Received: 4 November 2020 | Revised: 22 January 2021 | Accepted: 24 January 2021

DOI: 10.1111/bph.15397

Themed Issue: The second wave: are we any closer to efficacious pharmacotherapy for COVID 19? (BJP 75th Anniversary)

COMMISSIONED REVIEW ARTICLE - THEMED ISSUE

Neurological risks and benefits of cytokine-based treatments in coronavirus disease 2019: from preclinical to clinical evidence

Giuseppe Pignataro | **Mauro Cataldi** | **Maurizio Taglialatela**

Division of Pharmacology, Department of Neuroscience, University of Naples "Federico II", Naples, Italy

Correspondence
Maurizio Taglialatela, Division of Pharmacology, Department of Neuroscience, University of Naples "Federico II", Via Pansini 5, 80131, Naples, Italy.
Email: mtaglial@unina.it

Funding information
Ministero dell'Università e RIcerca, Grant/Award Number: PRIN 2017ALCR7C to MT; Ministero della Salute, Grant/Award Number: RF-2019-12370491; Ministero dell'Istruzione, dell'Università e della Ricerca, Grant/Award Number: PRIN 2017ALCR7C

Immunodeficiency and hyperinflammation are responsible for the most frequent and life-threatening forms of coronavirus disease 2019 (COVID-19). Therefore, cytokine-based treatments targeting immuno-inflammatory mechanisms are currently undergoing clinical scrutiny in COVID-19-affected patients. In addition, COVID-19 patients also exhibit a wide range of neurological manifestations (neuro-COVID), which may also benefit from cytokine-based treatments. In fact, such drugs have shown some clinical efficacy also in neuroinflammatory diseases. On the other hand, anti-cytokine drugs are endowed with significant neurological risks, mainly attributable to their immunodepressant effects. Therefore, the aim of the present manuscript is to briefly describe the role of specific cytokines in neuroinflammation, to summarize the efficacy in preclinical models of neuroinflammatory diseases of drugs targeting these cytokines and to review the clinical data regarding the neurological effects of these drugs currently being investigated against COVID-19, in order to raise awareness about their potentially beneficial and/or detrimental neurological consequences.

LINKED ARTICLES: This article is part of a themed issue on The second wave: are we any closer to efficacious pharmacotherapy for COVID 19? (BJP 75th Anniversary). To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v179.10/issuetoc

KEYWORDS
coronaviruses, COVID-19, neuroinflammation, SARS, viral encephalitis

1 | 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 a 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. They are severe acute respiratory syndrome (SARS) by the SARS-CoV, the

Abbreviations: BBB, blood–brain barrier; CAR-T, chimeric antigen receptor T; $CD4^+$, cluster of differentiation 4^+; $CD8^+$, cluster of differentiation 8^+; MAC, complement membrane attack complex; CoVs, coronaviruses; COVID-19, coronavirus disease 2019; KO, knockout; MHC, major histocompatibility complex; MERS, Middle East respiratory syndrome; PRRs, pattern recognition receptors; SARS, severe acute respiratory syndrome; TACE, TNF-α-converting enzyme; TNFRs, TNF-α receptors.

Giuseppe Pignataro and Mauro Cataldi contributed equally to this study.

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 most frequent and life-threatening symptoms affect the respiratory system. 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 centres 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, 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 have been classified as (i) encephalopathy, with delirium/psychosis and seizures and no distinct MRI or CSF abnormalities; (ii) meningoencephalitis, most commonly referred to as acute disseminated encephalomyelitis; (iii) ischaemic stroke, associated with a prothrombotic state and pulmonary thromboembolism; (iv) acute haemorrhagic necrotizing encephalopathy, a rare encephalopathy representing one of the remote complications of influenza and other viral infections and (v) peripheral neurological disorders, most often represented by the Guillain–Barré syndrome, a paralytic demyelinating disorder or by the Miller–Fisher syndrome, a Guillain–Barré syndrome variant characterized by the triad of ataxia, areflexia and ophthalmoplegia.

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 used against rheumatic diseases, which target cytokine-mediated inflammation and are currently being explored as potential therapeutic means in COVID-19, could also positively affect neuro-COVID manifestations. As a matter of fact, over the last two decades some of these drugs have already been investigated for the treatment of specific neuroinflammatory diseases and in some cases leading to an extension of their indications. On the other hand, the impairment of relevant physiological activities exerted by cytokines in the CNS caused by these drugs may pose a significant neurological risk in distinct patient categories. Therefore, the aim of the present review is to briefly describe the role of specific cytokines in neuroinflammation, to summarize the efficacy in preclinical models of neuroinflammatory diseases of drugs targeting these cytokines and to review the clinical data regarding the neurological effects of these drugs being investigated against COVID-19, in order to raise awareness about their potentially beneficial and/or detrimental neurological consequences.

To this aim, we researched 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 and analysed, and their main findings were 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-1β**, **IL-6**, **IL-7**, **TNF-α**, **INF-γ**, **Janus kinase/signal transducer and activator of transcription** (JAK/STAT, **granulocyte-macrophage colony stimulating factor (GM-CSF)** and the **complement system**.

2 | RATIONAL BASIS FOR TARGETING NEUROINFLAMMATORY MECHANISMS IN COVID-19

Neurological symptoms associated to SARS-CoV-2 infection may be triggered either by direct viral CNS invasion or by indirect attack on the CNS mediated by the cytokine storm induced by systemic SARS-CoV-2 infection (Cataldi et al., 2020). In fact, although evidence is scant for SARS-CoV-2, it has been demonstrated that several neurotropic CoVs may enter the brain through the fibres of olfactory and vagus nerves (neurogenic invasion) or through the systemic circulation, crossing the blood–brain barrier (BBB) directly or being carried by peripherally infected leukocytes (haematogenous invasion). Although *in vitro* data suggest that neurotropic CoVs may infect neuronal, glial and brain microvascular endothelial cells (Yamashita et al., 2005), evidence for CoV-induced cytopathic effect on neuronal or glial cells *in vivo* is limited and direct virus-induced cell loss may only have a role in acute or hyperacute forms of CoV-induced CNS damage, which occur with limited tissue inflammation. 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-1 receptor antagonist (IL-1ra)**, IL-6, **IL-10**, **IL-17**, **IFN-γ** and GM-CSF, among other soluble immune mediators (Huang et al., 2020). The triggering factor for this hyperinflammatory condition is probably the activation of the innate immune system, which occurs upon the interaction of viral RNA and structural proteins with cytosolic **pattern recognition receptors (PRRs)** (Jensen & Thomsen, 2012). PRR activation triggers the expression of both type I and type III IFNs and pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and **CXCL-8**. In addition, hyperactivated chemotaxis 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. Strong activation of innate immunity can cause CNS damage either through direct cytopathic effects of cytokines 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.

On average, 7–10 days after CoV infection, adaptive immune responses are activated and virus-specific cluster of differentiation 4^+ ($CD4^+$) and cluster of differentiation 8^+ ($CD8^+$) 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 the complete clearance of CoVs, which may persist for a very long time in infected cells and trigger a chronic inflammatory status, as demonstrated in experimental animals (Libbey & Fujinami, 2014).

Neuropathological studies may allow the identification of whether CNS damage during SARS-CoV-2 infection is due to direct viral invasion or to immune system overreaction, thereby providing important clues on the molecular pathogenesis of neuro-COVID. However, few exhaustive reports of the neuropathological findings in the brains from patients with COVID-19 are available. In a recent post-mortem case series, including 43 patients (Matschke et al., 2020), neuropathological changes seem to be mild, with pronounced neuroinflammatory changes in the brainstem being the most common finding (86% of the brains examined). Microglia activation and infiltration by cytotoxic T lymphocytes was often found in the meninges and in brainstem and cerebellum (79%). Ischaemic lesions of presumed thromboembolic origin were also found in 16% of the deceased patients. SARS-CoV-2 was detected by qRT-PCR or immunostaining in 53% of the examined brains, with SARS-CoV-2 viral proteins found in cranial nerves originating from the lower brainstem and in isolated cells of the brainstem. Noteworthy, the presence of SARS-CoV-2 in the CNS was not associated with the severity of neuropathological changes. The neuropathological finding of a predominant mild to moderate non-specific inflammation, with frequent acute hypoxic injury and focal microhaemorrhages or haemorrhagic suffusions, has been also confirmed in a recent review of 24 studies summarizing autoptic data from 149 COVID-19 individuals (Mukerji & Solomon, 2021).

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 transduction mechanisms) in COVID-19 patients (Figure 1). 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 of neuro-COVID. In these conditions, immunomodulatory approaches with cytokine-based treatments have already been investigated, leading to clinical improvement and in some cases to established uses, but 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

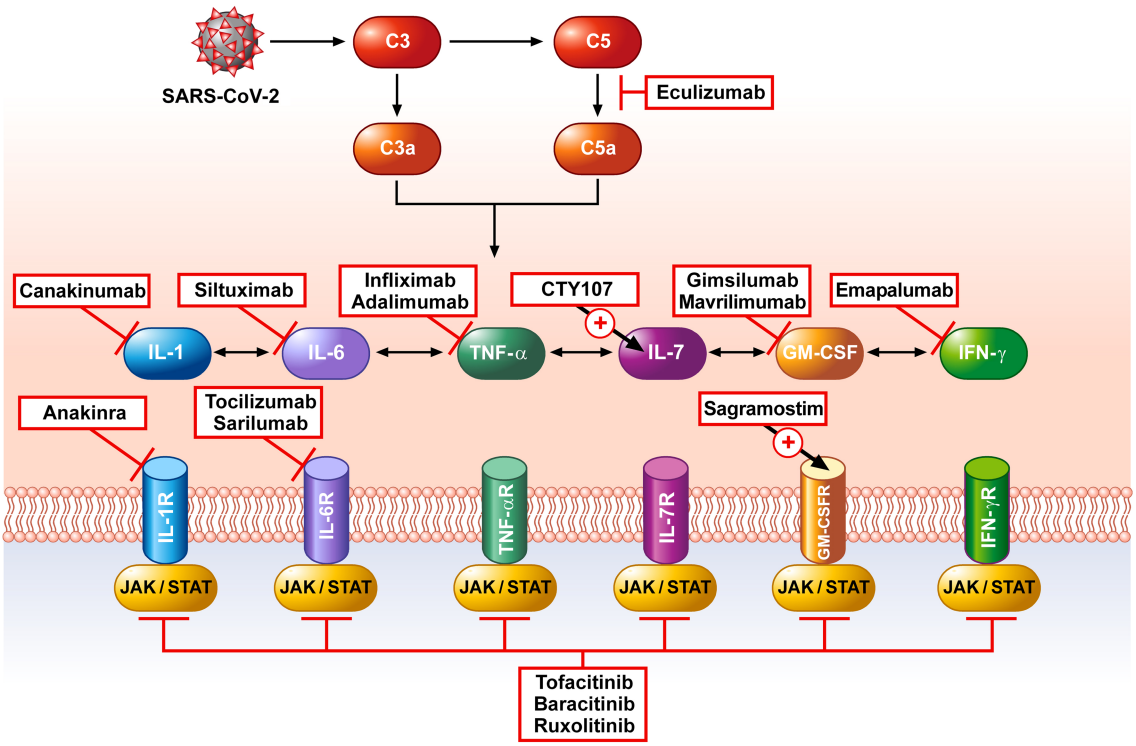

FIGURE 1 Schematic representation of cytokine-based drugs and their targets

to highlight and discuss their potentially beneficial or detrimental neurological impact, an issue of critical relevance when these drugs are used in COVID-19-affected patients.

3 | NEUROINFLAMMATION AND CYTOKINE-TARGETED INTERVENTIONS

3.1 | Targeting IL-1β: anakinra and canakinumab

IL-1β is a key mediator of innate immune response that also participates in triggering adaptive immunity (Cavalli & Dinarello, 2015). IL-1β activity can be pharmacologically blocked with anakinra, a recombinant form of the natural occurring antagonist IL-1ra, which has been approved for the treatment of **rheumatoid arthritis** and cryopyrin-associated periodic syndrome or with canakinumab, a high-affinity human monoclonal antibody against IL-1β, also approved for cryopyrin-associated periodic syndrome. IL-1β is generated by a **caspase-1**-mediated proteolytic cleavage of pro-IL-1β whose expression is induced by the activation of PRRs. These receptors are activated not only by *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 caused by infectious and non-infectious origins (Roh & Sohn, 2018). Therefore IL-1β, together with other cytokines may trigger the so-called "sterile" inflammation that accompanies non-infective neuroinflammatory diseases.

IL-1β has both physiological and pathological roles in the CNS where it can be released by microglial cells and by neurons (Wang et al., 2015). In physiological conditions, IL-1β potentiates the glutamatergic neurotransmission and is required for LTP, an elementary form of memory (Hewett et al., 2012). An excessive IL-1β-dependent activation of the glutamatergic neurotransmission may explain the detrimental role exerted by this cytokine in several animal models of neurodegenerative conditions including stroke, brain haemorrhage, spinal cord injury, experimental allergic encephalomyelis (a model of multiple sclerosis) and epilepsy (Hewett et al., 2012). In all these models, IL-1β antagonism with anakinra exerts protective effects (Cavalli & Dinarello, 2015).

Remarkably, single case reports have shown good clinical responses with IL-1β blockers in severe treatment-resistant forms of epilepsy (DeSena et al., 2018), also when secondary to febrile infections (Dilena et al., 2019; Kenney-Jung et al., 2016). Moreover, in a single-centre, double-blind, randomized, placebo-controlled Phase 2 trial in patients presenting within 5 h of ischaemic stroke onset, subcutaneous IL-1ra reduced plasma inflammatory markers and improved clinical outcome by reducing inflammation (Smith et al., 2018). In addition, treatment with canakinumab reduced the rates of serious cardiovascular events (including stroke) in patients with prior myocardial infarction and residual inflammatory risk (Everett et al., 2020). Finally, anti-IL-1β treatment was shown effective in three patients who developed neuromyelitis optica, a demyelinating disease of the optic nerve, as a complication of colchicine-resistant familial Mediterranean fever, a rare disease related to inflammosome hyperactivation (Ozdogan et al., 2020).

As for other cytokines, the neurodetrimental effects of IL-1β are partially counterbalanced by the positive consequences of activating innate and adaptive immunity (Cavalli & Dinarello, 2015). Viral CNS diseases well exemplify this principle, since IL-1β may limit viral multiplication and CNS damage in the case of highly cytopathic viruses such as the herpes simplex 1 (Sergerie et al., 2007), whereas it mainly promotes neuroinflammation and tissue damage for less severely cytopathic and long persistent viruses such as HIV (Brabers & Nottet, 2006). Studies performed with Theiler's murine encephalomyelitis virus, which remains latent in the CNS and induces a chronic demyelinating disease with similarities to human multiple sclerosis, 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 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 multi-organ injury depends 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 (Huang et al., 2020; Yang et al., 2020). Therefore several clinical studies are ongoing to evaluate the effect of anakinra and canakinumab on the course of this disease (Table 1A). 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, it will be of interest to evaluate whether IL-1β blockade will induce neurological improvement in COVID-19 patients showing evidence of CNS involvement.

3.2 | Targeting IL-6: tocilizumab, sarilumab and siltuximab

IL-6 is a pleiotropic Class I cytokine released by multiple cell types including macrophages, T and B cells, fibroblasts, and endothelial cells during the innate immunity response. As for IL-1, 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. IL-6 exerts both pro- and anti-inflammatory effects and has a crucial role in the activation of adaptive immunity. IL-6 biological effects occur via the binding of this cytokine to specific **IL-6 receptors** whose activation ultimately leads to the recruitment of JAK proteins and to STAT-dependent gene expression (Uciechowski & Dempke, 2020).

In physiological conditions, IL-6 is released at low concentrations in the CNS, being produced not only by infiltrating lymphocytes and macrophages but also by resident neurons, endothelial and microglial cells. IL-6 has a role in neuroendocrine regulation and in the control of body temperature, food intake and energy metabolism, and pain sensitivity. It is also involved in cognitive and emotional functions (Erta

TABLE 1 Neuroinflammation and cytokine-based interventions: targeting IL-1β and IL-6

A. IL-1β

Drug	Main indications	CT number, title, study protocol	Potential neurological implications
Anakinra Anti-IL-1β receptor antibody	Rheumatoid arthritis Cryopyrin-associated periodic syndrome	**NCT04341584** CORIMUNO-ANA: Trial Evaluating Efficacy Of Anakinra In Patients With Covid-19 Infection (CORIMUNO-ANA) **Interventional Phase 2** **NCT04366232** Efficacy of Intravenous Anakinra and Ruxolitinib During COVID-19 Inflammation (JAKINCOV) **Interventional Phase 2** **NCT04443881** Clinical Trial of the Use of Anakinra in Cytokine Storm Syndrome Secondary to Covid-19 (ANA-COVID-GEAS) **Interventional Phase 2/3** **NCT04462757** SCIL-1Ra in COVID-19 Feasibility & PK/PD **Interventional Phase 2** **NCT04412291** A Study in Patients With COVID-19 and Respiratory Distress Not Requiring Mechanical Ventilation, to Compare Standard-of-care With Anakinra and Tocilizumab Treatment The Immunomodulation-CoV Assessment (ImmCoVA) Study **Interventional Phase 2** **NCT04424056** A Trial Using ANAKINRA, TOCILIZUMAB Alone or in Association With RUXOLITINIB in Severe Stage 2b and 3 of COVID19-associated Disease (INFLAMMACOV) **Interventional Phase 3** **NCT04364009** Anakinra for COVID-19 Respiratory Symptoms (ANACONDA) **Interventional Phase 3** **NCT04357366** suPAR-guided Anakinra Treatment for Validation of the Risk and Management of Respiratory Failure by COVID-19 (SAVE) **Interventional Phase 2** **NCT04339712** Personalised Immunotherapy for SARS-CoV-2 (COVID-19) Associated With Organ Dysfunction (ESCAPE) **Interventional Phase 2** **NCT04324021**	Good clinical responses have been described in single cases of severe, drug-resistant epilepsies treated with IL-1β blockers (DeSena et al., 2018; Dilena et al., 2019; Kenney-Jung et al., 2016). In a single-centre, double-blind, randomized, placebo-controlled Phase 2 trial in patients presenting within 5 h of ischaemic stroke onset, subcutaneous IL-1ra reduced plasma inflammatory markers and improved clinical outcome by reducing inflammation (Smith et al., 2018). Moreover, anti-IL-1β treatment was shown effective in three patients who developed neuromyelitis optica as a complication of colchicine-resistant familial Mediterranean fever, a rare disease related to inflammosome hyperactivation (Ozdogan et al., 2020). Potential risks may include facilitation of viral replication by highly cytopathic viruses such as the herpes simplex 1 (Sergerie et al., 2007).

(Continues)

TABLE 1 (Continued)

A. IL-1β			
Drug	**Main indications**	**CT number, title, study protocol**	**Potential neurological implications**
		Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients With COVID-19 Infection **Interventional Phase 2/3** **NCT04362111** Early Identification and Treatment of Cytokine Storm Syndrome in Covid-19 **Interventional Phase 3** **NCT04408326** Efficacy and Safety of Angiotensin II Use in Coronavirus Disease(COVID)-19 Patients With Acute Respiratory Distress Syndrome (ACES) **Observational** **NCT04330638** Treatment of COVID-19 Patients With Antiinterleukin Drugs (COV-AID) **Interventional Phase 2/3**	
Canakinumab Anti-IL-1b antibody	Cryopyrin-associated periodic syndrome (CAPS)	**NCT04362813** Study of Efficacy and Safety of Canakinumab Treatment for CRS in Participants With COVID-19-induced Pneumonia (CAN-COVID) **Interventional Phase 3** **NCT04365153** Canakinumab in Covid-19 Cardiac Injury (The Three C Study) **Interventional Phase 2**	Beneficial effects have been observed in patients affected by drug-resistant epilepsy (DeSena et al., 2018), familial Mediterranean fever, and multiple sclerosis (Ozdogan et al., 2020). Its use has been explored as prophylactic agent in stroke patients (Everett et al., 2020).
B. IL-6			
Drug	**Main indications**	**CT number, title, study protocol**	**Neurological implications**
Tocilizumab Anti-IL-6 receptor monoclonal antibody	Rheumatoid arthritis Giant cell arteritis Cytokine release syndrome (CRS)	**NCT04377659** Tocilizumab for Prevention of Respiratory Failure in Patients With Severe COVID-19 Infection **Interventional Phase 2** **NCT04322773** Anti-il6 Treatment of Serious COVID-19 Disease With Threatening Respiratory Failure (TOCIVID) **Interventional Phase 2** **NCT04445272** Clinical Trial to Evaluate the Effectiveness and Safety of Tocilizumab for Treating Patients With COVID-19 Pneumonia **Interventional Phase 2** **NCT04479358** Low-dose Tocilizumab Versus Standard of Care in Hospitalized	It has been explored as a treatment in several neurological diseases, including neuromyelitis optica refractory to immunotherapy, immunosuppressants, and/or corticosteroids (Araki, 2019); multiple sclerosis (Hoshino et al., 2020); autoimmune encephalitis (Lee et al., 2016); new-onset refractory status epilepticus (Jun et al., 2018); Takayasu's arteritis with associated stroke (Osman et al., 2015); and amyotrophic lateral sclerosis (ALS) (Fiala et al., 2013). Favourable clinical response observed in severe acute necrotizing encephalopathy of childhood (Koh et al., 2019). Potential risks associated with IL-6 blockade include the occurrence of recurrent meningitis (Richebé

TABLE 1 (Continued)

B. IL-6			
Drug	**Main indications**	**CT number, title, study protocol**	**Neurological implications**
		Patients With COVID-19 (COVIDOSE-2) **Interventional Phase 2** **NCT04331795** Tocilizumab to Prevent Clinical Decompensation in Hospitalized, Noncritically Ill Patients With COVID-19 Pneumonitis (COVIDOSE) **Interventional Phase 2** **NCT04370834** Tocilizumab for Patients With Cancer and COVID-19 Disease **Interventional Phase 2** **NCT04335071** Tocilizumab in the Treatment of Coronavirus Induced Disease (COVID-19) (CORON-ACT) **Interventional Phase 2** **NCT04423042** Tocilizumab in Coronavirus-19 Positive Patients **Interventional Phase 2** **NCT04320615** A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA) **Interventional Phase 3** **NCT04315480** Tocilizumab for SARS-CoV2 (COVID-19) Severe Pneumonitis **Interventional Phase 2** **NCT04476979** Comparison of Tocilizumab Plus Dexamethasone vs. Dexamethasone for Patients With Covid-19 (TOCIDEX) **Interventional Phase 2** **NCT04435717** Efficacy of Tocilizumab in Modifying the Inflammatory Parameters of Patients With COVID-19 (COVITOZ-01) **Interventional Phase 2** **NCT04346355** Efficacy of Early Administration of Tocilizumab in COVID-19 Patients **Interventional Phase 2** **NCT04320615** A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA) **Interventional Phase 3** **NCT04412772**	et al., 2018), HTLV1-associated conditions (Terada et al., 2017), and multifocal and limbic encephalitis (Yamaguchi et al., 2014).

(Continues)

TABLE 1 (Continued)

B. IL-6			
Drug	**Main indications**	**CT number, title, study protocol**	**Neurological implications**
		A RCT—Safety & Efficacy of Tocilizumab—Tx of Severe COVID-19: ARCHITECTS (ARCHITECTS) **Interventional Phase 3** **NCT04361032** Assessment of Efficacy and Safety of Tocilizumab Compared to DefeROxamine, Associated With Standards Treatments in COVID-19 (+) Patients Hospitalized In Intensive Care in Tunisia (TRONCHER) **Interventional Phase 3** **NCT04403685** Safety and Efficacy of Tocilizumab in Moderate to Severe COVID-19 With Inflammatory Markers (TOCIBRAS) **Interventional Phase 3**	
Sarilumab Anti-IL-6 receptor monoclonal antibody	Rheumatoid arthritis	**NCT04357808** Efficacy of Subcutaneous Sarilumab in Hospitalised Patients With Moderate-severe COVID-19 Infection (SARCOVID) **Interventional Phase 2** **NCT04386239** Study on the Use of Sarilumab in Patients With COVID-19 Infection **Interventional Phase 1** **NCT04315298** Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19 **Interventional Phase 2/3** **NCT04359901** Sarilumab for Patients With Moderate COVID-19 Disease **Interventional Phase 2** **NCT04341870** Study of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients: Sarilumab, Azithromycin, Hydroxychloroquine Trial—CORIMUNO-19—VIRO (CORIMUNOVIRO) **Interventional Phase 2/3** **NCT04324073** Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients—Sarilumab Trial—CORIMUNO-19—SARI (CORIMUNO-SARI) **Interventional Phase 2/3**	Sarilumab treatment improved outcomes for pain, social functioning, and mood in patients affected by rheumatoid arthritis (Atzeni et al., 2019).

TABLE 1 (Continued)

B. IL-6			
Drug	**Main indications**	**CT number, title, study protocol**	**Neurological implications**
		NCT04357860 Clinical Trial of Sarilumab in Adults With COVID-19 (SARICOR) **Interventional Phase 2**	
Siltuximab Anti-IL-6 monoclonal antibody	Castleman disease	**NCT04329650** Efficacy and Safety of Siltuximab vs. Corticosteroids in Hospitalized Patients With COVID-19 Pneumonia **Interventional Phase 2**	A clinical trial in patients with rheumatoid arthritis (RA) or multicentric Castleman disease (MCD) showed that siltuximab was able to ameliorate depressive symptoms independently on anti-rheumatic effects (Sun et al., 2017).

et al., 2012). CNS IL-6 concentrations dramatically increase in a variety of animal models of neurological disorders including traumatic brain injury, stroke, Alzheimer's disease, multiple sclerosis and infective brain diseases (Uciechowski & Dempke, 2020). However, whether IL-6 participates in triggering damage or a homeostatic neuroprotective response strongly depends on the experimental model being considered. For example, preclinical evidence for both pro- and anti-convulsant actions of IL-6 are available. A higher susceptibility to chemically induced seizures was observed in both rats intranasally treated with IL-6 (Kalueff et al., 2004) and IL-6 knockout (KO) mice (De Sarro et al., 2004). On the other hand, preclinical studies suggest that IL-6 contributes to tissue damage in demyelinating conditions, as indicated 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 & Kurzrock, 2016) or with tocilizumab (Araki, 2019) and sarilumab (Scott, 2017), two monoclonal antibodies that bind and neutralize IL-6 receptors. Given the prominent role of IL-6 in systemic inflammation during SARS-CoV-2 infection, several controlled randomized trials are ongoing to evaluate the use of IL-6 modulators in COVID-19 patients (Table 1B). Noteworthy, tocilizumab efficacy has been already demonstrated in several human neurological diseases. The first example is given by neuromyelitis optica, in which the high concentrations of IL-6 observed in the CSF (Uzawa et al., 2013) promote the production of pathogenetically determinant AQP4 autoantibodies (Chihara et al., 2011). In several neuromyelitis optica patients refractory to immunotherapy, immunosuppressants and/or corticosteroids, tocilizumab was effective in preventing acute attacks and maintaining remission (Araki, 2019). Tocilizumab was also effective and safe in a retrospective, single-centre analysis of 91 patients with autoimmune encephalitis exhibiting inadequate clinical response to first-line immunotherapy and to rituximab (Lee et al., 2016), as well as in a small cohort of seven patients with new-onset refractory status epilepticus (Jun et al., 2018). IL-6 receptor blockade with tocilizumab improved outcome and prevented disability in three patients with severe acute necrotizing encephalopathy of childhood, a devastating parainfectious encephalopathy that occurs early during viral infections presumably due to massive release of cytokines including IL-6 (Koh et al., 2019). Finally, tocilizumab also attenuated inflammation and ameliorated symptoms in 33 patients affected by Takayasu's arteritis with associated stroke retrospectively identified in the literature (Osman et al., 2015) and in a single patient with fulminant multiple sclerosis (Hoshino et al., 2020). Three of five patients with sporadic amyotrophic lateral sclerosis receiving tocilizumab infusions showed time-limited attenuation of clinical progression (Fiala et al., 2013). Notably, clinical trials in rheumatoid arthritis showed that sarilumab treatment, independently from its anti-rheumatoid effect, improved outcomes for pain, social functioning and mood (Atzeni et al., 2019). In addition, siltuximab ameliorated depressive symptoms in patients with rheumatoid arthritis or multicentric Castleman disease, 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 the encephalitis caused by human enterovirus 71 in mice (Luo et al., 2019). In addition, in mice infected with Theiler's murine encephalomyelitis virus, 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). Thus, based on these results, anti-IL-6 strategies might 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 (Richebé et al., 2018), human T lymphotropic virus type 1-associated conditions such as uveitis and myelitis/tropical spastic paraparesis (Terada et al., 2017), and multifocal and limbic encephalitis (Yamaguchi et al., 2014), will require careful consideration.

3.3 | Targeting TNF-α: infliximab and adalimumab

TNF-α plays a key role in almost all acute inflammatory reactions by promoting oxidative stress and inflammation. TNF-α 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 (TNF membrane form), is subsequently

released from cells as a soluble cytokine (**TNF shed/soluble form**), via regulated cleavage by **TNF-α-converting enzyme (TACE/ADAM17)**. Both TNF membrane and shed form are biologically active and interact with two receptors, **TNFR1** and **TNFR2** which are expressed on different tissues. TNFR1 is expressed in all cell types and is preferentially activated by TNF shed form. It 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"). While TNFR2, which is expressed mainly in neurons, immune cells and endothelial cells, preferentially binds TNF membrane form and promotes cell survival, resolution of inflammation and myelination. These 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 immunosuppressive 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, ankylosing spondylitis and rheumatoid arthritis (Kalliolias & Ivashkiv, 2016).

Studies performed with SARS-CoV suggested that excessive TNF-α-dependent inflammation could be crucial in the genesis of this disease. In fact, the binding of SARS-**CoV spike glycoproteins** to the membrane bound **angiotensin-converting enzyme 2 (ACE2)** activates TACE and, consequently, increases TNF-α release and the activation of the TNF-dependent cytokine cascade (Haga et al., 2008). TNFR2 appears to play a critical role in SARS-CoV virulence in mice, as indicated by the observation that, when compared to wild-type mice, the severity of SARS-CoV infection is greatly attenuated in TNFR2 KO mice (McDermott et al., 2016).

Little data are available on the effect of anti-TNF-α drugs in SARS-CoV-2 infection, which is essentially limited to case reports. For instance, Bezzio et al. (2021) reported a favourable 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-inflammatory bowel disease database showed that patients with inflammatory bowel disease treated with anti-TNF-α drugs do no worse than those receiving **sulfasalazine** or **mesalazine** when they develop COVID-19 (Feldmann et al., 2020). At the time of writing, randomized clinical trials are ongoing with both infliximab and adalimumab in COVID-19 patients (Table 2A). In a recent review paper, Jamilloux et al. (2020) discussed the theoretical reasons supporting TNF-α blockade as a strategy for COVID-19 treatment. They emphasized that these drugs are expected not only to reduce cytokine release and inflammation, but also to down-regulate the production of **VEGF** and the expression of adhesion molecules in endothelial cells, thereby impeding vascular permeabilization that is crucially important in the pathophysiology of the cytokine storm.

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 & Ivashkiv, 2016). Therefore, anti-TNF-α drugs have been investigated, with promising results in preclinical models of several neurodegenerative disorders including multiple sclerosis (Kemanetzoglou & Andreadou, 2017), stroke (Jayaraj et al., 2019) and epilepsy (Vezzani et al., 2016). In addition, one small open-label pilot study has described a possible beneficial effect of adalimumab in 11 patients with Rasmussen's encephalitis (Lagarde et al., 2016). Whether beneficial effects of TNF-α blockade can be achieved also in neuro-COVID still remains to be addressed in experimental and clinical studies.

Contrasting data have been reported on the effect of anti-TNF-α drugs in CNS viral infections. In fact, these drugs seem to reduce disease severity in experimental murine models of herpes simplex (Boivin et al., 2013), Japanese encephalitis (Ye et al., 2014). On the contrary, serious encephalitis (Bradford et al., 2009) and meningitis (Ma et al., 2013), mainly of herpetic aetiology have been reported in patients treated with anti-TNF-α antibodies for inflammatory bowel disease or rheumatoid arthritis. The incidence of CNS herpetic infections recorded in pooled analysis of clinical trials with these drugs in autoimmune disorders was >1.5% (Ma et al., 2013). Moreover, several cases of herpetic CNS infections were reported to the Food and Drug Administration Adverse Events Reporting System during post-marketing surveillance of these drugs (Bradford et al., 2009).

An important reason of concern when using anti-TNF-α antibodies in the treatment of neurological disorders is that clinical experience with these drugs in rheumatology and dermatology has shown that they cause not only a variety of immune-mediated adverse events, such as urticaria, psoriasis, lupus-like syndrome and type I diabetes mellitus (Fischer et al., 2020) mainly affecting peripheral organs, but also neurological disorders in about 4% of patients (Kaltsonoudis et al., 2014). These include optic neuritis, chronic inflammatory demyelinating polyneuropathy, mononeuritis multiplex and Guillain–Barré syndrome (Kemanetzoglou & Andreadou, 2017). However, it is still debated whether treatment with TNF-α blockers triggered the development of these disorders or unmasked a pre-existing still silent disease status (Kaltsonoudis et al., 2014).

3.4 | Targeting IFN-γ: Emapalumab

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 major histocompatibility complex (MHC). These biological effects are exerted through the activation of plasma membrane IFN-γ receptors consisting of two subunits, **IFNGR1** and **IFNGR2**, which upon ligand binding, dimerize and activate **JAK1** and **JAK2** tyrosine

TABLE 2 Neuroinflammation and cytokine-targeted interventions: targeting TNF-α, IFN-γ and JAK1/2

A. TNF-α

Drug	Main indications	CT number, title, study protocol	Neurological implications
Adalimumab Anti-TNF-α antibody	Rheumatoid arthritis Juvenile idiopathic arthritis Psoriatic arthritis Plaque psoriasis Crohn's disease Ulcerative colitis Ankylosing spondylitis Hidradenitis suppurativa Uveitis	**ChiCTR2000030089** A randomized, open-label, controlled trial for the efficacy and safety of Adalimumab Injection in the treatment of patients with severe novel coronavirus pneumonia (COVID-19) **Interventional Phase 2**	Although not approved for any neurological condition in humans, its use has been successfully explored in Rasmussen's encephalitis (Lagarde et al., 2016). Demyelinating disorders, herpes zoster reactivation, and herpes zoster meningitis have been associated with its use (Bradford et al., 2009; Ma et al., 2013).

B. IFN-γ

Drug	Main indications	CT number, title, study protocol	Neurological implications
Emapalumab Anti-IFN-γ antibody	Primary haemophagocytic lymphohistiocytosis (HLH)	**NCT04324021** Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients With COVID-19 Infection **Interventional Phase 2/3**	In a single patient affected by adenosine deaminase deficiency-severe combined immunodeficiency (ADA-SCID), it reduced brain lesions caused by CNS tubercolosis infection (Tucci et al., 2020).

C. JAK1/2

Drug	Main indications	CT number, title, study protocol	Neurological implications
Tofacitinib Anti-Jak1 and anti-Jak3 receptor antibody	Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis	**NCT04415151** Tofacitinib for Treatment of Moderate COVID-19 (I-TOMIC) **Interventional Phase 2** **NCT04469114** Tofacitinib in Hospitalized Patients With COVID-19 Pneumonia **Interventional Phase 2** **NCT04390061** Tofacitinib Plus Hydroxycloroquine vs Hydroxycloroquine in Patients With COVID-19 Interstitial Pneumonia (TOFACoV-2) **Interventional Phase 2** **NCT04332042** Tofacitinib in SARS-CoV2 Pneumonia **Interventional Phase 2**	No studies on neurological implications. However, potential risks include occurrence of thromboembolic events and reactivation of latent viral infections (Scott et al., 2018).
Baricitinib Anti-Jak1 and anti-Jak2 receptor antibody	Rheumatoid arthritis	**NCT04340232** Safety and Efficacy of Baricitinib for COVID-19 **Interventional Phase 2/3** **NCT04421027** A Study of Baricitinib (LY3009104) in Participants With COVID-19 **Interventional Phase 3** **NCT04358614** Baricitinib Therapy in COVID-19 **Interventional Phase 2/3** **NCT04373044** Baricitinib, Placebo and Antiviral Therapy for the Treatment of Patients With Moderate and Severe COVID-19 **Interventional Phase 2**	Reverses HIV-associated neurocognitive disorders in preclinical animal models (Gavegnano et al., 2019). May induce thromboembolic events and promote new viral infections or the reactivation of latent infections (Scott et al., 2018).

(Continues)

TABLE 2 (Continued)

C. JAK1/2			
Drug	**Main indications**	**CT number, title, study protocol**	**Neurological implications**
		NCT04393051 Baricitinib Compared to Standard Therapy in Patients With COVID-19 **Interventional Phase 2** **NCT04362943** Clinical-epidemiological Characterization of COVID-19 Disease in Hospitalized Older Adults **Observational** **NCT04390464** mulTi-Arm Therapeutic Study in Pre-ICu Patients Admitted With Covid-19—Repurposed Drugs (TACTIC-R) **Interventional Phase 4** **NCT04401579** Adaptive COVID-19 Treatment Trial 2 (ACTT-2) **Interventional Phase 3** **NCT04346147** Clinical Trial to Evaluate Efficacy of 3 Types of Treatment in Patients With Pneumonia by COVID-19 **Interventional Phase 2** **NCT04321993** Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in Hospitalized Patients **Interventional Phase 2** **NCT04320277** Baricitinib in Symptomatic Patients Infected by COVID-19: an Open-label, Pilot Study **Interventional Phase 2/3** **NCT04399798** Baricitinib for coronavirus pneumonia (COVID-19): a therapeutic trial **Interventional Phase 2**	
Ruxolitinib Anti-Jak1 and anti-Jak2 receptor antibody	Myelofibrosis	**NCT04348071** Safety and Efficacy of Ruxolitinib for COVID-19 **Interventional Phase 2/3** **NCT04414098** Ruxolitinib in the Treatment of Covid-19 **Interventional Phase 2** **NCT04355793** Expanded Access Program of Ruxolitinib for the Emergency Treatment of Cytokine Storm From COVID-19 Infection **Expanded access** **NCT04377620**	Ameliorates HIV encephalitis in mice (Haile et al., 2016) Effective in a single patient with highly active refractory neuromyelitis optica (Hodecker et al., 2017). May induce thromboembolic events and promote new viral infections or the reactivation of latent infections (Ballesta et al., 2017; Reoma et al., 2019; Scott et al., 2018).

TABLE 2 (Continued)

C. JAK1/2			
Drug	**Main indications**	**CT number, title, study protocol**	**Neurological implications**
		Assessment of Efficacy and Safety of Ruxolitinib in Participants With COVID-19-Associated ARDS Who Require Mechanical Ventilation (RUXCOVID-DEVENT) **Interventional Phase 3** **NCT04334044** Treatment of SARS Caused by COVID-19 With Ruxolitinib **Interventional Phase 1/2** **NCT04331665** Study of the Efficacy and Safety of Ruxolitinib to Treat COVID-19 Pneumonia **NA** **NCT04337359** Ruxolitinib Managed Access Program (MAP) for Patients Diagnosed With Severe/Very Severe COVID-19 Illness **Expanded access** **NCT04361903** Ruxolitinib for the Treatment of Acute Respiratory Distress Syndrome in Patients With COVID-19 Infection (RESPIRE) **Observational** **NCT04338958** Ruxolitinib in Covid-19 Patients With Defined Hyperinflammation (RuxCoFlam) **Interventional Phase 2** NCT04374149 Therapeutic Plasma Exchange Alone or in Combination With Ruxolitinib in COVID-19 Associated CRS **Interventional Phase 2** **NCT04348695** Study of Ruxolitinib Plus Simvastatin in the Prevention and Treatment of Respiratory Failure of COVID-19. (Ruxo-Sim-20) **Interventional Phase 2**	

kinases, and, ultimately, STAT1-dependent gene transcription (Stark et al., 2018).

Preclinical evidence shows that IFN-γ may exert specific effects in the control of a variety of brain functions including sleeping behaviour, learning and memory, and mood (Monteiro et al., 2016), These effects may be explained at least in part by the regulation of the 5-hydroxytryptamine (5-HT; serotoninergic) neurotransmission through the activation of tryptophan-indoleamine-pyrrole 2,3-dioxygenase, an enzyme that degrades the 5-HT 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. IFN-γ promotes neurogenesis in adult animals and improves memory and spatial learning in wild-type mice and in a transgenic mouse model of Alzheimer's disease (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 **amyloid β_{1-42}** (Bate et al., 2006).

Opposing effects of IFN-γ have also been described in viral infections of the CNS. While anti-viral activity is, in fact, one of the major physiological role of IFN-γ and this cytokine is crucial for the anti-viral defence against many virus-induced encephalitis (Chesler & Reiss, 2002). 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 anti-viral system (Li et al., 2016). In addition, IFN-γ may contribute to viral damage of the CNS by enhancing the permeability of the BBB as demonstrated, for instance, in rabies virus infection (Chai et al., 2014). Pharmacological inactivation of IFN-γ exerted positive effects on disease progression in viral encephalitis triggered in neonatal mice by intracranial administration of an attenuated lymphocytic choriomeningitis virus (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, a rare clinical condition that 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 a single patient affected by adenosine deaminase deficiency-severe combined immunodeficiency, treatment with emapalumab reduced the size of brain lesions occurring during disseminated tuberculosis (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 2B). No data are yet available in humans on the effect of emapalumab in neuro-COVID or any other CNS disease.

3.5 | Targeting JAK1–2: tofacitinib, baricitinib and ruxolitinib

The JAK–STAT transduction pathway is a signalling cascade that mediates the response to numerous cytokines (e.g. IL-1, IL-6, and 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. Four different **JAK proteins** (JAK1, JAK2, JAK3 and TYK) may activate seven STAT proteins (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6) and the response to each cytokine is fingerprinted by the specific set of JAK/STAT proteins that they activate. The JAK–STAT signalling cascade can be pharmacologically blocked, with the intent to treat rheumatological and haematological 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 JAK2 (Schwartz et al., 2017).

Early studies on the JAK/STAT cascade demonstrated its critical role in immune response, inflammation and tumourigenesis. 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 signalling cascade is activated in response to many different infectious and non-infectious conditions of the CNS that cause cytokine release because of tissue damage. For instance, strong activation of STAT1 and STAT3, mainly occurring in reactive microglia and in macrophages, has been observed after cerebral ischaemia in experimental animals (Planas et al., 1997). Nevertheless, there is no evidence that JAK–STAT inhibitors could be beneficial in human stroke and these drugs could even be dangerous considering that they increase the risk of venous thromboembolism (Scott et al., 2018). The JAK–STAT pathway is also activated by a variety of epileptogenic conditions including exposure to proconvulsant drugs such as **kainate** or **pilocarpine** (Choi et al., 2003).

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 experimental allergic encephalomyelis (Chitnis et al., 2001; Liu et al., 2008), STAT1 KO mice are instead highly susceptible (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 experimental allergic encephalomyelis. 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 neuromyelitis optica refractory to other immunosuppressive drugs (Hodecker et al., 2017).

STAT1 is the downstream effector of all the members of the IFN family (Schneider et al., 2014) and as such, it is crucial in protecting from viral infections including those of the CNS. A high risk of developing herpes virus-1 encephalitis is observed in subjects with rare inactivating mutations in STAT1 (Sancho-Shimizu et al., 2007). The risk of opportunistic viral infection is significantly increased by JAK/STAT inhibitors, both in experimental animals and in patients taking these drugs for rheumatological or haematological disorders. For instance, it has been calculated that 5.6% of patients recruited in Phases II and III, and in subsequent long-term extension trials were treated with tofacitinib for ulcerative colitis caused by herpes zoster infections (Winthrop et al., 2018). Moreover, one case of herpes zoster encephalitis during treatment with oral tofacitinib has also been described (Hosking et al., 2018). One fatal case of encephalopathy (Reoma et al., 2019) and one of meningitis (Ballesta et al., 2017) by John Cunnigham polyomavirus (JCPyV) have been described during chronic immunosuppressive treatment with ruxolitinib.

While, 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, as in the case of 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 and HIV-associated neurocognitive disorder since it may prevent the effect of cytokines (such as IL-6) released during HIV infection of the CNS and promote viral replication and brain damage. As a matter of fact, ruxolitinib reduced HIV replication in an animal model of HIV encephalitis (Haile et al., 2016), whereas, in mice infected with HIV, baricitinib improved the neurobehavioural abnormalities that partially replicate the symptoms of human HIV-associated neurocognitive disorder (Gavegnano et al., 2019). Clinical data are yet unavailable on the effects of JAK/STAT inhibitors in CNS infection by neurotropic CoVs and, more specifically, by SARS-CoV-2-associated 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 2C) with the rationale of reducing cytokine effects and systemic inflammation. The ability of these drugs to induce thromboembolic events and promote new viral infections or the reactivation of latent infection is a matter of concern and will require careful monitoring (Scott et al., 2018).

3.6 | Targeting human GM-CSF: sargramostim; mavrilimumab and gimsilumab

GM-CSF is a pro-inflammatory 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 (Crotti et al., 2019). Recombinant forms of GM-CSF, such as sargramostim and **molgramostim**, have long been used in clinical conditions in which myelogenic support is needed, such as to counteract myelosuppression during cancer chemotherapy. More recently, the benefits of blocking GM-CSF pro-inflammatory effects in inflammatory diseases like rheumatoid arthritis 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 pathogenetic role has been suggested for the pro-inflammatory activity of GM-CSF also in SARS-CoV-2 infection because high circulating levels of this cytokine are found in the lung of COVID-19-affected patients (Bonaventura et al., 2020). Therefore, blocking GM-CSF could be beneficial in COVID-19, a hypothesis that is currently being investigated in clinical trials with either gimsilumab or mavrilimumab (Table 3A). On the other hand, it has also been observed that GM-CSF can help in fighting serious infection and its use has been suggested in sepsis of bacterial origin (Chousterman & Arnaud, 2018). Therefore, clinical trials are also ongoing to evaluate the effectiveness of sargramostim in COVID-19 patients (Table 3A). Although this may seem counterintuitive, both apparently opposing strategies might be effective, possibly depending on the disease stage, as the late stages of COVID-19 are thought to be driven by host overactive immunity rather than high viral load (Lang et al., 2020).

GM-CSF exerts biological effects in the CNS not only because peripherally synthesized circulating GM-CSF may cross the BBB but also because this cytokine is synthetized and released by resident CNS cells, mainly astrocytes. GM-CSF receptors are expressed in neurons, astrocytes, oligodendrocytes and microglia, which are considered the major target of this cytokine in the CNS (Aram et al., 2019). GM-CSF can act both as a pro-inflammatory 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 experimental allergic encephalomyelis (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 pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 may also participate (Bhattacharya et al., 2015). GM-CSF KO mice are protected from experimental allergic encephalomyelis (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, a hypothesis confirmed by the positive effects obtained by the intraperitoneal injection of an anti-GM-CSF mAb to experimental allergic encephalomyelis mice (McQualter et al., 2001). Consistent with these preliminary data, a randomized Phase Ib tolerability study performed with otilimab in patients with multiple sclerosis 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 and Phase 2 studies with lenzilumab in combination with CAR-T cell therapy are planned (Sterner et al., 2019). While these results are encouraging, the potential toxicity of anti-GM-CSF drugs, which includes an increased risk of opportunistic infection, the worsening of inflammatory bowel disease and alveolar proteinosis, will deserve the highest attention in further clinical development (Aram et al., 2019).

The effects of GM-CSF are predominantly neuroprotective in other animal models of neurological disorders including, for instance, traumatic brain injury, stroke, Parkinson's disease and Alzheimer's disease. Several 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 anti-apoptotic 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

TABLE 3 Neuroinflammation and cytokine-based interventions: targeting GM-CSF, IL-7 and the complement system

A. GM-CSF

Drug	Main indications	CT number, title, study protocol	Neurological implications
Mavrilimumab Anti-GM-CSF receptor-α (GM-CSFRα) antibody	Rheumatoid arthritis	**NCT04447469** Study of Mavrilimumab (KPL-301) in Participants Hospitalized With Severe Corona Virus Disease 2019 (COVID-19) Pneumonia and Hyper-inflammation **Interventional Phase 2** **NCT04492514** Mavrilimumab to Reduce Progression of Acute Respiratory Failure in COVID-19 Pneumonia and Systemic Hyper-inflation **Interventional Phase 2** **NCT04463004** Mavrilimumab to Reduce Progression of Acute Respiratory Failure in COVID-19 Pneumonia and Systemic Hyper-inflammation (Virginia) **Interventional Phase 2** **NCT04399980** Mavrilimumab to Reduce Progression of Acute Respiratory Failure in COVID-19 Pneumonia and Systemic Hyper-inflammation (Florida) **Interventional Phase 2** **NCT04397497** Mavrilimumab in Severe COVID-19 Pneumonia and Hyper-inflammation (COMBAT-19) **Interventional Phase 2**	No clinical data are available regarding the neurological implications of mavrilimumab treatment in humans; however, GM-CSF KO mice are protected from experimental allergic encephalomyelis (McQualter et al., 2001), whereas disease severity is increased in mice receiving the infusion of lymphocytes infected with adenoviruses carrying a GM-CSF transgene (Spath et al., 2017).
Gimsilumab Anti-GM-CSF antibody	Rheumatoid arthritis	**NCT04351243** A Study to Assess the Efficacy and Safety of Gimsilumab in Subjects With Lung Injury or Acute Respiratory Distress Syndrome Secondary to COVID-19 (BREATHE) **Interventional Phase 2**	MOR103 (otilimab), a human monoclonal antibody that binds GM-CSF, has shown moderate beneficial effects in multiple sclerosis patients (Constantinescu et al., 2015). GM-CSF neutralization with lenzilumab reduces chimeric antigen receptor T (CAR-T) cell therapy-induced neurotoxicity in in vitro and in vivo experimental models (Sterner et al., 2019).
Sargramostim Human recombinant GM-CSF	Acute myeloid leukaemia following chemotherapy Autologous peripheral blood progenitor cell mobilization and bone marrow transplantation Allogenic bone marrow transplantation	**NCT04411680** Study of Sargramostim in Patients with COVID-19 **Interventional Phase 2** **NCT04326920** Sargramostim in Patients With Acute Hypoxic Respiratory Failure Due to COVID-19 (SARPAC) **Interventional Phase 2** **NCT04400929**	Recombinant GM-CSF protects from HSV-1 encephalitis (Tsuboi et al., 1998), reduces brain infarct size (Schabitz et al., 2008), and is effective in experimental models of Parkinson's disease (Kim et al., 2009). Improved motor function in a small cohort of patients with Parkinson's disease (Gendelman et al., 2017). Is neuroprotective in a mouse model of Alzheimer's disease (Kiyota et al., 2018) and a clinical

TABLE 3 (Continued)

A. GM-CSF			
Drug	**Main indications**	**CT number, title, study protocol**	**Neurological implications**
		Using GM-CSF as a Host Directed Therapeutic Against COVID-19 **Interventional Phase 2**	trial in Alzheimer's disease patients (NCT01409915) has been completed (data not available yet).
B. IL-7			
Drug	**Main indications**	**CT number, title, study protocol**	**Neurological implications**
CYT-107 Recombinant IL-7	–	**NCT04379076** InterLeukin-7 (CYT107) to Improve Clinical Outcomes in Lymphopenic pAtients With COVID-19 Infection UK Cohort (ILIAD-7-UK) **Interventional Phase 2** **NCT04407689** InterLeukin-7 to Improve Clinical Outcomes in Lymphopenic pAtients With COVID-19 Infection FR BL Cohort (ILIAD-7-FR) **Interventional Phase 2** **NCT04426201** InterLeukin-7 to Improve Clinical Outcomes in Lymphopenic pAtients With COVID-19 Infection (ILIAD-7-US-O) **Interventional Phase 2** **NCT04442178** InterLeukin-7 to Improve Clinical Outcomes in Lymphopenic pAtients With COVID-19 Infection (ILIAD-7-US-I) **Interventional Phase 2**	IL-7 is effective in a single patient with progressive multifocal leukoencephalopathy caused by JC polyomavirus (Alstadhaug et al., 2014). May also exert pro-inflammatory activity during spinal trauma (Bao et al., 2018) and promote the autoimmune aggression of the CNS in multiple sclerosis-experimental allergic encephalomyelis mouse model (Lawson et al., 2015).
C. Complement system			
Drug	**Main indications**	**CT number, title, study protocol**	**Neurological implications**
Eculizumab Anti-C5 antibody	Paroxysmal nocturnal haemoglobinuria Atypical haemolytic uraemic syndrome Generalized myasthenia gravis Neuromyelitis optica spectrum disorder	**NCT04346797** CORIMUNO19-ECU: Trial Evaluating Efficacy and Safety of Eculizumab (Soliris) in Patients With COVID-19 Infection, Nested in the CORIMUNO-19 Cohort (CORIMUNO19-ECU) **Interventional Phase 2** **NCT04355494** SOLIRIS® (Eculizumab) Treatment of Participants With COVID-19 **Expanded access** **NCT04288713** Eculizumab (Soliris) in Covid-19 Infected Patients (SOLID-C19) **Expanded access**	Approved for neuromyelitis optica (Carpanini et al., 2019) and myasthenia gravis (Frampton, 2020). It has been effective in 4 patients with a genetic demyelinating neuropathy caused by CD59 mutation (Mevorach et al., 2016). It may aggravate progressive multifocal leukoencephalopathy caused by JC polyomavirus (Gomez-Cibeira et al., 2016).

reduces infarct size and neurological deficits in rats with middle cerebral artery occlusion (Schabitz et al., 2008). However, brain atrophy and behavioural 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 significant neuroprotection in primary neuronal midbrain cultures exposed to the parkinsonigenic toxin **1-methyl-4-phenylpyridinium (MPP^+)** and decreases dopaminergic neuron death in the substantia nigra and locomotor deficits in mice treated with this neurotoxic agent (Kim et al., 2009). Modest clinical improvement after 6 and 8 weeks of treatment was observed in a small randomized, placebo-controlled double-blind Phase 1 trial in which sargramostim was given subcutaneously to 20 Parkinson's disease patients (Gendelman et al., 2017). Neuroprotective effects have been observed after recombinant GM-CSF administration also in a mouse transgenic model of Alzheimer's disease (Kiyota et al., 2018) and a Phase II, placebo-controlled clinical trial (NCT01409915) has been completed (data not available yet) to assess the efficacy of this drug in 40 patients with Alzheimer's disease. It is worth mentioning that part of the protective effects triggered by GM-CSF in Alzheimer's disease could be exerted on the bone marrow and not directly in the brain since this cytokine could promote the release of monocytes that could then transmigrate in the CNS and phagocyte amyloid plaques (Heinzelman & Priebe, 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 pre-treatment with recombinant GM-CSF protects these animals from the ensuing HSV-1 encephalitis (Tsuboi et al., 1998). Most of this protective effect is the consequent of emergence haematopoiesis, 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 excessive activation may be lethal, leading to a massive inflammatory CNS damage. Evidence has been recently reported that IFN-γ is the major physiological down-regulator of GM-CSF release in viral encephalitis and contributes to limiting brain damage in this condition (Ramakrishna & Cantin, 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 of 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 the peripheral blood and in the CSF, whereas children with respiratory infections and no neurological symptom only had high GM-CSF in the peripheral blood, a result suggestive of a local CNS production of this cytokine (Li et al., 2016). No data have 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 (Table 3A) would improve or worsen CNS damage.

3.7 | Targeting interleukin-7 (IL-7): CYT107

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 (Mackall et al., 2011). Because of this effect on lymphocytes, recombinant IL-7 (CYT107) has been used experimentally 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 3B), 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 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 up-regulation of the suppressor of cytokine signalling 3, 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 a patient affected by idiopathic $CD4^+$ lymphocytopenia with the rationale of enhancing the immune response against the causative JCPyV (Alstadhaug et al., 2014).

While the effects IL-7 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 pro-inflammatory activity by inducing the release of TNF-α, IL-1β and IL-6 (Mackall et al., 2011). Such pro-inflammatory 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 expressed in neurons (Nunnari et al., 2005). Finally, IL-7 may promote the autoimmune aggression of the CNS and the blockade of **IL-7 receptor** with monoclonal antibodies may prevent or ameliorate experimental allergic encephalomyelis in mice (Lawson et al., 2015). Interestingly, individuals with specific allelic variants of the α subunit of IL-7 receptor have an increased risk of developing multiple sclerosis, further supporting the possible involvement of IL-7 in autoimmune demyelinating diseases (Gregory et al., 2007).

3.8 | 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 (Carpanini et al., 2019). 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. 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, also enhancing B-cell response to antigens, thus bridging adaptive and innate immunity (Carpanini et al., 2019). 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. As C5 is involved in the last stages of the complement cascade, its blockade with eculizumab impairs the formation of the prothrombotic and pro-inflammatory anaphylotoxin C5a and of the complement *MAC*, while leaving the upstream steps of the complement cascade unaffected (Cataldi & Cavaccini, 2011). Eculizumab has been originally approved for two rare haematological disorders, atypical haemolytic uraemic syndrome and paroxysmal nocturnal haemoglobinuria. More recently, its indications have been extended to include two immune-mediated and complement-dependent neurological disorders: (i) AQP4-IgG-seropositive neuromyelitis optica spectrum disorder, in which the Phase III PREVENT trial showed sustained improvements in neurological and functional disability, as well as in overall health-related quality of life (Frampton, 2020) and (ii) anti-ACh receptor antibody-positive refractory generalized myasthenia gravis, in which the Phase III REGAIN trial and subsequent open-label extension interim analysis revealed eculizumab's long-term safety and efficacy (Muppidi et al., 2019). Eculizumab has been shown to be effective also in four patients with a genetic demyelinating neuropathy caused by mutation in the glycosyl phosphatidylinositol-anchored cell surface membrane glycoprotein, CD59, a protein able to inhibit the final step of the complement MAC formation (Mevorach et al., 2016).

Several considerations suggest that the complement system could have a role in disorders of the CNS. In fact, 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. The endogenous CNS complement system takes part to synapse pruning and maturation and is involved in CNS development (Morimoto & Nakajima, 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 traumatic brain injury, spinal trauma, ischaemic stroke, Alzheimer's disease, Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis, 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, no human trials of anti-complement therapies for the most common CNS diseases have been yet carried out. 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. In addition, complement activation may help clearing protein precipitates such as β-amyloid plaques and therefore its inhibition may also be paradoxically detrimental in Alzheimer's disease and similar diseases (Carpanini et al., 2019).

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) and Venezuelan equine encephalitis virus (Brooke et al., 2012). Indeed, eculizumab, by blocking complement activation, may aggravate progressive multifocal leukoencephalopathy caused by the JCPyV (Gomez-Cibeira et al., 2016). Different mechanisms may account for complement anti-viral 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 anti-viral 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 susceptible cells (Agrawal et al., 2017). By using the latter mechanism, several viruses including HIV, Epstein–Barr virus, measles virus, Newcastle disease virus and Borna disease virus infect neurons and glia (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 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.

Favourable effects have been observed upon pharmacological blockade of C5a/C5aR axis in mice with experimental MERS infection (Jiang et al., 2018). On the other hand, it has been suggested that the complement-activating mannose-binding protein contributes to the first-line host defence 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 this 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 3C). However, the increased risk of life-threatening meningococcal infection associated to eculizumab use (McNamara et al., 2017) should be taken into consideration.

4 | CONCLUDING REMARKS

In the present review, we aimed to provide a general framework for understanding 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, firstly 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 secondly because early or late unwanted neurological effects may occur during COVID-19 treatment with these drugs.

Several points remain to be clarified. Probably the most fundamental question is how important are endogenous, CNS-synthesized cytokines for both anti-viral and neurotoxic 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 pharmacokinetic respect, JAK/STAT inhibitors appear as the privileged drugs

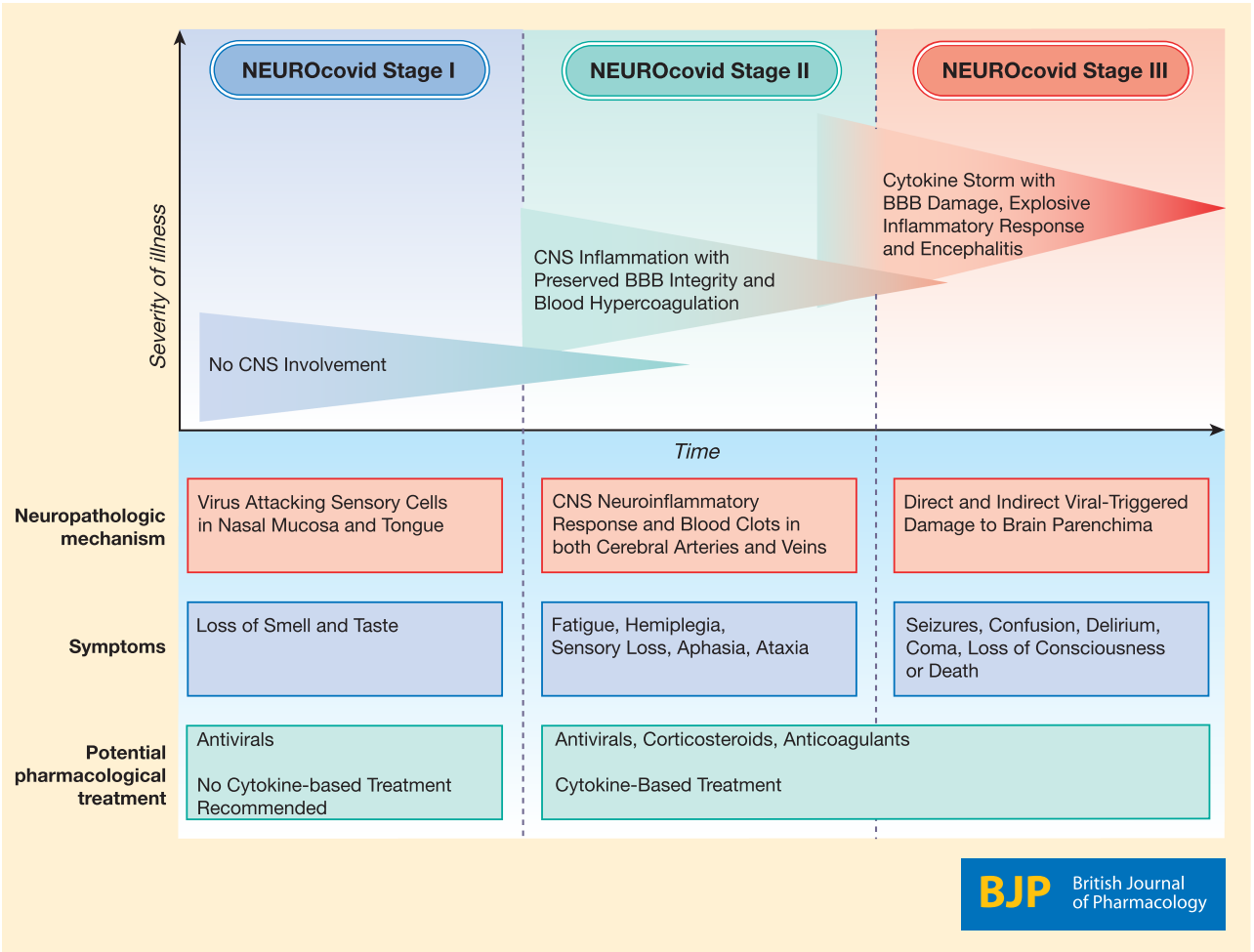

FIGURE 2 Neuropathological mechanisms, symptoms and potential therapeutic approaches in the three Neuro-COVID stages

because of their small size and physico-chemical 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 the CNS (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. Therefore, cytokine drugs are to be considered as double-edge sword 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, co-morbidities, …) 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*, the virus invades the brain parenchyma through the damaged BBB together with circulating cytokines and causes 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 from treatments boosting their immune response against the virus. On the contrary, in neuro-COVID Stages 2 and 3, a pharmacological intervention aiming to decrease neuroinflammation would likely be more effective (Figure 2). However, clinicians must be aware that a precise risk/benefit assessment is critical 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.

In conclusion, drugs affecting the cytokine system, which are currently being explored for their efficacy in COVID-19 patients, could also affect the CNS and be helpful against neuro-COVID manifestations. Emerging data begin to suggest that combination therapy of cytokine-based treatment with direct anti-viral drugs (**remdesivir**) may offer significant clinical advantage. In fact, in a recent double-blind, randomized, placebo-controlled trial carried out in 1033 hospitalized COVID-19 adults receiving high-flow oxygen or non-invasive mechanical ventilation, the use of the JAK inhibitor baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating clinical improvement, with fewer serious adverse events (Kalil et al., 2020). No data are yet available on the effects of cytokine-based treatment as alternative or complementary to corticosteroids, the most common anti-inflammatory drugs used in these patients (https://www.covid19treatmentguidelines.nih.gov/).

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019).

ACKNOWLEDGEMENTS

The present work was supported by grants from the Italian Ministry of Education, University and Research (Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) (PRIN 2017ALCR7C), Ministry of Health (Ministero della Salute) (RF-2019-12370491), the European Commission H2020 (UNICOM – 875299), and the European Joint Programme on Rare Disease JTC 2020 (TreatKCNQ) to M.T.

AUTHOR CONTRIBUTIONS

G.P. and M.C. searched and reviewed the literature, prepared the figures and tables, and drafted the manuscript. M.T. conceived the aims of the manuscript and revised the original manuscript draft. All authors critically analysed the data reported and their interpretation and gave final approval of the version to be published.

CONFLICT OF INTEREST

The authors declare no financial or other conflicts of interest that relate to the research covered in this article.

ORCID

Giuseppe Pignataro https://orcid.org/0000-0002-7290-4397
Mauro Cataldi https://orcid.org/0000-0001-7787-3406
Maurizio Taglialatela https://orcid.org/0000-0002-8202-0560

REFERENCES

Agrawal, P., Nawadkar, R., Ojha, H., Kumar, J., & Sahu, A. (2017). Complement evasion strategies of viruses: An overview. *Frontiers in Microbiology*, *8*, 1117. https://doi.org/10.3389/fmicb.2017.01117

Alexander, S. P. H., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., Sharman, J. L., Southan, C., Buneman, O. P., Cidlowski, J. A., Christopoulos, A., Davenport, A. P., Fabbro, D., Spedding, M., Striessnig, J., Davies, J. A., & CGTP Collaborators. (2019). The Concise Guide to PHARMACOLOGY 2019/20: Introduction and other protein targets. *British Journal of Pharmacology*, *176*(Suppl 1), S1–S20.

Al-Salama, Z. T. (2019). Emapalumab: First global approval. *Drugs*, *79*(1), 99–103.

Alstadhaug, K. B., Croughs, T., Henriksen, S., Leboeuf, C., Sereti, I., Hirsch, H. H., & Rinaldo, C. H. (2014). Treatment of progressive multifocal leukoencephalopathy with interleukin 7. *JAMA Neurology*, *71*(8), 1030–1035. https://doi.org/10.1001/jamaneurol.2014.825

Araki, M. (2019). Blockade of IL-6 signaling in neuromyelitis optica. *Neurochemistry International*, *130*, 104315. https://doi.org/10.1016/j.neuint.2018.10.012

Aram, J., Francis, A., Tanasescu, R., & Constantinescu, C. S. (2019). Granulocyte-macrophage colony-stimulating factor as a therapeutic target in multiple sclerosis. *Neurology and Theraphy*, *8*(1), 45–57.

Atzeni, F., Nucera, V., Masala, I. F., Sarzi-Puttini, P., & Bonitta, G. (2019). Il-6 involvement in pain, fatigue and mood disorders in rheumatoid

arthritis and the effects of Il-6 inhibitor sarilumab. *Pharmacological Research*, *149*, 104402.

Ballesta, B., Gonzalez, H., Martin, V., & Ballesta, J. J. (2017). Fatal ruxolitinib-related JC virus meningitis. *Journal of Neurovirology*, *23*(5), 783–785.

Bao, C., Wang, B., Yang, F., & Chen, L. (2018). Blockade of interleukin-7 receptor shapes macrophage alternative activation and promotes functional recovery after spinal cord injury. *Neuroscience*, *371*, 518–527. https://doi.org/10.1016/j.neuroscience.2017.10.022

Baron, R., Nemirovsky, A., Harpaz, I., Cohen, H., Owens, T., & Monsonego, A. (2008). IFN-γ enhances neurogenesis in wild-type mice and in a mouse model of Alzheimer's disease. *The FASEB Journal*, *22*(8), 2843–2852. https://doi.org/10.1096/fj.08-105866

Bate, C., Kempster, S., Last, V., & Williams, A. (2006). Interferon-γ increases neuronal death in response to amyloid-$\beta_{1\text{-}42}$. *Journal of Neuroinflammation*, *3*, 7. https://doi.org/10.1186/1742-2094-3-7

Benveniste, E. N., Liu, Y., McFarland, B. C., & Qin, H. (2014). Involvement of the Janus kinase/signal transducer and activator of transcription signaling pathway in multiple sclerosis and the animal model of experimental autoimmune encephalomyelitis. *Journal of Interferon & Cytokine Research*, *34*(8), 577–588. https://doi.org/10.1089/jir.2014.0012

Bettelli, E., Sullivan, B., Szabo, S. J., Sobel, R. A., Glimcher, L. H., & Kuchroo, V. K. (2004). Loss of T-bet, but not STAT1, prevents the development of experimental autoimmune encephalomyelitis. *Journal of Experimental Medicine*, *200*(1), 79–87. https://doi.org/10.1084/jem.20031819

Bezzio, C., Manes, G., Bini, F., Pellegrini, L., & Saibeni, S. (2021). Infliximab for severe ulcerative colitis and subsequent SARS-CoV-2 pneumonia: A stone for two birds. *Gut*, *70*(3), 623–624. https://doi.org/10.1136/gutjnl-2020-321760

Bhattacharya, P., Thiruppathi, M., Elshabrawy, H. A., Alharshawi, K., Kumar, P., & Prabhakar, B. S. (2015). GM-CSF: An immune modulatory cytokine that can suppress autoimmunity. *Cytokine*, *75*(2), 261–271.

Bibert, S., Piret, J., Quinodoz, M., Collinet, E., Zoete, V., Michielin, O., Menasria, R., Meylan, P., Bihl, T., Erard, V., & Fellmann, F. (2019). Herpes simplex encephalitis in adult patients with MASP-2 deficiency. *PLoS Pathogens*, *15*(12), e1008168.

Boivin, N., Menasria, R., Piret, J., Rivest, S., & Boivin, G. (2013). The combination of valacyclovir with an anti-TNF alpha antibody increases survival rate compared to antiviral therapy alone in a murine model of herpes simplex virus encephalitis. *Antiviral Research*, *100*(3), 649–653.

Bonaventura, A., Vecchie, A., Wang, T. S., Lee, E., Cremer, P. C., Carey, B., Rajendram, P., Hudock, K. M., Korbee, L., Van Tassell, B. W., & Dagna, L. (2020). Targeting GM-CSF in COVID-19 pneumonia: Rationale and strategies. *Frontiers in Immunology*, *11*, 1625.

Bordon, Y. (2011). Immune responses: IL-7 goes antiviral. *Nature Reviews Immunology*, *11*(3), 158.

Brabers, N. A., & Nottet, H. S. (2006). Role of the pro-inflammatory cytokines TNF-α and IL-1β in HIV-associated dementia. *European Journal of Clinical Investigation*, *36*(7), 447–458.

Bradford, R. D., Pettit, A. C., Wright, P. W., Mulligan, M. J., Moreland, L. W., McLain, D. A., Gnann, J. W., & Bloch, K. C. (2009). Herpes simplex encephalitis during treatment with tumor necrosis factor-α inhibitors. *Clinical Infectious Diseases*, *49*(6), 924–927. https://doi.org/10.1086/605498

Bright, J. J., Rodriguez, M., & Sriram, S. (1999). Differential influence of interleukin-12 in the pathogenesis of autoimmune and virus-induced central nervous system demyelination. *Journal of Virology*, *73*(2), 1637–1639.

Brooke, C. B., Schafer, A., Matsushima, G. K., White, L. J., & Johnston, R. E. (2012). Early activation of the host complement system is required to restrict central nervous system invasion and limit neuropathology during Venezuelan equine encephalitis virus infection. *The Journal of General Virology*, *93*(Pt 4), 797–806.

Carpanini, S. M., Torvell, M., & Morgan, B. P. (2019). Therapeutic inhibition of the complement system in diseases of the central nervous system. *Frontiers in Immunology*, *10*, 362. https://doi.org/10.3389/fimmu.2019.00362

Cataldi, M., & Cavaccini, A. (2011). Eculizumab. In S. J. Enna & D. B. Bylund (Eds.), *xPharm: The comprehensive pharmacology reference* (pp. 1–26). Amsterdam, Netherlands: Elsevier.

Cataldi, M., Pignataro, G., & Taglialatela, M. (2020). Neurobiology of coronaviruses: Potential relevance for COVID-19. *Neurobiology of Disease*, *143*, 105007. https://doi.org/10.1016/j.nbd.2020.105007

Cavalli, G., & Dinarello, C. A. (2015). Treating rheumatological diseases and co-morbidities with interleukin-1 blocking therapies. *Rheumatology (Oxford)*, *54*(12), 2134–2144.

Chai, Q., He, W. Q., Zhou, M., Lu, H., & Fu, Z. F. (2014). Enhancement of blood-brain barrier permeability and reduction of tight junction protein expression are modulated by chemokines/cytokines induced by rabies virus infection. *Journal of Virology*, *88*(9), 4698–4710.

Chesler, D. A., & Reiss, C. S. (2002). The role of IFN-γ in immune responses to viral infections of the central nervous system. *Cytokine & Growth Factor Reviews*, *13*(6), 441–454. https://doi.org/10.1016/S1359-6101(02)00044-8

Chihara, N., Aranami, T., Sato, W., Miyazaki, Y., Miyake, S., Okamoto, T., Toda, T., & Yamamura, T. (2011). Interleukin 6 signaling promotes anti-aquaporin 4 autoantibody production from plasmablasts in neuromyelitis optica. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(9), 3701–3706. https://doi.org/10.1073/pnas.1017385108

Chitnis, T., Najafian, N., Benou, C., Salama, A. D., Grusby, M. J., Sayegh, M. H., & Khoury, S. J. (2001). Effect of targeted disruption of STAT4 and STAT6 on the induction of experimental autoimmune encephalomyelitis. *The Journal of Clinical Investigation*, *108*(5), 739–747. https://doi.org/10.1172/JCI200112563

Choi, J. S., Kim, S. Y., Park, H. J., Cha, J. H., Choi, Y. S., Kang, J. E., Chung, J. W., Chun, M. H., & Lee, M.-Y. (2003). Upregulation of gp130 and differential activation of STAT and p42/44 MAPK in the rat hippocampus following kainic acid-induced seizures. *Brain Research. Molecular Brain Research*, *119*(1), 10–18. https://doi.org/10.1016/j.molbrainres.2003.08.010

Chousterman, B. G., & Arnaud, M. (2018). Is there a role for hematopoietic growth factors during sepsis? *Frontiers in Immunology*, *9*, 1015. https://doi.org/10.3389/fimmu.2018.01015

Constantinescu, C. S., Asher, A., Fryze, W., Kozubski, W., Wagner, F., Aram, J., Tanasescu, R., Korolkiewicz, R. P., Dirnberger-Hertweck, M., Steidl, S., Libretto, S. E., Sprenger, T., & Radue, E. W. (2015). Randomized phase 1b trial of MOR103, a human antibody to GM-CSF, in multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*, *2*(4), e117.

Cosenza-Nashat, M., Zhao, M. L., Marshall, H. D., Si, Q., Morgello, S., & Lee, S. C. (2007). Human immunodeficiency virus infection inhibits granulocyte-macrophage colony-stimulating factor-induced microglial proliferation. *Journal of Neurovirology*, *13*(6), 536–548.

Crotti, C., Agape, E., Becciolini, A., Biggioggero, M., & Favalli, E. G. (2019). Targeting granulocyte-monocyte colony-stimulating factor signaling in rheumatoid arthritis: Future prospects. *Drugs*, *79*(16), 1741–1755. https://doi.org/10.1007/s40265-019-01192-z

De Sarro, G., Russo, E., Ferreri, G., Giuseppe, B., Flocco, M. A., Di Paola, E. D., & De Sarro, A. (2004). Seizure susceptibility to various convulsant stimuli of knockout interleukin-6 mice. *Pharmacology Biochemistry and Behavior*, *77*(4), 761–766.

DeSena, A. D., Do, T., & Schulert, G. S. (2018). Systemic autoinflammation with intractable epilepsy managed with interleukin-1 blockade. *Journal of Neuroinflammation*, *15*(1), 38. https://doi.org/10.1186/s12974-018-1063-2

Dilena, R., Mauri, E., Aronica, E., Bernasconi, P., Bana, C., Cappelletti, C., Carrabba, G., Ferrero, S., Giorda, R., Guez, S., Catenacci, S. S., Triulzi, F., Barbieri, S., Calderini, E., & Vezzani, A. (2019). Therapeutic

effect of anakinra in the relapsing chronic phase of febrile infection-related epilepsy syndrome. *Epilepsia Open*, *4*(2), 344–350. https://doi.org/10.1002/epi4.12317

Erta, M., Quintana, A., & Hidalgo, J. (2012). Interleukin-6, a major cytokine in the central nervous system. *International Journal of Biological Sciences*, *8*(9), 1254–1266.

Everett, B. M., MacFadyen, J. G., Thuren, T., Libby, P., Glynn, R. J., & Ridker, P. M. (2020). Inhibition of interleukin-1β and reduction in atherothrombotic cardiovascular events in the CANTOS trial. *Journal of the American College of Cardiology*, *76*(14), 1660–1670.

Fajgenbaum, D. C., & Kurzrock, R. (2016). Siltuximab: A targeted therapy for idiopathic multicentric Castleman disease. *Immunotherapy*, *8*(1), 17–26.

Feldmann, M., Maini, R. N., Woody, J. N., Holgate, S. T., Winter, G., Rowland, M., Richards, D., & Hussell, T. (2020). Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *Lancet*, *395*(10234), 1407–1409.

Fiala, M., Mizwicki, M. T., Weitzman, R., Magpantay, L., & Nishimoto, N. (2013). Tocilizumabinfusiontherapynormalizesinflammation in sporadic ALS patients. *American Journal of Neurodegenerative Disease*, *2*(2), 129–139.

Fischer, R., Kontermann, R. E., & Pfizenmaier, K. (2020). Selective targeting of TNF receptors as a novel therapeutic approach. *Frontiers in Cell and Development Biology*, *8*, 401. https://doi.org/10.3389/fcell.2020.00401

Fotuhi, M., Mian, A., Meysami, S., & Raji, C. A. (2020). Neurobiology of COVID-19. *Journal of Alzheimer's Disease*, *76*(1), 3–19.

Frampton, J. E. (2020). Eculizumab: A review in neuromyelitis optica spectrum disorder. *Drugs*, *80*(7), 719–727.

Gavegnano, C., Haile, W. B., Hurwitz, S., Tao, S., Jiang, Y., Schinazi, R. F., & Tyor, W. R. (2019). Baricitinib reverses HIV-associated neurocognitive disorders in a SCID mouse model and reservoir seeding in vitro. *Journal of Neuroinflammation*, *16*(1), 182. https://doi.org/10.1186/s12974-019-1565-6

Gendelman, H. E., Zhang, Y., Santamaria, P., Olson, K. E., Schutt, C. R., Bhatti, D., Shetty, B. L. D., Lu, Y., Estes, K. A., Standaert, D. G., Heinrichs-Graham, E., Larson, L. A., Meza, J. L., Follett, M., Forsberg, E., Siuzdak, G., Wilson, T. W., Peterson, C., & Lee Mosley, R. (2017). Evaluation of the safety and immunomodulatory effects of sargramostim in a randomized, double-blind phase 1 clinical Parkinson's disease trial. *NPJ Parkinsons Disease*, *3*, 10. https://doi.org/10.1038/s41531-017-0013-5

Gomez-Cibeira, E., Ivanovic-Barbeito, Y., Gutierrez-Martinez, E., Morales, E., Abradelo, M., Hilario, A., Ramos, A., Ruiz-Morales, J., & Villarejo-Galende, A. (2016). Eculizumab-related progressive multifocal leukoencephalopathy. *Neurology*, *86*(4), 399–400.

Gralinski, L. E., Sheahan, T. P., Morrison, T. E., Menachery, V. D., Jensen, K., Leist, S. R., Whitmore, A., Heise, M. T., & Baric, R. S. (2018). Complement activation contributes to severe acute respiratory syndrome coronavirus pathogenesis. *MBio*, *9*(5), e01753–18.

Gregory, S. G., Schmidt, S., Seth, P., Oksenberg, J. R., Hart, J., Prokop, A., Caillier, S. J., Ban, M., Goris, A., Barcellos, L. F., Lincoln, R., McCauley, J. L., Sawcer, S. J., Compston, D. A. S., Dubois, B., Hauser, S. L., Garcia-Blanco, M. A., Pericak-Vance, M. A., Haines, J. L., & the Multiple Sclerosis Genetics Group. (2007). Interleukin 7 receptor α chain (IL7R) shows allelic and functional association with multiple sclerosis. *Nature Genetics*, *39*(9), 1083–1091.

Haga, S., Yamamoto, N., Nakai-Murakami, C., Osawa, Y., Tokunaga, K., Sata, T., Yamamoto, N., Sasazuki, T., & Ishizaka, Y. (2008). Modulation of TNF-α-converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF-α production and facilitates viral entry. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(22), 7809–7814. https://doi.org/10.1073/pnas.0711241105

Haile, W. B., Gavegnano, C., Tao, S., Jiang, Y., Schinazi, R. F., & Tyor, W. R. (2016). The Janus kinase inhibitor ruxolitinib reduces HIV replication in human macrophages and ameliorates HIV encephalitis in a murine model. *Neurobiology of Disease*, *92*(Pt B), 137–143.

Heinzelman, P., & Priebe, M. C. (2015). Engineering superactive granulocyte macrophage colony-stimulating factor transferrin fusion proteins as orally-delivered candidate agents for treating neurodegenerative disease. *Biotechnology Progress*, *31*(3), 668–677.

Hewett, S. J., Jackman, N. A., & Claycomb, R. J. (2012). Interleukin-1β in central nervous system injury and repair. *European Journal of Neurodegenerative Disease*, *1*(2), 195–211.

Hodecker, S. C., Stellmann, J. P., Rosenkranz, S. C., Young, K., Holst, B., Friese, M. A., & Heesen, C. (2017). Ruxolitinib treatment in a patient with neuromyelitis optica: A case report. *Neurol Neuroimmunology Neuroinflammation*, *4*(2), e328.

Hoshino, H., Shirai, Y., Konishi, H., Yamamura, T., & Shimizu, N. (2020). Efficacy of tocilizumab for fulminant multiple sclerosis with a tumefactive cervical lesion: A 12-year-old boy. *Multiple Sclerosis and Related Disorders*, *37*, 101460.

Hosking, A. M., Juhasz, M., & Mesinkovska, N. A. (2018). Suspected herpes zoster-associated encephalitis during treatment with oral tofacitinib in alopecia universalis. *International Journal of Trichology*, *10*(6), 286–288.

Hou, W., Jin, Y. H., Kang, H. S., & Kim, B. S. (2014). Interleukin-6 (IL-6) and IL-17 synergistically promote viral persistence by inhibiting cellular apoptosis and cytotoxic T cell function. *Journal of Virology*, *88*(15), 8479–8489. https://doi.org/10.1128/JVI.00724-14

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, *395*(10223), 497–506.

Ip, W. K., Chan, K. H., Law, H. K., Tso, G. H., Kong, E. K., Wong, W. H., To, Y. F., Yung, R. W., Chow, E. Y., Au, K. L., & Chan, E. Y. (2005). Mannose-binding lectin in severe acute respiratory syndrome coronavirus infection. *The Journal of Infectious Diseases*, *191*(10), 1697–1704.

Jamilloux, Y., Henry, T., Belot, A., Viel, S., Fauter, M., El Jammal, T., Walzer, T., François, B., & Sève, P. (2020). Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. *Autoimmunity Reviews*, *19*(7), 102567. https://doi.org/10.1016/j.autrev.2020.102567

Jayaraj, R. L., Azimullah, S., Beiram, R., Jalal, F. Y., & Rosenberg, G. A. (2019). Neuroinflammation: Friend and foe for ischemic stroke. *Journal of Neuroinflammation*, *16*(1), 142. https://doi.org/10.1186/s12974-019-1516-2

Jensen, S., & Thomsen, A. R. (2012). Sensing of RNA viruses: A review of innate immune receptors involved in recognizing RNA virus invasion. *Journal of Virology*, *86*(6), 2900–2910.

Jiang, Y., Zhao, G., Song, N., Li, P., Chen, Y., Guo, Y., Li, J., Du, L., Jiang, S., Guo, R., Sun, S., & Zhou, Y. (2018). Blockade of the C5a–C5aR axis alleviates lung damage in *hDPP4*-transgenic mice infected with MERS-CoV. *Emerg Microbes & Infections*, *7*(1), 77. https://doi.org/10.1038/s41426-018-0063-8

Jun, J. S., Lee, S. T., Kim, R., Chu, K., & Lee, S. K. (2018). Tocilizumab treatment for new onset refractory STATus epilepticus. *Annals of Neurology*, *84*(6), 940–945. https://doi.org/10.1002/ana.25374

Kalil, A. C., Patterson, T. F., Mehta, A. K., Tomashek, K. M., Wolfe, C. R., Ghazaryan, V., Marconi, V. C., Ruiz-Palacios, G. M., Hsieh, L., Kline, S., Tapson, V., Iovine, N. M., Jain, M. K., Sweeney, D. A., El Sahly, H. M., Branche, A. R., Pineda, J. R., Lye, D. C., Sandkovsky, U., … Beigel, J. H. (2020). Baricitinib plus remdesivir for hospitalized adults with Covid-19. *The New England Journal of Medicine*Epub ahead of print. https://doi.org/10.1056/NEJMoa2031994

Kalliolias, G. D., & Ivashkiv, L. B. (2016). TNF biology, pathogenic mechanisms and emerging therapeutic strategies. *Nature Reviews Rheumatology*, *12*(1), 49–62.

Kaltsonoudis, E., Zikou, A. K., Voulgari, P. V., Konitsiotis, S., Argyropoulou, M. I., & Drosos, A. A. (2014). Neurological adverse events in patients receiving anti-TNF therapy: A prospective imaging and electrophysiological study. *Arthritis Research & Therapy*, *16*(3), R125.

Kalueff, A. V., Lehtimaki, K. A., Ylinen, A., Honkaniemi, J., & Peltola, J. (2004). Intranasal administration of human IL-6 increases the severity of chemically induced seizures in rats. *Neuroscience Letters*, *365*(2), 106–110.

Kemanetzoglou, E., & Andreadou, E. (2017). CNS demyelination with TNF-α blockers. *Current Neurology and Neuroscience Reports*, *17*(4), 36. https://doi.org/10.1007/s11910-017-0742-1

Kenney-Jung, D. L., Vezzani, A., Kahoud, R. J., LaFrance-Corey, R. G., Ho, M. L., Muskardin, T. W., Wirrell, E. C., Howe, C. L., & Payne, E. T. (2016). Febrile infection-related epilepsy syndrome treated with anakinra. *Annals of Neurology*, *80*(6), 939–945. https://doi.org/10.1002/ana.24806

Kim, B. S., Jin, Y. H., Meng, L., Hou, W., Kang, H. S., Park, H. S., & Koh, C.-S. (2012). IL-1 signal affects both protection and pathogenesis of virus-induced chronic CNS demyelinating disease. *Journal of Neuroinflammation*, *9*, 217.

Kim, N. K., Choi, B. H., Huang, X., Snyder, B. J., Bukhari, S., Kong, T. H., Park, H., Park, H. C., Park, S. R., & Ha, Y. (2009). Granulocyte-macrophage colony-stimulating factor promotes survival of dopaminergic neurons in the 1-methyl-4-phenyl-1,-2,3,6-tetrahydropyridine-induced murine Parkinson's disease model. *The European Journal of Neuroscience*, *29*(5), 891–900. https://doi.org/10.1111/j.1460-9568.2009.06653.x

Kiyota, T., Machhi, J., Lu, Y., Dyavarshetty, B., Nemati, M., Yokoyama, I., Mosley, R. L., & Gendelman, H. E. (2018). Granulocyte-macrophage colony-stimulating factor neuroprotective activities in Alzheimer's disease mice. *Journal of Neuroimmunology*, *319*, 80–92. https://doi.org/10.1016/j.jneuroim.2018.03.009

Koh, J. C., Murugasu, A., Krishnappa, J., & Thomas, T. (2019). Favorable outcomes with early interleukin 6 receptor blockade in severe acute necrotizing encephalopathy of childhood. *Pediatric Neurology*, *98*, 80–84.

Kreutzfeldt, M., Bergthaler, A., Fernandez, M., Bruck, W., Steinbach, K., Vorm, M., Coras, R., Blümcke, I., Bonilla, W. V., Fleige, A., Forman, R., Müller, W., Becher, B., Misgeld, T., Kerschensteiner, M., Pinschewer, D. D., & Merkler, D. (2013). Neuroprotective intervention by IFN-γ blockade prevents $CD8^+$ T cell-mediated dendrite and synapse loss. *Journal of Experimental Medicine*, *210*(10), 2087–2103.

Kruger, C., Laage, R., Pitzer, C., Schabitz, W. R., & Schneider, A. (2007). The hematopoietic factor GM-CSF (granulocyte-macrophage colony-stimulating factor) promotes neuronal differentiation of adult neural stem cells in vitro. *BMC Neuroscience*, *8*, 88. https://doi.org/10.1186/1471-2202-8-88

Lagarde, S., Villeneuve, N., Trebuchon, A., Kaphan, E., Lepine, A., McGonigal, A., Roubertie, A., Barthez, M.-A. J., Trommsdorff, V., Lefranc, J., Wehbi, S., des Portes, V., Laguitton, V., Quartier, P., Scavarda, D., Giusiano, B., Milh, M., Bulteau, C., & Bartolomei, F. (2016). Anti-tumor necrosis factor alpha therapy (adalimumab) in Rasmussen's encephalitis: An open pilot study. *Epilepsia*, *57*(6), 956–966.

Lang, F. M., Lee, K. M., Teijaro, J. R., Becher, B., & Hamilton, J. A. (2020). GM-CSF-based treatments in COVID-19: Reconciling opposing therapeutic approaches. *Nature Reviews. Immunology*, *20*(8), 507–514.

Lawson, B. R., Gonzalez-Quintial, R., Eleftheriadis, T., Farrar, M. A., Miller, S. D., Sauer, K., McGavern, D. B., Kono, D. H., Baccala, R., & Theofilopoulos, A. N. (2015). Interleukin-7 is required for $CD4^+$ T cell activation and autoimmune neuroinflammation. *Clinical Immunology*, *161*(2), 260–269.

Lee, W. J., Lee, S. T., Moon, J., Sunwoo, J. S., Byun, J. I., Lim, J. A., Kim, T.-J., Shin, Y.-W., Lee, K.-J., Jun, J.-S., Lee, H. S., Kim, S., Park, K.-I., Jung, K.-H., Jung, K.-Y., Kim, M., Lee, S. K., & Chu, K. (2016). Tocilizumab in autoimmune encephalitis refractory to rituximab: An institutional cohort study. *Neurotherapeutics*, *13*(4), 824–832. https://doi.org/10.1007/s13311-016-0442-6

Li, Y., Li, H., Fan, R., Wen, B., Zhang, J., Cao, X., Wang, C., Song, Z., Li, S., Li, X., Lv, X., Qu, X., Huang, R., & Liu, W. (2016). Coronavirus infections in the central nervous system and respiratory tract show distinct features in hospitalized children. *Intervirology*, *59*(3), 163–169. https://doi.org/10.1159/000453066

Li, Y. C., Bai, W. Z., & Hashikawa, T. (2020). The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *Journal of Medical Virology*, *92*(6), 552–555. https://doi.org/10.1002/jmv.25728

Libbey, J. E., & Fujinami, R. S. (2014). Adaptive immune response to viral infections in the central nervous system. *Handbook of Clinical Neurology*, *123*, 225–247. https://doi.org/10.1016/B978-0-444-53488-0.00010-9

Liu, X., Lee, Y. S., Yu, C. R., & Egwuagu, C. E. (2008). Loss of STAT3 in $CD4^+$ T cells prevents development of experimental autoimmune diseases. *Journal of Immunology*, *180*(9), 6070–6076. https://doi.org/10.4049/jimmunol.180.9.6070

Liu, Y., Holdbrooks, A. T., De Sarno, P., Rowse, A. L., Yanagisawa, L. L., McFarland, B. C., Harrington, L. E., Raman, C., Sabbaj, S., Benveniste, E. N., & Qin, H. (2014). Therapeutic efficacy of suppressing the JAK/STAT pathway in multiple models of experimental autoimmune encephalomyelitis. *Journal of Immunology*, *192*(1), 59–72.

Luo, Z., Su, R., Wang, W., Liang, Y., Zeng, X., Shereen, M. A., Bashir, N., Zhang, Q., Zhao, L., Wu, K., Liu, Y., & Wu, J. (2019). EV71 infection induces neurodegeneration via activating TLR7 signaling and IL-6 production. *PLoS Pathogens*, *15*(11), e1008142. https://doi.org/10.1371/journal.ppat.1008142

Ma, C., Walters, B., & Fedorak, R. N. (2013). Varicella zoster meningitis complicating combined anti-tumor necrosis factor and corticosteroid therapy in Crohn's disease. *World Journal of Gastroenterology*, *19*(21), 3347–3351.

Mackall, C. L., Fry, T. J., & Gress, R. E. (2011). Harnessing the biology of IL-7 for therapeutic application. *Nature Reviews. Immunology*, *11*(5), 330–342. https://doi.org/10.1038/nri2970

Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Li, Y., & Hu, B. (2020). Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurology*, *77*(6), 683–690. https://doi.org/10.1001/jamaneurol.2020.1127

Marusic, S., Miyashiro, J. S., Douhan, J. 3rd, Konz, R. F., Xuan, D., Pelker, J. W., Ling, V., Leonard, J. P., & Jacobs, K. A. (2002). Local delivery of granulocyte macrophage colony-stimulating factor by retrovirally transduced antigen-specific T cells leads to severe, chronic experimental autoimmune encephalomyelitis in mice. *Neuroscience Letters*, *332*(3), 185–189.

Matschke, J., Lütgehetmann, M., Hagel, C., Sperhake, J. P., Schröder, A. S., Edler, C., Mushumba, H., Fitzek, A., Allweiss, L., Dandri, M., Dottermusch, M., Heinemann, A., Pfefferle, S., Schwabenland, M., Magruder, D. S., Bonn, S., Prinz, M., Gerloff, C., Püschel, K., … Glatzel, M. (2020). Neuropathology of patients with COVID-19 in Germany: A post-mortem case series. *Lancet Neurology*, *19*(11), 919–929.

McDermott, J. E., Mitchell, H. D., Gralinski, L. E., Eisfeld, A. J., Josset, L., Bankhead, A. 3rd, Neumann, G., Tilton, S. C., Schäfer, A., Li, C., Fan, S., McWeeney, S., Baric, R. S., Katze, M. G., & Waters, K. M. (2016). The effect of inhibition of PP1 and TNFα signaling on pathogenesis of SARS coronavirus. *BMC Systems Biology*, *10*(1), 93.

McNamara, L. A., Topaz, N., Wang, X., Hariri, S., Fox, L., & MacNeil, J. R. (2017). High risk for invasive meningococcal disease among patients

receiving eculizumab (Soliris) despite receipt of meningococcal vaccine. *MMWR. Morbidity and Mortality Weekly Report*, *66*(27), 734–737.

McQualter, J. L., Darwiche, R., Ewing, C., Onuki, M., Kay, T. W., Hamilton, J. A., Reid, H. H., & Bernard, C. C. (2001). Granulocyte macrophage colony-stimulating factor: A new putative therapeutic target in multiple sclerosis. *The Journal of Experimental Medicine*, *194*(7), 873–882. https://doi.org/10.1084/jem.194.7.873

Mehlhop, E., Whitby, K., Oliphant, T., Marri, A., Engle, M., & Diamond, M. S. (2005). Complement activation is required for induction of a protective antibody response against West Nile virus infection. *Journal of Virology*, *79*(12), 7466–7477.

Mevorach, D., Reiner, I., Grau, A., Ilan, U., Berkun, Y., Ta-Shma, A., Elpeleg, O., Shorer, Z., Edvardson, S., & Tabib, A. (2016). Therapy with eculizumab for patients with CD59 p.Cys89Tyr mutation. *Annals of Neurology*, *80*(5), 708–717. https://doi.org/10.1002/ana.24770

Monteiro, S., Ferreira, F. M., Pinto, V., Roque, S., Morais, M., de Sa-Calcada, D., Mota, C., Correia-Neves, M., & Cerqueira, J. J. (2016). Absence of IFNγ promotes hippocampal plasticity and enhances cognitive performance. *Translational Psychiatry*, *6*, e707. https://doi.org/10.1038/tp.2015.194

Moors, M., Vudattu, N. K., Abel, J., Kramer, U., Rane, L., Ulfig, N., Ceccatelli, S., Seyfert-Margolies, V., Fritsche, E., & Maeurer, M. J. (2010). Interleukin-7 (IL-7) and IL-7 splice variants affect differentiation of human neural progenitor cells. *Genes and Immunity*, *11*(1), 11–20. https://doi.org/10.1038/gene.2009.77

Morimoto, K., & Nakajima, K. (2019). Role of the immune system in the development of the central nervous system. *Frontiers in Neuroscience*, *13*, 916. https://doi.org/10.3389/fnins.2019.00916

Morrison, T. E., Fraser, R. J., Smith, P. N., Mahalingam, S., & Heise, M. T. (2007). Complement contributes to inflammatory tissue destruction in a mouse model of Ross River virus-induced disease. *Journal of Virology*, *81*(10), 5132–5143.

Mukerji, S. S., & Solomon, I. H. (2021). What can we learn from brain autopsies in COVID-19? *Neuroscience Letters*, *18*, 742:135528.

Muppidi, S., Utsugisawa, K., Benatar, M., Murai, H., Barohn, R. J., Illa, I., Jacob, S., Vissing, J., Burns, T. M., Kissel, J. T., Nowak, R. J., Andersen, H., Casasnovas, C., de Bleecker, J. L., Vu, T. H., Mantegazza, R., O'Brien, F. L., Wang, J. J., Fujita, K. P., … the Regain Study Group. (2019). Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. *Muscle & Nerve*, *60*(1), 14–24. https://doi.org/10.1002/mus.26447

Nicolas, C. S., Amici, M., Bortolotto, Z. A., Doherty, A., Csaba, Z., Fafouri, A., Dournaud, P., Gressens, P., Collingridge, G. L., & Peineau, S. (2013). The role of JAK-STAT signaling within the CNS. *JAKSTAT*, *2*(1), e22925.

Nunnari, G., Xu, Y., Acheampong, E. A., Fang, J., Daniel, R., Zhang, C., Zhang, H., Mukhtar, M., & Pomerantz, R. J. (2005). Exogenous IL-7 induces Fas-mediated human neuronal apoptosis: Potential effects during human immunodeficiency virus type 1 infection. *Journal of Neurovirology*, *11*(4), 319–328. https://doi.org/10.1080/13550280500187005

Okeke, F., Mone, A., & Swaminath, A. (2020). The course of SARS-COV2 infection was not severe in a Crohn's patient who administered maintenance anti-TNF therapy overlapping the early pre-symptomatic period of infection. *Antibodies (Basel)*, *9*(3), E42.

Osman, M., Emery, D., & Yacyshyn, E. (2015). Tocilizumab for treating Takayasu's arteritis and associated stroke: A case series and updated review of the literature. *Journal of Stroke and Cerebrovascular Diseases*, *24*(6), 1291–1298.

Oxenkrug, G. F. (2011). Interferon-gamma-inducible kynurenines/pteridines inflammation cascade: Implications for aging and aging-associated psychiatric and medical disorders. *Journal of Neural Transmission (Vienna)*, *118*(1), 75–85.

Ozdogan, H., Ugurlu, S., Uygunoglu, U., Tutuncu, M., Gul, A., Akman, G., & Silva, A. (2020). The efficacy of anti-IL-1 treatment in three patients with coexisting familial Mediterranean fever and multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *45*, 102332.

Paterson, R. W., Brown, R. L., Benjamin, L., Nortley, R., Wiethoff, S., Bharucha, T., Jayaseelan, D. L., Kumar, G., Raftopoulos, R. E., Zambreanu, L., Vivekanandam, V., Khoo, A., Geraldes, R., Chinthapalli, K., Boyd, E., Tuzlali, H., Price, G., Christofi, G., Morrow, J., … Zandi, M. S. (2020). The emerging spectrum of COVID-19 neurology: Clinical, radiological and laboratory findings. *Brain*, *143*(10), 3104–31208;awaa240. https://doi.org/10.1093/brain/awaa240

Planas, A. M., Justicia, C., & Ferrer, I. (1997). STAT1 in developing and adult rat brain. Induction after transient focal ischemia. *Neuroreport*, *8*(6), 1359–1362. https://doi.org/10.1097/00001756-199704140-00008

Ramakrishna, C., & Cantin, E. M. (2018). IFNγ inhibits G-CSF induced neutrophil expansion and invasion of the CNS to prevent viral encephalitis. *PLoS Pathogens*, *14*(1), e1006822.

Reoma, L. B., Trindade, C. J., Monaco, M. C., Solis, J., Montojo, M. G., Vu, P., Johnson, K., Beck, E., Nair, G., Khan, O. I., Quezado, M., Hewitt, S. M., Reich, D. S., Childs, R., & Nath, A. (2019). Fatal encephalopathy with wild-type JC virus and ruxolitinib therapy. *Annals of Neurology*, *86*(6), 878–884. https://doi.org/10.1002/ana.25608

Richardson, P. J., Ottaviani, S., Prelle, A., Stebbing, J., Casalini, G., & Corbellino, M. (2020). CNS penetration of potential anti-COVID-19 drugs. *Journal of Neurology*, *267*(7), 1880–1882. https://doi.org/10.1007/s00415-020-09866-5

Richebé, P., Bailly, F., Mariani, L. L., Pena, P. S., Pedespan, J. M., & Fautrel, B. (2018). Report of two cases of tocilizumab induced recurrent meningitis or meningoencephalitis. *Joint, Bone, Spine*, *85*(5), 643–644. https://doi.org/10.1016/j.jbspin.2018.01.002

Risner, K., Ahmed, A., Bakovic, A., Kortchak, S., Bhalla, N., & Narayanan, A. (2019). Efficacy of FDA-approved anti-inflammatory drugs against Venezuelan equine encephalitis virus infection. *Viruses*, *11*(12), 1151.

Roh, J. S., & Sohn, D. H. (2018). Damage-associated molecular patterns in inflammatory diseases. *Immune Network*, *18*(4), e27. https://doi.org/10.4110/in.2018.18.e27

Samoilova, E. B., Horton, J. L., Hilliard, B., Liu, T. S., & Chen, Y. (1998). IL-6-deficient mice are resistant to experimental autoimmune encephalomyelitis: Roles of IL-6 in the activation and differentiation of autoreactive T cells. *Journal of Immunology*, *161*(12), 6480–6486.

Sancho-Shimizu, V., Zhang, S. Y., Abel, L., Tardieu, M., Rozenberg, F., Jouanguy, E., & Casanova, J.-L. (2007). Genetic susceptibility to herpes simplex virus 1 encephalitis in mice and humans. *Current Opinion in Allergy and Clinical Immunology*, *7*(6), 495–505. https://doi.org/10.1097/ACI.0b013e3282f151d2

Schabitz, W. R., Kruger, C., Pitzer, C., Weber, D., Laage, R., Gassler, N., Aronowski, J., Mier, W., Kirsch, F., Dittgen, T., Bach, A., Sommer, C., & Schneider, A. (2008). A neuroprotective function for the hematopoietic protein granulocyte-macrophage colony stimulating factor (GM-CSF). *Journal of Cerebral Blood Flow and Metabolism*, *28*(1), 29–43.

Schneider, W. M., Chevillotte, M. D., & Rice, C. M. (2014). Interferon-stimulated genes: A complex web of host defenses. *Annual Review of Immunology*, *32*, 513–545.

Schwartz, D. M., Kanno, Y., Villarino, A., Ward, M., Gadina, M., & O'Shea, J. J. (2017). JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nature Reviews Drug Discovery*, *16*(12), 843–862. https://doi.org/10.1038/nrd.2017.201

Scott, I. C., Hider, S. L., & Scott, D. L. (2018). Thromboembolism with Janus kinase (JAK) inhibitors for rheumatoid arthritis: How real is the risk? *Drug Safety*, *41*(7), 645–653. https://doi.org/10.1007/s40264-018-0651-5

Scott, L. J. (2017). Sarilumab: First global approval. *Drugs*, *77*(6), 705–712. https://doi.org/10.1007/s40265-017-0724-2

Sergerie, Y., Rivest, S., & Boivin, G. (2007). Tumor necrosis factor-α and interleukin-1β play a critical role in the resistance against lethal herpes

simplex virus encephalitis. *The Journal of Infectious Diseases*, *196*(6), 853–860.

Sheng, J. R., Muthusamy, T., Prabhakar, B. S., & Meriggioli, M. N. (2011). GM-CSF-induced regulatory T cells selectively inhibit anti-acetylcholine receptor-specific immune responses in experimental myasthenia gravis. *Journal of Neuroimmunology*, *240-241*, 65–73.

Shultz, S. R., Tan, X. L., Wright, D. K., Liu, S. J., Semple, B. D., Johnston, L., Jones, N. C., Cook, A. D., Hamilton, J. A., & O'Brien, T. J. (2014). Granulocyte-macrophage colony-stimulating factor is neuroprotective in experimental traumatic brain injury. *Journal of Neurotrauma*, *31*(10), 976–983.

Smith, C. J., Hulme, S., Vail, A., Heal, C., Parry-Jones, A. R., Scarth, S., Hopkins, K., Hoadley, M., Allan, S. M., Rothwell, N. J., Hopkins, S. J., & Tyrrell, P. J. (2018). SCIL-STROKE (subcutaneous interleukin-1 receptor antagonist in ischemic stroke): A randomized controlled phase 2 trial. *Stroke*, *49*(5), 1210–1216. https://doi.org/10.1161/STROKEAHA.118.020750

Spath, S., Komuczki, J., Hermann, M., Pelczar, P., Mair, F., Schreiner, B., & Becher, B. (2017). Dysregulation of the cytokine GM-CSF induces spontaneous phagocyte invasion and immunopathology in the central nervous system. *Immunity*, *46*(2), 245–260. https://doi.org/10.1016/j.immuni.2017.01.007

Speth, C., Dierich, M. P., & Gasque, P. (2002). Neuroinvasion by pathogens: A key role of the complement system. *Molecular Immunology*, *38*(9), 669–679.

Stark, G. R., Cheon, H., & Wang, Y. (2018). Responses to cytokines and interferons that depend upon JAKs and STATs. *Cold Spring Harbor Perspectives in Biology*, *10*(1), a028555. https://doi.org/10.1101/cshperspect.a028555

Sterner, R. M., Sakemura, R., Cox, M. J., Yang, N., Khadka, R. H., Forsman, C. L., Hansen, M. J., Jin, F., Ayasoufi, K., Hefazi, M., Schick, K. J., Walters, D. K., Ahmed, O., Chappell, D., Sahmoud, T., Durrant, C., Nevala, W. K., Patnaik, M. M., Pease, L. R., … Kenderian, S. S. (2019). GM-CSF inhibition reduces cytokine release syndrome and neuroinflammation but enhances CAR-T cell function in xenografts. *Blood*, *133*(7), 697–709.

Sun, Y., Wang, D., Salvadore, G., Hsu, B., Curran, M., Casper, C., Vermeulen, J., Kent, J. M., Singh, J., Drevets, W. C., Wittenberg, G. M., & Chen, G. (2017). The effects of interleukin-6 neutralizing antibodies on symptoms of depressed mood and anhedonia in patients with rheumatoid arthritis and multicentric Castleman's disease. *Brain, Behavior and Immunity*, *66*, 156–164.

Tan, L., Wang, Q., Zhang, D., Ding, J., Huang, Q., Tang, Y. Q., Wang, Q., & Miao, H. (2020). Lymphopenia predicts disease severity of COVID-19: A descriptive and predictive study. *Signal Transduction and Targeted Therapy*, *5*(1), 33.

Terada, Y., Kamoi, K., Ohno-Matsui, K., Miyata, K., Yamano, C., Coler-Reilly, A., & Yamano, Y. (2017). Treatment of rheumatoid arthritis with biologics may exacerbate HTLV-1-associated conditions: A case report. *Medicine (Baltimore)*, *96*(6), e6021.

Tsuboi, K., Kimura, T., Sugiura, K., Hashimoto, I., Nishikawa, M., Uyama, M., & Fujisawa, J. I. (1998). Granulocyte-macrophage colony-stimulating factor expressed in T cells mediates immunity against herpes simplex virus type 1 encephalitis. *Journal of Infectious Diseases*, *178*(1), 16–26.

Tucci, F., Gallo, V., Barzaghi, F., Ferrua, F., Migliavacca, M., Calbi, V., Doglio, M., Fratini, E. S., Karakas, Z., Guner, S., Zambelli, M., Parisi, C., Milani, R., Gattillo, S., Mazzi, B., Oltolini, C., Barbera, M., Baldoli, C., Cirillo, D. M., … Bernardo, M. E. (2020). Treatment with emapalumab in an ADA-SCID patient with refractory hemophagocytic lymphohistiocytosis-related graft failure and disseminated BCGitis. *Haematologica*, Online Ahead of Print, 255620.

Uciechowski, P., & Dempke, W. C. M. (2020). Interleukin-6: A masterplayer in the cytokine network. *Oncology*, *98*(3), 131–137. https://doi.org/10.1159/000505099

Uzawa, A., Mori, M., Sawai, S., Masuda, S., Muto, M., Uchida, T., Ito, S., Nomura, F., & Kuwabara, S. (2013). Cerebrospinal fluid interleukin-6 and glial fibrillary acidic protein levels are increased during initial neuromyelitis optica attacks. *Clinica Chimica Acta*, *421*, 181–183.

van der Hoek, L. (2007). Human coronaviruses: What do they cause? *Antiviral Therapy*, *12*(4 Pt B), 651–658.

Veerhuis, R., Nielsen, H. M., & Tenner, A. J. (2011). Complement in the brain. *Molecular Immunology*, *48*(14), 1592–1603.

Vezzani, A., Fujinami, R. S., White, H. S., Preux, P. M., Blumcke, I., Sander, J. W., & Löscher, W. (2016). Infections, inflammation and epilepsy. *Acta Neuropathologica*, *131*(2), 211–234.

Wang, W. Y., Tan, M. S., Yu, J. T., & Tan, L. (2015). Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. *Annals of Translational Medicine*, *3*(10), 136.

Winthrop, K. L., Melmed, G. Y., Vermeire, S., Long, M. D., Chan, G., Pedersen, R. D., Lawendy, N., Thorpe, A. J., Nduaka, C. I., & Su, C. (2018). Herpes zoster infection in patients with ulcerative colitis receiving tofacitinib. *Inflammatory Bowel Diseases*, *24*(10), 2258–2265. https://doi.org/10.1093/ibd/izy131

Yamaguchi, Y., Furukawa, K., Yamamoto, T., Takahashi, Y., Tanaka, K., & Takahashi, M. (2014). Multifocal encephalopathy and autoimmune-mediated limbic encephalitis following tocilizumab therapy. *Internal Medicine*, *53*(8), 879–882.

Yamashita, M., Yamate, M., Li, G. M., & Ikuta, K. (2005). Susceptibility of human and rat neural cell lines to infection by SARS-coronavirus. *Biochemical and Biophysical Research Communications*, *334*(1), 79–85.

Yang, Y., Shen, C., Li, J., Yuan, J., Wei, J., Huang, F., Wang, F., Li, G., Li, Y., Xing, L., Peng, L., Yang, M., Cao, M., Zheng, H., Wu, W., Zou, R., Li, D., Xu, Z., Wang, H., … Liu, Y. (2020). Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. *The Journal of Allergy and Clinical Immunology*, *146*(1), 119, e114–127. https://doi.org/10.1016/j.jaci.2020.04.027

Ye, J., Jiang, R., Cui, M., Zhu, B., Sun, L., Wang, Y., Zohaib, A., Dong, Q., Ruan, X., Song, Y., He, W., Chen, H., & Cao, S. (2014). Etanercept reduces neuroinflammation and lethality in mouse model of Japanese encephalitis. *The Journal of Infectious Diseases*, *210*(6), 875–889.

How to cite this article: Pignataro, G., Cataldi, M., & Taglialatela, M. (2022). Neurological risks and benefits of cytokine-based treatments in coronavirus disease 2019: from preclinical to clinical evidence. *British Journal of Pharmacology*, *179*(10), 2149–2174. https://doi.org/10.1111/bph.15397