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1 **Translating IL-6 biology into effective treatments**

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18  
19 **ABSTRACT**

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

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

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## [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|

## [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.<sup>1,2</sup> 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

**Commented [A1]:** Original text, FYI: “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.”

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

63 The traditional approach of searching for small-molecule inhibitors proved challenging when  
64 the research team found that IL-6 signal transduction occurred through a hexameric high-  
65 affinity complex of IL-6, IL-6R and glycoprotein 130 (gp130) (Figure 2). Moreover, both  
66 soluble IL-6R (sIL-6R) and membrane-bound IL-6R (mIL-6R) can be part of the hexameric  
67 complex; hence, the binding region of IL-6–IL-6R–gp130 was considered too complex and  
68 broad for a small molecule compound to inhibit the IL-6 signal pathway.<sup>6,7</sup> The  
69 aforementioned mIL-6R and sIL-6R forms are associated with so-called classical and trans  
70 signalling pathways, respectively, the details of which and corresponding avenues for drug  
71 development have been reviewed extensively elsewhere.<sup>4</sup> Both signalling routes involve  
72 phosphorylation of Janus kinase 1 (JAK1), JAK2 and tyrosine kinase 2 (TYK2), which can  
73 also be targeted therapeutically with different molecules but are not the focus of this article.<sup>4</sup>

74 The decision to target sIL-6R rather than IL-6 itself was made taking into consideration that  
75 concentrations of the receptor have less interpatient variability than concentrations of IL-6,  
76 potentially simplifying dose and regimen selection.<sup>8,9</sup> With concurrent advances in  
77 biotechnology, the two groups decided to develop a humanized monoclonal antibody  
78 targeting IL-6R.<sup>10-12</sup> The resulting humanized anti-IL-6R antibody, tocilizumab, binds to  
79 mIL-6R and sIL-6R and inhibits IL-6 signalling by preventing IL-6 from binding to IL-6R.<sup>11</sup>  
80 <sup>12</sup> The therapeutic benefit of this anti-IL6R antibody led to the development of several anti-  
81 IL-6 antibodies (sirukumab, olokizumab and clazakizumab).

82

83 **[H1] Initial therapeutic applications**

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

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

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

106 6 neutralizing antibody to a patient with Castleman's disease seemed to be therapeutically  
107 effective.<sup>20</sup> Tocilizumab also had positive effects in a small case series of seven patients in  
108 2000 and in a multicentre prospective open-label study in 2005 that included 28 patients with  
109 Castleman's disease.<sup>21,22</sup> In the prospective study [Au:OK? Yes], bi-weekly treatment with  
110 tocilizumab consistently alleviated lymphadenopathy and improved all inflammatory  
111 parameters over 60 weeks.<sup>22</sup> A double-blind placebo-controlled trial of siltuximab also  
112 showed efficacy in this indication.<sup>23</sup> Subsequently, tocilizumab was approved for the  
113 treatment of Castleman's disease in Japan and siltuximab was approved for this indication in  
114 various countries.

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

127

128 **[H1] IL-6 inhibition in RA**

129 The development path for an IL-6 inhibitor for the treatment of rheumatoid arthritis (RA), the  
130 most common chronic autoimmune disorder that primarily affects joints, began in the early  
131 1990s, when cell-based experiments revealed that IL-6 might be involved in osteoporosis,  
132 cartilage destruction and synovial inflammation associated with RA.<sup>27-29,30</sup> In mouse models  
133 of collagen-induced and antigen-induced arthritis, IL-6 inhibition prevented the development  
134 of arthritis but did not ameliorate arthritis once the disease was established.<sup>31-33</sup> In a 1993  
135 study, the administration of a mouse anti-IL-6 monoclonal antibody to patients with RA  
136 resulted in improvements of disease symptoms and laboratory measures of disease activity,  
137 although the effects were transient.<sup>34</sup> In 2000, the efficacy and tolerability of tocilizumab was  
138 investigated in a case series of 11 patients with refractory RA; the treatment was well  
139 tolerated and led to both clinical and biochemical improvements.<sup>35</sup> On the basis of these  
140 results, larger and confirmatory double-blind RCTs of tocilizumab were conducted in patients  
141 with refractory RA.<sup>36-40</sup> Tocilizumab improved clinical signs and symptoms of RA,  
142 laboratory parameters and radiological manifestations, and also ameliorated the effects of RA  
143 on patient reported outcomes, activities of daily living and quality of life, when administered  
144 as monotherapy or in combination with conventional synthetic DMARDs (csDMARDs).<sup>41-45</sup>  
145 These and other studies led to tocilizumab receiving marketing authorization (Figure 1) for  
146 patients with early RA not previously treated with methotrexate and those with established  
147 RA and an inadequate response to previous treatment with DMARDs or TNF antagonists; in  
148 these patients, tocilizumab is administered in combination with methotrexate or as  
149 monotherapy if methotrexate is not tolerated or continued treatment with methotrexate is not  
150 appropriate.

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



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

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

179

180 **[H1] IL-6 inhibition in JIA and AOSD**

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

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

203 4 was achieved in ~61% of patients treated with tocilizumab, compared with ~31% of  
204 placebo-treated patients, although the difference was not statistically significant.<sup>94</sup> Patients in  
205 the tocilizumab group also had improvements in systemic symptoms and a decreased dose of  
206 glucocorticoids compared with the placebo group. On the basis of data from this trial,  
207 tocilizumab was approved for the treatment of AOSD in Japan in 2019.

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

216

#### 217 **[H1] IL-6 inhibition in SpA**

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

227 blind RCTs in 2014.<sup>103</sup> Sarilumab was also ineffective as a treatment for AS in a 2015 RCT.

228 <sup>104</sup> The conclusion from these RCTs is that IL-6 is not a therapeutic target in AS.

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

236

### 237 **[H1] IL-6 inhibition in SLE and SSc**

238 In 1990, a study in NZB/W F1 mice, an animal model of systemic lupus erythematosus  
239 (SLE), suggested that IL-6 could have a role in the pathogenesis of immune complex-  
240 mediated glomerulonephritis.<sup>109</sup> Moreover, IL-6 concentrations are elevated in serum and  
241 urine samples from patients with SLE or lupus nephritis, and correlate with disease activity.

242 <sup>110, 111</sup> In an open-label phase I study in 16 patients with SLE, treatment with tocilizumab  
243 improved disease activity; notably, arthritis improved in all seven patients who had arthritis at  
244 baseline and resolved in four of them.<sup>112, 113</sup> Levels of anti-double-stranded DNA antibodies  
245 decreased even after adjustment for the decrease in total IgG titres following tocilizumab  
246 treatment.<sup>112</sup> These changes, together with a decrease in the frequency of circulating plasma  
247 cells, suggested a specific effect of IL-6 inhibition on autoantibody-producing B cells.

248 However, further studies with sirukumab did not demonstrate a clinically meaningful benefit  
249 of IL-6 pathway inhibition in patients with lupus nephritis or SLE.<sup>114, 115</sup> These conflicting

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

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

269

#### 270 **[H1] IL-6 inhibition in vasculitis and PMR**

271 Takayasu arteritis and GCA are chronic, potentially life-threatening, primary systemic large-  
272 vessel vasculitides<sup>122, 123</sup>. Takayasu arteritis affects the aorta and its major branches in

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

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

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

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

297 monotherapy to be effective in new-onset PMR.<sup>132</sup> Additional trials of IL-6 pathway  
298 inhibition in PMR are ongoing, including phase III trials of tocilizumab and sarilumab.<sup>133,134</sup>

299

### 300 **[H1] IL-6 inhibition in CRS**

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

311

### 312 **[H1] Other potential indications**

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

320 syndrome, myocardial infarction, familial Mediterranean fever, COVID-19 pneumonia  
321 (caused by the novel coronavirus SARS-CoV-2) [Au:OK?Yes] and others.<sup>5, 139, 140</sup> It is hoped  
322 that findings from some of these studies will expand the application and medical value of IL-  
323 6 pathway inhibition to additional diseases in the future.

324

### 325 [H1] Safety of IL-6 inhibition

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

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

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

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



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

348 Monitoring of lipid profiles and treatment of hyperlipidemia according to clinical practice  
349 guidelines is recommended during treatment with IL-6 inhibitors, as IL-6 pathway inhibition  
350 is associated with increased serum lipid concentrations (LDL and triglycerides).<sup>151, 153</sup>

351 Interestingly, IL-6 inhibition modifies HDL lipoproteins towards an anti-inflammatory  
352 composition, thus the atherogenic index is unchanged [Au: edited sentence OK? Yes].<sup>167-169</sup>

353 In the ENTRACTE study, a head-to-head RCT comparing the cardiovascular safety of  
354 tocilizumab and the TNF inhibitor etanercept in RA, the rate of major adverse cardiovascular  
355 events was similar with both treatments (HR 1.05, 95% CI 0.77–1.43).<sup>170</sup>

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

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

367 design is unclear.<sup>172</sup> Additional studies are needed to further define the safety profile of  
368 sirukumab.

369 In general, monitoring for adverse events should always follow local labels, which are  
370 continuously updated with the latest safety information.<sup>161-164</sup>

371

### 372 **[H1] Conclusions**

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

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

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

394

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398

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418

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

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



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

				sparing effects <sup>94</sup>	
Ankylosing spondylitis	NA	NA	Serum concentrations of IL-6 are increased and correlate with disease activity <sup>102</sup>	Tocilizumab and sarilumab failed to show therapeutic benefit in RCTs <sup>103,104</sup>	None
Psoriatic arthritis	NA	NA	Serum and synovial fluid concentrations of IL-6 increased <sup>106,107</sup>	Clazakizumab improved arthritis, enthesitis, and dactylitis but not skin disease <sup>108</sup>	None
SLE	Increased production of IL-6 by B cells <sup>181</sup>	IL-6 implicated in autoimmune disease pathogenesis in NZB/W F1 mice <sup>109</sup>	IL-6 concentrations increased in cerebrospinal fluid <sup>110</sup>	IL-6 pathway inhibition affected autoantibody-producing cells but no clinically meaningful benefit demonstrated <sup>112,113</sup>	None
Systemic sclerosis	Increased production of IL-6 by PBMCs <sup>182</sup>	IL-6 blockade improved disease in the bleomycin	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 <sup>116</sup>	increased <sup>117, 118</sup>	function <sup>120, 121</sup>	
Giant cell arteritis	NA	NA	Serum concentrations of IL-6 increased in active disease <sup>124</sup>	Tocilizumab was superior to placebo with regard to sustained glucocorticoid-free remission <sup>126, 127</sup>	Tocilizumab
Takayasu arteritis	NA	NA	Serum concentrations of IL-6 increased in active disease <sup>125</sup>	Tocilizumab had some effect on time to relapse but primary end point not met <sup>129</sup>	Tocilizumab
CRS	NA	NA	Serum concentrations of IL-6 increased <sup>136</sup>	Tocilizumab used successfully to treat CRS occurring in trials of CAR-T cell therapy <sup>136, 137</sup>	Tocilizumab

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

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## 982 **Figure legend**

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

984 The timeline shows progress in the field of IL-6 pathway inhibition following the initial  
985 identification of a B cell stimulation factor in 1976, and the more definitive biochemical and  
986 molecular studies done in the 1980s and 1990s, to clinical trials and approvals in various  
987 diseases in 2000s and to the present day. AOSD: adult onset Still's disease; AS: ankylosing  
988 spondylitis; CRS: cytokine release syndrome; GCA: giant cell arteritis; gp130, glycoprotein  
989 130; IL-6R, IL-6 receptor; LVV, large vessel vasculitis; pJIA: polyarticular course juvenile  
990 idiopathic arthritis, RA, rheumatoid arthritis; SSc: systemic sclerosis; sJIA: systemic juvenile  
991 idiopathic arthritis; SLE: systemic lupus erythematosus; Takayasu arteritis.

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

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995 **IL-6 participates in a broad spectrum of biological events, such as synovial inflammation,**  
996 **immune responses, haematopoiesis and acute-phase reactions [Au: Is this sentence in the**  
997 **right place?Yes] . (a) IL-6 binds to IL-6 receptor (IL-6R) and glycoprotein 130 (gp130) to**  
998 **form a hexameric complex. Both membrane-bound IL-6R and soluble IL-6R (sIL-6R) can be**  
999 **part of the hexameric complex, and are associated with the classical and trans signalling**  
1000 **pathways, respectively. Intracellular signalling pathways involve the Janus kinase (JAK) and**  
1001 **signal transducer and activator of transcription (STAT) pathway. Pharmacological inhibitors**  
1002 **of IL-6 signalling prevents IL-6 from binding to IL-6R by targeting either the cytokine itself**  
1003 **or the receptor.**

1004 **(b) In the context of disease, IL-6 can have both local inflammatory and systemic effects.**  
1005 **Some of the manifestations of the diseases for which IL-6 inhibitors are approved could be**  
1006 **explained by the effects of IL-6, on the basis of both preclinical and clinical data. IL-6 has**  
1007 **been implicated in the pathogenesis of diseases including rheumatoid arthritis, systemic**  
1008 **juvenile idiopathic arthritis (sJIA), Castleman's disease, giant cell arteritis, Takayasu arteritis**  
1009 **and cytokine release syndrome, among others (c) [Au: If there will be a third part to this**  
1010 **figure, please provide the details (i.e. sketch and legend) via email, thanks by email]**

1011 CRP, C-reactive protein; MMP, matrix metalloprotease; RANKL, receptor activator of NF-  
1012 κB ligand; SAA, serum amyloid A; VEGF, vascular endothelial growth factor.

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