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

GIUSEPPE PIGNATARO[1], Mauro Cataldi[1], and Maurizio Taglialatela[1]

[1]Università degli Studi di Napoli Federico II

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Abstract

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

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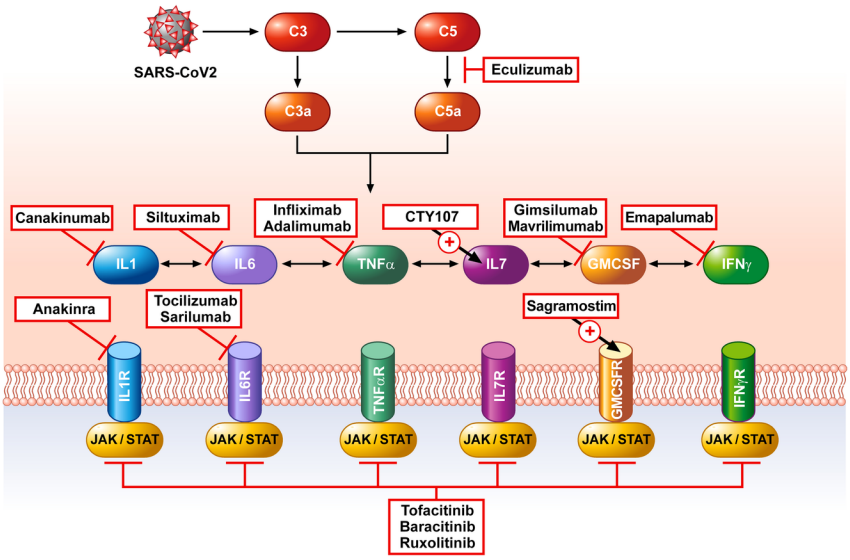

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Table 3. NEUROINFLAMMATION AND CYTOKINE-TARGETED INTERVENTIONS : Targeting TNF-α

Target	Drug	Main Indications	CT Number , Title, Study Protocol	Neurological Implications
TNF-α	**Infliximab** Anti-TNF-α antibody	•Rheumatoid Arthritis •Psoriatic Arthritis •Plaque Psoriasis •Crohn Disease •Ulcerative Colitis •Ankylosing Spondylitis •Idiopathic Pulmonary Fibrosis (Orphan)	**NCT04425538** A Phase 2 Trial of Infliximab in Coronavirus Disease 2019 (COVID-19). **Interventional Phase 2**	Not approved for any neurological condition. May cause a variety of neuroimmune adverse events, such as optic neuritis, chronic inflammatory demyelinating polyneuropathy, mononeuritis multiplex, Guillain-Barré syndrome (Kemanetzoglou et al., 2017), vasculitis and amyloidosis (Theibich et al., 2014), and serious encephalitis, mainly of herpetic etiology (Bradford et al., 2009). May cause herpes zoster reactivation (Strangfeld et al.,2009).
	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**	Athough not approved for any neurological condition, it has been successfully used in **Rasmussen encephalitis** (Lagarde et al., 2016). However, demyelinating disorders, herpes zoster reactivation and herpes zoster meningitis have been associated with its use (Bradford et al., 2009; Ma et al., 2013; Strangfeld et al.,2009; Zhu et al., 2016).

Table 4. NEUROINFLAMMATION AND CYTOKINE-TARGETED INTERVENTIONS : Targeting IFN-γ				
Target	**Drug**	**Main Indications**	**CT Number , Title, Study Protocol**	**Neurological Implications**
IFN-γ	**Emapalumab** Anti-IFN-γ antibody	•Primary Hemophagocytic 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 patients affected by Adenosine Deaminase Deficiency-Severe Combined Immunodeficiency (ADA-SCID), emapalumab reduced the size of brain lesions caused by CNS Tubercolosis infection (Tucci et al., 2020).

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Table 7. NEUROINFLAMMATION AND CYTOKINE-TARGETED INTERVENTIONS : Targeting IL-7

Target	Drug	Main Indications	CT Number , Title, Study Protocol	Neurological Implications
IL-7	**CYT-107** Recombinant Interleukin-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) (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) (ILIAD-7-US-I) **Interventional Phase 2**	IL-7 is effective in patients with **progressive multifocal leukoencephalopathy** caused by JC polyomavirus (Alstadhaug et al., 2014). May also exert proinflammatory activity (Ziegler et al., 1991) during spinal trauma (Bao et al., 2018), and promote the autoimmune aggression of the CNS in EAE mice (Lawson et al., 2015,Walline et al., 2011).

Table 8. NEUROINFLAMMATION AND CYTOKINE-TARGETED INTERVENTIONS : Targeting Complement System

Target	Drug	Main Indications	CT Number , Title, Study Protocol	Neurological Implications
Complement System	**Eculizumab** Anti-C5 antibody	• Paroxysmal nocturnal hemoglobinuria • Atypical hemolytic uremic 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** (Carparini et al., 2019), and **myasthenia gravis** (Frampton, 2020). Effective in 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).