

Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Anti-IL6R: Tocilizumab, Satralizumab, Sarilumab, Olokizumab, Vobarilizumab Anti-IL6: Siltuximab, Sirukumab, Clazakizumab

Evidence Summary

Beneficial for peripheral inflammatory conditions driven by IL-6 mediated pathology, but not well-suited for CNS compartmentalized inflammation, and suppress the immune system's ability to fight pathogens.

Neuroprotective Benefit: Can only reduce IL-6 mediated inflammation in the CNS if the BBB is disrupted. Effects of IL-6 in CNS are context dependent, so blocking IL-6 could improve or impair cognition in different patient populations.

Aging and related health concerns: Mixed effects on cardiovascular health by raising LDL-c, while reducing Lp(a) and improving the function of HDL-c. May protect against IL-6 mediated heart damage, but have no clear benefit in cancer.

Safety: Suppress immune system and pose risks for undetected infections that can become serious. Reduce blood cell counts and raise blood lipid levels. May also lead to gastrointestinal perforations or elevated liver transaminases.



Availability: Rx (tocilizumab, sarilumab, satralizumab, siltuximab) Clinical trials (clazakizumab, olokizumab)	Dose: Tocilizumab 8 mg/kg q4w IV or 162 mg SC qw/q2w Sarilumab 200 mg/1.14mL SC q2w Siltuximab 11 mg/kg IV q3w	Monoclonal Antibodies 144-148 kDa Nanobody (Vobarilizumab) 26 kDa
Half-life: Concentration dependent Tocilizumab: up to 13 days (8mg/kg dose) Sarilumab: up to 10 days (200 mg dose) Siltuximab: average 20.6 days Olokizumab: approx. 31 days Clazakizumab: approx. 30 days	BBB: Not penetrant	
Clinical trials: Successful Phase 3 RCTs for Tocilizumab: rheumatoid arthritis (range n= 499 to 1196) and giant cell arteritis (n=251); Sarilumab: rheumatoid arthritis (range n=369 to 1675) Satralizumab: neuromyelitis optica (n=83, 95); Olokizumab: rheumatoid arthritis (n=428)	Observational studies: Observational, cohort, and database studies on cardiovascular or malignancy risks of tocilizumab-treated arthritis patients	

What is it?

Interleukin-6 (IL-6) is a cytokine that has pleiotropic roles throughout the body, but is most frequently associated with inflammation. IL-6 can bind to the membrane bound or soluble IL-6 receptors (IL-6R) to activate the classical or trans signaling cascades, respectively. The IL-6R lacks intrinsic signaling capacity, and the activated IL-6/6R complex must bind to gp130 to initiate downstream signaling cascades, including the JAK/STAT, ERK, and P13K/AKT pathways [1]. The membrane bound IL-6R is only present on hepatocytes, monocytes, neutrophils, and leukocytes. In classical signaling, IL-6 binds to membrane bound IL-6R, which then binds to the ubiquitously expressed signal transducing membrane protein gp130, leading to its dimerization and activation. The classical pathway is associated with regenerative and protective effects. Meanwhile, in the trans pathway, circulating soluble IL-6R binds to IL-6 to form a complex that binds to gp130, and initiates pro-inflammatory signaling cascades.

Anti-IL-6 and IL-6R monoclonal antibodies (mAbs) have been developed to reduce chronic IL-6 mediated inflammatory signaling, however, these antibodies do not specifically target the trans signaling pathway, and thus can also negatively impact the beneficial functions of IL-6 [2]. These mAbs have **primarily been developed for chronic inflammatory autoimmune conditions** such as rheumatoid arthritis and neuromyelitis optica, but have also been tested in cancer, lymphoproliferative disorders, cardiovascular disease, depression, and schizophrenia.

Anti-IL-6R mAbs

Tocilizumab (trade name Actrema®) is the first-generation anti-IL-6R mAb. It is approved for adults with rheumatoid arthritis and inadequate response to one or more therapies, giant cell arteritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and cytokine release syndrome. It acts to inhibit binding between IL-6 and IL-6R [2].

Sarilumab (trade name Kevzara®) is approved for adults with rheumatoid arthritis and inadequate response to one or more therapies. It acts to inhibit binding between IL-6 and IL-6R [2].

Satralizumab is approved for neuromyelitis optica. It is a second-generation anti-IL-6R mAb designed to have enhanced antigen-neutralizing capacity and a longer plasma half-life relative to tocilizumab.

Olokizumab is being developed for rheumatoid arthritis. It acts to inhibit binding between the IL-6/6R complex with gp130, and increases systemic levels of free IL-6 to a lesser degree than mAbs that block the interaction between IL-6 with IL-6R [2].

Vobarilizumab (ALX-00061) is a nanobody that is six times smaller than the anti-IL-6R mAbs, which allows for better tissue penetration and bioavailability. It was projected to more specifically target the pathogenic IL-6 trans-signaling pathway because it has 2,500-fold higher affinity for the soluble IL-6R compared with tocilizumab. It was being developed for chronic inflammatory autoimmune conditions, including rheumatoid arthritis and lupus, however, development appears to have been discontinued following unsuccessful clinical trials for these indications.

Anti- IL-6 mAbs

Siltuximab (trade name Sylvant®) is approved for patients with multicentric Castleman's disease seronegative for HIV and HHV-8.

Sirukumab was being developed for rheumatoid arthritis, but development appears to have been discontinued following its failure to be approved due to safety concerns.

Clazakizumab is being developed for antibody mediated rejection in transplant patients. It blocks the interaction of IL-6 with IL-6R [2].

Neuroprotective Benefit: Can only reduce IL-6 mediated inflammation in the CNS if the BBB is disrupted. Effects of IL-6 in CNS are context dependent, so blocking IL-6 could improve or impair cognition in different patient populations.

Types of evidence:

- 1 meta-analysis: RCTs for cytokine therapy for chronic inflammatory disease for anti-depressant activity
- 5 clinical trials: RCTs for Depression [sirukumab], Schizophrenia [tocilizumab], Neuromyelitis optica [satralizumab]
- 1 post-hoc analysis of RCTs for sirukumab and siltuximab (for Depression)
- 2 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Depression: Benefit for people with chronic inflammatory disorder + comorbid depression

Inflammation is hypothesized to play a role in the etiology of depression based on the findings that people with major depressive disorder often have elevated levels of inflammatory cytokines, and that individuals with inflammation driven chronic physical diseases, such as rheumatoid arthritis, have higher rates of depression [3]. The cognitive dysfunction associated with depression has been found to be correlated with levels of these pro-inflammatory mediators, suggesting that reducing pro-inflammatory cytokine signaling may improve cognitive function [4]. Meta-analyses of clinical trials of chronic inflammatory conditions have shown that, relative to placebo, anti-cytokine treatments exert a significant anti-depressant effect [3]. Notably, the anti-depressant effect was not significantly associated with improvement in the chronic physical illness, but was associated with the severity of depression at baseline. While most of these trials tested TNF α inhibitors, other anti-cytokine therapies, including the anti-IL-6R mAb tocilizumab, also showed evidence for anti-depressant activity based on meta-analytic effect estimates (Standardized mean difference SMD: 0.31, 95% Confidence Interval (CI) 0.20 to 0.42) [3]. A post-hoc analysis of RCTs found that the anti-IL-6 mAbs, sirukumab and siltuximab, **improved depressive symptoms scores in patients with rheumatoid arthritis and Castleman's disease**, respectively [5]. Similar to tocilizumab, improvement was only seen in patients with baseline depression, was not associated with physical symptom responses, and correlated with baseline levels of IL-6R (>45 ng/mL).

Several meta-analyses have identified the cytokine IL-6 as one of the major pro-inflammatory mediators elevated in patients with depression [6; 7; 8; 9]. However, a 12-week double-blind placebo-controlled RCT testing sirukumab as an adjunct to antidepressant therapy in patients with **major depressive disorder** and high inflammation based on high-sensitivity C-reactive protein (hsCRP ≥ 3 mg/L) **failed to meet its primary endpoint** based on change on the Hamilton Depression Rating Scale (HDRS17) [10]. Sirukumab **did significantly improve anhedonia** (Least Squares Mean Difference 3.0; $p = 0.014$), with a greater effect seen in patients with the highest baseline hsCRP. These results suggest that IL-6 may be specifically related to anhedonia, or that the etiology of comorbid depression in patients with chronic inflammatory diseases may be distinct from those with depression alone. Tocilizumab will be tested in combination with whole body hyperthermia in an upcoming Phase 2 RCT in patients with major depressive disorder ([NCT03787290](https://clinicaltrials.gov/ct2/show/study/NCT03787290)).

Human research to suggest benefits to patients with dementia: None



Mechanisms of action for neuroprotection identified from laboratory and clinical research:

IL-6 is present at low levels in the brain under physiological conditions, and is increased in the context of various neurological and neurodegenerative conditions [11]. **IL-6 plays mixed roles within the CNS**, contributing to neural cell survival and synaptic function, as well as neuroinflammatory processes [12]. IL-6 mediated neurodegenerative processes are dependent on trans-signaling, while classical signaling may be neuroprotective. However, **the effects of IL-6 on CNS function and cognition depend on brain region, cell type, cytokine level, and physiological context**. The differences can likely be attributed to differences in downstream signaling following receptor activation, since IL-6 impinges on three major signaling pathways: JAK/STAT, ERK, and PI3K/AKT. A study in rodents found that physiological levels of IL-6 promote cognitive flexibility in the frontal cortex, but at higher concentrations the enhancement of cortical excitability could become pathogenic and result in excitotoxicity [13]. Consequently, under some conditions, the neutralization of IL-6 within the CNS could impair cognitive function. The context dependent diversity of functions for IL-6 may explain the underwhelming performance of anti-IL-6/6R mAbs for a variety of indications in clinical trials, as it would be expected that these therapies would only benefit the subset of patients in which disease pathology was driven by increased IL-6 signaling.

Cytokine-release mediated neurotoxicity: Mixed benefit/harm

Cytokine release syndrome involves systemic toxicity due to the rapid release of high levels of cytokines into the blood following treatment with some types of immunotherapy, particularly CAR-T cells [14]. Tocilizumab is approved for the management of severe cytokine release syndrome, however, in some patients, it can lead to a worsening of neurotoxicity. This may occur because **tocilizumab can increase peripheral free levels of IL-6** by saturating IL-6R, and this IL-6 can freely traverse into the CNS [15]. The inability of tocilizumab to cross the blood-brain barrier (BBB) at appreciable quantities means that the excess IL-6 can bind IL-6R and activate downstream inflammatory signaling pathways within the CNS. A study in rhesus monkeys confirmed that when the BBB is intact, the concentration of tocilizumab in the cerebrospinal fluid (CSF) (C_{max} 0.097 µg/mL) following intravenous (IV) administration (at Human equivalent dose (HED) 8 mg/kg) was far below the level necessary to completely inhibit IL-6R (4 µg/mL). Intraventricular administration (HED 40 mg) was necessary to obtain concentrations (C_{max} 6.95 µg/mL) associated with clinically significant IL-6R inhibition [15]. This suggests that **in the absence of BBB disruption, peripherally administered anti-IL-6R mAbs could potentially worsen IL-6 mediated neuroinflammation** in some cases, and direct CNS administration is necessary to have a therapeutic effect within the CNS.

Schizophrenia: No benefit for chronic stable disease

Inflammation has been implicated in the pathophysiology of schizophrenia. A meta-analysis found that IL-6 was significantly elevated in first episode or acutely relapsed schizophrenic patients, and that IL-6 levels decrease in response to treatment [16]. An open-label trial in 5 schizophrenic patients failed to find a significant improvement on psychopathology scores following 8 weeks of tocilizumab (4 mg/kg IV q4w) [17]. In a placebo controlled, double-blind, 12-week RCT in **clinically stable schizophrenic patients** (n=36), tocilizumab (8 mg/kg IV q4w) also **failed to meet its primary endpoint** of a significant effect on the Positive and Negative Symptoms Scale (PANSS) total score, and led to a worsening on the negative symptoms subscale relative to placebo (+1.93 points, p=0.004) [18]. Although tocilizumab treatment reduced CRP levels, the reduction in inflammatory markers was not associated with treatment outcomes. The lack of efficacy may stem from the inability of anti-IL6R mAbs to cross the BBB, so they may not adequately neutralize IL-6 signaling in the CNS. Alternatively, it may be related to the clinical population, as IL-6 was found to be associated with disease activity only in those with acute-relapse or unmedicated, and thus IL-6 may be less relevant to symptoms in clinically stable patients. Siltuximab is also being tested in an ongoing clinical trial in clinically stable schizophrenic patients as an adjunct to antipsychotics. It will be informative to see how the efficacy of the anti-IL-6 mAb compares to the anti-IL-6R mAb for this indication.

Demyelinating disorders: Benefit of anti-IL6R mAbs for NMOSD

TNF α inhibitors are reported to increase the risk for demyelinating disorders, meanwhile, non-TNF α targeted anti-cytokine biologics, including tocilizumab, are not associated with this increased risk, and may be beneficial [19]. Anti-IL6R mAbs have shown efficacy for neuromyelitis optica spectrum disorders (NMOSD), which are characterized by demyelination of the optic nerve and/or spinal cord. The biologics license application for satralizumab was approved in October 2019 based on the positive results of two Phase 3 RCTs (SAkuraSky and SAkuraStar) [20; 21]. Although these biologics are not BBB penetrant, patients with NMOSD have leaky CNS barriers, thus they would be expected to obtain higher CNS concentrations of anti-IL-6R mAbs. The reduction in IL-6 mediated signaling subsequently reduces the leakiness of the CNS barriers, and thus reduces the infiltration of pathogenic leukocytes.

Alzheimer's disease: Potential context dependent benefit (preclinical)

In male rats, intraventricular administration of tocilizumab (1.5 mg/kg) 1 hour prior to the induction of streptozotocin-induced cognitive impairment largely prevented the reduction in learning and memory based on the Morris water maze and passive avoidance test [22]. Tocilizumab pretreatment also

reduced the streptozotocin-mediated increase in amyloid in the cortex (1.3 ± 0.1 vs 3.5 ± 0.2 fold relative to control). It has not been established whether anti-IL6R mAbs would be protective in slowing cognitive decline after the onset of pathology, or whether chronic treatment may exacerbate cognitive decline in the context of established disease, particularly in individuals/models where IL-6 is not highly elevated. It is possible that only a subset of patients with Alzheimer's disease with pathologically high IL-6 mediated signaling may benefit from treatment with anti-IL-6 therapies which reduce but do not fully neutralize IL-6.

Post-operative cognitive decline: Potential benefit with CNS administration (preclinical)

IL-6 is sufficient to produce cognitive deficits in preclinical models, and IL-6 has been shown to be up-regulated in response to the trauma of surgery [23]. In aged male rats (24 months), tocilizumab (intracisternal) delivered at the time of surgery (laparotomy) attenuated cognitive deficits following surgery based on Morris water maze performance [24]. The protection was associated with an attenuation of pro-inflammatory cytokine induction.

APOE4 interactions:

The ApoE4 genotype is associated with higher levels of pro-inflammatory cytokines, suggesting that ApoE4 carriers may preferentially benefit from therapies that lower cytokine driven neuroinflammation. Transgenic mice expressing the ApoE4 allele have higher levels of the pro-inflammatory cytokines TNF α and IL-6 [25]. ApoE4 carriers in China (Han and She populations) were also found to have increased levels of TNF α , IL-6, and IL-1 β , which was associated with increased susceptibility for Alzheimer's disease [26]. Since anti-IL-6/6R mAbs are not BBB penetrant, they are unlikely to significantly reduce IL-6 mediated inflammatory signaling within the CNS, and are thus unlikely to be effective for reducing neuroinflammation. Furthermore, the rise in circulating levels of IL-6 following anti-IL-6R mAb administration could potentially exacerbate neuroinflammation in some people.

Aging and related health concerns: Mixed effects on cardiovascular health by raising LDL-c, while reducing Lp(a) and improving the function of HDL-c. May protect against IL-6 mediated heart damage, but have no clear benefit in cancer.

Types of evidence:

- 7 meta-analyses: RCTs for RA (n=14) using tocilizumab, sarilumab, or sirukumab; RCTs and cohort studies (n=19) for RA using DMARDs assessing cardiovascular adverse events; RCTs for RA using DMARDs assessing malignancy risk
- 1 Systematic review: RCTs for RA (n=10) using DMARDs assessing insulin resistance
- 37 clinical trials: Clazakizumab (n=2) for RA (Phase 2b) and psoriatic arthritis (Phase 2b); Olokizumab (n=2) Phase 3 for RA; Vobarilizumab (n=2) Phase 2b for RA; Siltuximab (n=15) Phase 1 and 2 for cancer and Castleman's disease; Tocilizumab (n=16) Phase 2 for myocardial infarction and giant cell arteritis, trials in RA assessing cardiovascular outcomes
- 4 observational studies: Tocilizumab in RA patients for cardiovascular risk and protection; pain and fatigue
- Numerous laboratory studies

Rheumatoid Arthritis: Benefit

The anti-IL-6R mAbs **tocilizumab** and **sarilumab** are approved for rheumatoid arthritis (RA) in patients who have failed one or more disease modifying anti-rheumatic drugs (DMARDs) and have similar efficacy based on the ACR50 response rate [27], while the anti-IL-6R mAbs clazakizumab and vobarilizumab, and anti-IL-6 mAbs sirukumab and olokizumab have also been tested in RA patients, and were found to have similar or lower efficacy relative to tocilizumab. Clazakizumab was found to have similar efficacy to a TNF α inhibitor in RA patients in a Phase 2b RCT (n=418), but was associated with higher rates of serious adverse events and discontinuations [28]. In a Phase 2b RCT (n=165) for active psoriatic arthritis, clazakizumab improved musculoskeletal but not skin manifestations, with no clear evidence of a dose response [29]. Sirukumab was denied approval due to safety concerns ([Drugs.com](https://www.fda.gov/drugs/development-resources/sirukumab-denied-approval)), and vobarilizumab failed its primary endpoint in a Phase 2b trial (n=345) ([Ablynx presentation](#)). Olokizumab was found to have similar efficacy to tocilizumab [30] and recently completed its first successful Phase 3 RCT [31]. Based on available evidence, there is **no indication that there is a significant clinical difference between targeting IL-6 or targeting IL-6R**.

Cardiovascular Disease: Potential benefit/Mixed

RA patients are at two times higher risk for cardiovascular disease relative to the general population due to a higher prevalence of cardiovascular risk factors and chronic low-grade inflammation [32]. It has been hypothesized that subclinical cardiovascular dysfunction could be part of the pathological profile of RA [33]. A prospective study found that RA patients without cardiac symptoms had higher levels of the heart failure biomarker NT-proBNP at baseline (median 109.0 pg/mL vs 42.5 pg/mL) relative to controls, and NT-proBNP levels decreased in association with the decrease in disease activity (DAS28 score) following 24 weeks of tocilizumab treatment [33]. The post-hoc analysis of an RCT for conventional DMARDs with or without tocilizumab found that the decline in NT-proBNP was modestly correlated with the decrease in the inflammation marker hsCRP in all patients, **suggesting that the reduction in cardiovascular risk is more closely related to optimal RA management** than to any particular DMARD [34]. Furthermore, it can be difficult to interpret reported cardioprotective effects from specific DMARDs, because the lowering of RA disease activity could increase the ability of patients to exercise and engage in other heart-healthy behaviors [35].

Although DMARDs may help lower some RA-related cardiovascular risk factors, some biologic DMARDs are also associated with an increased risk for heart failure, which is indicated on their FDA safety labels. Tocilizumab and other anti-IL-6/6R mAbs do not carry warnings for heart failure, but there is some controversy as to whether such a warning is warranted (STAT). A meta-analysis of 19 RCTs and cohort studies found that there were no significant differences in the rate of major cardiovascular adverse events, including myocardial infarction and stroke, for RA patients treated with tocilizumab, relative to those treated with TNF α inhibitors, or other biologic DMARDs [36]. While a meta-analysis of 14 observational studies found that tocilizumab may be associated with a lower risk of major cardiovascular adverse events relative to TNF α inhibitors (Odds Ratio OR: 0.59, 95% CI 0.34 to 1.00) [37], an additional real-world observational study based on insurance claims databases (n=88,463) found a trend toward a decrease but no significant differences in risk for cardiovascular events for tocilizumab relative to other biologic DMARDs for RA patients with or without a history of cardiovascular disease [38]. An open-label trial (n=3080) doing a head-to-head comparison found similar rates of major cardiovascular adverse events between tocilizumab and the TNF α inhibitor etanercept (Hazard Ratio HR: 1.05, 95% CI 0.77 to 1.43) [39].

There are several additional lines of evidence to suggest that IL-6R targeted therapies may indeed have cardioprotective properties.



IL-6R SNPs that mimic anti-IL-6R mAbs: Cardioprotective

People with the IL-6R Asp358Ala (A>C) variant have biochemical properties similar to people taking the anti-IL-6R mAb tocilizumab. A mendelian randomization analysis (n=133,449) found that the Asp358Ala IL-6R variant (rs8192284; rs222814) was associated with increased circulating IL-6 (9.45%, 95% CI 8.34 to 10.57 per allele), and decreased CRP (8.35%, 95% CI 7.31 to 9.38 per allele) and fibrinogen (0.85%, 95% CI 0.60 to 1.10 per allele) [40]. The IL-6R rs7529229 single nucleotide polymorphism (SNP) was associated with decreased odds of coronary heart disease events (OR: 0.95, 95% CI 0.93 to 0.97 per allele). A phenome-wide association study found that the Asp358Ala SNP is associated with reduced risk of aortic aneurysm (O: 0.87 to 0.90; 95% CI, 0.84 to 0.93) and ischemic heart disease (OR: 0.95; 95% CI 0.94 to 0.97) in a Veterans Affairs EHR biobank (n=332,799) [41]. These associations were replicated in the Vanderbilt University and UK Biobanks, respectively.

Insulin sensitivity: Potential benefit

The activation of IL-6R mediated signaling can lead to the induction of insulin receptor substrate 1 (IRS-1), which is associated with insulin resistance [42]. Both IL-6 levels and insulin resistance tend to increase with age. Tocilizumab treatment led to a significant decrease in insulin resistance based on the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in a sub-analyses of insulin resistant RA patients in the TOWARD (n=328) and TENDER (n=40) trials [43]. Insulin resistance (HOMA-IR) also decreased significantly following 3 months of tocilizumab treatment in non-diabetic RA patients in a small clinical study (n=11) [42]. A retrospective observational study (n=221) found that treatment with tocilizumab led a significantly greater reduction in glycated hemoglobin (HbA1c) levels within 3 months compared to TNF α inhibitors (OR: 5.59, 95% CI 2.56 to 12.2) [44]. A separate clinical study found that tocilizumab treatment was associated with a significant lowering of HbA1c levels in diabetic RA patients, and a non-significant decline in non-diabetics [35]. However, the degree of improvement in glucose metabolism attributable to tocilizumab may be difficult to parse out in many of these studies, because the onset of tocilizumab treatment often leads to the tapering of steroids, which are known to negatively affect glucose metabolism.

Dyslipidemia: Mixed

Concerns directed toward the cardiovascular safety of tocilizumab have primarily been associated with its **propensity to raise cholesterol levels**. The head-to-head trial between tocilizumab and etanercept found that tocilizumab-treated patients had significantly higher triglycerides (13.6%), LDL-c (11.1%), and HDL-c (5.7%) [39]. In non-diabetic RA patients (n=11), treatment with tocilizumab for 3 months led to

increases in serum triglycerides, LCL-c, and HDL-c, as well as significant decreases in Lp(a) from 34.5 ± 12.8 to 19.9 ± 6.3 mg/dl [42]. In a sub-study from the ROC trial (n=203), RA patients treated with tocilizumab had a greater decrease in Lp(a) levels and increase in the ApoA1 levels relative to other biologic DMARDs [32]. Notably, the effect was related to the RA disease-modifying activity, as the change in the ApoB100/ApoA1 level was driven by patients with a good clinical response to tocilizumab. In addition to modestly increasing total HDL-c levels, there is evidence to indicate that tocilizumab may also improve HDL function, namely its cholesterol removing capacity. Serum amyloid A (SAA) modifies the properties of HDL to make it less beneficial for vascular health [45]. One study (n=44) found that tocilizumab reduces SAA levels [46]. The prospective TOCRIVAR trial (n=27) found that tocilizumab treatment led to a sustained decrease in Lp(a) over 52 weeks, and an increase in serum cholesterol efflux capacity proportional to the decline in inflammation (hsCRP)[47]. A longitudinal study (n=70) also found that tocilizumab led to a significant improvement in cholesterol efflux capacity, but only in those that had an impairment at baseline [48]. The change in cholesterol efflux capacity was associated with the RA disease modifying activity (DAS28).

Myocardial infarction: Potential benefit

Tocilizumab (280 mg IV prior to coronary angiography) significantly reduced markers of inflammation (hsCRP) and acute coronary syndrome (hsTnT) in a double-blind, placebo-controlled Phase 2 RCT underpowered to assess clinical differences (n=117), but only in patients who also received a percutaneous coronary intervention [49]. In patients with hypercholesterolemia, tocilizumab reduced PCSK9, which is involved in LDL-c homeostasis by inhibiting its removal [50]. Tocilizumab was also associated with decreased expression of the complement anaphylatoxin receptors C5aR1 and C5aR2, but did not affect overall complement activation [51]. This suggests that anti-IL-6R mAbs may be beneficial in reducing inflammation following coronary angiography, but its ability to improve clinical outcomes remains unclear.

Giant cell arteritis: Potential benefit

Tocilizumab is approved for giant cell arteritis, an inflammatory vasculopathy. In an open-label study (n=21), tocilizumab for 3 months was more effective than prednisone alone at achieving sustained remission for 52 weeks, but some patients may require a longer treatment course to prevent relapse [52]. In a double-blind, placebo-controlled Phase 3 RCT (n=251) significantly more patients treated with tocilizumab (and tapered prednisone) for up to 52 weeks achieved sustained remission (tocilizumab qw 56% and q2w 53.1% vs placebo 14%). In a 52-week double-blind, placebo-controlled RCT (n=30), one third of patients in clinical remission continued to have evidence of vessel wall enhancement on



magnetic resonance angiography following treatment [53]. The clinical significance of this residual signal of vessel wall inflammation is not known.

Cancer: No increased risk with anti-IL-6R mAb, but no clear benefit

IL-6 can act as a growth factor to promote the growth and transformation of various human tumors, including multiple myeloma, ovarian, lung, bladder, breast, colon, and prostate cancers [54]. Therefore, anti-IL-6/6R mAbs have been tested in these cancers, primarily in combination, as a method to overcome chemoresistance. **Most of the trials** conducted thus far tested the anti-IL-6 mAb siltuximab and **failed to show significant benefits when added to conventional therapies**. The anti-IL-6R mAb tocilizumab continues to be tested in clinical trials as part of different combination therapies in various types of cancer ([Clinicaltrials.gov](https://clinicaltrials.gov)).

Since IL-6 plays multiple roles in regulating immune responses, its effects are tumor type dependent, and IL-6 can exert anti-tumor effects in some cancers by promoting the activation of the immune system [55]. Therefore, blocking IL-6 might be expected to exacerbate or increase the risk for some cancers. However, large cohort studies and meta-analyses of RCTs **do not show evidence for an increased risk of malignancies following treatment with tocilizumab** [54; 56; 57; 58; 59]. A meta-analysis of RCTs (n=4009 patients) testing tocilizumab in RA patients, found that the adjusted malignancy rate was 1.26 (95% CI 1.09 to 1.44) per 100 patient-years, and the standardized incidence rate (SIR) for all malignancies was 1.36 (95% CI 1.01 to 1.80) [54]. Although the rate was higher than the general population, RA patients are at elevated risk for certain types of cancer, and both the rate and cancer types of tocilizumab-treated patients are consistent with the general RA population. A cohort study of three US insurance claims databases including 130,102 tocilizumab-treated RA patients found that the incidence rate of malignancies was similar between patients initiating tocilizumab relative to those initiating TNF α inhibitors (HR: 0.97, 95%CI 0.74 to 1.27) [59]. A register based cohort study of RA patients in Sweden including 1798 tocilizumab-treated patients found that short-to-medium term use of tocilizumab was not associated with increased risk for hematological neoplasm (adjusted HR: 0.87, 95% CI 0.66 to 1.16) or solid neoplasm (adjusted HR: 0.92, 95% CI 0.69 to 1.23) [57]. These studies indicate that anti-IL-6R mAbs neither increase nor decrease the risk for cancer in RA patients.

Metastatic Castration-Resistant Prostate Cancer: No benefit

In an open-label Phase 1 trial siltuximab (n=37) in combination with docetaxel led to a $\geq 50\%$ decrease in prostate-specific antigen (PSA) levels in 62% patients, but only 2 patients had confirmed partial radiological responses [60]. As a monotherapy, only 3.8% of siltuximab (6 mg/kg IV q2w for 24 weeks)



treated patients (n=53) achieved $\geq 50\%$ reduction in PSA in a Phase 2 trial [61]. Siltuximab also failed to improve progression-free survival in an open-label Phase 2 RCT (n=106) when used in combination with mitoxantrone and prednisone [62].

Myeloma and Myelodysplastic Syndromes: No clear benefit

In a double-blind, placebo-controlled Phase 2 RCT (n=76) siltuximab (15 mg/kg IV q4w) failed to reduce red blood cell transfusions in anemic patients with myelodysplastic syndrome [63]. Siltuximab as a monotherapy or in combination failed to meet its primary endpoints in the majority of trials for relapsed refractory multiple myeloma. In a double-blind, placebo-controlled Phase 2 RCT (n=281), the addition of siltuximab (6 mg/kg IV q2w) failed to improve response rate, progression-free survival, or overall survival compared to bortezomib alone [64]. Siltuximab also failed to significantly improve response rates when added to bortezomib/melphalan/prednisone (n=106) [65], or dexamethasone (n=39) [66] in Phase 2 trials.

Castleman's Disease: Benefit for anti-IL-6 mAb in patients with IL-6 etiology

Castleman's disease is a rare lymphoproliferative disorder similar to lymphoma involving the overgrowth of cells in the lymph nodes often due to the hyperfunction of IL-6. The anti-IL-6 mAb siltuximab was approved for this indication in 2014 following a single positive double-blind, placebo-controlled Phase 2 RCT in patients with multicentric Castleman's disease seronegative for HIV and human herpesvirus 8 (HHV8) (n=79). Siltuximab (11 mg/kg IV q3w) achieved its primary outcome of durable tumor and symptomatic response (34% vs 0%, 95% CI 11.1 to 54.8, $p=0.0012$) [67; 68]. However, only individuals in which the disorder is driven by excess IL-6 adequately respond to anti-IL-6 therapy, thus only a subset of patients will achieve clinically meaningful benefit with siltuximab.

Pain and Fatigue: Potential benefit in RA

IL-6 is implicated in the regulation of pathological pain. Preclinical studies show that administering IL-6 can induce pain sensitization (allodynia), while anti-IL-6 mAbs can reduce pain-related behaviors [69]. Pain is an important feature of the chronic inflammatory conditions targeted by anti-IL-6/6R mAbs.

A prospective observational study in RA patients initiating tocilizumab (n=120), found that tocilizumab treatment led to significant improvements in fatigue (based on FACIT-F) and pain (based on VAS) [70]. These improvements are thought to be mediated by improvements in physical disease activity as well as psychological factors. Sarilumab treatment also led to improvements in FACIT-F and VAS scores in RCTs for RA [71]. Meanwhile, satralizumab led to improvements in disease activity for NMOSD patients,

but did not significantly impact fatigue or pain scores in RCTs [20; 21]. This suggests that the **ability of anti-IL-6R mAbs to alleviate pain and fatigue may depend on the patient population**. Since NMOSD is a CNS autoimmune disease, anti-IL-6R mAbs which are not CNS penetrant may be less effective at reducing disease-related pain, relative to RA, which is a peripheral autoimmune disease.

Safety: Suppress immune system and pose risks for undetected infections that can become serious. Reduce blood cell counts and raise blood lipid levels. May also lead to gastrointestinal perforations or elevated liver transaminases.

Types of evidence:

- 10 meta-analyses: RCTs for RA (n=14) using tocilizumab, sarilumab, or sirukumab; RCTs for sarilumab in RA; RCTs and cohort studies (n=19) for RA using DMARDs assessing cardiovascular adverse events; RCTs for RA using DMARDs assessing malignancy risk; Cochrane review of RCTs for biologic DMARDs for RA
- 6 clinical trials: Satralizumab Phase 3 RCTs for NMOSD, Clazakizumab Phase 2b RCTs for RA and psoriatic arthritis; Olokizumab Phase 2b and 3 RCTs for RA
- 5 observational studies: Tocilizumab in RA patients for cardiovascular risk and protection; RA patient characteristics and DMARD choice; Hospitalization risk based on DMARD type in RA patients
- FDA safety labels for tocilizumab, sarilumab, siltuximab
- Numerous laboratory studies

Infection: Increased risk

IL-6 is an important regulator of inflammatory immune system responses, therefore blocking IL-6 mediated signaling via IL-6R or IL-6 mAbs increases the risk for infections, and **serious infections are the most common severe adverse events** with these therapies. Patients taking anti-IL-6 therapy are at particular risk for stealth infections, because blocking IL-6 can obscure signs of infection such that symptoms are mild, which can lead severe infections to be left untreated, and ultimately lead to severe complications [44]. Live vaccinations are contraindicated in people taking anti-IL6/6R mAbs ([Drugs.com](https://www.drugs.com)).

Cytopenia: Increased risk

IL-6 plays multiple roles in stimulating the proliferation and activation of immune cells, including the induction of hematopoiesis, the differentiation of myeloid cells, antibody production, the migration of



neutrophils, and the activation of T-cells [72]. Consequently, loss of IL-6 signaling can lead to cytopenias, including **neutropenia, thrombocytopenia, lymphopenia, and leukopenia**. In clinical trials, neutropenia was generally not associated with increased rates of infection.

Infusion reactions: Mild

Intravenous and subcutaneous administered biologics are associated with infusion/injection site reactions, but these were found to be mild and range from 5 to 8% in clinical trials for approved anti-IL-6/6R mAbs (FDA safety labels [tocilizumab](#), [sarilumab](#), [siltuximab](#)).

Immunogenicity: Low risk

The development of anti-drug antibodies is also common with biologics, and can affect their efficacy and safety. Tocilizumab has low immunogenicity as either a monotherapy or in combination based on 13 Phase 3 clinical trials and 1 pharmacology safety study (8974 patients total), with anti-tocilizumab antibodies present in only 0.7-2% of patients, and had **no clear impact on drug pharmacokinetics, safety, or efficacy** [73]. Anti-drug antibodies were not found in patients treated in clinical trials for siltuximab, including a long-term safety study up to 7.2 years [68]. An open-label study evaluating the immunogenicity of sarilumab in RA patients (n=132) found that 6.1 to 12.3% of patients had persistent anti-sarilumab antibodies, but titers were low, and they were not associated with a meaningful loss of safety or efficacy [74]. Anti-sirukumab antibodies were not detected in healthy subjects in a Phase 1 study [75], and were detected in 3.8 to 4.9% of RA patients treated for 1 year, but did not affect response rates [76]. In a Phase 2 RCT in RA patient (n=345), anti-vobarilizumab antibodies developed in up to 31% of treated patients, but did not impact safety or efficacy (Ablynx [presentation](#)). Anti-clazakizumab antibodies were found in 1.7 to 10% of RA patients treated with clazakizumab for 24 weeks in a Phase 2b RCT [28], but the antibodies were also found in 3/165 patients with psoriatic arthritis at baseline in a separate trial [29]. The immunogenicity of olokizumab is unclear, since the rates of anti-olokizumab antibodies (9.8% vs 11.3%) were similar in olokizumab and placebo-treated RA patients in a Phase 2b trial [30]. Assessment of the immunogenicity of satralizumab was included in the trial protocol for its Phase 3 RCTs in NMOSD ([Clinicaltrials.gov](#)), but has not yet been reported.

Comparison between anti-IL-6 and IL-6R mAbs

There have not been enough head-to-head trials to indicate whether there is a meaningful difference in the safety profile between mAbs targeting IL-6 and IL-6R. Based on the currently available evidence, anti-IL-6 mAbs may be associated with a higher risk for serious adverse events and infections. The biologics application for the anti-IL-6 mAb sirukumab was denied by the FDA due to concerns over

increased mortality in RCTs relative to placebo ([Drugs.com](https://www.drugs.com)). However, since the anti-IL-6R mAb tocilizumab was the first drug approved in this class, there is far more safety data available for anti-IL-6R mAbs, so the risk for anti-IL-6 mAbs may appear elevated due to smaller dataset bias.

Comparison with other biologic DMARDs: Similar safety risk profile

Based on a Cochrane systematic review of 12 RCTs including 3364 RA patients, a network meta-analysis found no significant differences for withdrawals due to adverse events or serious adverse events across the different immune system targeting biologics approved for RA, including tocilizumab [77]. Real-world comparisons may be confounded by patient characteristics that negatively impact tocilizumab outcomes, since RA patients starting on non-TNF α biologics, including tocilizumab, tend to have higher disease activity, and higher comorbidity burden [78]. In contrast to TNF α inhibitors, tocilizumab does not appear to increase risk for adverse cardiovascular events in older RA patients, relative to younger patients [79].

Malignancy: Low risk

Meta-analyses indicate that treatment with biologic DMARDs is not associated with increased risk for malignancy in RA patients, and that tocilizumab is associated with similar risk relative to TNF α inhibitors [54; 56; 57; 58; 59].

Cardiovascular events: Moderate risk

Meta-analyses and real-world observational studies indicate that tocilizumab is associated with similar or slightly lower risk for adverse cardiovascular events in RA patients, relative to other biologic DMARDs. However, as featured in a [STAT](#) investigation, TNF α inhibitors contain warnings for heart failure as part of their FDA safety labels, thus, in this case, a comparable cardiovascular safety profile does not indicate that tocilizumab (anti-IL-6R mAbs) is safe. Anti-IL-6/6R mAbs are **associated with elevations in blood lipid levels**, primarily total cholesterol levels, and while short to medium term studies indicate that in spite of this atherogenic shift, the net effect of tocilizumab on cardiovascular health in RA patients appears to be neutral or slightly beneficial. Further studies are needed to fully understand the long-term risk. Phase 1 safety studies found that tocilizumab did not adversely affect cardiac repolarization, as measured by QTc prolongation in RA patients treated for 24 weeks at the therapeutic dose (8 mg/kg IV q4w) [80] or in healthy subjects following a supratherapeutic dose (20 mg/kg IV) [81]. Siltuximab (15 mg/kg IV q3w) also did not affect QTc prolongation in multiple myeloma patients in a Phase 1 study [82].

Drug interactions

Anti-IL-6/6R mAbs have drug interactions with other immunomodulatory/immunosuppressant drugs, including other biologic DMARDs.

Tocilizumab

The FDA safety [label](#) for tocilizumab contains warnings for **serious infections, gastrointestinal perforation**, and hypersensitivity reactions. It also recommends monitoring blood cell counts (neutrophils and platelets), blood lipid levels, and liver function tests.

The most common adverse events (at least 5% incidence) include upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased liver enzymes (ALT), and injection site reactions.

Sarilumab

The FDA safety [label](#) for sarilumab contains warnings for **serious infections, neutropenia, thrombocytopenia, elevated liver enzymes, lipid abnormalities, gastrointestinal perforations**, and hypersensitivity reactions.

The most common adverse events (at least 3% incidence) include neutropenia, increased liver enzymes (ALT), injection site reactions, upper respiratory infections, and urinary tract infections.

Siltuximab

The FDA safety [label](#) for siltuximab contains warnings for **serious infections, infusion related reactions, and gastrointestinal perforations**.

The most common adverse events (at least 10% incidence) include rash, pruritis, upper respiratory tract infection, increased weight, and hyperuricemia.

Satralizumab

In Phase 3 RCTs in NMOSD patients, there were similar numbers of adverse events and serious adverse events in placebo and satralizumab-treated arms, and there was no increased incidence of serious infections with satralizumab. **Infection** (urinary tract, respiratory tract, nasopharyngitis) was the most common adverse event in both groups [20; 21].

Clazakizumab

In a Phase 2b trial in RA patients, rates of serious adverse events ranged from 8.3 to 13.6% following clazakizumab treatment (monotherapy or in combination) [28]. These include **serious infections**, **increased levels of liver enzymes** (transaminase), **increased levels of lipids** (mean total cholesterol level) and hemoglobin, and **decreased counts of neutrophils and platelets**. Clazakizumab was similarly associated with elevated liver enzymes and lipid levels, and decreased neutrophil and platelet counts in a Phase 2b trial in psoriatic arthritis patients [29].

Olokizumab

In a Phase 2b RCT in RA patients, there were similar treatment-emergent adverse events in patients treated with olokizumab and tocilizumab [30]. The most common adverse events were **infections** (respiratory tract, urinary tract, nasopharyngitis) and **injection site reactions**. In a Phase 3 RCT in RA patients, there were more treatment-emergent adverse events with olokizumab relative to placebo, with more **serious infections** and one death due to septic shock in the high-dose group [31].

Sources and dosing:

Tocilizumab is marketed by Genentech (Chugai) under the trade name Actemra®, and is approved for adults with rheumatoid arthritis and inadequate response to one or more DMARDs (8 mg/kg IV every 4 weeks [q4w] or 162 mg subcutaneous [SC] qw/q2w), giant cell arteritis (162 mg SC qw), polyarticular juvenile idiopathic arthritis (8 or 10 mg/kg IV q4w), systemic juvenile idiopathic arthritis (8 or 12 mg/kg IV q2w), and cytokine release syndrome (8 or 12 mg/kg IV) ([Drugs.com](https://www.drugs.com)).

Sarilumab is marketed by Regeneron and Sanofi/Genzyme under the trade name Kevzara®, and is approved for adults with rheumatoid arthritis and inadequate response to one or more DMARDs. It comes as a pre-filled syringe and is administered SC at 150mg/1.14mL or 200 mg/1.14mL q2w ([Drugs.com](https://www.drugs.com)).

Siltuximab is marketed by Janssen Biotech under the trade name Sylvant®, and is approved for patients with multicentric Castleman's disease seronegative for HIV and HHV-8. It is administered IV at 11 mg/kg q3w ([Drugs.com](https://www.drugs.com)).

Satralizumab will be marketed by Genentech (Chugai), and was recently approved for neuromyelitis optica spectrum disorder ([Drugs.com](https://www.drugs.com)). In clinical trials it was dosed at 120 mg SC q2w for the first 4 weeks then q4w thereafter [20; 21].

Clazakizumab was created by Bristol Myers Squibb and Alder BioPharmaceuticals, and in 2016 was licensed to Vitaeris to commercialize it for chronic inflammatory conditions ([Press release](#)). [Viteris](#) is currently focused on developing clazakizumab for antibody-mediated rejection in kidney transplant patients, and clinical trials are ongoing for this indication. It is being dosed at 12.5 or 25 mg SC monthly in these trials ([Clinicaltrials.gov](#)). In a Phase 2b RCT for rheumatoid arthritis, the 25 mg dose was better tolerated and had the better therapeutic profile than the 100 mg or 200mg SC doses [[28](#)].

Olokizumab was created by UCB and was licensed to [R-Pharma](#) for development and commercialization. It is currently being developed for rheumatoid arthritis, and clinical trials are ongoing for this indication. In a Phase 3 RCT for rheumatoid arthritis it is being dosed at 64 mg SC q4w or q2w ([Clinicaltrials.gov](#)).

Sirukumab was developed by [Janssen](#) for rheumatoid arthritis, but development appears to have been discontinued following the failure of the FDA to approve the biologic due to an increased incidence of mortality compared to placebo.

Vobarilizumab was developed by [Ablynx](#) for chronic inflammatory autoimmune conditions. AbbVie declined the opportunity to license vobarilizumab for rheumatoid arthritis following its failure in Phase 2 RCTs ([Press release](#)). Ablynx was acquired by Sanofi/Genzyme in 2018 ([Press release](#)), but following the failure of vobarilizumab in a Phase 2 trial for lupus ([Topline](#) results), the development of vobarilizumab appears to have been discontinued.

Research underway:

According to [Clinicaltrials.gov](#), there are currently 88 active trials for tocilizumab for a variety of indications including rheumatoid arthritis, juvenile arthritis, type 1 diabetes, uveitis, giant cell arteritis, vasculitis, cancer, antibody-mediated rejection, graft vs host disease, myocardial infarction, colitis, scleroderma, cytokine release syndrome, Schnitzler's syndrome, Castleman's disease, depression, and schizophrenia.

There are 13 active trials for sarilumab on [Clinicaltrials.gov](#). It is being tested for rheumatoid arthritis, morphea, sarcoidosis, juvenile arthritis, systemic mastocytosis, and giant cell arteritis.

There are 2 active trials for satralizumab, which are extensions of the Phase 3 RCTs in neuromyelitis optica spectrum disorder ([Clinicaltrials.gov](#)).

There are 4 active trials for siltuximab on [Clinicaltrials.gov](https://clinicaltrials.gov). It is being tested for cancer and schizophrenia.

There are 5 active trials for clazakizumab on [Clinicaltrials.gov](https://clinicaltrials.gov) for antibody mediated rejection, and asthma.

There are 3 active trials for olokizumab on [Clinicaltrials.gov](https://clinicaltrials.gov) for rheumatoid arthritis.

Search terms:

Pubmed, Google:

- Alzheimer's disease, neurodegeneration, cognition, depression, inflammation, rheumatoid arthritis, cancer, cardiovascular, clinical trials, safety, immunogenicity

Websites visited for Anti-IL-6/IL-6R mAbs:

- Clinicaltrials.gov: [Tocilizumab](#), [Satralizumab](#), [Sirukumab](#), [Sarilumab](#), [Siltuximab](#), [Vobarilizumab](#), [Clazakizumab](#), [Olokizumab](#)
- Drugs.com: [Tocilizumab](#), [Sarilumab](#), [Siltuximab](#)
- WebMD.com: Tocilizumab [IV/Subcutaneous](#), [Sarilumab](#), [Siltuximab](#)
- DrugBank.ca: [Tocilizumab](#), [Sirukumab](#), [Sarilumab](#), [Siltuximab](#), [Vobarilizumab](#), [Clazakizumab](#), [Olokizumab](#)
- Cafepharma: [Tocilizumab](#), [Satralizumab](#), [Sirukumab](#), [Sarilumab](#), [Siltuximab](#), [Clazakizumab](#)

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