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REVIEW

Tocilizumab for the Treatment of Adults with Moderate to Severe Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is a chronic, autoimmune disorder primarily affecting the joints but is also associated with many systemic features. Inflammatory cytokines such as IL-6 are abundantly detected in the synovial fluid. IL-6 plays a role in autoimmunity by promoting antibody production and T cell proliferation. The chronicity of inflammation observed in RA can also be partly explained by the effect of IL-6 on leukocyte migration and angiogenesis. Additionally, joint destruction may be mediated by IL-6 dependent osteoclastogenesis. Collectively, these findings prompted the development of an anti IL-6 receptor antibody (tocilizumab). Currently, tocilizumab is indicated for treating patients with moderate to severe RA as monotherapy or in combination with methotrexate, in whom disease modifying anti-rheumatic drugs or anti-TNFs have failed. The side effect profile is manageable but includes infections, decrease in neutrophil, increases in cholesterol and liver transaminases. Tocilizumab has expanded the treatment options of RA.

Keywords: rheumatoid arthritis, tocilizumab, treatment, monoclonal antibody, biologic

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Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune disorder characterised by inflammatory infiltration, synoviocyte hyperplasia, pannus formation leading to subsequent cartilage and bone erosion.[1] Besides the polyarticular involvement, systemic inflammation may also occur as exemplified by acute phase response, fatigue and anaemia.[2] Although the aetiology underlying RA remains to be fully elucidated, it is widely accepted that cytokines are directly implicated in disease pathogenesis.[3]

The revelation of increased pro-inflammatory cytokines within the joints[4,5] led to the proposition of cytokine disequilibrium.[6] This model suggests that a relatively low proportion of anti-inflammatory cytokines like IL-10 and TGF-β are outweighed by pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1. Furthermore, TNF-α was seemingly the dominant control, its effects cascading down to induce other inflammatory cytokines such as IL-1 and IL-6.[7] Indeed, anti-TNF therapy has proven to be very successful in inducing remission in RA, including those refractory to conventional disease modifying anti-rheumatic drugs (DMARDS). Despite the efficacy of anti-TNF biologics, a population of patients discontinue therapy due to inadequate responses or intolerability. Continuous revelations of cytokine interactions challenged the simplistic TNF hierarchy hypothesis, instead proposing a complex parallel network of cytokines which work synergistically to induce hallmarks of RA. In particular, much evidence has implicated the importance of IL-6 in RA, leading to the development of an anti IL-6 receptor (IL-6R) antibody, tocilizumab.

The Role of IL-6 in the Pathogenesis of Rheumatoid Arthritis

Proof of concept studies

IL-6 was found to be elevated in the sera and synovia of rheumatoid patients[5] but not in non-inflammatory arthropathies such as osteoarthritis.[8] Additionally, it was demonstrated that the synoviocytes constitutively release IL-6[9] and its levels were positively correlated with disease progression in animal models of arthritis.[10] These critical findings provoked interest in identifying IL-6 as a culprit of RA pathogenesis. Subsequent studies using IL-6 knock out (KO) mice demonstrated milder arthritis in comparison to wild type mice following antigen induced arthritis.[11] Furthermore, immunohistochemical staining revealed near complete erosion of cartilage in wild type mice whilst IL-6 KO mice maintained cartilage integrity. Likewise, IL-6 KO mice also failed to develop collagen-induced arthritis (CIA).[12] In attempt to further clarify the role of IL-6 and establish a possibility to block the corresponding receptor, investigations were conducted utilizing an anti-mouse IL-6 receptor antibody (MR16-1) in a CIA model).[13] In agreement with the IL-6 KO mice, MR16-1 inhibited the development of CIA possibly by diminishing both the collagen specific serum levels of IgG and splenic lymphocyte responsiveness.

Aside from these conventional animal models of arthritis, a few interesting engineered mutant mice models have also been used to verify the pathological role of IL-6 in RA. The SKG mouse model spontaneously develops a $CD4^+$ T cell mediated chronic arthritis which mimics the human model in many aspects, including the presence of rheumatoid factor, proliferative synovitis and pannus formation.[14] SKG mice have a mutation in the gene encoding the Src homology 2 domain (SH2) of ZAP-70, a critical signal transduction molecule for T cells. Consequently, a lower threshold is established for T cells in thymic selection, increasing the likelihood of positive selection of self reactive T cells. In these mice, high titers of IL-6 have been observed in the synovial fluid[15] and the subsequent injection of MR16-1 could inhibit RA development.[16] Collaboratively, these animal models strongly implicate the role of IL-6 in RA development. This leads to the question as to how this cytokine can possess pathological roles in RA. In fact, there is sufficient evidence to demonstrate that IL-6 contributes to many characteristics of RA including autoimmunity, chronic inflammation, joint erosion as well as the systemic features.

IL-6 mediates autoimmunity

Initially, IL-6 was named B cell stimulatory factor-2 (BSF-2), responsible for the final differentiation stage of activated B cells into plasma cells which secrete antigen specific antibody.[17] The exact mechanism of plasma cell differentiation is not fully elucidated, but an indirect effect via the promotion of B-cell helper properties on $CD4^+$ T cells via IL-21 has been suggested.[18] By administering recombinant IL-6 into

mice, it was shown that IgM, IgA and IgG production was enhanced following pokeweed mitogen (PWM) stimulus, without a corresponding increase in B cell proliferation. As expected, anti-BSF-2 abrogated PWM specific antibodies but had no effect on mitogen specific B cell proliferation.[17] Considering this effect, one may imagine that an increased IL-6 expression in the synovia[5] could lead to augmented antibody production, including autoantibodies. Rheumatoid factor (RF), an antibody to constant region of self IgG, is the most prominently studied autoantibody.[19] Following RF binding with its cognate antigen, immune complexes may be initiated leading to complement activation. Subsequent complement factor release, such as C5a, promotes chemotaxis to the synovial joint, contributing to pannus formation.[20]

The biological effects of IL-6 are not only restricted to the humoral immune response but extend to T lymphocytes. Evidence has shown IL-6 can stimulate $CD4^+$ T cell proliferation by enhancing the expression of IL-2 receptor[21] and also promoting IL-2 secretion.[5] Indeed, $CD4^+$ T cells are widely implicated in RA development, not only capable of activating fibroblasts and macrophages via cell surface receptors to produce pro-inflammatory cytokines and matrix metalloproteinases (MMP), but also interacting with B cells to stimulate antibody production.[1] Giving this established role of T cells in RA, the high titres of IL-6 within the synovium could activate autoreactive T cells which would provoke RA pathogenesis.

Another mechanism by which IL-6 can affect autoimmunity is via T regulatory cells (Tregs). In the absence of IL-6, $CD4^+$ T cells preferentially shift to the differentiation of Tregs if TGF-β is available.[22] Tregs are required for controlling the balance between tolerance and immunity. Failure in Treg function can subsequently lead to a prolonged immune response and ultimately chronic inflammation. It remains a possibility that IL-6 blockade can alleviate symptoms by re-establishing Treg numbers.

IL-6 maintains chronic joint inflammation

Typically, acute inflammation is dominated by the extravasation of neutrophils, followed by mononuclear cells 48 hours later. Neutrophils are short lived and die by apoptosis; on the contrary monocytes differentiate to other immune cells including macrophages and dendritic cells. For this reason, the transition to monocytes is a critical step in mediating a chronic immune response.[23] The exact mechanism of this transition is unknown but evidence has suggested IL-6 may be important in orchestrating this shift.[24] The cascade is thought to begin with IL-8 production by endothelial cells which are responsible for the initial neutrophil recruitment.[25] Activated neutrophils then shed soluble IL-6R (sIL-6R) from the cell surfaces[26] which in turn interact with locally produced IL-6 to stimulate monocyte chemotactic protein from endothelial cells.[27] This chemokine preferentially attracts monocytes to the site of inflammation which initiates a chronic immune response.

Once evolution to a chronic inflammatory state has occurred, maintenance is aided by several factors. A cardinal feature of a rheumatic joint is synovial hyperplasia which increases the demand for nutrient/metabolic exchange and hence evokes angiogenesis.[28] Angiogenic factors such as vascular endothelial growth factor (VEGF) can promote migration and endothelial proliferation[29] and have indeed been identified to be raised in RA.[30] Interestingly IL-6 alone, but not TNF-α, could induce VEGF slightly from synovial cells. This induction was much enhanced in the presence of IL-1, suggesting a synergistic interaction.[31] Accordingly, anti IL-6R antibody effectively reduced serum concentrations of VEGF and this was correlated to disease amelioration as measured by disease activity scores. Another study verified the importance of IL-6 and sIL6R in promoting angiogenic activity via VEGF production from fibroblast like synoviocytes whilst TNF-α actually appeared to exert an anti-angiogenic effect.[32]

Effects of IL-6 on joint erosion

Bone erosion is a prominent occurrence in RA patients, resulting in joint deformities. Osteoclasts, being macrophage derived cells responsible for bone resorption, are heavily implicated in coordinating the erosion of joint architecture in RA. Indeed, IL-6 has been suggested to be a pro-resorptive cytokine, along with TNF-α and IL-1. The simultaneous presence of sIL-6R and IL-6 induces the formation of multinucleated cells with characteristic phenotype of osteoclasts in vitro[33] which were capable of stimulating mineral and matrix release from bone extracts.[34] Accordingly,

the use of neutralising antibodies for IL-6R led to a marked reduction in osteoclast generation in mice[35] whilst IL-6 KO mice demonstrated comparatively less osteoclast recruitment to sites of joint disease than wild type mice.[36] The exact mechanism of osteoclastogenesis cannot be defined with certainty, but involves the RANK/RANKL system. Antigen stimulated arthritis in IL-6 KO mice expressed less RANKL on $CD4^+$ T cells relative to its soluble decoy receptor, osteprotegerin (OPG). Soluble OPG acts to neutralise RANKL on T cells thus preventing interaction with RANK on pre-osteoclasts which are vital for osteoclast generation.[37]

Besides the bones, IL-6 may also exert its effect on articular cartilage. In order for cartilage to be damaged, its structural constituents such as proteoglycans must be depleted. Primarily, this catabolism is mediated by cytokines such as IL-1, but IL-6 together with sIL-6 was also reported to inhibit proteoglycan synthesis in human chrondocyte culture.[38]

IL-6 induces systemic effects of RA

As already discussed, IL-6 plays a pivotal role in the local inflammatory processes but in fact evidence shows involvement of IL-6 in systemic manifestations. As part of the acute inflammatory response, alongside leucocytosis and fever, is an increase in liver derived proteins called acute phase proteins. Examples include α1-acid glycoprotein, α1-antitrypsin, α1-antichymotrypsin, haptoglobin and C reactive protein (CRP). IL-6, once known as hepatocyte stimulating factor, is the most potent inducer of acute phase proteins.[39] Experimental evidence has shown that the acute phase response is markedly compromised in IL-6 deficient mice[40] whilst administration of IL-6 to cynomolgus monkeys raised CRP levels in the serum.[41]

An additional hepatic effect mediated by IL-6 is the increased synthesis of hepcidin, a peptide central to iron homeostasis.[42] Upon expression, this peptide antagonises the functional activity of ferroportin, an iron exporter molecule. In turn, this diminishes iron absorption from the small intestines and iron mobilisation from macrophages. The end biological effect is hypoferriaemia which translates clinically to anaemia of chronic inflammation.[43] Indeed IL-6 KO mice exhibited lower levels of hepcidin and an increase in serum iron compared to wild type mice on stimulation with turpentine.[44] This implies that the IL-6-hepcidin axis may partly be responsible for the anaemia associated with many RA patients.

Fatigue is also commonly associated with RA and could be attributed to IL-6. Administration of IL-6 to healthy volunteers resulted in increased fatigue, reduced concentrations and activity. In IL-6 treated volunteers, increase serum level of adrenocorticotropic hormone (ACTH) and cortisol were detected with a concomitant decrease in thyroid stimulating hormone (TSH). Therefore, IL-6 seemingly mediates fatigue via the hypothalamic-pituitary-adrenal (HPA) axis.[45]

In summary, the pleiotropic nature of IL-6 can explain the key features of RA. Not only can IL-6 mediate chronic inflammation by antiapoptotic T cells and monocyte recruitment, but it plays a vital role in autoimmunity, integrating the effects of reduced Tregs and increased autoantibodies. Furthermore, systemic manifestation of RA including acute phase proteins, anaemia and fatigue can be explained by the action of IL-6. The apparent joint destruction in RA may also in part be attributed to IL-6. These diverse mechanisms of action of IL-6 highlighted IL-6R as a potential therapeutic target capable of alleviating the many hallmarks of RA (Fig. 1). This led to the successful development of an anti IL-6R antibody named tocilizumab.

IL-6R Antibody: Tocilizumab

A humanized monoclonal antibody for IL-6R was developed by grafting the complementarity determining region of mouse anti IL-6R Fab_2 onto a human IgG1 framework, using recombinant DNA technology.[47] Ideally, the anti IL-6R antibody should have the capability to neutralize membrane IL-6R (mIL-6R) and soluble IL-6R (sIL-6R) as both receptors contribute to RA pathogenesis. ELISA assay revealed that tocilizumab could bind to sIL-6R in a dose dependent manner but in addition could dissociate the IL-6: sIL-6R complex. Having established the binding capacity, it was also important to confirm IL-6R binding did not lead to stimulation. Antagonistic effects of tocilizumab on mIL-6R were confirmed using a human myeloma cell line KPMM2 which proliferates in response to IL-6. Furthermore, the

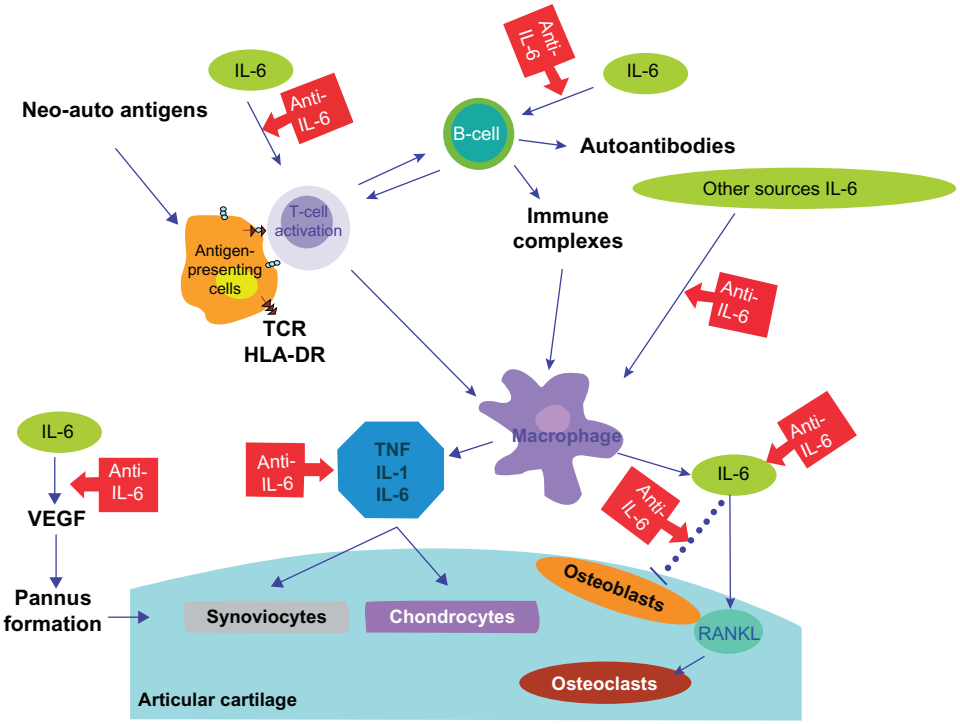

Figure 1. A schematic diagram representing the numerous potential sites of action of anti IL-6 at the joint level. Anti IL-6 may diminish the initial autoimmune events which produce self reactive T cells and antibodies. In addition, IL-6 blockade inhibits the later stages involved in bone erosion by the preferential generation of osteoblasts over osteoclasts as well as reduced synviocyte/chrondocytes stimulation. The pannus formation, which is responsible for joint erosion, may also be hindered by anti IL-6 which would reduce VEGF synthesis and therefore angiogenesis.[46]
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results suggested tocilizumab was specific for IL-6, despite other members of the superfamily using the same signaling molecule, gp130. Together these results confirm tocilizumab inhibits IL-6 signaling via mIL-6R and sIL-6R specifically without affecting other IL-6 superfamily members.

Pharmacokinetics of Tocilizumab

Population pharmacokinetic analyses were assessed based upon intravenous administration of 4 and 8 mg/kg tocilizumab for 1 hour every 4 weeks for a duration of 24 weeks (n = 1793).[48] Patients receiving 8 mg/kg tocilizumab every 4 weeks achieved an average steady state area under the curve (AUC), maximum concentration (C_{max}) and trough concentration (C_{min}) of 35 mg ± 15500 h/ml, 9.74 ± 10.5 µg/ml and 183 ± 85.6 µg/ml respectively. Although steady state C_{max} was reached after the first dosage, steady state C_{min} and AUC attainment was delayed till 8 and 20 weeks respectively. Interestingly, a more than dose-proportional increase in the AUC and C_{min} (2.7 and 6.5 fold higher respectively) were observed for doses of 4 and 8 mg/kg tocilizumab whereas C_{max} increased dose-proportionally. As the dose responsiveness of tocilizumab plateaus at high exposure (>800 mg per infusion), incremental increases in tocilizumab did not translate to clinically improved efficacy. Accordingly, doses exceeding 800 mg per infusion are not recommended.

The elimination of tocilizumab from the circulation is biphasic.[48] The total clearance is concentration dependent and is the sum of both linear and non-linear clearance. Non-linear clearance is the main mechanism of removal of tocilizumab from the circulation, however this pathway becomes saturated at higher concentrations, leaving linear clearance to dominate. Although no formal studies assessing the effect of renal or hepatic impairment on the pharmacokinetics of tocilizumab have been performed, patients which participated in the population pharmacokinetic analysis had normal to mild renal impairment (creatinine clearance based on Cockcroft-Gault <80 ml/min and ≥50 ml/min) and demonstrated no difference in the clearance of tocilizumab.

Clinical Efficacy

A European randomized, double blind control trial, CHARISMA, evaluated the comparative effectiveness of tocilizumab monotherapy and combination with methotrexate (MTX) relative to the control (placebo plus MTX).[49] The primary endpoint was measured using the American College of Rheumatology 20 criteria (ACR20). This is defined as a 20% improvement in both the tender/swollen joints and in at least 3 of 5 core measures: pain, acute phase proteins, physical disability, and patient/physician assessments.[49] ACR20 was achieved in 63% of volunteers who received 8 mg/kg tocilizumab monotherapy compared to 41% of control treated patients. Combination therapy of tocilizumab 8 mg/kg with MTX was observed to increase the number of patients achieving ACR20 to 74%. Besides synovial improvement, a reduced CRP and erythrocyte sedimentation rate (ESR) was also noted in tocilizumab treated but not control treated patients.

Subsequently, a multicenter, 24 week double blind, phase III trial, OPTION, verified the clinical benefit of tocilizumab used in combination with MTX.[50] The 623 patients recruited with active RA were either randomized for treatment every four weeks with tocilizumab 8 mg/kg (n = 205), tocilizumab 4 mg/kg (n = 214) or placebo (n = 204). All patient groups were also treated with a fixed weekly dose of methotrexate (10–25 mg/week). It was reported that 58.8% of patients achieved ACR20 when given tocilizumab 8 mg/kg plus MTX. In comparison, this benefit was only measured in 47.9% and 26.5% of tocilizumab 4 mg/kg and placebo treated patients respectively. Furthermore, ACR50 and ACR70 response were also statistically superior in patients treated with tocilizumab 8 mg/kg (44 and 22% respectively) compared to tocilizumab 4 mg/kg (31 and 12%) and placebo control (11 and 2%). Importantly, fatgue which was measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score showed statistically significant greater reduction by 8.6 and 7.29 respectively in the 8 mg/kg and 4 mg/kg compared with 4.01 in the placebo group ($P < 0.0001$ and $P < 0.0063$).

The findings from the OPTION study were further corroborated by the LITHE study, a randomized, double blinded, placebo control trial with 1196 RA patients.[51] Similar to OPTION, the objective of this study was to compare the achievement of ACR20 response after 24 weeks in patients treated with tocilizumab (4 or 8 mg/kg every 4 weeks) to patients treated with placebo. All patient groups were also administered MTX (10–25 mg weekly). In the tocilizumab 8 mg/kg group in combination with MTX group (n = 398), 56% of patients attained ACR20 response after 24 weeks whilst only 25% of the placebo control patients (n = 393) reached ACR20. After 52 weeks treatment, significantly more patients treated with tocilizumab 8 mg/kg (47%) attained DAS28 remission and compared to the control group (8%). Joint destruction and physical conditions after 52 weeks were also assessed. Significantly less radiographic progression was documented in patients treated with 8 mg/kg tocilizumab plus MTX compared to the control (Mean change of total Genant-modified Sharp score was 0.29 and 1.13 respectively; $P < 0.0001$). Furthermore, analysis of the area under the curve for change from baseline in HAQ-DI revealed more reduction with tocilizumab 8 mg/kg (−144.06 U) than placebo (−58.11 U; $P < 0.0001$), demonstrating that tocilizumab plus MTX results in more improvement in physical function.

The double-blind, placebo controlled, multicentre TOWARD trial, which included 1220 patients, demonstrated that dual therapy with tocilizumab (8 mg/kg every 4 weeks) plus DMARD was more effective than placebo combined with DMARD (ACR20 in 61% and 25% of patients respectively $P < 0.0001$).[52] Concomitantly, an improvement of systemic inflammatory effects in tocilizumab plus DMARD treated patients was observed as measured by reduced CRP and increase in haemoglobin levels (average increase of 0.98 g/dl) compared to placebo and DMARD combination.

In the RADIATE study, the efficacy of tocilizumab with methotrexate was evaluated in 499 patients with inadequate response to TNF-α inhibitor.[53] After 24 week, 50% of the patients treated with tocilizumab 8 mg/kg achieved ACR20 response compared with 30.4% in the Tocilizumab 4 mg/kg group, and 10.1% in the placebo group.

In AMBITION, a 24-week double-blind, placebo control trial, 673 patients with RA were randomized to either tocilizumab 8 mg/kg monotherapy or oral

methotrexate (target dose 20 mg/week).[54] Statistically significant more patients treated with tocilizumab monotherapy achieved an ACR20 (69.9% versus 52.5%), ACR50 (44.1% versus 33.5%) and ACR70 responses (28% versus 15.1%) compared with methotrexate. This is the first time a biologic agent used as monotherapy has been shown to be superior to methotrexate in improving symptoms and signs in RA. FACIT-Fatigue score showed greater reduction in patients treated by tocilizumab compared with the methotrexate arm (9.2 vs. 6.5) at week 24.

In the SAMURAI trial, 8 mg/kg tocilizumab and DMARDS were compared for efficacy in diminishing joint damage.[55] This randomized, multicentre trial recruited 306 participants with active RA. Patients were randomized to either tocilizumab 8 mg/kg monotherapy or DMARD. Radiographic assessments, as measured by modified total sharp score (TSS), of the hands and feet were undertaken at baseline, week 28 and week 52. At week 52, 56% of patients receiving 8 mg/kg tocilizumab experienced no radiographic progression compared to 39% of DMARD treated patients ($P < 0.01$). The mean change in TSS was 2.3 and 6.1 respectively for the two arms of the study ($P < 0.01$). Long term studies are required to assess whether the reduced change in TSS scores measured in tocilizumab treated patients will ultimately correlate with diminished disability.

Adverse Events

All of the aforementioned clinical trials firmly established the clinical benefit of tocilizumab therapy in RA (Table 1) and also profiled the safety data. Akin to other immunosuppressive agents, infections were the most common adverse drug reaction (ADR) reported in tocilizumab treated patients. As described above, IL-6 activates macrophages, neutrophils and upregulates antibody production leading to an enhanced immune reaction; IL-6 inhibition therefore interferes with defence mechanisms. In a pooled analysis of 4 double blind, 6 month controlled studies (AMBITION, LITHE, OPTION, TOWARD), the rate of all infections with tocilizumab 8 mg/kg plus DMARD was 127 events per 100 patient years compared to 112 events per 100 patient years in the placebo plus DMARD cohort.[48] Most notably, mild to moderate infections involving the skin, subcutaneous and upper respiratory tract were reported. The occurrence of serious infections were also greater in the 8 mg/kg tocilzumab treated patients compared to controls (Odds Ratio (OR) 1.78; confidence interval (CI) 0.98, 3.23) and included pneumonia, herpes zoster, acute bronchitis and pyelonephritis.[56] In comparison to the OR of serious infections for anti-TNFs (OR 2.0; CI 1.3, 3.1). In the long-term exposure population (up to 3 years treatment), the incidence of serious infections was comparable to the short-term trials (5.3 and 4.7 events per 100 patient years respectively), suggesting no increase in infection risk with extended exposure time. As a consequence, tocilizumab should not be initiated in patients with active infections. Risks to benefit assessments are necessary for patients with predisposing factors such as recurrent or chronic infections, co-morbidities (eg, diabetes, diverticulitis) and those with foreign materials in the body (eg, catheters, prosthesis). In common with other biologic agents, it is advisable to screen for tuberculosis and treat with standard therapy, if required, prior to initiating tocilizumab. Furthermore, special vigilance is required when evaluating tocilizumab treated patients for infections as IL-6 inhibition masks the standard clinical signs of infections (eg, fever, CRP elevation) by blunting the acute phase responses.

Tocilizumab plus DMARD therapy (3.4%) was also found to lower neutrophil counts below 1×10^9/l significantly more compared to placebo plus DMARD (<0.1%).[48] Although no clear association between decreases in neutrophil and the occurrence of serious infections were found, caution should be exercised in initiating tocilizumab therapy in patients with low neutrophil counts. In addition, monitoring every 4 to 8 weeks should be conducted.

Another concern regarding biological therapies is the development of neutralising antibodies that may lead not only lead to diminished efficacy but also the occurrence of allergic type adverse events. In a pooled analysis of four phase III trials with a total of 1747 tocilizumab treated patients, 24 patients developed neutralizing (n = 18), Ig class (n = 9), uncharacterized (n = 4) or multiple categories of anti-tocilizumab antibodies (ATA).[58] Despite the presence of neutralizing ATAs, no reductions in clinical efficacy, as measured by CRP and DAS28, were experienced. Allergic ADRs were documented in 6 patients; however, 4 of

Table 1. Proportion of patients achieving the primary and secondary efficacy endpoints in five principal tocilizumab trials. Tocilizumab was consistently more efficacious than the placebo and active control groups.

Intervention	CHARISMA			OPTION		
	P + MTX	T4 + MTX*	T8 + MTX**	P + MTX	T4 + MTX	T8 + MTX*
Intention to treat (n)	49	49	50	204	213	205
Baseline DAS-28 score	6.75	6.34	6.47	6.8	6.8	6.6
Primary endpoint [n(%)]						
ACR-20	20 (41)	31 (63)	37 (74)	54 (26)	102 (48)	120 (59)
**P* value*	<0.005			<0.0001		
***P* value*	<0.001					
Secondary endpoint [n(%)]						
ACR-50	14 (29)	18 (37)	27 (53)	22 (11)	67 (31)	90 (44)
**P* value*	Not stated			<0.0001		
ACR-70	784 (16)	6 (12)	19 (37)	4 (2)	26 (12)	45 (22)
**P* value*	Not stated			<0.0001		
DAS-28 < 2.6	4 (8)	8 (17)	17 (34)	1 (0.8)	21 (13)	47 (27)
**P* value*	Not stated			<0.0001		

these patients developed ATAs preceding the allergic event. Of the 4 patients, 3 patients were withdrawn due to severe anaphylactic reaction and infusion reactions.

The effect of tocilizumab on hepatic aminotransferases and bilirubin levels in five phase III trials were pooled for analysis.[48] The incidence of transient elevations in liver transaminases were highest in the 8 mg/kg tocilizumab plus DMARDs group (6.5%) followed by methotrexate treated patients (4.9%), 8 mg/kg tocilizumab monotherapy (2.1%) and placebo plus DMARDs (1.5%). It is evident that concurrent use of hepatotoxic drugs, such as MTX, with tocilizumab results in an increased prevalence of liver abnormalities. Although 0.7% and 1.4% of tocilizumab monotherapy and tocilizumab plus DMARD treated patients experienced greater than 5 times the upper limit of normal for liver transaminases, this did not translate clinically to hepatitis or hepatic impairment. The liver profile should be monitored every 4 to 8 weeks for the first 6 months followed by every 12 weeks thereafter.

Tocilizumab is also associated with alterations in lipid parameters, with elevations in high density lipoprotein (HDL), low density lipoprotein (LDL), cholesterol and triglycerides from baseline reported across various studies.[48] In a pooled analysis, 24% and 15% of tocilizumab treated patients had cholesterol levels exceeding 6.2 mmol/l and LDL levels surpassing 4.1 mmol/l respectively. Corresponding increases in the incidence of cardiovascular events have neither been reported in short term studies nor in the 5 year extension STREAM study.[59] However, patients should be regularly monitored and therapeutic intervention initiated if hyperlipidaemia persists.

Immunomodulating agents are associated with the potential for increased risk of malignancies. To date, there has been no correlation between tocilizumab treatment and malignancies. Although a minority of tocilizumab participants in the clinical trials developed cancer, the prevalence was insignificant compared to MTX and DMARD treated control groups.[51] In addition, the increased prevalence of cancer in the tocilizumab 4 mg/kg treated group plus MTX (1.9 events per 100 patient years) compared to both tocilizumab 8 mg/kg treated (0.9 events per 100 patient years) and control (0.4 events per 100 patient years) in the LITHE trial.[51] Nevertheless, the limited participants and short term exposure does not evaluate the risks of delayed events after long term exposure and post marketing surveillance is ongoing. In the interim, tocilizumab therapy is not recommended in patients with a history of malignancy and discontinuation should be considered if cancer develops during therapy.

Overall the safety profile of tocilizumab is manageable. Whilst awaiting additional safety data from post marketing surveillance, vigilance, regular screening and monitoring for liver abnormalities,

LITHE			TOWARD		AMBITION	
P + MTX	T4 + MTX	T8 + MTX*	P + DMARD	T8 + DMARD*	MTX	T8*
393	399	398	413	803	284	286
6.5	6.5	6.6	6.6	6.7	6.8	6.8
97 (25)	186 (47)	222 (56)	103 (25)	490 (61)	149 (53)	200 (70)
<0.0001			<0.0001		<0.0001	
39 (10)	116 (29)	145 (36)	37 (9)	305 (38)	95 (33.5)	126 (44.1)
<0.0001			<0.0001		0.0023	
15 (4)	65(16)	80 (20)	12 (3)	169 (21)	43 (15.1)	80 (28)
<0.0001			<0.0001		0.0002	
12 (8)	70(30)	127 (47)	12 (3)	241 (30)	34 (12.1)	96 (33.6)
<0.0001			<0.0001		Not stated	

Abbreviations: P, placebo; MTX, methotrexate; T4, 4 mg/kg tocilizumab; T8, 8 mg/kg tocilizumab; DMARD, disease modifying anti-rheumatic drug.

lipid profiles and infections are imperative in tocilizumab treated patients.

Drug Interactions

In vitro studies of cultured human hepatocytes have demonstrated that IL-6 downregulates cytochrome P450 enzyme (CYP450) expression, including isoenzymes CYP1A2, CYP2C9, CYP2C19 and CYP3A4.[48] Subsequent administration of tocilizumab may consequently restore CYP450 activity, leading to increased metabolism of CYP450 substrates. Prior to initiating or discontinuing tocilizumab therapy, dose adjustments may be necessary for concomitant medications metabolised by CYP450, in particular those with a narrow therapeutic window. Therapeutic monitoring of the effect (eg, warfarin) or serum concentrations (eg, theophylline, ciclosporin) of CYP450 substrates should be conducted and dose adjusted as appropriate to maintain therapeutic effect. Prescribers should also exercise caution with medications where a decrease in effectiveness is undesirable, such as statins, benzodiazepines and oral contraceptives. Given the long elimination half life of tocilizumab (up to 14 days), the effect on CYP450 enzyme activity may persist for several weeks after discontinuation.[48]

Place in Therapy

Tocilizumab recently gained licensing within Europe by EMA for the treatment of moderate to severe RA as monotherapy or in combination with MTX, in whom DMARDS or anti-TNFs have failed and in USA by FDA for the treatment of RA in combination with MTX after anti-TNF failure. In terms of scientific rationale, IL-6 is implicated in many RA manifestations (Table 2). The question as to whether this translates to improved clinical efficacy cannot be answered due to the absence of a direct head to head comparison of anti-TNF and anti IL-6R therapy. Meta analyses have implied no significant differences in safety or efficacy of anti-TNF and tocilizumab.[60] Nevertheless, the RADIATE trial clearly demonstrated that anti IL-6R can be effective in patients who were refractory to anti-TNFs,

Table 2. Qualitative comparison of the relative contributions of the pro-inflammatory cytokines to the manifestations of RA. The symbols + and – indicates a positive effect and no effect respectively.

Features	IL-6	TNF-α	IL-1
Levels in blood and synovial fluid	++++	+	+
Local effects			
Neutrophil migration	++	+	+
MMPs	+	++	+++
B cell function	+++	–	+
Osteoclast activity	++	+	+
Systemic effects			
Acute phase proteins	+++	+	+
Anaemia	++	+	+
Fatigue	+++	++	++

with 50% of this patient cohort achieving ACR20 when administered tocilizumab.[53] Furthermore, anti-TNFs have been associated with reactivation of latent tuberculosis by destabilising the granulomas compartmentalising the mycobacteria.[61] In comparison, IL-6 does not appear to have an established role in granuloma formation or maintenance. It is therefore encouraging that a new and efficacious treatment option exists for patients who are refractory to or intolerant of DMARDs and/or anti-TNF therapy.

Conclusion

IL-6 is the most abundant proinflammatory cytokine present in the sera and synovia of RA patients. Its pleiotropic effects are mediated by the ubiqitious availability of sIL-6R and mIL-6R. Animal proof of concept studies have validated that reduced IL-6 can alleviate disease pathogenesis, whilst IL-6 overexpression exacerbates the condition. The IL-6 involvement in RA was found to be multifunctional, capable of explaining the main manifestations of the disease. Not only did IL-6 maintain chronicity of inflammation within the joints but IL-6 could orchestrate autoimmunity. In addition, IL-6 mediates joint destruction. At the systemic level, IL-6 is involved in acute phase proteins, anaemia, fatigue as well as increased cardiovascular risk. In combination, these identified IL-6 to be a logical therapeutic target for RA and prompted an anti IL-6R antibody to be developed. This new therapeutic agent has gained licensing after proving safety and efficacy in clinical trials. Tocilizumab was consistently more efficacious compared to placebo or MTX in reducing disease activity. Additional benefits in reducing joint damage have also been demonstrated. IL-6 blockade is a new treatment options for RA patients refractory to conventional treatment.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. EC has received research grants, and served as member of advisory boards and speaker bureaus of Roche. The rest of the authors and peer reviewers report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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