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ABSTRACT

Background Targeting interleukin (IL)-6 has become a major therapeutic strategy in the treatment of immune-mediated inflammatory disease. Interference with the IL-6 pathway can be directed at the specific receptor using anti-IL-6Rα antibodies or by directly inhibiting the IL-6 cytokine. This paper is an update of a previous consensus document, based on most recent evidence and expert opinion, that aims to inform on the medical use of interfering with the IL-6 pathway.

Methods A systematic literature research was performed that focused on IL-6-pathway inhibitors in inflammatory diseases. Evidence was put in context by a large group of international experts and patients in a subsequent consensus process. All were involved in formulating the consensus statements, and in the preparation of this document.

Results The consensus process covered relevant aspects of dosing and populations for different indications of IL-6 pathway inhibitors that are approved across the world, including rheumatoid arthritis, polyarticular-course and systemic juvenile idiopathic arthritis, giant cell arteritis, Takayasu arteritis, adult-onset Still's disease, Castleman's disease, chimeric antigen receptor-T-cell-induced cytokine release syndrome, neuromyelitis optica spectrum disorder and severe COVID-19. Also addressed were other clinical aspects of the use of IL-6 pathway inhibitors, including pretreatment screening, safety, contraindications and monitoring.

Conclusions The document provides a comprehensive consensus on the use of IL-6 inhibition to treat inflammatory disorders to inform healthcare professionals (including researchers), patients, administrators and payers.

INTRODUCTION

When looking back at the first two decades of the new millennium, patients with rheumatoid arthritis (RA) and rheumatologists as well as other stakeholders can be quite pleased with the advances made since the 2000. While at the end of the preceding century, only conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs) were available and many patients with RA and other inflammatory diseases often could not attain optimal disease control, the last 20 years have allowed five tumour necrosis factor (TNF)-inhibitors (1), two interleukin (IL)−6 receptor (R) blockers, one T cell costimulation inhibitor, an IL-1 receptor antagonist and an antibody to the CD20 surface antigen of B-lymphocytes to become approved and successfully applied in RA[1] and other biologic agents have been developed and approved for other inflammatory disorders. In addition to these biological (b) DMARDs, most recently, five Janus kinase (JAK) inhibitors have been introduced into the armamentarium for treating RA, designated as targeted synthetic (ts) DMARDs that can be taken orally.[2]

In addition to the introduction of these new medications, the performance of trials on treatment strategies[3–9] has informed both the validity of the treat-to-target recommendations[10] and management recommendations of major international organisations.[11–13] These management recommendations provide important general guidance to rheumatologists, patients and other stakeholders on what is regarded to be an optimal treatment approach based on evidence and expert opinion. However, since these recommendations have to cover the totality of the therapeutic area, they do not always well describe specific aspects of individual drugs.

Therefore, additional consensus statements on the use of individual agents or classes of agents have been developed by various expert groups.[2 14–16] In 2013, one of these consensus statements addressed inhibition of the IL-6 receptor, detailing the important aspects of efficacy and safety in patients with RA.[17] Importantly, however, rheumatology has spearheaded therapeutic developments in other medical areas and, therefore, the indications for agents originally developed for RA have expanded over the years. Consequently, some consensus statements also embraced diseases beyond RA and beyond rheumatology.[2 15]

Many therapeutics successfully applied in patients with inflammatory rheumatic diseases target proinflammatory cytokines, their receptors or their signal transduction. Among these cytokines IL-6 stands out by virtue of its very high serum concentration and its pivotal role in the induction of the acute phase response.[18 19] IL-6 is a cytokine with multiple effects that is produced by most cell types.[20] Due to its pleiotropic nature, IL-6 is involved in many fundamental processes of cell growth and cell activation, such as embryonic development, hematopoiesis, bone metabolism, immune responses and inflammation.[21] Immunologically, IL-6 is an important factor-regulating B-cell growth, maturation and activation (previously referred to as B-cell stimulating factor) and is also involved in the generation of T helper (h) 17 cells, which produce IL-17.[22 23] In the context of RA and other immune-mediated inflammatory diseases, IL-6 is pivotal in the generation of the overall inflammatory response, inducing joint damage by activating matrix metalloproteinases and osteoclasts,[24 25] and driving the production of acute phase reactants (APR).[26]

A brief look at the molecular aspects of blocking the IL-6 receptor or its ligand is warranted. The monoclonal anti-IL-6R antibodies tocilizumab, sarilumab and satralizumab all target domain 2 of the IL-6R molecule, which is the main point of engagement with its ligand IL-6.[27] Thus, these monoclonal antibodies prevent the binding of IL-6 to its soluble and cell surface receptors; as a consequence of this inhibition, circulating IL-6 levels increase, without leading to inflammatory responses. ALX-0061, a nanobody, targets the same site but has not yet been fully evaluated in clinical studies.[27 28] However, the IL-6R also has other domains, including domain 3, which is the site of its interaction with gp130; this region can be targeted by the mAb NI-1201, which also has yet to be tested in a clinical trial.[29]

The IL-6 cytokine has several functional regions.[30] Site 1 is the main binding site to the cognate IL-6R and is inhibited by, among other molecules, siltuximab, sirukumab (the human version of siltuximab)[31] and clazakizumab.[27] Site 3 of IL-6, however, is the binding region of the IL-6R-IL-6 complex to gp130 and is blocked by olokizumab. An antibody to site 2, EBI-029,[27] which also interacts with gp130, has not yet been studied for human disease.[32]

IL-6 is an abundant cytokine in the circulation, which reflects its systemic functional profile mediated via its unique ability to bind to and activate target cells either directly or indirectly. IL-6 binds to its cognate receptor IL-6Rα, which is located either on the cell surface or cleaved into a soluble form. The IL-6Rα chain, even if membrane bound, has no intracellular signalling moiety and requires a coreceptor, gp130 or IL-6Rβ, to transmit information to the nucleus. To this end, JAKs, a series of non-receptor tyrosine kinases, are activated on IL-6 binding, and phosphorylate signal transducer and activator of transcription proteins, the respective transcription factors. Signalling ensues after engagement of two IL-6 ligand molecules with two IL-6Rα molecules and two gp130 moieties, forming a hexameric structure on the cell surface.[33] Of note, many cells express gp130 without the IL-6Rα chains. However, soluble IL-6R, which is present at high levels in the blood, can bind IL-6 in the circulation and then interact with membrane gp130 on various cell populations, a process called trans-signalling (as opposed to classical signalling). More recently, a third signalling mechanism, transpresentation, has been recognised, through which IL-6Rα present on a cell surface, after having bound IL-6, can interact with a gp130 molecule expressed on another cell.[21 34]

Table 1 IL-6 pathway blocking agents and their targets

Biological agent	Molecular type	Target	Diseases for which the agent is approved
Tocilizumab	Humanised MAb	IL-6R	RA, JIA, sJIA, GCA, others
Sarilumab	Human MAb	IL-6R	RA
Satralizumab	Humanised MAb	IL-6R	NMOSD
Siltuximab	Chimeric MAb	IL-6, site 1	Castleman's disease
Sirukumab	Human MAb	IL-6, site 1	N.a.
Clazakizumab	Humanised MAb	IL-6, site 1	N.a.
Olokizumab	Humanised MAb	IL-6, site 3	N.a.
EBI-028	scFv fragment	IL-6, site 2	N.a.
Olamkizept	sgp130-Fc	IL-6-sIL-6R complex	N.a.
JAK 1,3-inhibitors	Small chemical	IL-6R signalling	RA, PsA, AS, PsO, others

AS, ankylosing spondyloarthritis; Fc, IgG-Fc fragment; GCA, giant cell arteritis; JIA, juvenile inflammatory arthritis; Mab, monoclonal antibody; NMOSD, neuromyelitis optica spectrum disorder; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; sgp, soluble glycoprotein; sJIA, systemic juvenile inflammatory arthritis.

Targeting IL-6 has become a major therapeutic strategy in reducing inflammation, either by interfering with IL-6 directly or preventing its binding to the specific receptor using anti-IL-6Rα antibodies (table 1). As far back as the 1990s xenogeneic monoclonal antibodies against IL-6 were evaluated[35] and humanised and human anti-IL-6 molecules, such as sirukumab, olokizumab and clazakizumab, were evaluated in multiple clinical trials; however, none of these medications has been approved. In contrast, a humanised monoclonal antibody targeting IL-6Rα, tocilizumab, was licensed more than a decade ago for RA, more recently for giant cell arteritis (GCA), and has been used successfully in these and other indications. Sarilumab, a human antibody against IL-6Rα, was recently approved for RA, further expanding the options for specifically inhibiting IL-6-mediated inflammation. A third mechanism for interfering with the effects of IL-6 is by inactivating the 'IL-6–IL-6Rα complex' with a sgp130 Fc receptor construct such as olamkicept. This molecule is in the early phase of development and may also affect other members of the IL-6 family. Interference with IL-6 signal transduction can also be accomplished using JAK inhibitors; however, their effect is not confined to just IL-6, as multiple other cytokines and growth factors use the JAK-STAT pathways, as described in a recent consensus statement on the use of JAK inhibitors.[2]

Thus, binding IL-6 can be multifaceted as one can block the ligand or the receptor, which can occur at different sites within these molecules. The multiple therapeutic approaches to interfere with the IL-6 pathway are further enhanced by the ability to inhibit signal transduction with JAK inhibitors, but these compounds will not be addressed in the present consensus statement as the focus here will be solely on the respective bDMARDs.

At the time of the first consensus statement on IL-6 and IL-6Rα inhibition almost one decade ago, the only approved molecule targeting this pathway was tocilizumab and the

approved indications were RA, systemic juvenile idiopathic arthritis (sJIA)[17] and, in Japan, Castleman's disease (CD). Since then, several antibodies directed against IL-6 have undergone phase III trials. Tocilizumab was licensed for many more indications, sarilumab was approved as the second anti-IL-6Rα for RA, satralizumab was approved for neuromyelitis optica spectrum disorder (NMOSD). In addition, since the previous consensus statement, much more safety information is available, including information from registries. For all these reasons, it was deemed timely to revisit and update the previous consensus statement with the most recent insights into indications, efficacy and safety of IL-6 blockade by assessing the evidence accrued since the previous version of the statement, to discuss this evidence among experts in immune mediated inflammatory diseases and patient representatives, and to develop an updated consensus document to reflect the current state of known medical science.

METHODS

Two convenors (DA and JSS) created a task force (TF) of members with complementary expertise for the specific task of developing an update of the Consensus Statement on the use of IL-6 inhibition. The work of the TF adhered to the EULAR standard operating procedures for recommendations.[36] In contrast to the previous version, due to the expansion of indications, this TF included experts from areas beyond rheumatology, such as hepatology and infectious diseases. First, a steering committee (SC) was formed, which consisted of a patient representative (MV), a healthcare professional (TAS), a gastroenterologist (MT), a cardiologist and metabolism expert (NS), an infectious disease specialist (KLW), a paediatric rheumatologist (AR), nine adult rheumatologists with various scientific focus from basic to clinical research, a fellow (KK) and a methodologist (AK). The SC members came from several European Countries, Asia (TT) and North America (KLW). The SC was charged to first develop questions for the systematic literature research (SLR). Once the fellow performed the SLR under the supervision of the methodologist, and with oversight from the convenors, the SC critically discussed the SLR and developed a proposal for the updated bullet points of the consensus statement.

The TF included all SC members plus two additional patient representatives (NB and MdW), seven additional rheumatologists from North America (MKC, RF, JMK, PM), Latin America (EFM, Asia (YT) and Australia (PN), and 14 additional rheumatologists from several European countries. The expertise of several of the rheumatologists included other rheumatic diseases like vasculitis and systemic lupus erythematosus as well as colleagues with vast experience in leading registries and studying cardiovascular aspects. At the TF meeting, the fellow presented the SLR results and the convenors the proposal for the individual statements as developed by the SC. These proposals were further discussed, reformulated as needed and underwent online voting. All items received an adjudication of the level of evidence (LoE) and Strength of Recommendation according to the Oxford Evidence-Based Medicine approach.[37]

As suggested in the EULAR standard operating procedure, for each bullet point, the first vote had to arrive at a 75% majority for acceptance; if further discussions were needed, a next proposal of the respective bullet point had to reach a two-thirds majority and, if still needed, the final wording had to be approved by more than 50% of the TF members. Due to the COVID-19 pandemic, all discussions and voting took place remotely. The TF meeting was scheduled to provide ample time for all members to actively participate in all discussions. Anonymity of the voting process was ensured during the TF meeting. Notes captured the contents of the discussions and the reasoning behind each decision. These discussions are represented in the manuscript as comments accompanying each individual item.

After the meeting, the TF members received all statements in a table format and submitted their level of agreement with each of the items by assigning a vote between 0 and 10 (0 meaning no agreement at all and 10 full agreement); the mean of these responses was calculated as the mean level of agreement (LoA; table 2).

The details of the SLR are published separately.[38] Of note, drugs that had not yet undergone regulatory assessment or formal approval, but for which evidence from clinical trials was available, were part of the SLR and could be considered in the recommendations with the respective caveats.

The individual statements are presented in the wording of the final vote (table 2). The results of the last ballot for each statement are presented as percentage of voting members present in the virtual room (table 2).

The convenors drafted the initial version of the manuscript with the help of the methodologist and the fellow. This draft was sent to all TF members for their comments. All comments were considered for the next version of the paper and all authors provided their final approval prior to submission of the manuscript.

RESULTS

Consensus statement on the use of IL-6-pathway inhibitors to treat inflammatory diseases

The components of the consensus statement covering specific indications, management, safety, and other aspects, are shown in table 2. The following section addresses some details of the TF's deliberations and conclusions.

Indications, considerations, preinitiation of treatment screening, and dosing by indication

Adult RA (level 1a, grade A)

In line with the current licensed indication in Europe, sarilumab and tocilizumab may be used in adult patients with active RA, normally with at least moderate disease activity according to a validated composite measure, who have had an inadequate response to, or intolerance of, at least one DMARD. EULAR recommends use of csDMARDs in combination with short-term glucocorticoids before deciding that the csDMARD treatment is insufficiently effective.[12]

Sarilumab and tocilizumab fulfilled the requirements for the above indication as a consequence of the results of several clinical trials (level 1a, grade A). The data for tocilizumab were detailed in the previous version of this consensus statement; however, further studies performed since then are addressed in the SLR.[38] Superiority of tocilizumab and sarilumab monotherapy[39 40] over monotherapy of TNF-inhibitors as well as similarity of all bDMARD mechanisms in combination with methotrexate (MTX) were reported in SLRs for the EULAR management recommendations for RA.[41 42] This latter finding was recently confirmed in a head-to-head trial in which three bDMARDs, tocilizumab, certolizumab pegol and abatacept, when combined with MTX and glucocorticoids, showed similar efficacy.[43] This conclusion was further supported by a recent study comparing tocilizumab with rituximab.[44] Registry data reveal similar efficacy of all bDMARDs.[45]

Outside the USA, the approved dose of tocilizumab is 162 mg subcutaneous (sc) weekly and the intravenous dose is 8 mg/kg

Table 2 Consensus statements on the use of IL-6 blocking agents with levels and grades of evidence, levels of agreement and last voting results

Statement	Level of agreement (0–10)	Last voting results
Indication—Rheumatoid arthritis (level 1 a, grade A)		
Population: Active RA (at least moderate disease activity according to a validated composite measure) characterised by an inadequate response to (or intolerance of) ► at least one conventional synthetic disease modifying antirheumatic drug (csDMARDs) or ► a biological DMARD (bDMARD) or ► a targeted synthetic (ts) DMARD (JAK-inhibitor)	**9.8±0.5**	**100%**
Dosing scheme: ► sarilumab: 200 mg s.c. every 2 weeks (level 1 a, grade A) ► tocilizumab: 162 mg s.c. weekly or 8 mg/kg every 4 weeks as intravenous infusion, usually over 1 hour (level 1 a, grade A) ► sarilumab/tocilizumab should be used in combination with methotrexate (MTX) (alternatively in combination with other csDMARDs) or, if MTX or another csDMARD is inappropriate, as monotherapy. (level 1 a, grade A)	**9.9±0.3**	**100%**
Dose reduction: ► As a shared decision between patients and their rheumatologist ► Indication: – occurrence of certain adverse events; – in patients with sustained remission, after having tapered GC; discontinuation of concomitant csDMARDs (especially MTX) can also be considered. ► Scheme: sarilumab from 200 to 150 mg or tocilizumab from 8 to 4 mg/kg, or dosing interval increase.	**9.5±0.8**	**91%**
Indication—Polyarticular-course juvenile idiopathic arthritis (level 1b, grade A)		
Population: Active pcJIA (≥5 active joints,≥3 with limitation of motion), characterised by an inadequate response to MTX.	**9.6±0.8**	**94%**
Dosing (tocilizumab): ► IV dosing every 4 weeks: 8 mg/kg for weight ≥30 kg; 8–10 mg/kg for weight <30 kg ► SC dosing:>=30kg: 162 s.c. / 2 weeks;<30kg: 162 mg s.c. / 3 weeks ► In combination with MTX (unless not tolerated)	**9.9±0.3**	**94%**
Indication—Systemic juvenile idiopathic arthritis (level 1b, grade A)		
Population: Active sJIA, refractory to NSAIDs and GC	**9.8±0.5**	**94%**
Dosing (tocilizumab): ► IV dosing every 2 weeks: 8 mg/kg for weight≥30 kg; 12 mg/kg for weight <30 kg ► SC dosing:≥30 kg: 162 mg s.c. / week;<30 kg: 162 mg s.c. / 2 weeks ► Use as monotherapy	**9.9±0.3**	**94%**
Indication—Giant cell arteritis (level 1b, grade A)		
Population: New onset or relapsing GCA, especially those at high risk of GC-related AE	**9.7±0.7**	**90%**
Dosing (tocilizumab): ► 162 mg s.c. weekly ► always start in combination with GCs, but alongside GC tapering	**9.7±0.7**	**90%**
Indication—Takayasu arteritis (level 2 a, grade B)		
Population: Patients aged ≥12 years with relapsing and refractory to GC TAK	**9.6±1.0**	**93%**
Dosing (tocilizumab, only in Japan): ► 162 mg s.c. weekly ► In combination with GCs, but alongside GC tapering	**9.7±0.7**	**93%**
Indication—Adult-onset Still's disease (level 1b, grade A)		
Population: - AoSD refractory to GC	**9.5±0.8**	**93%93%**
Dosing (tocilizumab, only in Japan): - only IV dosing at 8 mg/kg every 2 weeks	**9.5±0.9**	
Indication—Castleman's disease (level 2b/1b, grade B)		
Population: Human herpesvirus-8-seronegative patients with symptomatic multicentric Castleman's disease	**9.8±0.6**	**93%**
Dosing (tocilizumab in Japan, and Siltuximab in EU and USA): ► tocilizumab: IV dosing: 8 mg/kg every 2 weeks; SC dosing: 162 mg weekly (level 2b, grade B) ► Siltuximab: IV dosing: 11 mg/kg every 3 weeks (level 1b, grade B)	**9.7±0.6**	**93%**
Indication—CAR-T-cell induced cytokine release syndrome **(level 2c, grade B)**		
Population: Severe or life-threatening grades of CRS in adults and paediatric patients≥2 years of age	**9.7±0.6**	**93%**
Dosing: IV tocilizumab dosing: once 8 mg/kg (12 mg/kg for pts<30 kg)	**9.7±0.6**	**93%**

Continued

Table 2 Continued

Statement	Level of agreement (0–10)	Last voting results
Indication—Neuromyelitis optica spectrum disorder (NMOSD) **(level 1b, grade A)**		
Population: AQP4-IgG seropositive or seronegative relapsing NMOSD	**9.7±0.5**	**93%**
Dosing (Satralizumab in USA and Japan, in USA only seropositive adults): - Satralizumab: SC dosing: 120 mg at weeks 0, 2 and 4 and every 4 weeks as monotherapy or as combination therapy with immunosuppressant	**9.7±0.5**	**93%**
Disease management		
► Follow-up of clinical response: outcome measures that do not include acute phase reactants should be used to evaluate disease activity. ► Risk of delaying diagnosis of infection because of APR normalisation by IL-6R	**9.8±0.6**	**100%**
Pre-treatment screening (level 5, grade D)		
► History and physical examination – Consider possible contraindications – Consider radiograph of the chest – Assess history of infections (especially history of hepatitis), diverticulitis, GI perforations and malignancies ► Routine laboratory testing, including lipid levels ► Testing for hepatitis B and hepatitis C viral infections (persistence of HBsAg, anti-HBc) ► Screening for Tb ► Assess necessity of vaccination; vaccination should be updated according to local recommendations	**9.4±1.0**	**94%**
Contraindications (level 5, grade D)		
► Allergy to IL-6 inhibiting drug ► Clinically relevant co-morbidities, particularly active infections, diverticulitis	**9.6±0.7**	**94%**
Safety (level 2b, grade B)		
► Serious bacterial infections and opportunistic infections occurred about twice as frequently with tocilizumab compared with placebo populations (similar to other bDMARDs) – Risk of delaying diagnosis of infection because of APR normalisation by IL-6R ► Hepatic transaminase elevations ► Gastrointestinal perforations, risk factors include a history of diverticulitis, older age, GC and/or NSAID intake; no reported cases in children. ► Neutropenia and rarely thrombocytopenia ► Infusion reactions (~7%) ► Severe infusion (hypersensitivity) reactions may occur but are rare (0.3%); they are more frequent with the 4 mg/kg than the 8 mg/kg dose iv / 162 mg dose sc ► Children with sJIA: possible risk for development of macrophage activation syndrome	**9.6±0.9**	**94%**

anti-HBc, antibody against hepatitis B core antigen; APR, acute phase reactant; AQP4, aquaporin 4; bDMARDs, biological disease modifying antirheumatic drugs; CAR, chimaeric antigen receptor; csDMARDs, conventional synthetic DMARDs; HBsAg, hepatitis B surface antigen; NSAID, non-steroidal anti-inflammatory drugs; Tb, tuberculosis; tsDMARDs, targeted synthetic DMARDs (for more detailed definition see ref.[176]).

every 4 weeks. In the USA, the recommended starting dose is 162 mg sc every other week or 4 mg/kg intravenous every 4 weeks to be followed by 162 mg sc weekly or 8 mg/kg intravenous if there is insufficient response to the lower dose. The reasoning behind the 162 mg every other week and 4 mg/kg dosing was based on the FDA's concerns about safety, despite the much lower efficacy of the lower doses; the lower dose has also been associated with more hypersensitivity reactions. The approved dose of sarilumab is 200 mg sc, every 2 weeks. Dose reductions (interval increase for tocilizumab sc; reduction to 4 mg/kg for tocilizumab intravenous; or decrease to 150 mg sarilumab sc every 2 weeks) should be considered in cases of serious infections or persistent cytopenia. Interval increases or dose decreases should also be considered when patients reach stable ACR-EULAR Boolean or index-based remission,[46] in line with the respective management recommendations.[12 47]

With respect to efficacy after failure of TNF inhibitors, results from some open-label clinical trials suggest that non-TNF inhibitors, including tocilizumab, were more efficacious than a second TNF inhibitor,[48] but the EULAR SLRs did not identify convincing high-level evidence to suggest any bDMARDs over another after insufficient response to TNF blockers. The efficacy of tocilizumab is higher when combined with MTX compared with tocilizumab monotherapy based on the results from several studies[49–51] and is, therefore, the treatment of choice. While some studies suggest non-inferiority of withdrawing versus continuing MTX in combination with tocilizumab, the evidence favours better efficacy for tocilizumab combination than monotherapy. In addition, it is difficult to understand why MTX should be withdrawn if it is well tolerated and leads to better efficacy, as shown in all these studies. Nevertheless, if there is a strong patient preference or if all csDMARDs are contraindicated, monotherapy of monoclonal antibodies against the IL-6R has an advantage over monotherapies with other bDMARDs.[12 52] Details of studies on dose tapering and combination are provided in the SLR paper.[38]

One question raised in the research agenda from the previous edition of the consensus addressed the use and efficacy of JAK inhibitors after IL-6R blockade has failed. This question is now answered as there was no difference in efficacy of JAK inhibition whether patients failed TNF inhibitors or failed tocilizumab.[53]

Response rates according to the American College of Rheumatology (ACR) improvement criteria for RA[54] as observed in phase III clinical trials have consistently shown superiority of IL-6 and IL-6R inhibitors compared with control arms. A significant decrease in the disease activity score (DAS) using 28 joint counts (DAS28) and high proportions of EULAR moderate and good response as well as DAS28 remission (DAS28 <2.6) rates were observed. However, interpretation of these data is difficult because of the high weight of the APR component in the DAS28 formula[55 56] and the prominent effect of IL-6 inhibition on the hepatic APR production, which can lead to exaggerated improvement of response rates if this instrument is employed. Nevertheless, the pre-eminent requirement for improvement in both swollen and tender joints to fulfil ACR improvement criteria and published clinical trial data showing a decrease in disease activity across all variables studied, including functional improvement and structural effects, provide solid evidence that tocilizumab is an effective bDMARD for the treatment of RA. When looking at the clinical disease activity index (CDAI), a score that does not contain an APR in its formula,[57] sarilumab and tocilizumab were also significantly more efficacious compared with the respective comparators, placebo or anti-TNF as a monotherapy.[39 40 50] As mentioned previously, in combination with MTX, the efficacy of anti-IL-6R agents appears to be of a similar magnitude to that of TNF inhibitors, abatacept or rituximab[1 41–43] (level 1 a, grade A).

Other indications for IL-6 blockade

IL-6R and IL-6 blockades are also approved for a variety of other diseases. The various studies are detailed in the SLR paper[38] and will not be broadly addressed here.

Polyarticular-course idiopathic juvenile arthritis (pcJIA; level 1b, grade A), sJIA (level 1b, grade A) and adult-onset Still's disease (level 1b, Grade A)

As for the other indications, the approval for pcJIA, sJIA and adult-onset Still's disease (AoSD) was based on randomised controlled clinical trial data. However, the number of trials available are fewer than those for RA.

For children older than 2 years with active *pcJIA* non-responsive to MTX, tocilizumab is approved at an intravenous dose of 8 mg/kg every 4 weeks at a weight of 30 kg or more, and 10 mg/kg every 4 weeks at a weight of <30 kg. These data are based on the CHERISH trial.[58 59] The sc dosing is 162 mg every 2 weeks for children ≥30 kg and every 3 weeks for those <30 kg.[60] It is recommended to combine tocilizumab with MTX (whether seropositive or seronegative), unless not tolerated. A trial of sarilumab for the treatment of pcJIA (NCT02991469) has not yet been completed.

In *sJIA*, the recommended intravenous dose is 8 mg/kg every 2 weeks at a weight of 30 kg or more and 12 mg/kg every 4 weeks at a weight of <30 kg.[61 62] The sc dose is 162 mg weekly or every other week for children ≥30 kg and <30 kg, respectively.[60]

For *AoSD* with insufficient response to glucocorticoids, tocilizumab is approved in Japan at an intravenous dose of 8 mg/kg every 2 weeks with a possibility of weekly infusions if the response is inadequate.[63 64]

Giant cell arteritis (level 1b, Grade A), and Takayasu arteritis (TAK; level 2a, Grade B)

Two studies in patients with GCA (Giant-Cell Arteritis Actemra (GiACTA)) were successful and the basis for approval of tocilizumab for patients with new-onset or relapsing disease, particularly those at risk of glucocorticoid-related adverse events.[65 66] The approved dose is 162 mg sc weekly to be started in combination with glucocorticoids but alongside subsequent glucocorticoid tapering; in the USA, tocilizumab is also approved at 162 mg every other week. In addition to the pivotal clinical trial, many case series and one other but small randomised controlled trial (RCT) have been published.[67]

IL-6R inhibition with tocilizumab is also approved for glucocorticoid resistant TAK in Japan, although the primary endpoint of the confirmatory trial was missed.[68] A dose of 162 mg weekly sc is recommended, similar to GCA, and it should be started in combination with glucocorticoids but associated with subsequent glucocorticoid tapering.

Chimeric antigen receptor T cell-induced cytokine release syndrome (level 2c, grade B)

Treatment with chimeric antigen receptor T cells (CAR-T cells), approved for acute lymphoblastic leukaemia and various lymphomas, is associated with a life-threatening cytokine release syndrome. IL-6R inhibition dramatically interferes with the development of this syndrome[69] and has been approved for patients 2 years or older with this indication at a dose of 8 mg/kg (intravenous; 12 mg/kg if weight is <30 kg).[70]

CD, level 2b/1b, grade B

Idiopathic multicentric CD (MCD) is a lymphoproliferative disorder characterised by dramatic overproduction of IL-6. For many years, it has been known that IL-6R inhibition can be successfully used to interfere with the disease.[71] Tocilizumab is approved for the treatment of MCD in Japan at an intravenous dose of 8 mg/kg every 2 weeks or 162 mg sc weekly. The approval was based on the results of an open-label prospective study. IL-6 blockade with siltuximab is efficacious in treating MCD, as demonstrated in a RCT,[72 73] and this therapy has been approved in Europe, the USA and other areas at an intravenous dose of 11 mg/kg every 3 weeks.

Neuromyelitis optica spectrum disorder (level 1b, grade A)

Satralizumab, a humanised anti-IL-6R antibody, has proven efficacious in this disease[74 75] and has been approved in the USA and Japan at an SC dose of 120 mg at weeks 0, 2 and 4 and every 4 weeks thereafter with or without immunosuppressive agents.

Further potential indications

IL-6R inhibition has been studied in polymyalgia rheumatic (PMR). Case series and a subgroup analysis of patients with GCA with PMR symptoms suggested efficacy[76 77] and a recent phase II/III RCT provided clarity regarding good efficacy and acceptable safety in PMR.[78]

Tocilizumab was also studied in systemic sclerosis and current data suggest an effect on lung function but not skin changes[79 80]; it was recently (after the consensus meeting) approved by the FDA for slowing the rate of decline in pulmonary function in adults with systemic sclerosis-associated interstitial lung disease.

IL-6 blockade has been studied in many other diseases. IL-6R or IL-6 inhibition clearly failed to show efficacy in axial spondyloarthritis,[81–83] psoriasis, psoriatic arthritis[84] and Sjögren's syndrome,[85] and its role in systemic lupus erythematosus is still unclear; phase I/II studies showed some benefit but did not provide convincing results.[86 87] All these trials are mentioned in the SLR publication and will not be further addressed here.[38]

Finally, given that severe COVID-19 is associated with hyperinflammation[88] and IL-6R blockade with tocilizumab and sarilumab has a significant beneficial effect in critically sick patients

in retrospectively and prospectively evaluated patients,[89–92] sarilumabS-CoV-2 infection with severe pulmonary manifestations may be yet another indication for IL-6 blockade. After the TF meeting, on 6 July 2021, the WHO recommended the use of IL-6 receptor blockade for severely ill patients with COVID-19.[93] The US FDA (emergency authorisation) and European Medicines Agency (EMA) have approved IL-6R blockade for this indication.[94 95]

Disease management and outcome (with a focus on RA)

Disease management in the context of IL-6 pathway inhibition involves several considerations. First, the right indication must be present. Then appropriate precautions need to be taken to ensure optimal patient safety. Finally, monitoring and the choice and performance of outcome measures need to be considered. The indications and precautions are discussed in sections above and below. In addition, however, it would be desirable to have biomarkers available that may predict efficacy and/or toxicity. Moreover, clinical assessment also requires specific considerations when applying IL-6 pathway blockers. The available evidence for predictive biomarkers and outcome measures in the context of treatment with IL-6 blocking agents is summarised below.

Current evidence suggests associations of some biomarkers with response to IL-6 blockade: these include that low pretreatment IL-6 levels are predictive of response to tocilizumab or to sustained effectiveness after its cessation.[96 97] High pretreatment C reactive protein (CRP) level may serve as an indicator of better response compared with low baseline CRP levels, contrasting with other drugs.[98] Interestingly, the data on CRP levels as predictive of a good respone to tocilizumab[98] find a correlate in IL-6 levels as also being predictive for a good response to sarilumab.[99] Data on obesity and lower treatment response are controversial.[100–102]

The preferred tool for assessing activity in patients with RA treated with IL-6 blockade is a composite measure, such as the simplified disease activity index (SDAI) and/or CDAI. CDAI is preferred, since SDAI includes an APR; other measures like the DAS or DAS using 28 joint counts (DAS28) also incorporate levels of APRs, although at a high weight,[55 56] which is problematic given the effect of IL-6 inhibition on CRP levels and ESR. An improvement of APR in response to IL-6 blockade may be profound despite lack of clinical improvement, thus confounding the interpretation of the response. One should be vigilant for the timely detection of serious infection, as signs and symptoms of acute inflammation may be lessened during treatment with IL-6 pathway inhibitors; patients consequently are at risk of undetected infection because of the effects of IL-6R inhibitors on CRP, neutrophils and signs and symptoms of infection, such as fever. This is particularly relevant in younger children with sJIA or pJIA who may be less able to communicate their symptoms. In summary, it is recommended to thoroughly and cautiously evaluate patients on these treatments and use the CDAI as the preferred metric (level 5, grade D) to measure disease activity in RA. The issues related to use of IL-6 blockade and interference with disease assessment tools are also relevant for several other diseases for which IL-6 blockade is indicated or is being investigated.

In line with prior recommendations, assessment of disease activity in RA should be done every 3 months, aiming at a significant improvement (>50%) within 3 months and attaining low disease activity (CDAI ≤10, SDAI≤11, DAS28 <3.2) or remission (using ACR-EULAR remission criteria[46] within 6 months (level 5, grade D)).[12] If a patient does not achieve low disease activity within 6 months at an adequate dose (or does not experience a significant improvement of disease activity within 3 months) another treatment option should be considered (level 5, grade D).

With respect to patient adherence, one study in RA identified low initial CRP, high Health Assessment Questionnaire Disability Index (HAQ), high fatigue and pain, smoking and prior exposure to bDMARD as predictors of discontinuation of tocilizumab.[103] Persistence with tocilizumab was not different between monotherapy or for combination with methotrexate versus monotherapy.[104] Tocilizumab-treated patients exhibited a similar response to those receiving other bDMARDs, among patients with RA who had previously received ≥1 bDMARD.[105] As expected, patients who were biologic naive showed numerically better improvements in all patient-reported outcomes (pain, fatigue, patient global assessment of disease activity, morning stiffness) than patients previously exposed to bDMARDs. Patients treated with tocilizumab or sarilumab monotherapy reported greater improvements across multiple patient reported outcomes (PROs) compared with csDMARD or TNFi (adalimumab) monotherapy in clinical trials.[106–108] With respect to the route of administration, one small observational study showed that patients with JIA switching from intravenous to sc route experienced better efficacy and quality of life, school successand reduced school absenteeism.[109]

A final management aspect relates to the use of glucocorticoids when IL-6 pathway blockade is used. Glucocorticoids, especially if used at doses >5 mg prednisone equivalent per day or for prolonged periods of time, are associated with significant adverse events, not the least of which is cardiovascular adverse events.[110 111] However, it has been observed that many patients with RA in registries or who enter clinical trials continue their glucocorticoid therapy at doses of 5 mg/day or higher. There are increasing data that even prolonged so-called 'low-dose' daily glucocorticoids is associated with a substantial increase in the risk of infections.[112 113] In a recent study, among patients with RA on tocilizumab who either continued or tapered glucocorticoids one third experienced a flare of disease activity on withdrawal of glucocorticoids, but in two-thirds no flares were observed.[114] Similarly, the importance of using IL-6R inhibition in patients with other diseases, such as GCA, relates to the need of prolonged glucocorticoid use and consequent adverse events, especially in the elderly population of patients with GCA,[115] allowing for the reduction and possible discontinuation of glucocorticoids more rapidly. The appropriate duration of treatment for GCA with IL-6R inhibition remains unclear. However, data from an open-label extension study of the GiACTA trial demonstrated that among those patients who were taking tociliuzmab in the double-blind portion of the trial and remained in remission at the end of 1 year, 42% remained in remission off glucocorticoids and tocilizumab during 2 years of follow-up.[116] This implies that although long-term remission can be seen after the use of IL-6 inhibition for GCA, relapses still occur in the majority of patients once treatment is discontinued. The pest treatment strategy for patients with GCA, therefore, remains elusive with options including low-dose glucocorticoids, methotrexate, tocilizumab or some combination of these drugs.

Cost-effectiveness of the use of IL-6 inhibition

The evaluation of cost-effectiveness of compounds is complex and ever-changing, as costs of expensive drugs vary considerably across and within countries, healthcare systems, insurance plans

and especially when biosimilars become available in a given market. While cost-effectiveness studies are important, these were mostly if not exclusively industry-sponsored and most of these studies came from the USA.[105 117–120] Therefore, we will not address these studies further here. Once biosimilars of the first IL-6R inhibitor, tocilizumab, become available new analyses may provide valuable information.

Pretreatment screening (level 5, grade D) and contraindications associated with the use of IL-6 blocking agents (level 5, grade D)

As with all agents for the treatment of inflammatory diseases, to mitigate and minimise the risk of adverse effects, several investigations need to be undertaken prior to initiating treatment with IL-6 blockade. These screening procedures include a history and physical examination to evaluate the presence of contraindications or settings where the compound needs to be used cautiously. True contraindications are limited to: (1) hypersensitivity to the active substance or to any of the excipients, (2) active severe infections or a history of recurring or chronic infections or (3) specific underlying conditions, especially including diverticulitis.[121] There are several special warnings and clinical scenarios that are relevant for consideration before initiating therapy with an inhibitor of IL-6R. It is advised to screen for latent tuberculosis, active hepatitis B or C virus infection, severe hepatic disease, a history of gastrointestinal ulcers (or symptoms suggestive of such), altered blood cell counts, severe lipid disorder or a history of malignancies.

Vaccinations should be performed according to established recommendations and ideally before the administration of tocilizumab; live vaccines should be avoided during therapy with tocilizumab. Several recent open-label studies of vaccination suggested that IL-6R inhibition with tocilizumab did not hamper antibody response to influenza, pneumococcal vaccine or tetanus toxoid vaccine.[122–125] Concomitant methotrexate had a negative effect on antibody response when tocilizumab was used.[123] The efficacy of influenza vaccination did not differ significantly between the tocilizumab-treated patients with sJIA and healthy controls.[126] EULAR strongly recommends the use of COVID-19 vaccination and, to date, there is no indication that IL-6R agents hamper the development of an immune response to SARS-CoV-2 vaccines.[127–129]

Safety (level 2b, grade B)

Safety issues are the major concern with any type of new treatment, and this is raised due to a lack of sufficient power to detect all relevant signals from short-term RCTs, the unique populations generally recruited to clinical trials and the usually prolonged absence of long-term data from extension studies or real-life evidence from registries or market data. For IL-6R blockade, all these sources exist and, thus, evidence-based consensus conclusions are presented here.

Infections

Infectious adverse events of particular significance include severe infections, opportunistic infections and infections of special interest (eg, hepatitis, herpes virus infection). Tocilizumab showed an increased risk for septicemia, diverticulitis, pneumonia/upper respiratory tract infections and skin infections, with statistical significance in individual studies comparing these rates to TNF inhibitors, but without consistent replication across those studies, and with significant variability.[130–133] Overall, serious infectious adverse events and the risk of hospitalisation for infection were comparable to other biologics. Similarly, IL-6 inhibition with tocilizumab did not show an increased risk for herpes zoster, opportunistic infections or tuberculosis compared with TNF inhibition or abatacept.[130 134 135] No new data since the previous consensus statement exist to modify the respective conclusions about hepatitis B or C viruses and the use of tocilizumab, where it should either be avoided or antiviral treatment should be used. In postmarketing data from Japanese patients who had a history of hepatitis B or C viruses or who were carriers, none of these patients experienced virus reactivation (with or without hepatitis) after exposure to tocilizumab.[136] To reiterate a previously made point, when treatment with IL-6-inhibitors is applied, clinicians should be aware that the diagnosis of infectious events may be delayed secondary to the absence of elevations of acute-phase response markers and potential interference with signs and symptoms of infections.

The risk of serious infection does not appear elevated with the use of tocilizumab for the treatment of GCA or systemic sclerosis; however, the size of the relevant populations with these diseases studied has been quite small and include patients selected for inclusion in clinical trials.[66 116 137 138] More research is needed to better understand the risk of infection in these patients, who are often particularly vulnerable to the impact of infection.

Malignancies

Sources of data on any association of IL-6R inhibition with malignancies come from registries and claims databases that indicate no increased risk for the overall incidence of cancer, or specific types of cancer. In general, with the notable exception of non-melanoma skin cancer, compared with csDMARD-treated patients in the general RA population, tocilizumab was associated with a reduced HR of developing a malignancy.[139 140]

Gastrointestinal and hepatic events

The increased risk for gastrointestinal perforations requiring hospitalisation, and, particularly, lower gastrointestinal tract perforations with treatment with tocilizumab, compared with other bDMARDs, have been confirmed in recent studies.[141 142] Therefore, approaches for continuous risk mitigation are required, including an evaluation for risk factors for perforations such as a history of diverticulitis or gastro-intestinal (GI) ulcers, older age or use of glucocorticoids or non-steroidal anti-inflammatory drugs. Transaminase elevations >1–3 × upper limit of normal (ULN) occurred in more than half of patients treated with tocilizumab in one large pooled RCT cohort and were more frequently observed when combined with MTX than as a monotherapy; rates of severe hepatic adverse events occurred in 0.04/100 patient years.[143]

Lipid levels (level 1b, grade A)

The MEASURE trial investigated the effects on lipid levels of tocilizumab compared with placebo in a MTX-IR population.[144] The median total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglyceride levels increased in patients treated with tocilizumab compared with placebo. Similar findings were made when comparing tocilizumab to adalimumab, with LDL-C and HDL-C both increasing significantly more with tocilizumab than with adalimumab.[145] However, tocilizumab likely favourably modified the lipid profile towards an anti-inflammatory composition.

Haematologic events

Effective treatment of chronic inflammatory systemic disease is expected to improve anaemia of chronic disease; this effect may be blunted by negative or adverse effects on the red blood cell count. Compared with other biologic and non-biologic DMARDs, IL-6 inhibition with tocilizumab has been shown to significantly increase haemoglobin and hematocrit levels in anaemic and non-anaemic patients with RA[146]: this is, at least partly, due to interference with the hepatic production of hepcidin, an acute phase protein which inhibits gastrointestinal iron absorption.[147] In a pooled analysis of phase III and IV trials of tocilizumab, more tocilizumab-treated than placebo-treated patients were observed to have grade 1/2 or 3/4 neutropenia.[148] Rates of serious infections were similar in patients with normal neutrophil counts, and those with grade 1/2 or grade 3/4 neutropenia. In generl, neutrophil counts decreased through week 6 from baseline and remained stable thereafter; thrombocytopenia may also occasionally occur. Data from the phase 2 dose-ranging study (CHARISMA) suggest both neutropenia and thrombocytopenia are pharmacodynamic effects with a 'sawtooth' pattern of dipping 2 weeks after an infusion and recovery by the next dose.[149] Tocilizumab can also induce macrophage activation syndrome (MAS), especially in children.[150] While MAS has also been reported with other IL-6 blocking agents,[151] it is of concern primarily with IL-6R blockade and requires rapid recognition and appropriate therapeutic interventions.

Cardiovascular safety and venous thromboembolism (including pulmonary embolism; level 1b, grade A)

Evaluation of the existing evidence suggests that, in the general RA population, IL-6 inhibition with tocilizumab is not associated with an increased risk of cardiovascular events compared with other DMARDs, particularly TNF-inhibitors, abatacept or rituximab. The ENTRACTE trial was designed to rule out a higher risk for cardiovascular events with tocilizumab versus etanercept.[152] The results showed that cardiovascular risk is not increased with tocilizumab but that there were also no differences in deep vein thrombosis or pulmonary embolism (events per 100py: 0.2/0.06 for tocilizumab; 0.3/0.2 for etanercept (ETN)). Additional analyses based on claims databases also concluded that there was no increase in MACE in tocilizumab patients.[153–155]

Other adverse events of interest

IL-6 inhibition does not appear to worsen diabetes mellitus.[156] In a study of sarilumab, an even greater reduction in serum haemoglobin A1c (HbA1c) was seen compared with placebo (PBO) or adalimumab at week 24 in patients with a baseline HbA1c ≥7%0.[157] Similarly, tocilizumab demonstrated a stable safety and tolerability profile in patients with RA and renal insufficiency, regardless of MTX use,[158] and may, thus, be a treatment option for patients with RA and concomitant renal insufficiency. Recent observational studies of tocilizumab did not detect an increased risk of interstitial lung disease,[159] demyelinating disease or idiopathic facial nerve palsy[160]; on the contrary, IL-6R inhibition was shown to be efficacious in one open-label trial in demyelinating disease.[161] There was no difference in the incidence of osteoporotic fractures in patients treated with tocilizumab compared with those receiving TNF inhibitors[162]; tocilizumab has been found to positively affect bone turnover and improve bone mineral density, also in patients positive for anticitrullinated peptide antibodies.[163 164]

Safety considerations with other biological IL-6 pathway inhibitors

Sarilumab and sirukumab are the two other IL-6 pathway inhibitors with the largest body of data. Sarilumab, an IL-6R-inhibitor, is approved for RA based on several phase-3 clinical trials and extension data. The data from these trials suggest that its safety and tolerability profiles are consistent across studies and comparable with tocilizumab, with no new safety signals emerging.[165] This is different from sirukumab, a direct inhibitor of the IL-6 cytokine, which was not approved by the FDA in 2017 because of a numerically higher mortality rate among patients treated with sirukumab compared with controls.[166 167] Cardiovascular events, infections and malignancies were the most common causes of mortality.[168 169]

Hypersensitivity reactions

In a study on more than 3000 patients with subcutaneous tocilizumab and almost 6000 patients with intravenous tocilizumab, there were approximately 1% hypersensitivity reactions (not injection site reactions), observed with both formulations; however, claims data suggest much more frequent hypersensitivity reactions with the intravenous route with 20%–40% of the reactions considered serious.[170] The reactions were not related to the presence of antidrug antibodies.[171] For sarilumab, which is only available in a subcutaneous formulation, 0.3% of patients had hypersensitivity reactions leading to treatment discontinuation.[172]

Safety in pregnancy

Analyses of pregnant women exposed to tocilizumab from the global safety database revealed that preterm birth (before week 37) occurred in about one-third of the prospectively reported pregnancies; elective termination was performed in 17.2% of pregnancies, and 21.7% of pregnancies ended in spontaneous abortion.[173] These data are not different from observations with anti-TNF agents[174] and may be mostly due to higher disease activity in patients on biologic agents; disease activity is a known risk factor for preterm delivery.[175] There is no increased risk of malformations. No increased risk of adverse pregnancy outcomes for fathers exposed to IL-6R blockade has been observed.[173]

Research agenda

As always, when deriving a consensus statement or recommendations, one finds many questions which have not been answered sufficiently in the literature. However, many questions have been addressed and the respective information can be found in the SLR paper. Questions that were posed in the first version of this statement but have not received satisfactory answers will be repeated here as well other questions that arose in the course of the present deliberations.

1. Different drugs targeting the same molecule are approved for different diseases. Can one extrapolate from one anti-IL-6R inhibitor to another one regarding clinical efficacy and safety in the different indications?
2. In RA, can one use anti-IL-6R blockers effectively and safely after one or more JAKinibs have failed?
3. In RA, what is the comparative efficacy of JAK-inhibitors and anti-IL-6, in monotherapy and combination therapy with csDMARDs?
4. What is the efficacy and safety when IL-6 pathway inhibitors are given to patients previously treated with rituximab (with or without persistent B-cell depletion) or abatacept?
5. Does the concomitant use of isoniazid lead to significant increases in liver function test abnormalities in patients with IL-6 inhibitor mono and combination therapy?
6. Is there a need to stop therapy with IL-6-blockers in men before their sperm is used to conceive a child?
7. What is the molecular effect of IL-6R antibodies on target cells?

DISCUSSION

This update of a consensus statement originally compiled almost 10 years ago[17] covers a variety of novel developments. First, two additional IL-6R blockers, sarilumab, silltuximab and satralizumab, have been licensed and are in clinical use for the approved indications. Second, new indications for IL-6R inhibition have been approved, such as GCA, CART-cytokine release syndrome, NMOSD, interstitial lung disease in systemic sclerosis and severe COVID-19. While sarilumab is only approved for RA, satralizumab only for NMOSD and siltuximab only for Castleman's disease, it can be assumed that all these agents have efficacy across the indication profile. Third, expectations that IL-6 ligand inhibitors would become available were not met when the development of sirukumab was stopped after the results of several phase 3 trials were completed. Another monoclonal antibody to IL-6, olokizumab, is already approved in Russia and currently in late-phase development for other regions. Fourth, and most importantly, much more information on the long-term adverse event profile both from clinical trials and registries is available today than a decade ago, providing reassurance of the safety of IL-6R blockade.

This update, like the original version, is primarily based on evidence from clinical trials and, therefore, most of the items have a high LoE and grade of recommendation. However, clinical trials do not provide data for substantial numbers of adverse events or long-term outcomes. For this reason, results from observational studies were included. Only a few points are based on low evidence levels or expert opinion. Those with low evidence need to be clarified by further research.

This consensus statement, like others, has been developed to provide guidance to not only rheumatologists and other experts but also patients and administrators, on what the TF regards as state-of-the-art in the context of managing patients with the use of drugs blocking the IL-6 pathway. The individual points presented in table 2 constitute a summary of the discussions and the text in the Results section should be considered as an integral part of these recommendations. The TF did not include JAKinibs, since (1) a consensus statement on the use of these agents was published recently[2] and (2) JAKinibs inhibit not only signal transduction of IL-6 but also interferons and other cytokines; consequently, JAKinibs have a different profile and other safety issues may be relevant.

In summary, blocking the IL-6R is a major therapeutic advance for many diseases in adults and children. This article summarises the current state of these agents in terms of efficacy and safety, and the data regarding these areas have significantly advanced since the time of the first version of this consensus statement. Future research will provide even more insights and allow further expansion of these drugs' profile for the benefit of patients with a large spectrum of inflammatory diseases.

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