Translating IL-6 biology into effective treatments

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ABSTRACT

In 1973, IL-6 was identified as a soluble factor that is secreted by T cells and is important for antibody production by B cells. Since its discovery more than 40 years ago, the IL-6 pathway has emerged as a pivotal pathway involved in immune regulation in health and dysregulation in many diseases. Targeting of the IL-6 pathway has led to innovative therapeutic approaches

for various rheumatic conditions such as rheumatoid arthritis, juvenile idiopathic arthritis, adult onset Still's disease, giant cell arteritis, Takayasu arteritis, and others such as Castleman's disease or cytokine release syndrome. Targeting this pathway [Au:OK?Yes] has also identified avenues for potential expansion into several other indications, such as uveitis and neuromyelitis optica. To mark the tenth anniversary of anti-IL-6-receptor therapy worldwide, we discuss the history of research into IL-6 biology and the development of therapies that target IL-6 signalling, including the successes and challenges and with an emphasis on rheumatic diseases.

[H1] Introduction

Cytokine inhibitors have transformed the outcome of many chronic inflammatory diseases. A decade has passed since the approval of anti-IL-6-receptor (anti-IL-6R) therapy, which is now used worldwide in various rheumatic conditions such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), adult onset Still's disease (AOSD), giant cell arteritis (GCA) and Takayasu arteritis, as well as other conditions such as Castleman's disease and cytokine release syndrome (CRS). To mark this anniversary, we discuss the 40-year history of translational research into IL-6 biology and the subsequent development of therapies targeting this pivotal cytokine pathway, which helps to inform future biologic and clinical research. **[Au: Edits have been made to clarify this introductory text, to break up a very long sentence and to avoid repeating wording used in the abstract – edited text OK?Yes]**

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"To mark the tenth anniversary of approved anti-IL-6-receptor therapy worldwide, we discuss the 40 year history of translational research into IL-6 biology and the subsequent development of therapies targeting this pivotal cytokine pathway which include various rheumatic conditions such as rheumatoid arthritis, juvenile idiopathic arthritis, adult onset Still's disease, giant cell arteritis, Takayasu arteritis, and others such as Castleman's disease or cytokine release syndrome that helps to inform future biologic and clinical research."

[H1] From signalling to drug discovery

The journey from the discovery of IL-6 biology to the development of an IL-6 pathway inhibitor as a potential treatment for various diseases started coincidentally with the meeting of two research groups in Japan. In 1973, researchers at Osaka University led by Tadamitsu Kishimoto first reported that a soluble factor secreted by T cells was important for antibody production by B cells (Figure 1); subsequently, this soluble factor was cloned as IL-6, which turned out to have various roles in several autoimmune diseases.[1, 2] At the same time, researchers at Chugai Pharmaceutical were exploring new avenues for drug development for autoimmune diseases. In the late 1980s, the two groups started to collaborate to further

advance the understanding of the biological role of IL-6 in various autoimmune diseases and the development of IL-6 inhibitors as treatment options. To increase their collaborative potential, the two research groups even moved to adjoined laboratories at Osaka University. The university researchers led efforts to identify IL-6 signalling mechanisms and the biologic effects of IL-6, whereas the company focused on developing and characterizing IL-6 inhibitors as potential new treatments for autoimmune diseases. [3-5]

The traditional approach of searching for small-molecule inhibitors proved challenging when the research team found that IL-6 signal transduction occurred through a hexameric high-affinity complex of IL-6, IL-6R and glycoprotein 130 (gp130) (Figure 2). Moreover, both soluble IL-6R (sIL-6R) and membrane-bound IL-6R (mIL-6R) can be part of the hexameric complex; hence, the binding region of IL-6–IL-6R–gp130 was considered too complex and broad for a small molecule compound to inhibit the IL-6 signal pathway.[6, 7] The aforementioned mIL-6R and sIL-6R forms are associated with so-called classical and trans signalling pathways, respectively, the details of which and corresponding avenues for drug development have been reviewed extensively elsewhere.[4] Both signalling routes involve phosphorylation of Janus kinase 1(JAK1), JAK2 and tyrosine kinase 2 (TYK2) , which can also be targeted therapeutically with different molecules but are not the focus of this article.[4] The decision to target sIL-6R rather than IL-6 itself was made taking into consideration that concentrations of the receptor have less interpatient variability than concentrations of IL-6, potentially simplifying dose and regimen selection. [8, 9] With concurrent advances in biotechnology, the two groups decided to develop a humanized monoclonal antibody targeting IL-6R.[10-12] The resulting humanized anti-IL-6R antibody, tocilizumab, binds to mIL-6R and sIL-6R and inhibits IL-6 signalling by preventing IL-6 from binding to IL-6R.[11, 12] The therapeutic benefit of this anti-IL6R antibody led to the development of several anti-IL-6 antibodies (sirukumab, olokizumab and clazakizumab).

[H1] Initial therapeutic applications

As IL-6 is well known to have various physiological roles, in considering IL-6 as a therapeutic target its homeostatic role versus its pathogenic role in various autoimmune diseases was extensively debated. [3, 4] However, utilizing cell-based assays, animal models and ex vivo serum and tissue analyses, scientists identified several candidate diseases that might benefit from the use of IL-6 inhibition (Table 1).

A 1988 publication reported that IL-6 is an important growth factor in myeloma cells. [13] Oncologists in France conducted an open-label clinical trial of a mouse anti-IL-6 antibody in patients with multiple myeloma, the second most common type of blood cancer after leukemia.[14] Although none of the patients treated had an improved outcome or achieved remission in the initial report of the trial, post hoc analysis revealed that treatment with the anti-IL-6 antibody showed some efficacy in those patients who produced low concentrations of IL-6 .[15] More than 20 years later, a clinical trial evaluated whether the addition of a different chimeric anti-IL-6 monoclonal antibody, siltuximab, to the bortezomib–melphalan–prednisone regimen would be beneficial to patients with newly diagnosed multiple myeloma; however, this IL-6 inhibitor also failed to improve outcomes. [16]

In 1989, a publication described constitutive overproduction of IL-6 from the germinal centers of hyperplastic lymph nodes in patients with Castleman's disease**,** a lymphoproliferative disorder, and a correlation of serum IL-6 concentrations with clinical abnormalities.[17] Consistent with these observations, transgenic mice carrying the human *IL6* gene, under the control of an immunoglobulin promoter, developed clinical features of Castleman’s disease including splenomegaly, lymph node enlargement, and high concentrations of IL-6 and IgG.[18, 19] In a 1994 case report, administration of a mouse anti-IL-

6 neutralizing antibody to a patient with Castleman's disease seemed to be therapeutically effective.[20] Tocilizumab also had positive effects in a small case series of seven patients in 2000 and in a multicentre prospective open-label study in 2005 that included 28 patients with Castleman's disease.[21, 22] In the prospective study [Au:OK? Yes], bi-weekly treatment with tocilizumab consistently alleviated lymphadenopathy and improved all inflammatory parameters over 60 weeks.[22] A double-blind placebo-controlled trial of siltuximab also showed efficacy in this indication. [23] Subsequently, tocilizumab was approved for the treatment of Castleman's disease in Japan and siltuximab was approved for this indication in various countries.

A 1995 study reported that serum concentrations of IL-6 and sIL-6R were elevated in patients with Crohn's disease, a type of inflammatory bowel disease, and correlated with C-reactive protein levels. [24] On the basis of these observations, tocilizumab was evaluated in a phase II randomized placebo-controlled trial (RCT) with patients with active Crohn's disease (defined as Crohn's Disease Activity Index [CDAI] score $\geq$150. [25] The primary end point, a reduction of CDAI $\geq$70 points, was met by 80% of the patients who received bi-weekly tocilizumab, compared with 31% of the placebo-treated patients, demonstrating the substantial efficacy of tocilizumab. However, the development of tocilizumab for Crohn's disease did not proceed owing to rare reports of gastrointestinal perforations observed in concurrent clinical trials in arthritis and because of an increased understanding of the homeostatic role of IL-6 in the intestinal epithelium. [26] Together, these findings suggested that patients with Crohn's disease might be at increased risk of potential detrimental effects of IL-6 inhibition.

[H1] IL-6 inhibition in RA

The development path for an IL-6 inhibitor for the treatment of rheumatoid arthritis (RA), the most common chronic autoimmune disorder that primarily affects joints, began in the early 1990s, when cell-based experiments revealed that IL-6 might be involved in osteoporosis, cartilage destruction and synovial inflammation associated with RA.[27-29,30] In mouse models of collagen-induced and antigen-induced arthritis, IL-6 inhibition prevented the development of arthritis but did not ameliorate arthritis once the disease was established.[31-33] In a 1993 study, the administration of a mouse anti-IL-6 monoclonal antibody to patients with RA resulted in improvements of disease symptoms and laboratory measures of disease activity, although the effects were transient.[34] In 2000, the efficacy and tolerability of tocilizumab was investigated in a case series of 11 patients with refractory RA; the treatment was well tolerated and led to both clinical and biochemical improvements.[35] On the basis of these results, larger and confirmatory double-blind RCTs of tocilizumab were conducted in patients with refractory RA.[36-40] Tocilizumab improved clinical signs and symptoms of RA, laboratory parameters and radiological manifestations, and also ameliorated the effects of RA on patient reported outcomes, activities of daily living and quality of life, when administered as monotherapy or in combination with conventional synthetic DMARDs (csDMARDs).[41-45] These and other studies led to tocilizumab receiving marketing authorization (Figure 1) for patients with early RA not previously treated with methotrexate and those with established RA and an inadequate response to previous treatment with DMARDs or TNF antagonists; in these patients, tocilizumab is administered in combination with methotrexate or as monotherapy if methotrexate is not tolerated or continued treatment with methotrexate is not appropriate.

A notable finding of further clinical investigation in several RCTs and real-world data was that, unlike TNF inhibitors, tocilizumab monotherapy was superior to methotrexate or other csDMARDs for reducing the signs, symptoms and radiographic progression of RA. [39, 40, 46-59]

In particular, a head-to-head, double-blind, double-dummy RCT found that, when used as monotherapy, tocilizumab was superior to the TNF inhibitor adalimumab in measures of disease activity and several other outcomes. [46] On the basis of these results, EULAR recommendations for the management of RA named IL-6 pathway inhibitors as one of the preferred treatment options for patients for whom methotrexate is inappropriate.[60] Interestingly, the clinical benefits of IL-6 inhibition might be attributable, in part, to the beneficial effects of IL-6 inhibition on bone and cartilage turnover, which are supported by data from prospective cohort studies showing that tocilizumab monotherapy achieves better repair of focal bone erosions than TNF inhibition in patients with RA.[60-70] Besides promoting joint inflammation and damage through effects on chondrocytes, osteoclasts, macrophages and fibroblasts, IL-6 mediates systemic inflammation in RA. IL-6 affects T and B cell differentiation, and is the key driver of the acute phase response in RA. Key symptoms and comorbidities such as pain, fatigue, anxiety, depression, anaemia and cardiovascular disease can be mediated by IL-6 [refs [71, 72]], as shown in Figure 3.

Since tocilizumab was approved for RA, sarilumab, an alternative anti-IL-6R monoclonal antibody, has also demonstrated efficacy and safety and has been approved for the treatment of RA.[73-75] Three other anti-IL-6 monoclonal antibodies, sirukumab, olokizumab and clazakizumab, have also been tested in clinical trials in RA. In phase III RCTs that included patients with RA refractory to treatment with csDMARD and biologic DMARDs, sirukumab was superior to placebo in improving disease activity, physical function and health related quality of life, as well as inhibiting radiographic disease progression. [76, 77] However, monotherapy with sirukumab was similar but not superior to adalimumab and efforts to obtain regulatory approval in RA were terminated. [78] Phase II trials of olokizumab demonstrated therapeutic benefit and phase III trials are ongoing.[79] However, the development of clazakizumab as a treatment for RA has also been terminated.

[H1] IL-6 inhibition in JIA and AOSD

JIA is a term encompassing all forms of chronic arthritis affecting children younger than 16 years of age. [80] JIA exists as several different subtypes: oligoarticular JIA, polyarticular JIA, juvenile psoriatic arthritis, enthesitis-related arthritis and systemic JIA (sJIA). In sJIA, arthritis is associated with prominent systemic features, including high spiking fever, rash, serositis, and inflammatory signs. This disease is further characterized by high morbidity and mortality rates, joint destruction, functional disability, and growth retardation.[80] Concentrations of IL-6 are markedly elevated in the serum and synovial fluid of patients with sJIA and a vast body of evidence from cell-based experiments and animal models demonstrates that IL-6 overproduction seems to explain most, if not all, of the clinical and laboratory features of the disease including fever spikes, acute phase response, anaemia, growth retardation and systemic osteoporosis.[81-85] In 2005, clinical trials of tocilizumab in patients with sJIA conducted in the UK and Japan provided proof of principle of the efficacy of IL-6 inhibition in this severe pediatric condition.[86, 87] Two subsequent trials of tocilizumab in >150 children with sJIA confirmed extensive improvements in the signs and symptoms of disease following treatment with tocilizumab and demonstrated clinically relevant glucocorticoid-sparing potential of IL-6 inhibition.[88-92] The efficacy and safety of IL-6 inhibition in sJIA has also been confirmed in real-world studies.[93] Reversal of sJIA-associated growth retardation has also been demonstrated with IL-6 inhibition, with patients experiencing catch-up growth during treatment with tocilizumab. [92]

AOSD and sJIA are increasingly considered to be the same disease, with AOSD occurring in adulthood and sJIA in childhood. In a double-blind RCT of 27 patients with AOSD refractory to treatment with glucocorticoids, an ACR50 response (reflecting 50% improvement) at week

4 was achieved in ~61% of patients treated with tocilizumab, compared with ~31% of placebo-treated patients, although the difference was not statistically significant.[94] Patients in the tocilizumab group also had improvements in systemic symptoms and a decreased dose of glucocorticoids compared with the placebo group. On the basis of data from this trial, tocilizumab was approved for the treatment of AOSD in Japan in 2019.

Polyarticular JIA is characterized by a potentially destructive disease course. Trials of tocilizumab were undertaken in polyarticular JIA from 2009 on the basis of results obtained in RA. In a small trial in 19 patients, 100% of patients met the criteria for a good response after 48 weeks of treatment with tocilizumab.[95] In a pivotal phase III trial and its subsequent long-term extension study in 188 patients, inhibition of IL-6 led to sustained and clinically meaningful improvements after 2 years and skeletal growth was also improved by treatment with tocilizumab.[96, 97] Another anti-IL-6R antibody, sarilumab, is in phase II trials for polyarticular JIA.[98] and sJIA[99].

[H1] IL-6 inhibition in SpA

Seronegative spondyloarthritis (SpA) is a group of inflammatory rheumatic diseases includin ankylosing spondylitis (AS) and psoriatic arthritis (PsA) with common clinical and aetiological features such as axial and peripheral inflammatory arthritis, enthesitis and extra-articular manifestations. [100] The absence of the serological markers rheumatoid factor (RF) and antibodies against cyclic citrullinated peptides differentiate SpA from RA. AS is a chronic, debilitating and gradually progressive inflammatory rheumatic disease that primarily affects the axial skeleton and sacroiliac joints but can also affect the peripheral joints. [101] Serum IL-6 concentrations are elevated in patients with AS and correlate with disease activity. [102] However, tocilizumab failed to show therapeutic benefit in AS in two double-

blind RCTs in 2014. [103] Sarilumab was also ineffective as a treatment for AS in a 2015 RCT. [104] The conclusion from these RCTs is that IL-6 is not a therapeutic target in AS.

PsA is a chronic immune-mediated disease characterized by widespread musculoskeletal inflammation and is the major comorbidity associated with psoriasis. [105] The rationale for inhibiting IL-6 in PsA was based on a small number of studies that demonstrated elevated concentrations of IL-6 in both the serum and synovial fluid of patients with PsA.[106, 107] In a placebo-controlled phase II RCT, clazakizumab improved arthritis, enthesitis and dactylitis in patients with PsA but with minimal improvements in skin disease.[108] Currently, development of clazakizumab for this indication seems to have been terminated.

[H1] IL-6 inhibition in SLE and SSc

In 1990, a study in NZB/W F1 mice, an animal model of systemic lupus erythematosus (SLE), suggested that IL-6 could have a role in the pathogenesis of immune complex-mediated glomerulonephritis.[109] Moreover, IL-6 concentrations are elevated in serum and urine samples from patients with SLE or lupus nephritis, and correlate with disease activity. [110, 111] In an open-label phase I study in 16 patients with SLE, treatment with tocilizumab improved disease activity; notably, arthritis improved in all seven patients who had arthritis at baseline and resolved in four of them. [112, 113] Levels of anti–double-stranded DNA antibodies decreased even after adjustment for the decrease in total IgG titres following tocilizumab treatment. [112] These changes, together with a decrease in the frequency of circulating plasma cells, suggested a specific effect of IL-6 inhibition on autoantibody-producing B cells. However, further studies with sirukumab did not demonstrate a clinically meaningful benefit of IL-6 pathway inhibition in patients with lupus nephritis or SLE. [114, 115] These conflicting

results in SLE have tempered further clinical development. Whether IL-6 inhibition might be effective for some manifestations of SLE and not others requires further studies.

IL-6 is also implicated in the pathogenesis of systemic sclerosis (SSc). In the bleomycin mouse model of SSc, IL-6 blockade reduced skin fibrosis, α smooth-muscle actin protein expression, hydroxyproline content, and myofibroblast counts.[116] Dermal fibroblasts from patients with SSc constitutively express more IL-6 than those from healthy controls, and serum IL-6 concentrations are elevated in patients with early SSc.[117, 118] In a 2010 report, softening of skin sclerosis was observed in two patients with diffuse cutaneous SSc who received tocilizumab treatment.[119] In a double-blind phase II RCT in 87 patients with active diffuse SSc, fewer patients in the tocilizumab group had a decline in forced vital capacity compared with the placebo group, but improvements in skin thickening (measured by modified Rodnan skin score) with tocilizumab were not statistically significant.[120] Results of a follow-up phase III double-blind, placebo-controlled trial in 212 patients with progressive SSc again showed a numerical reduction in skin score with tocilizumab at week 48 but the difference did not reach statistical significance.[121] Regarding the mean change in forced vital capacity from baseline to week 48, tocilizumab performed better than placebo, suggesting a potentially clinically important effect of tocilizumab on preservation of lung function.[121] Studies with larger sample size will better define clinical benefit and identify specific SSc patient population for IL-6 inhibition.

[H1] IL-6 inhibition in vasculitis and PMR

Takayasu arteritis and GCA are chronic, potentially life-threatening, primary systemic large-vessel vasculitides [122, 123]. Takayasu arteritis affects the aorta and its major branches in

adolescents and young adults, whereas GCA affects large and medium-sized arteries and usually affects individuals above the age of 50 years.

IL-6 has been implicated as an important factor in the pathogenesis of both GCA and Takayasu arteritis in the 1990s. First, serum level of IL-6 correlated with disease activity in both diseases.[124, 125] Second, tocilizumab improved disease signs and symptoms in patients with refractory GCA or refractory Takayasu arteritis in case series. Subsequently, a single-centre phase II RCT and a phase III multicenter, double-blind RCT investigated whether tocilizumab could sustain remission and enable glucocorticoid tapering.[126, 127] In the phase III RCT, sustained glucocorticoid-free remission at 52 weeks was achieved in more patients treated with tocilizumab weekly (56%) or every other week (53%) (in combination with a prednisone taper over 26 weeks) than in patients who received placebo plus a prednisone taper over 26 weeks (14%) or placebo plus a prednisone taper over 52 weeks (18%).[127] Consequently, tocilizumab was approved for the treatment of patients with GCA by the FDA and EMA in 2017, making this the first drug approved for the treatment of GCA other than glucocorticoids. A phase III trial evaluating the efficacy and safety of sarilumab in patients with GCA is currently ongoing.[128]

In Takayasu arteritis, a double-blind RCT in Japan showed that, compared with placebo, tocilizumab treatment prolonged the time to relapse during glucocorticoid tapering.[129] Although the primary end point of the study was not met, tocilizumab has been approved in Japan for the treatment of Takayasu arteritis refractory to existing therapies.

Polymyalgia rheumatica (PMR) is a disease closely related to GCA, with stiffness and muscle pain being the predominant symptoms. Several case reports and a small, prospective, open-label phase II trial of tocilizumab in patients with PMR suggested that this drug might have a steroid-sparing effect. [130, 131] Another prospective open-label study found tocilizumab

monotherapy to be effective in new-onset PMR.[132] Additional trials of IL-6 pathway inhibition in PMR are ongoing, including phase III trials of tocilizumab and sarilumab.[133,134]

[H1] IL-6 inhibition in CRS

Tocilizumab was approved by the FDA (in 2017) and EMA (in 2018) for the treatment of severe or life threatening chimeric antigen receptor (CAR) T cell−induced cytokine release syndrome (CRS) in adults and children. CAR T cells are ex vivo modified T cells from patients with cancer, which are reprogrammed to lyse tumour cells when bound to a specific cancer cell surface protein. However, ~70% of patients treated with a CD19 CAR T cell therapy develop CRS. [135] CRS leads to headache, fever, chills, severe nausea, vomiting, diarrhoea, musculoskeletal pain, dyspnea, hypotension and tachycardia, and in severe cases can be fatal. The approval of tocilizumab for the treatment of CAR T cell-induced CRS was based on retrospective analysis of data showing the efficacy of tocilizumab treatment in patients who developed CRS after CAR T cell therapy in prospective clinical trials. [136-138]

[H1] Other potential indications

Unraveling the therapeutic potential of IL-6 pathway inhibition for indications other than those discussed above is a matter of ongoing basic and clinical research spanning various therapeutic areas. [4,5] Several investigator-initiated studies are either planned or ongoing or have already been published as proof-of-concept studies. A detailed representation of all of these studies is beyond the scope of this article but briefly, they encompass conditions such as uveitis, thyroid-eye disease, neuromyelitis optica, graft-versus-host disease, erosive hand osteoarthrtitis, various oncological indications, depression, schizophrenia, Schnitzler

syndrome, myocardial infarction, familial Mediterranean fever, COVID-19 pneumonia (caused by the novel coronavirus SARS-CoV-2) [Au:OK?Yes] and others.[5, 139, 140] It is hoped that findings from some of these studies will expand the application and medical value of IL-6 pathway inhibition to additional diseases in the future.

[H1] Safety of IL-6 inhibition

The safety profile of IL-6R inhibition is derived mainly from clinical trials of tocilizumab and sarilumab, as well as data from real-world registries of more than 1 million patients worldwide who have been treated with tocilizumab, including patients with RA, JIA and GCA. [26, 53, 141-164]

Consistent with expectations for a biologic DMARD for RA, serious infections, including bacterial serious infections, are among the most common serious adverse events reported in clinical trials, post-marketing surveillance studies, short-term studies and open-label extension studies. The overall rate of serious infections in patients with long-term exposure to IL-6 pathway inhibitors is in line with rates seen in studies with a short duration of exposure. [58, 142, 156, 158, 161-166]

Treatment with IL-6 pathway inhibitors has been associated with elevations in serum concentrations of transaminases. These elevations did not seem to result in permanent or clinically evident hepatic injury in clinical trials. An increased frequency and magnitude of transaminase elevations was observed when potentially hepatotoxic drugs (for example, methotrexate) were used in combination with IL-6 pathway inhibitors. [161-164]

Pancreatitis is among the adverse reactions identified during post-approval use of tocilizumab and sarilumab[161, 163] Gastrointestinal perforations have also been associated with use of these drugs; most such events occurred in patients with pre-existing risk factors (such as pre-

existing diverticulitis or use of oral glucocorticoids); thus, IL-6 pathway inhibitors should be used with caution in patients with a history of gastrointestinal perforation, intestinal ulcers or diverticulitis. The overall rate of gastrointestinal perforations in populations with long-term exposure was in line with rates seen in short-duration studies. [26, 161-164]

Monitoring of lipid profiles and treatment of hyperlipidemia according to clinical practice guidelines is recommended during treatment with IL-6 inhibitors, as IL-6 pathway inhibition is associated with increased serum lipid concentrations (LDL and triglycerides). [151, 153] Interestingly, IL-6 inhibition modifies HDL lipoproteins towards an anti-inflammatory composition, thus the atherogenic index is unchanged **[Au: edited sentence OK?Yes]** .[167-169] In the ENTRACTE study, a head-to-head RCT comparing the cardiovascular safety of tocilizumab and the TNF inhibitor etanercept in RA, the rate of major adverse cardiovascular events was similar with both treatments (HR 1.05, 95% CI 0.77–1.43). [170]

One safety concern of biologic therapies is the development of anti-drug antibodies, which can lead to loss of efficacy and/or immune-mediated adverse reactions.[171] A study evaluating the immunogenicity of tocilizumab in patients with RA found that the incidence of anti-tocilizumab antibodies was low **[Au: Study description added, edit OK? Yes]**, regardless of the route of administration of tocilizumab or whether it was used as monotherapy or in combination with csDMARDs; moreover, anti-tocilizumab antibodies were mostly transient, and their development did not correlate with pharmacokinetics, safety events or loss of efficacy. [171]

For sirukumab, the FDA declined to approve the drug for use in RA owing to concern about an imbalance in all-cause mortality between the sirukumab and placebo groups in phase III studies, although whether this imbalance was a true safety signal or a result of the study

design is unclear. [172] Additional studies are needed to further define the safety profile of sirukumab.

In general, monitoring for adverse events should always follow local labels, which are continuously updated with the latest safety information. [161-164]

[H1] Conclusions

Substantial advances have been made in translating the biology of IL-6 to the treatment of patients with autoimmune diseases. Accumulating safety data on IL-6 pathway inhibitors have provided clinicians with the necessary knowledge for assessing the risk of using them. IL-6 pathway inhibitors have shown benefit in patients with RA, JIA, AOSD, GCA, Castleman's diseases and CRS, and might also be beneficial in patients with other autoimmune diseases and even beyond. However, the limitations of preclinical studies for predicting clinical success in patients is a major barrier and necessitates early human proof-of-concept studies. Case reports or series have proved useful in some conditions such as GCA, Takayasu arteritis, AOSD and CRS. In the future, trials to assess the efficacy and safety of a specific treatment within a biomarker-positive subgroup in heterogeneous patient populations (for example, a basket trial) to confirm and generate hypotheses might be an option. However, a reliable biomarker for predicting treatment response in many rheumatic diseases has not been identified.

Several questions relating to IL-6 biology remain unanswered. For example, why does IL-6 over-production occur and why does IL-6 signal inhibition lead to clinical meaningful benefits for patients with some diseases associated with IL-6 over-production (such as RA) but not all (such as AS)? Answering these questions would help to further progress our understanding of how various autoimmune diseases are regulated in the context of IL-6

pathway biology and help in developing additional, personalized treatment options for individual patients or patient subgroups. It seems that the journey of realizing the therapeutic potential of IL-6 pathway inhibition is far from over.

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Competing interests

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Table 1. Evidence for the effects of IL-6 inhibition on diseases.

Disease	Cell based assays	Animal models	Biomarkers	Clinical trials	Drug(s) indicated
Multiple myeloma	IL-6 promotes myeloma cell proliferation [13]	In the KPMM2 xenograft model, growth is IL-6-dependent [173]	Serum concentrations of IL-6 correlate with disease severity in plasma cell leukemia [174]	No improvement in clinical outcomes [14, 16]	None
Crohn's disease	IL-6 activates mucosal T cells[175]	IL-6R blockade promotes T cell apoptosis, which contributes chronic intestinal inflammation in the CD4 adoptive transfer colitis model [175]	Serum concentrations of sIL-6R are increased in active disease[24] Concentrations of IL-6 and sIL-6R are increased in colonic organ cultures using specimens from patients with active disease[176]	Tocilizumab had a clinical effect in a pilot study[25]	None
Castleman's disease	IL-6 is produced by affected germinal centres[17]	*IL6* transgenic mice develop clinical features of	Increased serum concentrations of IL-6 in active disease[17]	Tocilizumab and siltuximab showed efficacy in	Tocilizumab Siltuximab

		Castleman's disease[19]		clinical studies[22,23]	
RA	IL-6 involved in osteoporosis, cartilage destruction and synovial inflammation associated with RA[27-29]	IL-6 inhibition prevented development of arthritis in CIA [31, 32] and AIA [33]	Serum concentrations of IL-6 elevated in active RA	IL-6 pathway inhibition effective in many clinical trials[36-52, 54-57, 62]	Tocilizumab Sarilumab
Systemic JIA	Increased production of IL-6 by PBMCs[177]	*IL6* transgenic mice develop a skeletal phenotype resembling abnormalities observed in children with chronic inflammatory diseases [84]	Serum concentrations of IL-6 increased in patients with JIA and correlate with disease activity[81, 178]	Tocilizumab improved disease activity and reversed growth retardation [86-91, 93, 95, 179]	Tocilizumab
Adult-onset Still's disease	NA	NA	Serum concentrations of IL-6 increased[180]	Tocilizumab showed some clinical benefit and steroid-	Tocilizumab

				sparing effects[94]	
Ankylosing spondylitis	NA	NA	Serum concentrations of IL-6 are increased and correlate with disease activity[102]	Tocilizumab and sarilumab failed to show therapeutic benefit in RCTs [103,104]	None
Psoriatic arthritis	NA	NA	Serum and synovial fluid concentrations of IL-6 increased[106] [107]	Clazakizumab improved arthritis, enthesitis, and dactylitis but not skin disease[108]	None
SLE	Increased production of IL-6 by B cells[181]	IL-6 implicated in autoimmune disease pathogenesis in NZB/WF1 mice [109]	IL-6 concentrations increased in cerebrospinal fluid[110]	IL-6 pathway inhibition affected autoantibody-producing cells but no clinically meaningful benefit demonstrated[112, 113]	None
Systemic sclerosis	Increased production of IL-6 by PBMCs[182]	IL-6 blockade improved disease in the bleomyci	Production of IL-6 increased in dermal fibroblasts and serum concentrations of IL-6	Tocilizumab had a potentially clinically important effect on preservation of lung	None

		n mouse model[116]	increased[117, 118]	function[120, 121]	
Giant cell arteritis	NA	NA	Serum concentrations of IL-6 increased in active disease[124]	Tocilizumab was superior to placebo with regard to sustained glucocorticoid-free remission[126, 127]	Tocilizumab
Takayasu arteritis	NA	NA	Serum concentrations of IL-6 increased in active disease[125]	Tocilizumab had some effect on time to relapse but primary end point not met[129]	Tocilizumab
CRS	NA	NA	Serum concentrations of IL-6 increased[136]	Tocilizumab used successfully to treat CRS occurring in trials of CAR-T cell therapy[136, 137]	Tocilizumab

AIA, antibody-induced arthritis; CIA: collagen induced arthritis; CRS, cytokine release syndrome; JIA, juvenile idiopathic arthritis; NA, not available; PBMC, peripheral blood mononuclear cell; RA, rheumatoid arthritis; sIL-6R, soluble IL-6 receptor; SLE, systemic lupus erythematosus.

Figure legend

Figure 1: Timeline of the discovery of IL-6 and IL-6-targeted therapies.

The timeline shows progress in the field if IL-6 pathway inhibition following the initial identification of a B cell stimulation factor in 1976, and the more definitive biochemical and molecular studies done in the 1980s and 1990s, to clinical trials and approvals in various diseases in 2000s and to the present day. AOSD: adult onset Still's disease; AS: ankylosing spondylitis; CRS: cytokine release syndrome; GCA: giant cell arteritis; gp130, glycoprotein 130; IL-6R, IL-6 receptor; LVV, large vessel vasculitis; pJIA: polyarticular course juvenile idiopathic arthritis, RA, rheumatoid arthritis; SSc: systemic sclerosis; sJIA: systemic juvenile idiopathic arthritis; SLE: systemic lupus erythematosus; Takayasu arteritis.

Figure 2: Cell signalling pathways and physiological role of IL-6 in diseases.

IL-6 participates in a broad spectrum of biological events, such as synovial inflammation, immune responses, haematopoiesis and acute-phase reactions **[Au: Is this sentence in the right place?Yes]** . (a) IL-6 binds to IL-6 receptor (IL-6R) and glycoprotein 130 (gp130) to form a hexameric complex. Both membrane-bound IL-6R and soluble IL-6R (sIL-6R) can be part of the hexameric complex, and are associated with the classical and trans signalling pathways, respectively. Intracellular signalling pathways involve the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway. Pharmacological inhibitors of IL-6 signalling prevents IL-6 from binding to IL-6R by targeting either the cytokine itself or the receptor.

(b) In the context of disease, IL-6 can have both local inflammatory and systemic effects. Some of the manifestations of the diseases for which IL-6 inhibitors are approved could be explained by the effects of IL-6, on the basis of both preclinical and clinical data. IL-6 has been implicated in the pathogenesis of diseases including rheumatoid arthritis, systemic juvenile idiopathic arthritis (sJIA), Castleman's disease, giant cell arteritis, Takayasu arteritis and cytokine release syndrome, among others (c) **[Au: If there will be a third part to this figure, please provide the details (i.e. sketch and legend) via email, thanks by email]**

CRP, C-reactive protein; MMP, matrix metalloprotease; RANKL, receptor activator of NF-κB ligand; SAA, serum amyloid A; VEGF, vascular endothelial growth factor.