio. Finally, given the current treatment guidelines for COVID-19 patients with pneumonia (Bai et al., Eur. Resp. Rev. 2020), future trials investigating the potential effectiveness of the described cytokine-based therapies as alternative or complementary approaches to direct antiviral drugs (remdesivir) or corticosteroids are likely to be carried out in the near future.

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LEGEND OF FIGURE

Figure 1:
Schematic representation of cytokine-based drugs and their targets