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Review

What have we learnt from the inhibition of IL-6 in RA and what are the clinical opportunities for patient outcomes?

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Peter C. Taylor, Eugen Feist, Janet E. Pope, Peter Nash, Jean Sibilia, Roberto Caporali and Alejandro Balsa

***Abstract*:** Rheumatoid arthritis (RA) is an autoimmune disease characterised by persistent inflammation of the synovial joints as well as other tissues and organs. Left untreated, it can lead to joint damage, disability and even increased mortality. The disease is driven by inflammatory cytokines that contribute to the chronic inflammation seen in RA. Interleukin-6 (IL-6) is a key pathological cytokine and a target for treatments aiming to alleviate local and systemic inflammation. Despite advances in understanding RA and the introduction of new treatments, achieving sustained remission remains challenging. This review explores the role of IL-6 in RA pathogenesis, its potential as a treatment target and the significance of personalised medicine in RA management. IL-6 has a dual signalling mechanism, classical and trans-signalling, which influences various intracellular pathways. While several targeted therapies have emerged, no single mechanism-based therapy is universally effective due to the diversity and complexity of the disease. Different approaches to targeting IL-6 have been tested, including biologic blockade of receptors or ligands, and inhibition of IL-6 signalling. IL-6 receptor inhibitors have been validated as RA therapeutics, either alone or in combination with other treatments. Tocilizumab, the first approved IL-6 inhibitor, blocks both soluble and membrane-bound IL-6 receptors, reducing the inflammatory cascade. Clinical trials confirm the efficacy and safety of tocilizumab and its role as a treatment option for patients unresponsive to conventional therapies. The benefits of IL-6 inhibition extend beyond reduced joint inflammation to the amelioration of comorbidities like anaemia, cardiovascular disease, depression and osteoporosis. Tailoring treatment to patients' profiles and comorbidities is essential for optimal outcomes. A 'treat-to-profile' approach, focusing on a holistic view of the patient, could improve personalised medicine strategies. Biosimilars – lower-cost alternatives to biologics – further enhance the accessibility and cost-effectiveness of treatment. IL-6 inhibitors present a valuable treatment option for RA management, particularly for patients with specific comorbidities.

Plain language summary

What have we learnt from the inhibition of IL-6 in RA and identifying the clinical opportunities for patient outcomes?

Rheumatoid arthritis (RA) is a condition where joints become swollen and painful due to long-term (chronic) inflammation. If left untreated, it can cause severe joint damage, disability and even increase the risk of death. The disease is driven by cytokines, which are proteins in the body that help control the immune system and can cause inflammation. One important cytokine is interleukin-6 (IL-6), and scientists are studying ways to block its effects to help people with RA.

Correspondence to:
Peter C. Taylor
Botnar Research Centre, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Windmill Road, Oxford OX3 7LD, UK
peter.taylor@kennedy.ox.ac.uk

Eugen Feist
Department of Rheumatology, Helios Clinic Vogelsang-Gommern, Cooperation Partner of the Otto-von-Guericke University Magdeburg, Magdeburg, Germany

Janet E. Pope
Department of Medicine, Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON, Canada

Peter Nash
School of Medicine, Griffith University, Brisbane, QLD, Australia

Jean Sibilia
Service de rhumatologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

Roberto Caporali
Department of Rheumatology and Medical Sciences, ASST Gaetano Pini-CTO, Milan, Italy

Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy

Alejandro Balsa
Rheumatology Department, Hospital Universitario La Paz, Madrid, Spain

Inmuno-Rheumatology Research Group, Hospital La Paz, Institute for Health Research – IdiPAZ, Madrid, Spain

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This review looks at how IL-6 works in RA and how blocking it might help. Despite new treatments, it is still hard to fully control RA. Researchers are trying to find better ways to personalise treatments based on the symptoms of individual patients.

One drug called tocilizumab stops IL-6 from working by attaching to its receptor. A receptor is a part of a cell that receives signals from substances like cytokines. When IL-6 attaches to its receptor, it triggers inflammation. Tocilizumab stops IL-6 from attaching to its receptor, reducing pain and inflammation in people with RA. This drug not only helps the joints but may also improve other problems like anaemia, heart disease and even depression that often come with RA.

The review suggests that treating RA should involve looking at the person's overall health, not just the joints. IL-6 blockers might be particularly useful for patients with other health issues or for those who have not responded well to other treatments.

Biosimilars, which are similar to the original IL-6 blocking drug but less expensive, have expanded the treatment options. Combining personalised treatments with more affordable options could help improve the lives of people with RA.

Overall, IL-6 blockers seem to be a promising way to help people with RA, especially when used in a personalised approach that considers the whole person and their overall health.

Keywords: biological therapy, interleukin-6, personalized medicine, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterised by persistent chronic inflammation of the synovial joints, that if left untreated can result in progressive joint degeneration, causing disability, poor quality of life and a higher mortality rate.[1,2] While the hallmark feature of RA is the involvement of the peripheral joints, clinical manifestations are variable and can occur in other organ systems including the bronchopulmonary, skin, ocular, neuropsychiatric, haematological, hepatic, renal and vascular systems.[3] RA is driven by inflammatory cytokines. These signalling proteins bind to various cell types and contribute to acute and chronic inflammatory processes inherent in RA.[4] Interleukin (IL)-6 is a key immunomodulatory cytokine in RA and a major mediator of both local and systemic inflammation, and therefore an important target for treatments that aim to improve both the local and systemic inflammatory features of RA.[5–7]

Despite advances in understanding the pathology and immunological systems underpinning RA and the introduction of a significant number of novel treatments, sustained RA remission remains difficult to achieve.[1] This increases the need to understand the pathophysiology at a cellular level, how the various treatment options work and the patient's comorbidities and preferences in an attempt to select the most appropriate therapy.[2]

This perspective review describes the role of IL-6 in the pathogenesis of RA, the risk–benefit ratio based on comorbidities that may influence IL-6 inhibitor use and highlights the importance of applying personalised medicine principles in RA.

Enhancing IL-6 inhibition strategies

Advances in understanding the pathology of RA have enabled the development of targeted treatments for clinical application. However, the wide variability in therapeutic responses achieved has prevented any single mechanism-focused therapy from becoming the definitive standard for all patients.[8] So far, IL-6 receptor inhibitors have shown promising results in managing RA, in combination therapy with conventional synthetic

disease-modifying antirheumatic drugs (csDMARDs) and as a monotherapy, and in patients with an inadequate response to methotrexate (MTX) and/or tumour necrosis factor inhibitors (TNFis).[2] However, the potential exists to enhance and expand the utilisation of IL-6 inhibition in the context of RA to improve the quality of care and overall treatment outcomes for patients.[9]

Role of IL-6 in local and systemic inflammation responses

Despite the tight regulation of cytokine expression by transcriptional and post-transcriptional mechanisms, dysregulated continuous production of IL-6 in RA causes detrimental effects on chronic inflammation and autoimmune disease.[10]

IL-6 is the most abundant cytokine in a family of related molecules comprising IL-6, IL-11, ciliary neurotrophic factor, leukaemia inhibitory factor, oncostatin M, cardiotrophin 1, cardiotrophin-like cytokine and IL-27.[11] It is produced by a wide variety of cell types, including immune, non-immune, epithelial, liver, kidney, cartilage and nerve, and is essential for controlling the development of cancer, inflammation, haematopoiesis, liver regeneration, metabolic regulation and bone metabolism,[11] and plays a significant role in immunological control.[12]

A unique feature of IL-6 is the dual signalling mechanism known as classical signalling and trans-signalling. The classical pathway occurs via the membrane-bound IL-6 receptor, while the trans-pathway is activated via the soluble IL-6 receptor (sIL-6R).[13] IL-6 classical or trans-signalling ligand–receptor complex formation results in the activation of many different intracellular signalling pathways, including the Janus kinase (JAK)-STAT route, the Ras-MAPK pathway, the p38 and JNK MAPK pathways, the PI 3-K-Akt pathway and the p-ERK pathway.[7,11,13] A simplified schematic of classical and trans-signalling pathways is illustrated in Figure 1.

Classical IL-6 signalling starts with IL-6 attaching to the membrane-bound form of the IL-6-specific receptor alpha subunit (IL-6Rα) causing it to associate with the signal-transducing gp130 receptor subunit. Hepatocytes, macrophages, neutrophils and resting lymphocytes are the only cells that can express membrane-bound IL-6Rα, which is essential for classical IL-6 signalling.[6,11]

For the IL-6 trans-pathway, signalling occurs through membrane-bound gp130 when it becomes associated with complexes formed by IL-6 and sIL-6R. This requires IL-6 binding to IL-6Rα in a soluble form, which can be produced by either alternative splicing or proteolytic cleavage.[11] In gp130-expressing cells, the IL-6-soluble IL-6Rα complex can then trans-activate IL-6 signalling pathways.[11] Trans-signalling enables a greater variety of cells to react to IL-6 due to the ubiquitous expression of gp130.[11] Although both the classical and trans-signalling receptor complexes activate similar intracellular signalling pathways, several studies have suggested that IL-6 trans-signalling, rather than classical signalling, promotes pro-inflammatory disease pathogenesis.[11]

In theory, antibodies can target any part of the receptor signalling complex to inhibit IL-6 signalling. This alone is sufficient to entirely silence IL-6-mediated signalling. While IL-6 inhibition is the current focus of a number of therapeutic interventions, gp130 inhibitors will likely be a viable target for future innovation in RA treatments.[14] Another feasible strategy to inhibit IL-6 activity involves using small molecule inhibitors that target JAKs, which work downstream of gp130.[11] However, according to clinical experts, multiple cytokines, in addition to IL-6, signal via JAK enzymes. Therefore, it would be undesirable to completely block the activity of some of these, such as erythropoietin, as anaemia would be the result. By contrast, inhibition of IL-6R rapidly reverses the anaemia of chronic disease that may be associated with RA.

Pharmacological approaches to IL-6 inhibition in RA

The unique mechanisms and properties of biologic and small molecule IL-6 inhibitors help to inform their risk/benefit profiles. Originator biologics with specificity for IL-6R target the critical trans-signalling IL-6 pathway (some also target the classical pathway), inhibiting pro-inflammatory disease pathogenesis. The IL-6 inhibitor drugs do not all have the same actions; blocking of IL-6 ligands, receptors and signalling pathways occurs in different ways and has different effects, as illustrated in Table 1.[6,7,15] For example, biologics like tocilizumab, a humanised monoclonal antibody, and sarilumab, a fully human monoclonal antibody, target IL-6Rα.[1] Sirukumab, olokizumab and clazakizumab are anti-IL-6 monoclonal antibodies that bind to various locations

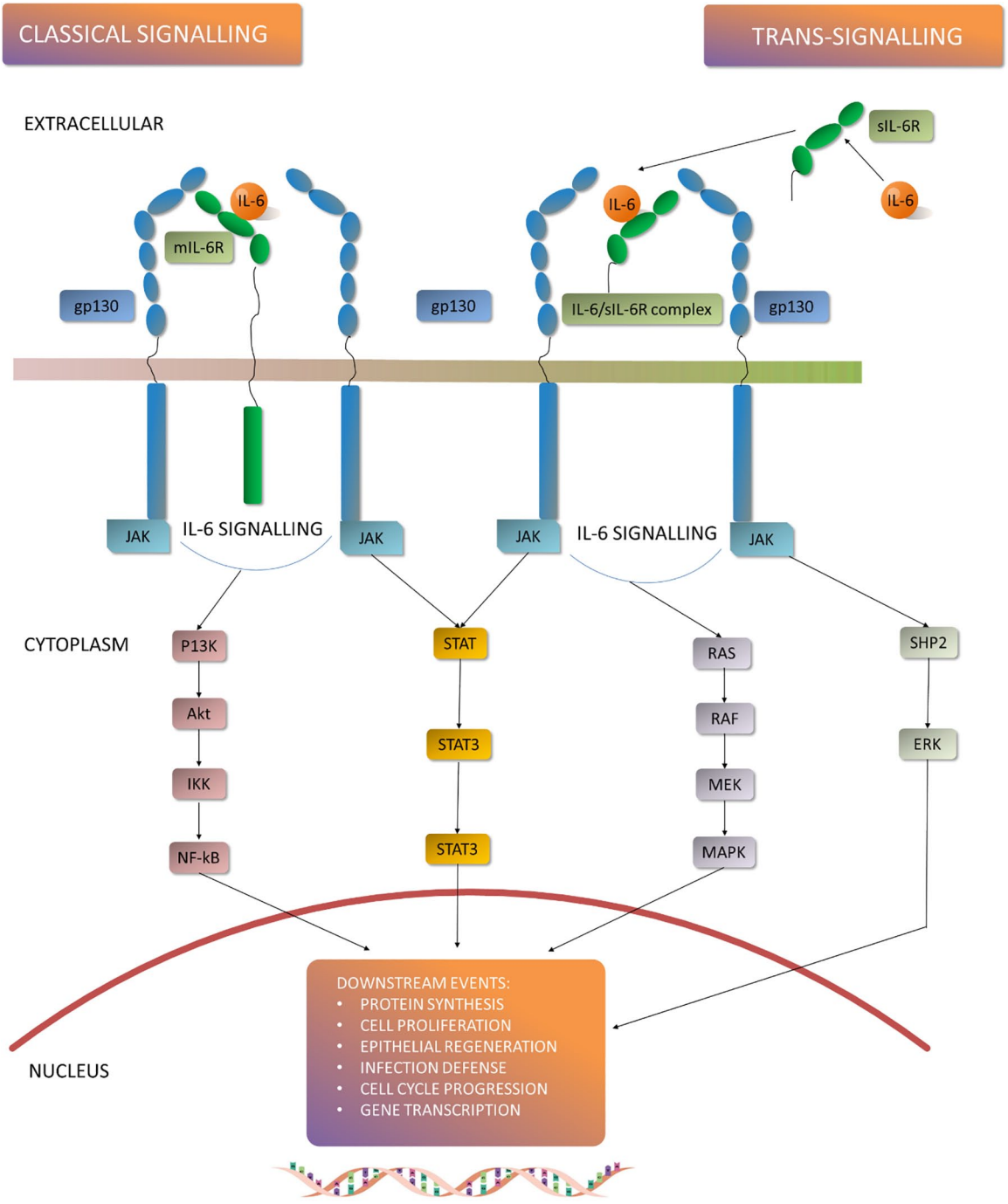

Figure 1. IL-6 classical and trans-signalling pathways.
Akt, protein kinase B; ERK, extracellular signal-regulated kinase; gp130, glycoprotein 130; IKK, IκB kinase; IL-6, interleukin 6; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase/ERK kinase; mIL-6, membrane-bound interleukin 6; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; SHP2, Src homology 2 domain-containing phosphatase 2; sIL-6R, soluble interleukin 6 receptor; STAT, signal transducer and activator of transcription.

on IL-6, halting the signalling process.[16] Olamkicept takes yet a different route and targets and inactivates the IL-6–sIL-6Rα complex structure.[16]

JAK inhibitors competitively inhibit the JAK enzymes responsible for IL-6 signal transduction, as well as other cytokines and interferons, thereby interfering with the signalling of various

Table 1. IL-6 inhibitors: types, mechanisms and examples.

Type of IL-6 inhibitor	Target molecule	Mechanism of action	Examples
Humanised and human monoclonal antibody	IL-6Rα	Binds specifically to the IL-6Rα, inhibiting IL-6-mediated signal transduction. They interfere with IL-6 binding to both membrane-bound and soluble forms of IL-6Rα, blocking downstream JAK-STAT signalling. This inhibits the production of acute-phase reactants and pro-inflammatory cytokines.	Tocilizumab Sarilumab (human) Levilimab (human)
Human monoclonal antibody	IL-6 ligand	Binds directly to IL-6, inhibiting its interaction with both membrane-bound and soluble IL-6Rs. By preventing IL-6 from binding to its receptors, sirukumab disrupts the activation of JAK-STAT signalling, which is essential for mediating the inflammatory response. This leads to reduced production of pro-inflammatory cytokines.	Sirukumab
Human monoclonal antibody	IL-6, site 1	Binds to site 1, blocking the initial interaction between IL-6 and its receptor complex, which includes IL-6Rα and gp130. This prevents the activation of downstream signalling cascades, including JAK-STAT, MAPK and PI3K/Akt pathways, which are critical for mediating inflammatory responses.	Clazakimumab
Chimeric monoclonal antibody	Soluble IL-6	Binds specifically to soluble IL-6, preventing its interaction with the IL-6R complex. By blocking IL-6 binding, siltuximab inhibits the downstream activation of JAK-STAT signalling, which regulates the expression of genes involved in inflammation and immune responses. This leads to the suppression of cytokine production.	Siltuximab
Humanised monoclonal antibody	IL-6–sIL-6Rα complex	As a decoy receptor for IL-6, olamkicept binds to the IL-6–sIL-6Rα complex, sequestering IL-6 and preventing its interaction with membrane-bound IL-6Rs. By inhibiting IL-6 signalling through both classical and trans-signalling pathways, olamkicept effectively suppresses the production of pro-inflammatory cytokines and mitigates inflammatory responses in conditions such as RA.	Olamkicept
Humanised monoclonal antibody	IL-6 cytokine	Binds to the IL-6 cytokine, specifically its epitope or binding site, preventing its interaction with both membrane-bound IL-6R and sIL-6R. By disrupting IL-6 binding, olokizumab interferes with downstream JAK-STAT signalling, which regulates the expression of inflammatory genes. This results in the attenuation of inflammatory responses and tissue damage.	Olokizumab
Humanised monoclonal antibody	gp130	By targeting the gp130 subunit, which is shared by the receptor complexes of various cytokines, including IL-6, vobarilizumab disrupts IL-6 signalling pathways. Specifically, vobarilizumab inhibits the activation of JAK-STAT signalling downstream of gp130, leading to reduced cytokine production and dampened inflammatory responses.	Vobarilizumab

Akt, protein kinase B; gp130, glycoprotein 130; IL-6R, IL-6 receptor; IL-6Rα, IL-6 receptor alpha; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; RA, rheumatoid arthritis; sIL-6R, soluble IL-6 receptor; STAT, signal transducer and activator of transcription.

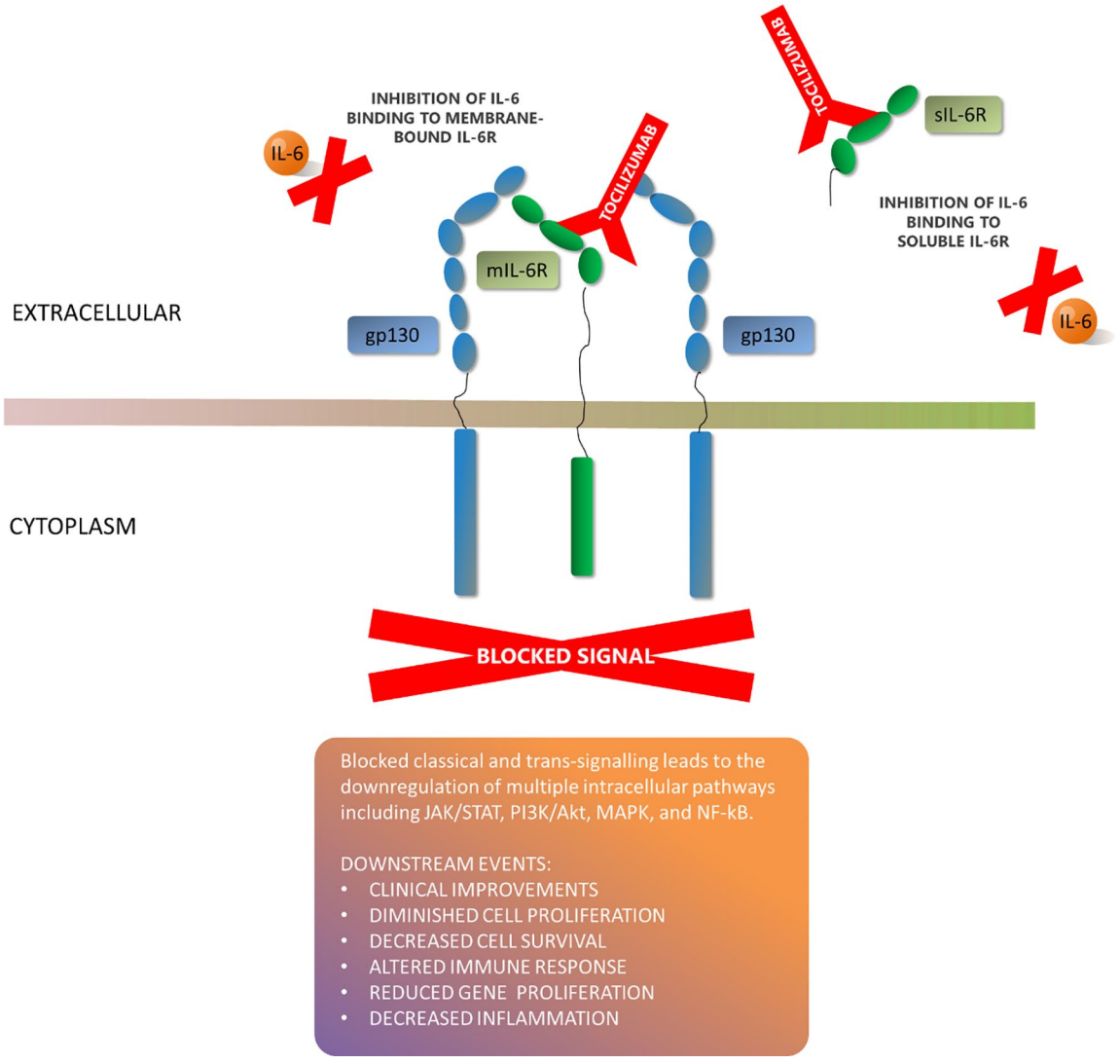

Figure 2. Tocilizumab inhibits classical and trans-signalling.
gp130, glycoprotein 130; IL-6, interleukin 6; mIL-6R, membrane-bound IL-6 receptor; sIL-6R, soluble IL-6 receptor.

type I/II cytokines depending on the enzymatic selectivity of the specific inhibitor in question.[16] The JAK inhibitors currently approved for the treatment of RA all inhibit IL-6, among other cytokines. Small molecules such as JAK inhibitors are simpler than biologics to administer as they are taken orally and offer no immunogenic risks.[17] A review of JAK inhibitors in RA has been previously published that addresses the anti-inflammatory properties.[18]

There have been attempts to manufacture small molecule inhibitors of IL-6 itself, but none have reached clinical practice.[19]

Tocilizumab

Tocilizumab was the first approved IL-6R inhibitor introduced in 2008 as a monotherapy and combination therapy option for adults with RA and an inadequate response to DMARDs.[20] Tocilizumab is also the first humanised recombinant IgG1 monoclonal antibody that binds to both the soluble and membrane-bound IL-6 receptors, blocking its action and leading to a decrease in the inflammatory response cascade (Figure 2).[1]

Trials conducted in 23,725 patients have confirmed the efficacy and safety of tocilizumab, and

in some cases, demonstrated that it has higher efficacy than other treatment options.[5] Additionally, clinical improvement with tocilizumab was comparable to findings in 4770 patients trialled on other biologic IL-6 inhibitors.[5]

Efficacy

Tocilizumab has demonstrated efficacy in early progressive RA, both as a monotherapy and in combination with MTX.[21] This combination approach has been reported to be more effective than monotherapy using MTX (45% of patients taking tocilizumab and MTX achieved remission at week 24 compared to 15% taking MTX alone), thereby providing an additional treatment option for patients with inadequate responses to csDMARDs.[21] Of particular interest this study showed that tocilizumab was also effective as a monotherapy (39% remission at week 24).[21] In another study, tocilizumab as a monotherapy showed superior results in reducing RA symptoms compared to adalimumab alone in patients intolerant to MTX or inappropriate for continued MTX.[22] Based on the robust efficacy data for tocilizumab when used as a monotherapy for RA, European Alliance of Associations for Rheumatology (EULAR) management recommendations highlight IL-6R inhibition as the biologic of choice in patients for whom MTX is contraindicated. The versatility and impressive efficacy of tocilizumab when used in combination with concomitant MTX or as a monotherapy in MTX-naïve patients with RA challenges current recommendations to use MTX or a combination of csDMARDS as the initial treatment strategy in early RA.[1,23]

Safety

Safety is a key factor in treatment decision-making. Although tocilizumab is generally well tolerated, it has been associated with an elevated likelihood of infections, as well as diverticulitis and resultant gastrointestinal perforation.[24] Additionally, a meta-analysis of tocilizumab clinical trials suggested that the use of tocilizumab in combination with MTX for RA was linked to a slightly elevated risk of adverse events compared with controls receiving MTX alone, which is in line with the risks associated with other biologic therapies (odds ratio (OR): 1.53; 95% confidence interval (CI): 1.26–1.86).[25] However, there was a significantly higher risk of infections in this combination therapy group compared to controls receiving MTX alone (OR: 1.30; 95% CI: 1.07–1.58), suggesting a need for greater vigilance to mitigate untoward effects.[25] In particular, because tocilizumab is associated with decreased C-reactive protein levels,[26] the early detection of any infectious complications may potentially be masked. Other safety considerations for tocilizumab in patients with RA include elevated liver transaminases,[27] elevated lipid levels[26] and neutropenia.[28] No increased risk of malignancy[26,29] or cardiac events[30] have been confirmed by long-term studies or registers. On the other hand, tocilizumab carries minimal or negligible risk of tuberculosis reactivation,[31] and a post-marketing global study suggested a decreased risk of cardiovascular disease over time.[29]

A head-to-head study, the ENTRACTE trial, was powered to compare safety endpoints between tocilizumab and the biologic TNFi etanercept. In this trial, tocilizumab did not significantly increase the risk of major adverse cardiac events compared to etanercept.[32] Based on measured changes in cardioprotective lipids, it has also been suggested that tocilizumab may have more cardioprotective characteristics compared to TNFis.[33]

Role in clinical practice

IL-6 inhibitors have predominantly been positioned as second-line biologic agents for patients who do not adequately respond to TNFis,[2] primarily due to considerations of cost-effectiveness and historical precedent, as suggested by clinical experts. Although TNF is a valuable target in patients with severe RA, 30%–40% of patients taking TNFis discontinue them due to an inadequate response or intolerance.[34] When TNF inhibition fails, the evidence supports switching to an alternate category of targeted therapy with a different mechanism of action.[34] For those non-responders, targeting IL-6 is a valuable therapy option that can enhance the overall response to pharmacological management.[35]

According to clinical experts, variable clinical responses to IL-6R inhibition and inter-individual variability of IL-6 levels highlight the heterogeneity of the inflammatory processes inherent in RA. In addition, there can be widely variable diurnal changes in peripheral blood IL-6 levels. Despite this, IL-6 levels and those of C-reactive protein (which is a surrogate for IL-6 production over time) show associations with the likelihood

of treatment response.[36] Measurement of blood levels of IL-6 has not entered routine practice, but C-reactive protein levels are widely assayed and, with other principle clusters of cytokines, may help inform personalised treatment plans in the future.[37]

Extra-articular RA manifestations, comorbidities and effects of IL-6 inhibition

Persistent inflammation, a characteristic of RA, can lead to various extra-articular manifestations and comorbidities, which, in turn, contribute to increased morbidity and mortality.[38,39]

Extra-articular manifestations are a direct result of the inflammatory process and present as non-joint symptoms that occur in about 40% of patients with RA.[40] Examples include bronchopulmonary, muscular (sarcopenia), psychological, fatigue, pain, anaemia and vascular (arteriosclerosis and vasculitis) manifestations.[13] Of particular interest, a 40-year population-based study found that the presence of extra-articular manifestations and comorbidities were the strongest predictor of mortality in RA.[41] This link is of vital importance as is the strategic management of these manifestations to improve mortality rates in patients with RA.

Comorbidities, on the other hand, are conditions that can be related to RA, caused by RA or completely unrelated but occurring alongside RA.[38,39] While RA is usually thought of as a disease affecting mostly the joints, patients with this disease often present with, or are at a higher risk of developing, several comorbidities, such as cardiovascular disease, type II diabetes and depression.[39]

Table 2 outlines the most common inflammatory manifestations and comorbidities in patients with RA, the associated incidence/prevalence rates and the effect of IL-6 inhibition.

Table 2. Inflammatory manifestations and comorbidities in patients with RA and effect of IL-6 inhibition.

Inflammatory manifestations	Incidence, prevalence or risk in patients with RA	Effect of IL-6 inhibition
Bronchopulmonary	Prevalence of 39%–60%[42]	Reduced pulmonary artery pressure and pulmonary hypertension[43] No increase in reactivation risk of tuberculosis infection[31]
Endocrine	Dyslipidaemia prevalence: 30.1%[44]	Notably increased total cholesterol, high-density lipoprotein and triglyceride levels[4,45] Lowered plasma concentrations of low-density lipoprotein(a)[46] Reduced C-reactive protein levels[26]
Gastrointestinal	Incidence rate of gastrointestinal perforation: 0.17/100 patient-years[47]	Increased risk of gastrointestinal perforations and elevated liver enzymes/transaminases[27,48]
Haematological	Anaemia: up to 60% lifetime incidence[49] Thrombocytopenia: incidence between 3% and 10%[50] Treatment-related neutropenia episodes: recorded in 7.5% of patients with RA; mostly transient (75.8%)[51]	Improved RA-associated anaemia through reduction of hepcidin and haptoglobin levels and increased iron availability and binding capacity[4,52] Increased serum haemoglobin levels and reduced proportion of patients with anaemia from baseline to week 24 (sarilumab)[53] Reduced platelet count, usually low-grade thrombocytopenia without bleeding complications[22,54] Can increase neutropenia and neutrophil migration, but usually transient[55,56]
Musculoskeletal	Prevalence of sarcopenia: 66%[57] Prevalence of fatigue: 40%–70%[58] Prevalence of osteoporosis: up to a maximum of 62%[59] Two-fold increase in the risk of osteoporotic hip fracture in patients with RA[60]	Improved muscle function, potential muscle gain and decreased bone loss[13,61,62] Minimised risk and disability associated with sarcopenia by inhibiting protein catabolism caused by inflammatory cytokines and increased lean muscle mass[57] Improved fatigue, increased mean functional assessment and functional improvement[63–65] Improved muscle function, bone density, osteoporosis and biomarkers of bone resorption[61,62] Reversal of bone and muscle loss associated with RA[61,62]

(Continued)

Table 2. (Continued)

Inflammatory manifestations	Incidence, prevalence or risk in patients with RA	Effect of IL-6 inhibition
Neuropsychiatric	Prevalence of anxiety (19.0%), depression (12.2%)[66] and moderate to severe pain (38.4%) despite biological treatments for RA[67]	Improved depressive symptoms with IL-6 inhibition, especially with tocilizumab[68] Significantly improved Hamilton Depression and Anxiety scores[69] and rapid sustained improvement of multiple patient-reported outcomes[63] Pain improved by approximately 50%,[65] indicating significant improvement compared to placebo at week 24[63]
Systemic	Prevalence of amyloid A amyloidosis: 5%–78%[70] Serious infections: incidence rate of 1.5–12.1/100 patient-years[47]	Reduced risk of amyloidosis, reduced serum amyloid A content[39,71] Serious infections noted,[1] but no additional increase reported with long-term use (tocilizumab)[48] Increased risk of skin and soft tissue infections and complications[4]
Vascular	1.5-fold increased risk of atherosclerotic cardiovascular manifestations compared to the general population[72]	In giant cell arteritis, IL-6 inhibition is an approved approach[28] Reduced risk of cardiovascular disease, and potential as a treatment option after an atherosclerotic event[72] Favourable cardiometabolic function[61]
Comorbidities	Incidence, prevalence or risk in patients with RA	Effect of IL-6 inhibition
Cancer	The occurrence of cancer is higher than in the general population, with an odds ratio of 1.632 (95% CI: 1.239–2.151; $p = 0.0005$)[73] The most prevalent cancer types were breast cancer (16.22%) and prostate cancer (16.22%)[73]	Several pro-oncogenic signalling pathways are deactivated, anti-cancer immune responses are regulated and a genotoxic stress response is induced, promoting an anti-tumour immune response[74,75]
Cardiac	The risk for cardiovascular disease in patients with RA is two to three times higher than in the general population, which appears to be directly affected by IL-6 levels[76] Congestive heart failure: 34% cumulative incidence at 30 years and significant excess risk versus those without RA (HR: 1.87; 95% CI: 1.47–2.39)[77] Congestive heart failure adjusted risk versus those without RA higher is seen only in patients with RA who are rheumatic factor positive (HR: 2.59; 95% CI: 1.95–3.43), not those who are rheumatoid factor negative[77] Coronary artery disease risk in patients with RA: 35.2% have low risk, 38.9% have moderate and 25.9% have high risk[76]	Increased coronary flow reserve, ventricular remodelling, cardiac function and ejection fraction and slowed progression of heart failure[78] Decreased plaque production and destabilisation, and increased myocardial remodelling and contractility[78] Decreased lipoprotein levels and improved endothelial function and arterial flexibility[13] Positive association between cardiovascular disease activity and IL-6 ($p = 0.028$) and leptin concentrations ($p = 0.047$)[76] Reduced systemic inflammation and lowered risk of a cardiac event[13] Rapidly improved insulin resistance and insulin sensitivity in non-diabetic RA patients, suggesting a positive impact on processes involved in developing metabolic syndrome and cardiovascular disease in RA patients with IV tocilizumab[79] Reduced lipoprotein(a) levels, potentially lowering the risk of cardiovascular disease, with IV tocilizumab[46]
Diabetes	Incidence is at least twice that of the general population[13] Prevalence 11.8%[44] The increased risk associated with higher levels of IL-6[13]	Decreased HbA1c and improved insulin sensitivity[13] Greater reduction in HbA1c than with TNFi (with tocilizumab)[80] and csDMARDs (with sarilumab)[81] Comparing baseline data to 1 h after intravenous tocilizumab administration, a significant decrease in serum insulin levels and insulin/glucose ratio was noted. There was also a marked reduction in insulin resistance (HOMA-IR: 2.62 ± 2.03 to 1.65 ± 1.15, $p < 0.01$) and an increase in insulin sensitivity (QUICKI: 0.34 ± 0.03 to 0.37 ± 0.04, $p < 0.01$). These improvements contribute to the cardiometabolic efficacy of tocilizumab in RA patients[79]

CI, confidence interval; csDMARDs, conventional disease-modifying agents; HbA1c, glycosylated haemoglobin; HOMA-IR, homeostatis model assessment of insulin resistance; HR, hazard ratio; IL-6, interleukin 6; IV, intravenous; QUICKI, quantitative insulin sensitivity check index; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

A common systemic benefit of IL-6 inhibition in patients with RA is seen in the rapid reversal of anaemia of chronic disease. It is estimated that 16% of patients with newly diagnosed RA have anaemia[82] and 60% will experience it within their lifetime.[49] Anaemia also can be seen as an independent predictor of disease severity and progression of RA.[4] The benefit of IL-6 inhibition is that it counteracts the effects of IL-6 on iron metabolism, reducing hepcidin levels and improving anaemia (increase in haemoglobin of 1.1 g/dL using tocilizumab at 12 weeks).[83]

Cardiovascular disease is also particularly common in populations with RA (two to three times higher risk than the general population), which appears to be directly affected by IL-6 levels.[76] Congestive heart failure (CHF)[77] and comorbid diabetes[13] are also common. When compared to those without RA, patients with RA experience almost twice the risk of CHF,[77] and twice the incidence of diabetes has been reported in patients with RA.[13] Beneficially, IL-6 inhibition reduces glycosylated haemoglobin and systemic inflammation associated with atherosclerosis, lowering the risk of a cardiac event and improving glycaemic control in patients with RA.[13] In one study, intravenous IL-6 blockage with tocilizumab has shown a rapid reduction in serum insulin levels and insulin resistance in non-diabetic RA patients, which highlights the benefits of IL-6 inhibition in the processes that lead to metabolic syndrome and cardiovascular disease in RA patients.[79] In another 10-year prospective study, RA patients treated with tocilizumab were compared with patients who did not receive biologic therapy.[46] The findings revealed that those treated with tocilizumab had lower plasma concentrations of lipoprotein(a) compared to those not receiving biologic therapy, with statistically significant differences observed (β: −0.303, 95% CI: −0.558 to −0.047; $p = 0.02$).[46] Lowering plasma concentrations of lipoprotein(a) may reduce cardiovascular risk because high levels are associated with increased risk of atherosclerosis and thrombosis, both major contributors to cardiovascular disease.[46] However, elevation of total cholesterol and triglyceride levels, as well as potentially protective high-density lipoprotein levels, have been noted after IL-6 inhibitor treatments.[45] Interestingly, the cardiovascular effects of IL-6 inhibition were similar when compared to those of TNFis.[84]

The impact of RA extends to a well-documented significant emotional burden. Studies have reported that 22% of patients with RA take antidepressants,[44] 19% report anxiety[66] and 44% experience fatigue,[58] all of which could be improved with IL-6 inhibition.[13,68] Other benefits of IL-6 inhibition include mitigating the two-fold increase in the risk of osteoporotic fractures in patients with RA,[60] improvement in muscle function, bone density, osteoporosis and biomarkers of bone resorption.[13,61,62]

In summary, many favourable benefits of IL-6 inhibition extend well beyond reducing synovial inflammation in RA to include systemic, extra-articular and comorbid gains. By combining the added health advantages of IL-6 inhibition, the risk–benefit profile of treatment options and the clinical profile of an individual patient, stratification of treatment options can usually inform a personalised approach to the most suitable therapy choice. For those patients where efficacy based on measures of disease activity is expected to be similar for biologic IL-6 inhibitors versus other treatment options, the effect of each treatment class not only on RA but also on the individual patient's comorbidities may dictate which option is the most appropriate.

Comorbidities and treat-to-profile approach

While a treat-to-target approach is widely accepted,[85] a paradigm shift to a treat-to-profile approach may also have advantages. Treat-to-target focuses on achieving RA remission or low disease activity, as recommended by EULAR.[85] Also recommended is the importance of managing comorbidities in patients with RA, which may have a differential response to RA treatments depending on the particular mechanism of action and, in some cases, may preclude dose tapering.[85]

Unlike treat-to-target, treat-to-profile embraces a more personalised and holistic medical approach with the choice of treatment based on a patient's characteristics, including sociodemographic, clinical and serological.[86,87] This broadens the scope of understanding to better predict the patient's baseline probability of responding to treatment.[86] Treating RA by reviewing the entire patient profile can also improve the utilisation of health resources and clinical outcomes.[87]

Patient profiles of individuals with RA are complex, with approximately one-quarter of patients

having a family history of RA, in addition to multiple comorbidities.[88] Furthermore, studies have shown that certain patient subgroups with specific comorbidities may benefit more or less from IL-6 inhibition (Table 2).[2,4,13,20,21,39,49,52,53,61–65,68,69,71,74–76,80,81,89–92]

In RA, patient profiles or specific patient subgroups that would benefit the most from IL-6 inhibition include those patients with associated high inflammatory markers, high disease activity, anaemia, coronary artery disease, depression, diabetes mellitus, early RA, elevated baseline IL-6 levels, fatigue, pain, osteoporosis and/or amyloidosis. However, even those with low inflammatory markers and high disease activity can benefit from IL-6 inhibitor treatment.[2,4,13,20,21,39,52,53,61–65,68,69,71,74–76,80,81,89–92] In subgroups of patients with comorbidities that include diverticulitis or an increased risk of gastrointestinal perforation, neutropenia or leukopenia, or thrombocytopenia, IL-6 inhibition should be used with caution or avoided. If the patient experiences hyperlipidaemia, which has been well documented in the literature, lipid-lowering treatment should be considered according to recommended guidelines.[1,4,13,22,48,55,56,93]

Notably, it is beyond the scope of this review to summarise all the published and ongoing research in detail. Research in different therapeutic fields – both basic and clinical – is ongoing to uncover the therapeutic potential of IL-6 pathway inhibition for diseases other than those mentioned above, such as giant cell arteritis, polymyalgia rheumatica, other vasculitis and progressive systemic sclerosis. However, with the increasing understanding of mechanisms involved in the pathogenesis of RA, there is a growing clinical opportunity to explore the risk–benefit ratio of each RA therapy on a deeper level to improve all relevant outcomes.

Where do IL-6 biosimilars fit within the therapeutic landscape?

RA places a significant financial and resource burden on patients, with up to one-third of patients with RA not working due to disability.[94] Even if patients can overcome this access barrier, biologics are still among the most expensive prescription drug therapies currently available.[95]

However, similar versions of biologics – biosimilars – provide lower-cost options, often making these treatments more accessible to prescribers and increasing the chances of improving health outcomes for patients with RA.[95] Some RA therapies, including adalimumab, infliximab, etanercept, tocilizumab and rituximab do have biosimilar equivalents and these have shown comparable efficacy and safety results in patients with RA when compared to the originator.[96–100]

The added benefit of these biosimilars, beyond cost-effectiveness and accessibility, is the equivalent reduction in RA-associated comorbidities.[4] Biosimilars aimed at IL-6R are currently in development, demonstrating comparable efficacy to originator biologics, with the first tocilizumab biosimilars undergoing approval processes and preparing for launch.

Clinical opportunities

IL-6 inhibitors, either as a monotherapy or in combination with a csDMARD, for active RA which is failing with csDMARDs and/or other advanced therapies, should be considered more often to reduce the burden of the disease.[9] Beyond minimising structural damage, inducing remission and easing joint symptoms, IL-6 inhibitors have the added benefits of improving extra-articular symptoms and have a favourable impact on many RA comorbidities.[13,78,83]

With decision-making becoming more complex, patient profiles are critical in informing personalised medicine and contributing to improved patient outcomes, safety and quality of care.[87] Personalised medicine and therapeutic choices that target both RA and the associated comorbidities work towards the joint goal of both stable remission and decreased morbidities. Several factors need to be considered when choosing a treatment for an individual patient, including safety and effectiveness, drug retention rate (RR) and comorbidities – some of which have already been discussed.

Retention is commonly measured from the time the treatment starts to when it is discontinued,[101] and is a good indicator of the balance between drug effectiveness and adverse events.[102] In the case of tocilizumab in the ACTRA-RI cohort study, an RR of 48.3 months for monotherapy was reported as satisfactory and comparable to that of combination therapy with MTX (50.0 months).[101] This suggests that the outcomes for both treatment approaches – monotherapy and combination therapy – were deemed satisfactory and similar, as the difference in reported RR

was not considered meaningful. The TANDEM real-world multicentre study also confirmed RRs comparable to those seen in clinical trials for subcutaneous tocilizumab,[103] and other research has indicated 86.6% retention at 12 months for tocilizumab.[104] These findings suggest that tocilizumab administered subcutaneously demonstrated real-world tolerability and sustained treatment benefits similar to those seen in controlled trials, with a significant proportion of patients continuing to use tocilizumab for at least 1 year. Interestingly, tocilizumab monotherapy showed higher crude median retention than tocilizumab combination therapy (2.31 vs 1.98 years), TNFi monotherapy (1.31 years) and TNFi combination therapy (1.37 years).[105]

Other studies have compared the effectiveness of RA treatment options, helping to assess the improvement in symptoms and well-being. In one such study, the comparative effectiveness of rituximab, abatacept and tocilizumab was measured over 2 years in 3162 adults with RA and showed higher rates of EULAR outcome improvements for both tocilizumab and rituximab compared to abatacept.[102] Of note is that a longer disease duration has been a particularly strong predictor of reduced treatment response.[106] This trend has also been reported with prior use of DMARDs, higher function disease class, lower disease activity and female sex.[106]

As already highlighted, critically evaluating RA comorbidities affords the clinician a more comprehensive risk–benefit assessment, weighing the positive outcomes on the patient's health beyond RA against the potential negative consequence of the treatment choice. From a safety perspective, the cardiovascular effects of tocilizumab were not statistically different from those of TNFis, as per findings of the ENTRACTE trial.[32]

The use of biosimilars is recommended in the current RA guidelines (TNFi biosimilars as the first biologic), largely due to affordability.[85,107,108] A biosimilar of tocilizumab may change the current treatment landscape, and as a result, change clinical practice.

In clinical practice, it is therefore essential to consider the prevention or treatment of comorbidities as part of the overall management of RA. As the number of novel RA medications and biosimilar products is expected to increase, patients will have wider and earlier access to sophisticated therapies.[39] It is also important to note that comorbidities and the patient profile may change during the course of the disease and its treatment, which may impact the therapy choice.[71]

AI and the future of personalised medicine

AI, encompassing machine learning and deep learning, is rapidly advancing in healthcare, with significant potential in managing chronic rheumatological conditions like RA.[109] Leveraging vast datasets, AI tools can analyse patient data comprehensively, aiding in decision-making and outcome prediction.[110] Several studies have highlighted the benefits of integrating AI into RA management.

Rehberg et al.[111] used machine learning to develop a rule predicting response to sarilumab versus adalimumab, in patients with RA, focusing on clinically feasible blood biomarkers. The decision tree model GUIDE was trained using data from the sarilumab trial MOBILITY, identifying a rule predicting disease activity after sarilumab 200 mg. Testing across four trials (MOBILITY, MONARCH, TARGET and ASCERTAIN) confirmed the rule's ability to predict response to sarilumab for many efficacy parameters, although its applicability was reduced in individuals refractory to TNFi.[111] Creagh et al.[112] in the weARable-PRO study, investigated how digital health technologies, like smartphones and wearables, could enhance patient-reported outcomes in determining RA status and severity. Using machine learning, the researchers developed a framework to distinguish RA status and estimate severity. Results showed that combining standard patient-reported outcomes assessments with sensor-based features improved the detection of RA severity levels, highlighting the value of machine learning in RA management and the development of patient-centric measurements for clinical trials.[112] Hirano et al.[113] developed a deep-learning model to assess radiographic finger joint destruction in RA, achieving high sensitivity (95.3%) in joint detection and moderate accuracy in scoring joint space narrowing (49.3%–65.4%) and erosion (70.6%–74.1%). Bai et al.[114] employed an artificial neural network for RA diagnosis, demonstrating improved accuracy (F1 = 0.916) compared to traditional methods and identifying anti-cyclic citrullinated peptide as the most influential diagnostic marker. Lastly, Gossec et al.[115] investigated the association between patient-reported flares and physical activity in RA and

axial spondyloarthritis using machine learning. The machine-generated models accurately predicted patient-reported flares (mean sensitivity 96%, specificity 97%), indicating potential for remote monitoring of disease activity with minimal patient burden.[115]

These findings underscore the value of machine learning in enhancing RA diagnosis, assessing disease progression and monitoring treatment response, with implications for personalised patient care and remote disease management.

Conclusion

The therapeutic options for RA have improved dramatically over the past three decades, from only a few options to several classes of pharmacologics. While there are distinct differences in the risk–benefit profiles of RA treatment options, IL-6 inhibition is an effective therapeutic strategy that may have important benefits based on the patient profile, particularly for patients who are intolerant of, or in whom MTX is contraindicated. Using a treat-to-profile approach, the symptoms of RA may respond to IL-6 inhibitors in both managing articular and extra-articular symptoms of RA with or without comorbidities or elevated inflammatory markers. In the future, conducting trials to evaluate the efficacy and safety of IL-6 inhibitors in distinct patient subgroups, considering specific comorbidities and utilising AI to analyse vast datasets, could prove invaluable in confirming findings and developing useful stratification tools. To date, a reliable biomarker for predicting treatment response in rheumatic diseases has not been identified.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Peter C. Taylor: Conceptualisation; Methodology; Writing – original draft; Writing – review & editing.

Eugen Feist: Writing – original draft; Writing – review & editing.

Janet E. Pope: Writing – review & editing.

Peter Nash: Writing – review & editing.

Jean Sibilia: Writing – review & editing.

Roberto Caporali: Writing – review & editing.

Alejandro Balsa: Writing – original draft; Writing – review & editing.

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ORCID iD

Peter C. Taylor https://orcid.org/0000-0001-7766-6167

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