Consensus statement on blocking interleukin-6 receptor and interleukin-6 in inflammatory conditions: An update

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Abstract

Background. Targeting IL-6 has become a major therapeutic strategy in 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 inhibiting the IL-6 cytokine directly. This is an update of a previous consensus document aiming to inform on the interference with the IL-6 pathway based on evidence and expert opinion.

Methods. A systematic literature search was performed that focused on IL6-pathway inhibitors in rheumatoid arthritis and other 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 covers 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 disease, adult-onset Still's disease, Castleman's disease, CAR-T-cell induced cytokine release syndrome, neuromyelitis optica spectrum disorder. Furthermore they cover aspects of pre-treatment screening, safety, contraindications, and monitoring.

Conclusions. The document provides a comprehensive consensus on IL-6 pathway inhibitors to inform patients, administrators and payers.

Introduction

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

In addition to all these medicines, strategic trials have been performed[3-9] which not only inspired the development of treat-to-target recommendations,[10] but also informed 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 dwell deeply in 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 over the years.[2;14-16] One of these consensus statements addressed inhibition of the IL-6 receptor, dealing in detail with all important aspects of efficacy and safety in patients with RA.[17]

Importantly, however, rheumatology has spearheaded therapeutic developments in other 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 of the 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 even called B-cell stimulating factor), and it is also

importantly involved in the generation of T helper (h) 17 cells which produce IL-17.[22;23] In the context of rheumatoid arthritis and other immune mediated inflammatory diseases (IMIDs), it is pivotal in the generation of the overall inflammatory response, joint damage based on its capacity to activate matrix metalloproteinases and osteoclasts,[24;25] aside from being the major driver of acute phase reactant production.[26]

IL-6 is not only the most abundant cytokine in the circulation, it also uses a variety of means to bind to and activate target cells either directly or indirectly. IL-6 always binds to its cognate receptor IL-6Rα, but this receptor is located either on the cell surface or cleaved into a soluble form. The IL-6Rα chain, even if membrane bound, has no intracellular signaling moiety and requires a co-receptor, gp130 or IL-6Rβ, to transmit information to the nucleus. To this end, Janus kinases (JAKs), a series of non-receptor tyrosine kinases, are activated which phosphorylate signal transducer and activator of transcription proteins (STATs), the respective transcription factors. Signaling 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.[27] Interestingly, many cells express gp130 without the IL-6Rα chains. However, soluble IL-6R (sIL-6R) is present at high blood levels, can bind IL-6 in the circulation, and then interact with membrane gp130 on various cell populations, a process called transsignaling (as opposed to classical signaling). More recently, a third signaling mechanism has been recognized, namely trans-presentation, where IL-6Rα present on a cell surface, after having bound IL-6, can interact with a gp130 molecule expressed on another cell.[21;28]

Targeting IL-6 has become a major therapeutic opportunity to combat inflammation. Generally, one can interfere with IL-6 directly or prevent its binding to the specific receptor using anti-IL-6Rα antibodies. While , already in very early days xenogeneic monoclonal antibodies against IL-6 have been tested,[29] humanized and human anti-IL-6 molecules, such as sirukumab, olekizumab or clazakizumab, have been developed and tested in various clinical trials since then, but none has been approved hitherto. In contrast, a humanized monoclonal antibody targeting IL-6Rα, tocilizumab, has been licensed more than a decade ago for RA and has been used successfully in this and other indications. More recently, a human antibody against IL-6Rα, sarilumab, has also been approved for RA, a further expansion of the specific approach to inhibit IL-6 mediated inflammation. A third possibility to interfere with IL-6 effects is by inactivating the “IL-6 - IL-6Rα complex” with a sgp130 Fc receptor construct like Olamkicept. However, this molecule is in early phase development and likely would 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 many more cytokines and growth factors use the JAK-STAT pathway, as described in a recent consensus statement on the use of JAK inhibitors.[2]

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. Since then, several IL-6 directed antibodies underwent phase III trials; tocilizumab was licensed for many more indications; and sarilumab was approved as the second anti-IL-6Rα for RA and several head-to-head trials employing anti-IL-6Rα antibodies have been performed. In addition, much more safety information is available today, including information from registries, since the previous consensus statement.

For all these reasons it was deemed timely to revisit the previous consensus statement and to advance it to include the most recent insights into indications, efficacy and safety by assessing the evidence accrued since the previous version of the statement, discussing this evidence among experts in IMIDs as well as patient representatives and developing an updated consensus document to reflect the current state of the art.

MOLECULAR ASPECTS OF IL-6R and IL-6 INHIBITION

Before dwelling on the updated consensus statement, 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.[30] Thus, these monoclonal antibodies prevent the binding of IL-6 to its soluble and cell surface receptors; as a consequence of this inhibition, IL-6 levels increase in the circulation (without leading to inflammatory responses). ALX-0061, a nanobody, targets the same site but has not yet undergone clinical studies in detail.[30;31] 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 of yet not undergone clinical trials.[32]

The IL-6 cytokine has several functional regions.[33]A Site 1 is the main binding site to the cognate IL-6R and is inhibited, among others, by siltuximab, sirukumab (the human version of siltuximab[34]) and clazakizumab.[30] 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,[30] which also interacts with gp130, has not yet been studied for human disease but is available for experimental work.[35]

Thus, there is an inherent complexity not only regarding the potential interactions between IL-6 and the various forms of its receptors, but agents blocking the ligand, or the receptor can interact with different sites of these molecules. This complexity regarding therapeutic approaches to interfere with the IL-6 pathway is further enhanced by our ability to inhibit signal transduction with JAK-

inhibitors, but these compounds will not be addressed in the present consensus statement; rather, the focus here will be solely on the respective bDMARDs.

METHODS

Two convenors (DA and JS) brought a Task Force (TF) together based on the expertise regarding the specific task to develop an update of the Consensus Statemen 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 task force had to include experts from areas beyond adult rheumatology. First, a Steering Committee (SC) was formed which consisted of a patient representative (MV), a health professional (TS), a gastroenterologist (MT), a cardiologist and metabolism expert (NS), an infectious disease specialist (KW), a pediatric rheumatologist (AR), nine adult rheumatologists with various scientific focusses from basic to clinical research, a fellow (KK) and a methodologist (AK). The SC members came from several European Countries, Japan (TT) and USA (KW). The SC was charged to first develop questions for the systematic literature research (SLR). Once the fellow had 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, MdW), seven additional rheumatologists from North America, Japan (YT) and Australia (PN), and 14 additional rheumatologists from several European countries. The special research focus of several of the rheumatologists span from vasculitis to systemic lupus erythematosus and included colleagues with a vast experience in leading registries and cardiovascular medicine. 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 (SoR) according to the Oxford Evidence Based Medicine approach.[37]

As suggested in the EULAR standard operating procedure, 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. 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 items.

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 respective last ballot 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 task force 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.

CONSENSUS STATEMENT ON THE USE OF IL-6-PATHWAY INHIBITORS

The consensus statement on the use of IL-6 pathway inhibition covering indications, management, safety, and other aspects, are shown in Table 1. In the following, we will address some details of the task force's deliberations and conclusions.

Indications, considerations and screening for treatment initiation, dosing

Indication

ADULT RA

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 were performed since then and are addressed in the SLR as detailed in the respective document.[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 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 was further supported by a recent study comparing tocilizumab with rituximab.[44] Registry data reveal similar efficacy among bDMARDs.[45]

Outside the USA, the approved dose of TCZ should is 162mg sc weekly and the iv dose is 8mg/kg every 4 weeks. In the USA, the recommended starting dose is 162mg sc every other week or 4mg/kg iv every 4 weeks to be followed by 162mg sc weekly or 8mg/kg iv with insufficient response to the lower dose. The reasoning behind the 162 mg every other week and 4mg/kg dosing was based on the FDA's perceived safety concerns despite being much less efficacious in clinical trials; the lower dose has also been associated with more hypersensitivity reactions. The approved dose of SAR is 200mg sc, every 2 weeks. Dose reductions (interval increase for TCZ sc; reduction to 4mg/kg for TC iv; or decrease to 150mg SAR sc every 2 weeks) should be considered in case of serious infections or persistent cytopenia. Interval increases or dose decreases should be considered when patients reach stable ACR-EULAR Boolean or index-based remission, in line with the respective management recommendations. Combination with MTX is the treatment of choice and more efficacious than monotherapy with both SAR and TCZ. Details on dose tapering and combination are provided in the SLR paper.

With respect to efficacy after failure of TNF-inhibitors, some open label clinical trials suggested that non-TNF-inhibitors including tocilizumab were more efficacious than a second TNF-inhibitor,[46] 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 TCZ is higher when combined with MTX compared with TCZ monotherapy according to several studies.[47-49] While other studies suggest non-inferiority of withdrawing versus continuing MTX in combination with tocilizumab, the evidence favors the demonstration of 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 have an advantage over other bDMARDs.[12;50]

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, since there was no difference in efficacy if patients failed TNF inhibitors or tocilizumab.[51]

Response rates according to the American College of Rheumatology (ACR) improvement criteria[52] as observed in phase III clinical trials, have consistently shown superiority compared with control arms. A significant decrease in the disease activity score using 28 joint counts (DAS28) and high proportions of European League Against Rheumatism (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 acute phase reactant (APR) component in the DAS28 formula[53;54] and the prominent effect of IL-6 inhibition on the hepatic APR production, which can lead to exaggerated improvement of response rates if this measure is employed. Nevertheless, the pre-eminent requirement for improvement in both swollen and tender joints to fulfill ACR improvement criteria and the published clinical trial data showing a decrease in disease activity across all variables studied as well as functional improvement and structural effects, provided solid evidence that tocilizumab is an effective bDMARD. Indeed, when looking at the clinical disease activity index (CDAI), a score that does not comprise an APR in its formula,[55] sarilumab and TCZ were also significantly more efficacious compared to the respective comparators, placebo or anti-TNF as a monotherapy.[39;40;48] Of note, as mentoned previously, in combination with MTX, the efficacy of anti-IL-6R agents appears to be of similar magnitude as that of TNF-inhibitors, abatacept and rituximab[1;41-43] (level 1a, grade A).

OTHER INDICATIONS

IL-6R and IL-6 blockade is 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), systemic JIA (sJIA; level 1b, Grade A) and adult-onset Still's disease (AoSD; level 1b, Grade A)

As for the other indications, the approval for pcJIA, sJIA and AoSD is based on randomized controlled clinical trial data. However, the number of trials available are fewer than those for RA.

For children above 2 years with active *pcJIA* non-responsive to MTX, TCZ is approved at an iv dose of 8mg/kg every 4 weeks at a weight of 30kg or more and 10mg/kg every 4 weeks at a weight of <30kg. These data are based on the CHERISH trial.[56;57] The s.c. dosing is 162mg every 2 weeks for children ≥30kg and every 3 weeks for those <30kg.[58] It is recommended to combine TCZ with MTX (whether

seropositive or seronegative), unless not tolerated. It is expected that sarilumab will show similar efficacy as tocilizumab in pcJIA, but the trial (NCT02991469) has not yet been completed.

In *sJIA* the recommended iv dose is 8mg/kg every 2 weeks at a weight of 30kg or more and 12mg/kg every 4 weeks at a weight of <30kg.[59;60] The s.c. dose is 162mg weekly or every other week for children ≥30kg and <30kg, respectively.[58]

For *AoSD* with insufficient response to glucocorticoids, tocilizumab is approved in Japan at an iv dose of 8mg/kg every 2 weeks with a possibility of weekly infusions if the response is inadequate.[61;62]

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

A large study in GCA patients (GiACTA) was successful and was the basis for approval of TCZ for patients with new onset or relapsing disease, particularly those at risk of glucocorticoid-related adverse events.[63] The approved dose is 162mg s.c. weekly to be started in combination with glucocorticoids but alongside subsequent glucocorticoid tapering. Inaddition to the pivotal clinical trial, many case series and one other but small randomized controlled trial (RCT) have been published.[64]

IL-6R inhibition with TCZ is also approved for glucocorticoid resistant TAK in Japan, although the primary endpoint of the confirmatory trial was missed.[65] A dose of 162mg weekly s.c. is recommended; similar to GCA, it should be started in combination with glucocorticoids but associated with subsequent glucocorticoid tapering.

CAR-T cell induced cytokine release syndrome (CART-CRS; level 2c, Grade B)

Treatment with chimeric antigen receptor T cells (CAR-T cells), approved for acute lymphoblastic leukemia and various lymphomas, is associated with a life-threatening cytokine release syndrome. IL-6R inhibition dramatically interferes with the development of this syndrome[66] and has been approved for patients 2 years or older with this indication at a dose of 8mg/kg (iv; 12mg/kg if weight is <30kg).[67]

Castleman's disease (CD, level 2b/1b, Grade B)

Idiopathic multicentric CD (MCD) is a lymphoproliferative disorder characterized 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.[68] TCZ is approved for the treatment of MCD in Japan at an iv dose of 8mg/kg every 2 weeks or 162mg 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,[69;70] and this therapy has been approved in Europe, US and other areas at an iv dose of 11mg/kg every 3 weeks.

Neuromyelitis optica spectrum disorder (NMOSD; level 1b, Grade A)

NMOSD is an autoimmune demyelinating disease distinct from multiple sclerosis. Inflammatory lesions are located in the optic nerve, brainstem, and cerebrum, but can also be found in the spinal cord. Motor and sensory impairment, bladder dysfunction and vision loss are some of the symptoms of this disease.[71] In contrast to IL-6 pathway inhibition, the various therapies for multiple sclerosis are not effective in NMOSD.[72;73] Indeed, satralizumab, a humanised anti-IL-6R antibody, has proven efficacious in this disease and has been approved in the USA and Japan at a 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 GCA patients with PMR symptoms suggested efficacy[74;75] and a recent phase II/III RCT provided clarity regarding good efficacy and acceptable safety in PMR(REF).

Tocilizumab was also studied in systemic sclerosis and current data suggest an effect on lung function but not skin changes;76;77 it has recently (after the consensus meeting) been approved by the FDA for slowing the rate of decline in pulmonary function in adults with systemic sclerosis-associated interstitial lung disease.

Many other diseases have been studied. IL-6R or IL-6 inhibition clearly failed to show efficacy in axial spondyloarthritis[78-80] and psoriatic arthritis, but its role in systemic lupus erythematosus is still unclear, though phase I/II studies did not provide overwhelmingly convincing results[81;82]. 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[83] and IL-6R blockade with tocilizumab and sarilumab has a significant beneficial effect in critically sick patients in retrospectively and prospectively evaluated patients,[84-87] SARS-CoV-2 infection with severe pulmonary manifestations may be yet another indication, and indeed, after the meeting, on July 6, 2021, the World Health Organization recommended the use of IL-6 receptor blockade for severly ill COVID-19 patients.[88] The US FDA (emergency authorization) and EMA have meanwhile approved IL-5R blockade for this indication.[89;90]

DISEASE MANAGEMENT AND OUTCOME (with a focus on RA)

Disease management in the context of IL-6 pathway inhibition concerns 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 dedirable to have biomarkers available that may predict efficacy and/or safety issues. Moreover, clinical assessment also requires specific considerations when applying IL-6 pathway blockers. The available evidence for predictive biomarkers and outcome measures will be summarized in the following.

Current evidence suggest association of some biomarkers with response: these include low pre-treatment IL-6 levels that are predictive of response to tocilizumab or to sustained effectiveness after its cessation.[91;92] High pre-treatment C-reactive protein level may serve as an indicator of better response compared with low baseline CRP-levels, contrasting other drugs.[93] Interestingly, the data on predictive CRP-levels for a good tocilizumab response[93] find a correlate in predictive IL-6 levels for a good sarilumab response.[94]Data on obesity and lower treatment response are more controversial.[95-97]

Disease activity assessment should be typically done using composite measures of disease activity, such as DAS, DAS28, SDAI and/or CDAI. CDAI is the preferred metric, as the others include a measure of the APR which Is problematic given the effect of IL-6 inhibition on CRP levels and ESR. An improvement of APR may be profound despite lack of clinical improvement confounding the interpretatioin 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 may be at risk of undetected infection, because of the effects of IL-6R inhibitors on CRP, neutrophils as well as signs and symptoms of infection. 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 either thoroughly and cautiously evaluate patients on these treatments, and alternatively use the CDAI (level 5, grade D).

In line with prior recommendations, disease activity assessment 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[98]) 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 RA study identified low initial CRP, high HAQ, high fatigue and pain, smoking and prior exposure to bDMARD as predictors of TCZ discontinuation.[99] Persistence with tocilizumab was not different in combination with methotrexate than as a monotherapy[100] and tocilizumab treated patients exhibited a similar response as those receiving other bDMARDs, among patients with RA who had previously received ≥1 bDMARD.[101] As expected, patients who were biologic naive showed numerically better improvements in all patient reported outcomes (pain, fatigue, patients global assessment of disease activity, morning stiffness) than patients who were were already exposed to bDMARDs. Patients treated with tocilizumab or sarilumab monotherapy reported greater improvements across multiple PROs compared to csDMARD or TNFi (adalimumab) monotherapy in clinical trials.[102-104] With respect to the administration, one small observational study showed that patients with JIA switching from IV to SC route experienced better efficacy and quality of life, school success, and reduced school absenteeism.[105]

A final aspect relates to the use of glucocorticoids when IL-6 pathway blockade is applied. Glucocorticoids, especially if used at doses >5mg 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. [106;107] However, it has been observed that many RA patients in registries or who enter clinical trials continue their glucocorticoid therapy at doses of 5mg daily or higher. In a recent study, among RA patients on TCZ who either continued or tapered glucocorticoids one third experienced and increase of disease activity upon withdrawal of glucocorticoids, but in two thirds no flares were observed.[108] 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 GCA patients,[109] allowing for the reduction and possible discontinuation of glucocorticoids more rapidly.

COST EFFECTIVENESS

The evaluation of cost-effectiveness of compounds has become a moving target, as costs of expensive drugs change in the competitive field as soon as biosimilars become available. Based on an analysis of MarketScan/Medicare datasets, tocilizumab had the lowest real-world healthcare costs, compared to originator infliximab and abatacept.[110] Tocilizumab plus methotrexate showed to be a cost-effective initial biologic treatment for patients with moderate-to-severe RA after failure of one or more csDMARDs,[111] while first line combination therapy of tocilizumab plus methotrexate was not superior to a step-up strategy from methotrexate using a T2T approach over 2 to 5 years in early RA.[112] Using data from the ADACTA trial, costs to achieve clinical response were lower in patients

with RA who received tocilizumab monotherapy than in those who received branded adalimumab monotherapy;[101] In addition, hospitalization costs were lower in patients who received tocilizumab than in those who received adalimumab. In a cost-effectiveness analysis of patients with insufficient response to csDMARDs reported by the manufacturer, sarilumab 200mg plus methotrexate outperformed other bDMARD and tsDMARD treatments (adalimumab, certolizumab, golimumab and tofacitinib) by resulting in lower costs and greater health benefit.[113] However, cost-effectiveneyy studies have mostly been performed among RA patients and more data need to be assembled in other indications. Moreover, comparisons between IL-6R blockers and other bDMARDs were made at a time before biosimilars became available and, therefore, these data are not pertinent for all agents for whom bsDMARDs have been approved. On the other hand, once biosimilars of the first IL-6R inhibitor, tocilizumab, will become available, they may again provide valuable information.

PRE-TREATMENT SCREENING (Level 5, Grade D) and CONTRAINDICATIONS (Level 5, Grade D)

As before all newly introduced therapies, several investigations need to be undertaken to mitigate and minimize the risk of adverse effects. This includes a history and physical examination to evaluate the presence of contraindications or settings where the compound needs to be used cautiously. According to the summary of product characteristics true contraindications are limited to hypersensitivity to the active substance or to any of the excipients, as well as active, severe infections, or a history of recurring or chronic infections; predisposing underlying conditions, such as diverticulitis and diabetes need to be considered.[114] Nevertheless, there exist several special warnings and clinical scenarios that are relevant for consideration before initiating therapy with an inhibitor of IL-6R: it is therefore advised to screen for latent tuberculosis, hepatitis B/C, severe hepatic disease, a previous history of intestinal ulceration or diverticulitis (or symptoms suggestive of such), altered blood cell counts, severe lipid disorder or a history of malignancies.

Vaccinations should be performed in accordance with respective recommendations ideally before the administration of TCZ; live vaccines should be avoided during TCZ therapy. Several recent open label vaccination studies indicated that that IL-6R inhibition with tocilizumab did not hamper antibody response to influenza, pneumococcal vaccine, or tetanus toxoid vaccine.[115-118] EULAR strongly recommends the use of COVID-19 vaccination and except for rituximab there is no indication that biologic agents hamper the development of an immune response to SARS-CoV-2 vaccines.[119-121] Concomitant methotrexate had a negative effect on antibody response when tocilizumab was used.[116] The efficacy of influenza vaccination did not differ significantly between the tocilizumab treated sJIA patients and healthy controls.[122]

SAFETY (Level 2b, Grade B)

Safety issues are the major concern with any type of new treatment modality, and this is linked to a lack of sufficient power to detect all relevant signals from short-term RCTs, and the usually prolonged absence of long-term data from extension studies or real-life evidence from registries or market data. For IL-6 Inhibition with tocilizumab all these sources exist and evidence-based consensus conclusion are presented here.

Infections. Infectious adverse events of major interest include severe infections, opportunistic infections, and infections of special interest (e.g., hepatitis, herpes virus infection). TCZ 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, with significant variability.[123-126] Overall, serious infectious AE and the risk of hospitalisation for infectious AE was comparable to other biologics. Similarly, IL-6 inhibition with TCZ did not show an increased risk for herpes zoster, opportunistic infections or tuberculosis in comparison to TNF-inhibition or abatacept.[123;127;128] No new data exist to modify the conclusion about Hepatitis B/C and the use of TCZ, where it should either be avoided or antiviral treatment should be used. In post-marketing data from Japanese patients who had a history of hepatitis B/C virus or who were carriers, none of these patients experienced virus reactivation (with or without hepatitis) after exposure to TCZ.[129] When treatment with IL6-inhibitors is considered, clinicians should be aware that the diagnosis of infectious events may be delayed secondary to the absence of elevations of acute phase response markers.

Malignancies. For malignancies sources of new data on IL-6R inhibition come from registries and claims databases which indicate no increased risk for overall cancer incidence, or specific cancer types. In general, with the notable exception of non-melanoma skin cancer, compared to csDMARD treated patients in the general RA population, TCZ was associated with a reduced hazard ratio of developing a malignancy.[130;131]

Gastrointestinal and hepatic events. The increased risk for gastro-intestinal perforations requiring hospitalization, and particularly lower GI tract perforations with TZC treatment compared to other bDMARDs has been confirmed in recent studies. Therefore continuous risk mitigation approaches are required, including an evaluation for risk factors such as a history of diverticulitis or GI ulcers, older age, glucocorticoid or NSAID use. Transaminase elevations >1-3x ULN occurred in more than half of patients treated with TCZ in one large pooled RCT cohort. They were more frequently observed when

combined with MTX than as a monotherapy; rates of severe hepatic AEs occurred in 0.04/100 patient years.[132]

Lipid levels (Level 1b, Grade A). The MEASURE trial investigated the effects of TCZ on lipid outcomes in comparison to placebo in an MTX-IR population.[133] It was found that the median total-cholesterol, low-density lipoprotein-cholesterol (LDL-C) and triglyceride levels increased in TCZ in comparison to PBO. Similar findings were made in a comparison of TCZ to ADA, with LDL-C and HDL-C both increased significantly more with TCZ than with ADA.[134] However, TCZ likely favourably modified the lipid profile towards an anti-inflammatory composition.

Haematologic Events. Effective treatment of chronic inflammatory systemic disease is expected to improve anemia of chronic disease; this effect may be blunted by negative or adverse effects on the red blood cell count. IL-6 inhibition with TCZ showed significant increase in hemoglobin and hematocrit levels in anaemic and non-anaemic patients with rheumatoid arthritis, compared to other biologic and nonbiologic DMARDs.[135] In a pooled analysis of phase III and IV trials of TCZ, more TCZ- than placebo-treated patients were observed to have grade 1/2 or 3/4 neutropenia.[136] Rates of serious infections were similar in patients with normal neutrophil counts, and those with grade 1/2 or grade 3/4 neutropenia. Generally, neutrophil counts decreased through week 6 from baseline and remained stable thereafter. Tocilizumab can also induce macrophage activation syndrome (MAS), especially in children[137]). While MAS has also been reported with other IL-6 blocking agents,[138] 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 would suggest that IL-6 inhibition with tocilizumab is not associated with an increased risk of cardiovascular events compared to other DMARDs, particularly TNF-inhibitors, abatacept, or rituximab in the general RA population. The ENTRACTE trial compared tocilizumab to etanercept in a dedicated trial designed to rule out a higher risk for cardiovascular events with tocilizumab versus etanercept.[139] The results showed that cardiovascular risk is not increased with tocilizumab but also that there were no differences in deep vein thrombosis (DVT) or pulmonary embolism (PE) (events per 100py: 0.2/0.06 for TCZ; 0.3/0.2 for ETN). Additional analyses based on claims databases also concluded that there was no increase in MACE in TCZ patients.[140-142]

Other adverse events of interest. IL-6 inhibition does not appear to facilitate worsening of diabetes.[143] In a study of sarilumab, an even greater reduction in HbA1c was seen compared to PBO or ADA at week 24 in patients with baseline HbA1c ≥ 7%.[144] Similarly, TCZ demonstrated a stable safety and tolerability

profile in patients with RA and renal insufficiency, regardless of MTX use,[145] and may thus be a treatment option for patients with RA and concomitant renal insufficiency. Recent observational studies of TCZ did not detect an increased risk of interstitial lung disease,[146] demyelinating disease or idiopathic facial nerve palsy;[147] on the contrary, IL-6R inhibition was shown to be efficacious in one open-label trial in demyelinating disease.[148] There was no difference in the incidence of osteoporotic fractures in patients treated with TCZ as compared to those receiving TNF-inhibitors;[149] TCZ has been found to positively affect bone-turnover and improve bone mineral density in ACPA positive patients.[150;151]

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 with a based on several phase-3 clinical trials and extension data. The data from these trials suggest that its safety and tolerability profiles is consistent across studies and comparable with tocilizumab, with no new safety signals emerging.[152] 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 rate in mortality among patients treated with sirukumab compared to controls.[153;154] Cardiovascular events, infections and malignancies were the most common causes of mortality.[155;156]

Hypersensitivity reactions. In a study on more than 3000 patients with sc and almost 6000 patients with iv TCZ, there were approximately 1% hypersensitivity reactions, observed with both formulations (not injection site reactions); however, claims data suggest much more frequent hypersensitivity reactions with iv compared to sc application.[157] Of these, 20-40% were serious. The reactions were not related to the presence of anti-drug antibodies.[158] For sarilumab, which is only available in a sc formulation, 0.3% of patients had hypersensitivity reactions leading to treatment discontinuation.[159]

Safety in pregnancy. Analyses of TCZ exposed pregnant women from the global safety database revealed that preterm birth (before week 37) occurred in about one-third of the prospectively reported pregnancies; elective termination of pregnancy was performed in 17.2% of pregnancies, 21.7% of pregnancies ended in spontaneous abortion.[160] These data are not different from observations with anti-TNF agents[161] and may mostly be due to higher disease activity in patients on biologic agents; disease activity is a known risk factor for pre-term delivery. There is no increased risk of malformations and also no increased risk of adverse pregnancy outcomes for fathers exposed to IL-6R blockade.[160]

RESEARCH AGENDA

As always when deriving 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. Those questions that were posed in the first version of this statement but have not received satisfactory answers will be repeated here. Other questions 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. Can one use anti-IL-6R blockers effectively and safely after one or more JAKinibs have failed?
3. What is the comparative efficacy of JAK-inhibitors and anti-IL-6 principles in monotherapy and combination therapy?
4. In the USA, an initial dose of 4mg/kg is recommended: what are the risks and benefits of this approach?
5. 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?
6. Are IL-6 inhibitors safe when used with or immediately after Jak inhibitors?
7. Does the use of isoniazid lead to significant increases in liver function tests in patients with IL-6 inhibitor mono- and combination therapy?
8. Is there a need to stop therapy with IL-6-blockers before fathering a child?
9. What is the molecular effect of IL-6R antibodies on target cells? Reverse signaling?

DISCUSSION

This update of a consensus statement compiled almost ten years ago[17] covers a variety of novel developments. Firstly, additional IL-6R blockers have been licensed and are in clinical use for the approved indications: sarilumab and satralizumab. Secondly, new indications for IL-6R inhibition have been approved, such as giant cell arteritis, CAR-T CRS and NMOSD, and interstitial lung disease in systemic sclerosis patients, and while sarilumab is only approved for RA, satrilzumab only for NMOSD and siltuximab only for Castelman's disease, it can be assumed that all these agents have efficacy across the indication profile. Thirdly, expectations existing that IL-6 ligand inhibitors may become available around the middle of the last decade were not met when the development of sirukumab was stopped after several phase 3 trials had been completed; another monoclonal antibody to IL-6, olokizumab, is currently in late phase development and one will see if this molecule is approved. Fourthly, 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 level of evidence and grade of recommendation. Only a few points are based on low evidence levels or expert opinion. Those with low evidence need to be clarified by further research.

The research agenda included in the first version of this consensus document was long and several questions raised then have been answered by new data. Other questions have still not been answered. Rather than repeating those, we have provided a new research agenda in the current statement.

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

In summary, blocking the IL-6R is a major therapeutic advance for many diseases in adulthood and children. We have summarized the current state of these agents in terms of efficacy and safety has been summarized which has 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 in a large spectrum of inflammatory diseases.

Table 1. IL-6 pathway blocking agents and their targets

Table 2. Consensus Statements on the use of IL-6 blocking agents.

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Table 1. Molecules that interfere with the IL-6 pathway. Mab, monoclonal antibody; sgp, soluble glycoprotein; Fc, IgG-Fc fragment; other abbreviations see text.

Biological agent	Molecular type	Target	Approval for
Tocilizumab	Humanized MAb	IL-6R	RA, JIA, sJIA, GCA, others
Sarilumab	Human MAb	IL-6R	RA
Satralizumab	Humanized MAb	IL-6R	NMOSD
Siltuximab	Chimeric MAb	IL-6, site 1	Castleman's disease
Sirukumab	Human MAb	IL-6, site 1	N.a.
Clazakizumab	Humanized MAb	IL-6, site 1	N.a.
Olokizumab	Humanized 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 signaling	RA, PsA, AS, PsO, others

Table 2. Consensus statements with levels and grades of evidence, levels of agreement and last voting results

Statement	**Level of Agreement (0-10)**	**Last voting results**
INDICATION - <u>Rheumatoid arthritis</u> (Level 1a, Grade A)		
Population: Active RA (at least moderate disease activity according to a validated composite measure) characterized 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: - SAR: 200mg s.c. every 2 weeks (Level 1a, Grade A) - TCZ: 162mg s.c. weekly or 8 mg/kg every 4 weeks as intravenous infusion, usually over 1 h (Level 1a, Grade A) - SAR/TCZ 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 1a, Grade A)	**9.9±0.3**	**100%**
Dose reduction: - As a shared decision between patients and their rheumatologist - Indication: o occurrence of certain adverse events;	**9.5±0.8**	**91%**

○ in patients with sustained remission, after having tapered GC; discontinuation of concomitant csDMARDs (especially MTX) can also be considered. - Scheme: SAR from 200 to 150mg or TCZ from 8 to 4 mg/kg, or interval increase.		
INDICATION - <u>Polyarticular-course juvenile idiopathic arthritis</u> (Level 1b, Grade A)		
Population: Active pcJIA (≥ 5 active joints, ≥ 3 with limitation of motion), characterized by an inadequate response to MTX.	**9.6±0.8**	**94%**
Dosing (TCZ): - IV dosing every four weeks: 8mg/kg for weight >=30kg; 8-10mg/kg for weight <30kg - SC dosing: >=30kg: 162 s.c. / 2 weeks; <30kg: 162mg s.c. / 3 weeks - In combination with MTX (unless not tolerated)	**9.9±0.3**	**94%**
INDICATION - <u>Systemic juvenile idiopathic arthritis</u> (Level 1b, Grade A)		
Population: Active sJIA, refractory to NSAIDs and GC	**9.8±0.5**	**94%**
Dosing (TCZ): - IV dosing every two weeks: 8mg/kg for weight >=30kg; 12mg/kg for weight <30kg - SC dosing: >=30kg: 162mg s.c. / week; <30kg: 162mg s.c. / 2 weeks - Use as monotherapy	**9.9±0.3**	**94%**
INDICATION - <u>Giant cell arteritis</u> (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 (TCZ): - 162mg s.c. weekly - always start in combination with GCs, but alongside GC tapering	**9.7±0.7**	**90%**
INDICATION - <u>Takayasu Arteritis</u> (Level 2a, Grade B)		
Population: Patients aged ≥12 years with relapsing and refractory to GC TAK	**9.6±1.0**	**93%**
Dosing (TCZ, only in Japan): - 162mg s.c. weekly - In combination with GCs, but alongside GC tapering	**9.7±0.7**	**93%**
INDICATION - <u>Adult-onset Still's disease</u> (Level 1b, Grade A)		
Population: - AoSD refractory to GC	**9.5±0.8**	**93%93%**
Dosing (TCZ, only in Japan): - only IV dosing at 8mg/kg every 2 weeks	**9.5±0.9**	
INDICATION - <u>Castleman's disease</u> (Level 2b/1b, Grade B)		
Population:	**9.8±0.6**	**93%**

Human herpesvirus-8-seronegative patients with symptomatic multicentric Castleman's disease		
Dosing (TCZ in Japan, and Siltuximab in EU and USA): - TCZ: IV dosing: 8mg/kg every 2 weeks; SC dosing: 162mg weekly (Level 2b, Grade B) - Siltuximab: IV dosing: 11mg/kg every 3 weeks (Level 1b, Grade B)	**9.7±0.6**	**93%**
INDICATION - <u>CAR-T-Cell induced Cytokine Release Syndrome</u> (Level 2c, Grade B)		
Population: Severe or life-threatening grades of CRS in adults and pediatric patients ≥ 2 years of age	**9.7±0.6**	**93%**
Dosing: IV TCZ dosing: once 8 mg/kg (12 mg/kg for pts <30 kg)	**9.7±0.6**	**93%**
INDICATION – <u>Neuromyelitis optica spectrum disorder NMOSD</u> (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 which do not include acute phase reactants should be used to evaluate disease activity. - Risk of delaying diagnosis of infection because of APR normalization by IL-6R	**9.8±0.6**	**100%**
PRE-TREATMENT SCREENING (Level 5, Grade D)		

- History and physical examination
  o Consider possible contraindications
  o Consider radiograph of the chest
  o Assess history of infections (especially history of hepatitis?), diverticulitis, any history of GI perforations (including peptic ulcer?) 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 IL6 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 TCZ compared to placebo population (similar to other bDMARDs)
  o Risk of delaying diagnosis of infection because of APR normalization by IL-6R
- Hepatic transaminase elevations
- Gastrointestinal perforations, risk factors include a history of diverticulitis or GI ulcers, older age, GC and/or NSAID intake, no reported cases in children.
- Neutropenia and rarely thrombocytopenia
- Infusion reactions (~7%)
  o 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 / 162mg dose sc
- Children with sJIA: possible risk for development of macrophage activation syndrome
	9.6±0.9	**94%**