

Table 2. NEUROINFLAMMATION AND CYTOKINE-TARGETED INTERVENTIONS : Targeting IL-6

Target	Drug	Main Indications	CT Number , Title, Study Protocol	Neurological Implications
<p>IL-6</p>	<p>Tocilizumab Anti-IL-6- Receptor monoclonal antibody</p>	<ul style="list-style-type: none"> • Rheumatoid arthritis • Giant cell arteritis • Cytokine release syndrome (CRS) 	<p>NCT04377659 Tocilizumab for Prevention of Respiratory Failure in Patients With Severe COVID-19 Infection Interventional Phase 2</p>	<p>Effective in several neurological diseases, including neuromyelitis optica (Araki et al., 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 (Fiala et al., 2013; Mizwicki et al., 2012). Favorable clinical response also 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 (Richebè et al., 2018), HTLV1-associated myelopathy/tropical spastic paraparesis (Terada et al., 2017), and multifocal and limbic encephalitis (Yamagouchi et al., 2014), each shown in a few case reports.</p>
			<p>NCT04322773 Anti-il6 Treatment of Serious COVID-19 Disease With Threatening Respiratory Failure (TOCIDVID) Interventional Phase 2</p>	
			<p>NCT04445272 Clinical Trial to Evaluate the Effectiveness and Safety of Tocilizumab for Treating Patients With COVID-19 Pneumonia Interventional Phase 2</p>	
			<p>NCT04479358 Low-dose Tocilizumab Versus Standard of Care in Hospitalized Patients With COVID-19 (COVIDOSE-2) Interventional Phase 2</p>	
			<p>NCT04331795 Tocilizumab to Prevent Clinical Decompensation in Hospitalized, Non-critically Ill Patients With COVID-19 Pneumonitis (COVIDOSE) Interventional Phase 2</p>	
			<p>NCT04370834 Tocilizumab for Patients With Cancer and COVID-19 Disease Interventional Phase 2</p>	
			<p>NCT04335071 Tocilizumab in the Treatment of Coronavirus Induced Disease (COVID-19) (CORON-ACT) Interventional Phase 2</p>	
			<p>NCT04423042 Tocilizumab in Coronavirus-19 Positive Patients Interventional Phase 2</p>	
			<p>NCT04320615 A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA) Interventional Phase 3</p>	

Table 2 Continued (I)

Target	Drug	Main Indications	CT Number , Title, Study Protocol	Neurological Implications
IL-6	Tocilizumab		<p>NCT04315480 Tocilizumab for SARS-CoV2 (COVID-19) Severe Pneumonitis Interventional Phase 2</p>	
			<p>NCT04476979 Comparison of Tocilizumab Plus Dexamethasone vs. Dexamethasone for Patients With Covid-19 (TOCIDEX) Interventional Phase 2</p>	
			<p>NCT04435717 Efficacy of Tocilizumab in Modifying the Inflammatory Parameters of Patients With COVID-19 (COVIT0Z-01) (COVIT0Z-01) Interventional Phase 2</p>	
			<p>NCT04346355 Efficacy of Early Administration of Tocilizumab in COVID-19 Patients Interventional Phase 2</p>	
			<p>NCT04317092 Tocilizumab in COVID-19 Pneumonia (TOCIDVID-19) (TOCIDVID-19) Interventional Phase 2</p>	
			<p>NCT04412772 A RCT - Safety & Efficacy of Tocilizumab - Tx of Severe COVID-19: ARCHITECTS (ARCHITECTS) Interventional Phase 3</p>	
			<p>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</p>	
			<p>NCT04403685 Safety and Efficacy of Tocilizumab in Moderate to Severe COVID-19 With Inflammatory Markers (TOCIBRAS) Interventional Phase 3</p>	

Table 2 Continued (II)

Target	Drug	Main Indications	CT Number , Title, Study Protocol	Neurological Implications
<p>IL-6</p>	<p>Sarilumab Anti-IL-6- Receptor monoclonal antibody</p>	<ul style="list-style-type: none"> • Rheumatoid Arthritis 	<p>NCT04357808 Efficacy of Subcutaneous Sarilumab in Hospitalised Patients With Moderate-severe COVID-19 Infection (SARCOVID) (SARCOVID) Interventional Phase 2</p>	<p>Sarilumab treatment improved outcomes for pain, social functioning, and mood in patients affected by rheumatoid arthritis (Atzeni et al., 2019).</p>
			<p>NCT04386239 Study on the Use of Sarilumab in Patients With COVID-19 Infection Interventional Phase 1</p>	
			<p>NCT04315298 Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19 Interventional Phase 2/3</p>	
			<p>NCT04359901 Sarilumab for Patients With Moderate COVID-19 Disease Interventional Phase 2</p>	
			<p>NCT04341870 Study of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients: Sarilumab, Azithromycin, Hydroxychloroquine Trial - CORIMUNO-19 - VIRO (CORIMUNO-VIRO) Interventional Phase 2/3</p>	
			<p>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</p>	
			<p>NCT04357860 Clinical Trial of Sarilumab in Adults With COVID-19 (SARICOR) Interventional Phase 2</p>	
	<p>Siltuximab Anti-IL-6 monoclonal antibody</p>	<ul style="list-style-type: none"> • Castleman Disease 	<p>NCT04329650 Efficacy and Safety of Siltuximab vs. Corticosteroids in Hospitalized Patients With COVID-19 Pneumonia Interventional Phase 2</p>	<p>A clinical trial in patients with rheumatoid arthritis or multicentric Castleman’s disease showed that siltuximab was able to ameliorate depressive symptoms independently on anti-rheumatic effects (Sun et al., 2017).</p>