New biologic for treating rheumatoid arthritis: clinical trial experience with tocilizumab

The aim of rheumatoid arthritis management is to control the signs and symptoms of disease, radiographic progression, functional decline, quality of life and to reduce the premature mortality associated with the condition. The early initiation of disease-modifying antirheumatic drugs (DMARDs) is recommended, preferably before the first radiographic evidence of erosions, and methotrexate should be used first-line in patients at risk of developing persistent disease. The optimal objective of treatment is to achieve remission. However, many patients do not achieve long-term remission with methotrexate monotherapy and only approximately 10% of patients who do not respond to methotrexate monotherapy are likely to respond adequately to other conventional DMARDs. Clinical outcomes can be improved by adding biological response modifiers that target specific molecules in the inflammatory cascade. The European League Against Rheumatism (EULAR) treatment guidelines recommend that anti-TNF therapy be considered instead of, or in addition to, treatment with conventional DMARDs for patients who do not achieve a satisfactory clinical response to one conventional DMARD. EULAR guidelines also state that anti-TNF agents may be appropriate first-line therapy in patients with severe disease or for those in whom conventional DMARDs are contraindicated. However, anti-TNF agents are not efficacious in all patients and, thus, other effective therapies have a role to play. IL-6 has been demonstrated to have a pivotal role in the pathogenesis of rheumatoid arthritis. Tocilizumab (Actemra®/RoActemra®; Roche, Basel, Switzerland/Chugai, London, UK) is the first agent developed to target this molecule specifically by inhibiting the binding of IL-6 to its receptor (an IL-6 receptor antagonist). Therapy with tocilizumab is indicated to reduce the signs and symptoms of rheumatoid arthritis in adult patients with moderate-to-severe active rheumatoid arthritis. Tocilizumab has shown efficacy in patients who have had an inadequate response to one or more DMARDs and in patients who have an inadequate response to anti-TNF agents or who were intolerant to them. It has also been demonstrated to be effective as monotherapy. Clinical trials demonstrated that tocilizumab is generally well tolerated.

KEYWORDS: biologic therapy ■ IL-6 ■ IL-6 receptor ■ rheumatoid arthritis ■ tocilizumab

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Rheumatoid arthritis (RA) is a chronic, disabling autoimmune disease that affects 0.5–1% of the population and is three-times more prevalent in women than in men [101]. Treatment options include a combination of pharmacological and nonpharmacological interventions, including disease-modifying antirheumatic drugs (DMARDs), NSAIDs, corticosteroids, analgesics, surgery, physiotherapy and occupational therapy. Only DMARDs (and glucocorticoids, to some extent) can delay or stop inflammation and joint destruction [1]. Conventional DMARDs, such as methotrexate (MTX) and sulfasalazine have been the mainstay of treatment for decades. More recently, biological drugs have been developed to target the cytokine mediators, such as TNF, IL-1 and IL-6, involved in the inflammatory cascade. Anti-TNF agents are effective for both the improvement of symptomatic disease and for the prevention of structural damage in patients with RA who have active disease in spite of treatment with conventional DMARDs, including MTX [2–6]. However, approximately a third of patients treated after DMARD failure show a lack of response to anti-TNF agents, either owing to lack of efficacy or following the development of adverse events [7].

New treatment options have been developed in recent years to treat patients with RA refractory to anti-TNF therapy. Tocilizumab (TCZ) is an intravenously administered monoclonal antibody that acts as an IL-6 receptor (IL-6R) antagonist. IL-6 is a logical target for drug therapy as patients with RA have elevated serum levels of this cytokine.

Tocilizumab is licensed in Europe for reducing the signs and symptoms of moderate-to-severe RA in adults. The US FDA accepted a resubmission for a Biologics License Application

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in July and plans to review this by the beginning of 2010. The Arthritis Advisory Committee of the US FDA voted 10–1 to recommend approval of TCZ.

IL-6: a new therapeutic target

Tocilizumab is a recombinant humanized anti-IL-6R monoclonal antibody that inhibits IL-6 signal transduction. IL-6 is a pleiotropic cytokine that acts as a biochemical messenger between cells that play a role in regulating acute and chronic inflammation throughout the body. It has been found in the synovial joints of patients with active RA, elevated levels correlating with clinical and laboratory indices of arthritis [8,9]. Overproduction of IL-6 leads to increases in acute phase reactants, such as serum amyloid and C-reactive protein (CRP) [10].

Clinical pharmacology

IL-6 binds either to a membrane-expressed IL-6R or to a soluble receptor (sIL-6Rα) [11]. The membrane-bound receptor is composed of two subunits: an IL-6Rα chain (gp80), which forms a low-affinity complex with IL-6, and a signal transducing subunit (gp130). These receptors are found on more limited cell types, including hepatocytes, monocytes, macrophages and some lymphocytes. The soluble form of the IL-6Rα bound to IL-6 can form a signaling competent complex with gp130 expressed on cells lacking the membrane IL-6Rα (transmembrane signaling). Soluble IL-6R is found in most body fluids. TCZ, administered by intravenous infusion, binds both to the soluble and to the membrane-bound IL-6R, blocking the receptor complex, leading to the prevention of all transmembrane signaling by IL-6 [11]. Formation of the IL-6R complex leads to the activation of signaling cascades (Jak-STAT, MPAK and P12K pathways), resulting in gene expression cell differentiation, proliferation, apoptosis or migration [12].

Pharmacokinetics

The total clearance of TCZ is concentration dependent. Once IL-6Rs are saturated, clearance becomes linear and is mediated by the reticuloendothelial system [13].

A small Phase I/II study demonstrated that repetitive treatment with TCZ normalized acute phase response in patients with RA. The authors noted that the optimal dosing schedule was not defined in their study, but that maintenance of serum concentration appeared to be important to achieve efficacy [14].

Patients treated with drugs that are metabolized by different CYP450 isoforms, such as CYP3A4 (simvastatin), CYP2D6 (dextromethorphan) and CYP2C19 (omeprazole), may require monitoring after concomitant therapy with TCZ owing to the effect of TCZ on CYP450 levels.

Clinical efficacy

Phase I/II

A dose-escalation trial (0.1, 1, 5 or 10 mg/kg) in 45 patients with active RA was the first randomized, controlled trial to show that inhibition of IL-6R improved the signs and symptoms of RA and normalized the acute-phase reactants [15]. The 5 mg/kg dose arm was the only arm with a significantly higher proportion of patients achieving an American College of Rheumatology (ACR) 20% improvement criteria (ACR20) response, observed at week 2, compared with placebo. No anti-TCZ antibodies were detected in treated patients. (Details of diagnostic criteria of RA can be seen in Box 1.)

In Nishimoto's dose-finding study of repetitive treatment with TCZ [14], 15 patients were randomized to receive biweekly infusions of 2, 4 or 8 mg/kg of TCZ for 6 weeks. Only patients who had detectable trough concentrations of TCZ achieved reductions to normal levels in CRP and erythrocyte sedimentation rate (ESR). ACR responses did not differ between the dosing groups and no patients had detectable levels of anti-TCZ antibodies. In another study led by Nishimoto, patients with active RA and prior failure of at least one DMARD or immunosuppressant were randomized (n = 164) to receive TCZ or placebo every 4 weeks following a washout period [16]. A total of 95% of the patients completed TCZ treatment compared with 53% of the patients receiving placebo. ACR20 was achieved in significantly more patients in the 4- and 8-mg/kg treatment arms versus the placebo arm. Two patients were withdrawn due to the development of anti-TCZ IL-6 antibodies.

The Chugai Humanised Antihuman Recombinant Interleukin-6 Monoclonal Antibody (CHARISMA) trial evaluated the efficacy of repeat infusions of TCZ alone and in combination with MTX in 359 patients with active RA in whom the response to MTX was inadequate [17]. Patients were randomized to one of seven groups: TCZ 2, 4 or 8 mg/kg as monotherapy; TCZ in combination with MTX; or MTX plus placebo. ACR20 was achieved by 61 and 63% of patients receiving 4 and 8 mg/kg of TCZ as monotherapy, respectively, and by 63 and 74% of patients receiving those doses of TCZ plus MTX, respectively,

compared with 41% of patients receiving placebo plus MTX. Statistically significant ACR50 and ACR70 responses were observed in patients receiving combination therapy with either 4 or 8 mg/kg of TCZ plus MTX.

In this trial, 17% of TCZ-treated patients versus 8% of MTX-treated patients achieved clinical remission at week 16. Significantly more patients whose previous MTX therapy had failed achieved a clinical response at week 16 with a combination of TCZ 8 mg/kg plus MTX than with MTX alone.

Phase III

A total of seven, large, randomized published studies have investigated the effect of treatment with TCZ in adult patients with moderate-to-severe RA [18–24]. All the studies evaluating the efficacy of TCZ were of double-blind design, except for the Study of Active Controlled Monotherapy Used for RA Patients, an IL-6 Inhibitor (SAMURAI) trial [18], which was x-ray reader-blinded, and performed in Japanese patients. With the exception of the Actemra Versus Methotrexate Double-Blind Investigative Trial In Monotherapy (AMBITION) study [20], which evaluated TCZ monotherapy in MTX-naive patients, the other trials assessed the effect of therapy in patients who had experienced an inadequate clinical response to previous therapy with MTX, at least one conventional DMARD or at least one anti-TNF agent.

The AMBITION study demonstrated that monotherapy with TCZ 8 mg/kg was superior to MTX with rapid improvement in the signs and symptoms of RA in patients who had not previously failed MTX or biologics treatment. The Tocilizumab Safety and the Prevention of Structural Joint Damage (LITHE) study [24,25], presented at this year's ACR meeting demonstrated that a greater proportion of RA patients treated with TCZ in combination with MTX experienced a significant inhibition on the progression of structural joint damage compared with patients treated with MTX alone.

SAMURAI & SATORI studies

In the SAMURAI study [18], 306 patients suffering from RA of less than 5 years' duration (mean disease duration: 2.3 years) who had had an inadequate response to at least one DMARD or immunosupressant therapy were treated with either 8 mg/kg of TCZ or continued with their conventional DMARDs for 52 weeks. At week 52, significantly more subjects in the TCZ group versus the DMARD group had no radiographic disease progression (56 vs 39%; $p < 0.01$) and improved total Sharp score ($p < 0.01$) and erosion score ($p < 0.001$). More TCZ subjects achieved ACR20, ACR50 and ACR70 responses, as well as reductions in the Disease Activity Score 28 (DAS28). In the Study of Active Controlled TCZ Monotherapy for RA Patients with an Inadequate Response to MTX (SATORI), the clinical efficacy and safety of TCZ monotherapy in active RA patients with an inadequate response to low-dose MTX was assessed [19].

Tocilizumab in treatment-refractory patients with established RA

A total of four Phase III trials have demonstrated that TCZ treatment is effective in treatment-refractory patients with established RA [21–24].

Box 1. Diagnostic criteria and key efficacy parameters in rheumatoid arthritis.

ACR criteria

- RA is defined by four or more of the following: morning stiffness in and around joints lasting at least 1 h; soft tissue swelling of three or more joint areas; swelling of the proximal interphalangeal, metacarpophalangeal or wrist joints; symmetric swelling; rheumatoid nodules; presence of rheumatoid factor; and radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints. Active disease is defined as having a swollen joint count of 6 or more, a tender joint count of 8 or more, and C-reactive protein levels of over 1 mg/dl or ESR above 28 mm/h.

ACR improvement criteria

- ACR20, ACR50 and ACR70: these represent the percentage of disease activity improvement (20, 50 or 70%) by the reduction in certain RA symptoms. For example, ACR20: patients achieve a 20% improvement in tender and swollen joint counts and 20% improvement in three of the five remaining ACR core set measures.

DAS28

- This records information from 28 tender and swollen joints, Ritchie Articular Index (a scoring system for recording joint tenderness), ESR and general health. DAS28 counts discriminate between high and low disease activity. Serial measurements of DAS28 are predictors of physical disability and radiologic progression. Low disease activity (DAS28 <3.2), moderate ($3.2 \geq$ DAS28 ≤ 5.1) and high disease activity (DAS28 >5.1). DAS28 less than 2.6 indicates clinical disease remission.

EULAR criteria

- Criteria evaluate improvements of disease activity in a core set of outcome measures in RA patients.

HAQ-DI

- Scores patient-reported physical functional status or ability to perform normal daily activities and discomfort during the past week. It contains 20 questions in eight domains. Final score ranges from 0 to 3, with higher values reflecting greater disability.

SF-36

- Health Survey is a measure of health-related quality of life based on 36 items.

TSS & TSGS

- The van der Heijde's modified TSS and the TSGS are modifications of the Sharp score, assessing disease progression in the radiographs of RA patients. Joint damage is measured on erosions and joint space narrowing.

ACR: American College of Rheumatology; DAS28: Disease Activity Score 28; ESR: Erythrocyte Sedimentation Rate; EULAR: The European League Against Rheumatism; HAQ-DI: Health Assessment Questionnaire Disability Index; RA: Rheumatoid arthritis; SF-36: Short Form-36; TSGS: Total Sharp-Genant score; TSS: Total Sharp score.

OPTION study

The Tocilizumab Pivotal Trial in MTX Inadequate Responders (OPTION) [21] randomized, controlled trial was performed in 73 centers in South America, Canada, Europe, Asia and Australia. It was designed to assess safety and efficacy of TCZ (either 4 or 8 mg/kg TCZ) plus MTX compared with MTX monotherapy in moderate-to-severe active RA patients. The study found that a higher proportion of patients receiving TCZ plus MTX had significantly lower RA activity compared with patients receiving placebo plus MTX (ACR20: 59%, 48 vs 26%; ACR50: 44%, 31 vs 11%; ACR70: 22%, 12 vs 2%; DAS28 < 2.6: 27%, 13 vs 0.8%; good or moderate EULAR responses: 80%, 62 vs 35%, respectively for 8 and 4 mg/kg of TCZ plus MTX vs placebo plus MTX; $p < 0.0001$ for all parameters of TCZ plus MTX vs placebo plus MTX, except $p = 0.0002$ for DAS28 remission for 4 mg/kg TCZ plus MTX vs placebo plus MTX; Table 1).

TOWARD study

The Tocilizumab in Combination With Traditional DMARD Therapy (TOWARD) study was performed in over 1000 patients from the USA, Europe, Latin America and Asia [22]. It evaluated the efficacy of 8 mg/kg TCZ every 4 weeks plus DMARDs compared with DMARDs alone in adult RA patients with moderate-to-severe active disease. At week 24, ACR20, ACR50 and ACR70 responses were significantly higher in all the TCZ groups ($p < 0.0001$). Remission (DAS28 < 2.6) was achieved in significantly more patients in the TCZ group than in the control group (30.0 vs 3.0%; $p < 0.0001$).

RADIATE study

The Research on Actemra Determining Efficacy After Anti-TNF Failures Trial (RADIATE) was a Phase III randomized, double-blind, placebo-controlled, parallel group study conducted throughout North America, Western Europe, Latin America and Australia [23]. It was the first study to demonstrate the efficacy of TCZ plus MTX in patients who had had an inadequate response to anti-TNF agents. Patients responded regardless of which anti-TNF agent they were intolerant or responding inadequately to, or the number of failed treatments (Table 2).

The trial included 499 adult patients with moderate-to-severe active RA who had failed to respond or who were intolerant to one or more anti-TNF drugs and were on MTX. Patients were treated with TCZ 8 or 4 mg/kg or with a placebo infusion for 24 weeks. All patients were treated with stable doses of MTX (10–25 mg weekly) and folate.

Table 1. Clinical response to tocilizumab treatment in the OPTION study.

Efficacy parameter	Patient response		
	4 mg/kg TCZ	*8 mg/kg TCZ*	*Placebo*
ACR20			
n (%)	102 (48)	120 (59)	54 (26)
p-value versus placebo	<0.0001	<0.0001	–
Odds ratio (95% CI)	2.6 (1.7–3.9)	4.0 (2.6–6.1)	–
ACR50			
n (%)	67 (31)	90 (44)	22 (11)
p-value	<0.0001	<0.0001	–
Odds ratio (95% CI)	3.8 (2.3–6.5)	6.6 (3.9–11.2)	–
ACR70			
n (%)	26 (12%)	45 (22%)	4 (2)
p-value	<0.0001	<0.0001	–
Odds ratio	7.0 (2.4–20.4)	14.2 (5.0–40.4)	–
DAS28 < 2.6			
n (%)	21/156 (13)	47/171 (27)	1/121 (0.8)
p-value	0.0002	<0.0001	–
Odds ratio (95% CI)	18.8 (2.5–142.2)	45 (6.1–331.6)	–

ACR: American College of Rheumatology improvement criteria; DAS: Disease Activity Score; OPTION: Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders; TCZ: Tocilizumab.
Data from [21].

Table 2. American College of Rheumatology response by previous anti-TNF treatment in the RADIATE study.

Anti-TNF agent	Patient response (%)		
	8 mg/kg TCZ plus MTX	*4 mg/kg TCZ plus MTX*	*Placebo plus MTX*
ACR20			
Adalimumab	26/49 (53.1)	19/55 (34.5)	3/62 (4.8)
Etanercept	35/67 (52.2)	17/61 (27.9)	8/49 (16.3)
Infliximab	24/54 (44.4)	13/43 (30.2)	5/47 (10.6)
ACR50			
Adalimumab	19/49 (38.8)	13/55 (23.6)	0/62 (0.0)
Etanercept	19/67 (28.4)	6/61 (9.8)	3/49 (6.1)
Infliximab	11/54 (20.4)	8/43 (18.6)	3/47 (6.4)
ACR70			
Adalimumab	6/49 (12.2)	5/55 (9.1)	0/62 (0.0)
Etanercept	10/67 (14.9)	0/61 (0.0)	1/49 (2.0)
Infliximab	5/54 (9.3)	3/43 (7.0)	1/47 (2.1)

ACR: American College of Rheumatology improvement criteria; MTX: Methotrexate; RADIATE: Research on Actemra Determining Efflcacy After Anti-TNF Failures; TCZ: Tocilizumab.
Data from [23].

Patients who had failed to respond at week 16 were offered rescue therapy with 8 mg/kg TCZ and MTX. ACR20 was seen in 50% of TCZ 8 mg/kg patients, 30.4% of TCZ 4 mg/kg patients and 10.1% of the placebo patients ($p < 0.0001$ for both TCZ doses vs placebo). DAS28 remission occurred in significantly more patients who received 8 mg/kg doses of TCZ compared with placebo (30.1 vs 1.6%; $p = 0.0001$). These results were consistent with those obtained in previous trials in different patient populations. Table 3 shows adverse events by class in the RADIATE study.

LITHE study

The 1-year results from the 2-year Phase III LITHE study, presented at EULAR in June 2009, demonstrated that TCZ with MTX inhibited the progression of structural joint damage and improved physical function and clinical disease activity significantly more than MTX alone in RA patients who respond inadequately to MTX [24]. Patients treated with 4 and 8 mg/kg TCZ plus MTX experienced a change in the mean Genant-modified Sharp score compared with patients treated with MTX plus placebo (0.29, 0.34 vs 1.1, respectively; $p < 0.001$). More patients treated with 4 and 8 mg/kg TCZ experienced no progression of structural joint damage from baseline compared with MTX plus placebo-treated patients (81, 85 vs 67%, respectively; $p \leq 0.0001$). DAS28 less than 2.6 was demonstrated in 30 and 47% of patients treated with 4 and 8 mg/kg TCZ, respectively, compared with 8% of patients treated with placebo plus MTX. The 2-year data presented at this year's annual ACR meeting in Philadelphia (PA, USA) demonstrated that TCZ in combination with MTX inhibited progression of joint damage in 83% of RA patients after 2 years compared with 66% of patients treated with placebo plus MTX ($p \leq 0.0025$).

The effect of 8 mg/kg TCZ treatment also increased over time with 65% of patients achieving remission after 2 years compared with 48% of patients treated for 1 year [25].

Tolerability

In general, TCZ treatment was well tolerated when administered as monotherapy or in combination with MTX or DMARDs to treat patients with RA in clinical trials. The adverse effects reported in clinical trials suggest that TCZ has a manageable safety profile. Withdrawal rates due to treatment-emergent adverse events were generally low. The most common clinical adverse effects observed in trials of TCZ therapy were upper respiratory tract infections, gastrointestinal complaints (i.e., diarrhea, vomiting, dyspepsia and abdominal pain), musculoskeletal disorders, headache and cutaneous adverse effects. Laboratory abnormalities involving liver enzymes, cholesterol levels and neutrophils occurred with greater frequency in TCZ-treated patients compared with placebo patients.

Alanine aminotransferase levels increased in a dose-dependent way and peaked within a few weeks of treatment then fell before the next dose.

Table 3. Summary of adverse events by class in more than 5% of patients and lipid changes in the RADIATE study.

Adverse event	Patient response		
	8 mg/kg TCZ plus MTX	*4 mg/kg TCZ plus MTX*	*Placebo plus MTX*
Adverse event by class in over 5% of patients n(%)			
Infections and infestations	86 (49.1)	76 (46.46)	66 (41.3)
Gastrointestinal	64 (36.6)	53 (32.5)	31 (19.4)
Skin	38 (21.7)	50 (30.7)	23 (14.4)
Musculoskeletal	27 (15.4)	34 (20.9)	34 (21.3)
Nervous	32 (18.3)	32 (19.6)	27 (16.9)
Respiratory	21 (12)	24 (14.7)	21 (13.1)
Vascular	14 (8)	18 (11)	8 (5)
Eye	11 (6.3)	11 (6.7)	3 (1.9)
Metabolism	9 (5.1)	7 (4.3)	7 (4.4)
Hematological	9 (5.1)	4 (2.5)	4 (2.5)
Total cholesterol (mmol/l)			
Baseline, mean (SD)	5.09 (1.07)	4.96 (1.12)	4.92 (0.99)
Week 24, mean (SD)	5.99 (1.25)	5.38 (1.09)	4.99 (1.07)
HDL-cholesterol n (%)			
No change	112 (64.7)	100 (61.3)	104 (65)
Elevation	29 (16.6)	22 (13.5)	6 (3.8)
LDL-cholesterol n (%)			
No change	90 (51.4)	76 (46.6)	104 (65)
Elevation	21 (12)	25 (15.3)	6 (3.8)

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; MTX: Methotrexate; RADIATE: Research on Actemra Determining Efficacy After Anti-TNF Failures Trial; SD: Standard deviation; TCZ: Tocilizumab.
Data from [23].

Lipid abnormalities were common in TCZ-treated patients, but the atherogenic index (total cholesterol-HDL-C/HDL-C) either remained unchanged or increased in a small number of patients. Neutrophil counts decreased in a dose-dependent way and normalized when TCZ was withdrawn.

The clinical consequences of increases in lipid levels, together with decreases in CRP and inflammation, have yet to become clear, but it may be that this effect requires treatment with statins. Other laboratory abnormalities reported on TCZ treatment include neutropenia and increases in liver enzymes, which may be related to a reduction of the inflammatory response. Consistent with its mechanism of action, infections were slightly increased with TCZ treatment, but the rate of serious treatment-emergent infections was generally low in trials and similar to rates observed in comparator groups.

Conclusion

Therapy with TCZ is indicated to reduce the signs and symptoms of RA in adult patients with moderate-to-severe active RA at a dose of 8 mg/kg in a 60-min intravenous infusion every 4 weeks, given either as monotherapy or in combination with MTX or other conventional DMARDs.

Well-designed studies have demonstrated that TCZ is efficacious when administered as monotherapy or in combination with conventional DMARDs in adult RA patients regardless of disease duration or prior therapy. TCZ is also efficacious in patients who have an inadequate response to anti-TNF agents or who were intolerant to them. TCZ is the first available agent to target IL-6 as a mediator of inflammation. In clinical practice, TCZ is likely to be used in RA patients for whom anti-TNF agents are contraindicated and in RA patients who have failed to respond to anti-TNF agents.

It may also be used first-line in RA patients when MTX is contraindicated, but support for this practice will be dependent on reimbursement policies and local guidelines.

Future perspective

Recent trials have demonstrated that DMARDs and DMARD combinations slow disease progression and that biological treatments result in rapid and sustained disease control associated with the prevention of joint destruction.

New, effective treatments for RA and new conceptual approaches have led to a shift in practice, with an emphasis now on treating arthritis as early as possible to a defined target where possible to achieve remission. Although this is a recommended approach to the management of RA, practice varies among countries. In the future, management efforts will focus more on the earlier phase of the disease. Patient-reported outcomes and patient concerns, such as being able to continue working, are also likely to receive more attention in the next few years. Future changes to treatment strategies are likely to involve the earlier use of biological treatments, the use of more targeted therapy to predefined end points and the consideration of the place of small molecules in the treatment of RA. Pharmacogenetics is also likely to play a role in the future to inform individualized treatment approaches and strategies.

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Executive summary

Aims of rheumatoid arthritis management

- Suppress inflammation.
- Prevent or to control joint damage.
- Prevent functional impairment.
- Minimize pain.
- Achieve remission.
- Reduce premature mortality.

Rationale for new treatment options

- A significant proportion of rheumatoid arthritis (RA) patients do not respond to anti-TNF therapy.
- Response to treatment is individual and more treatment options means more choice to offer patients the chance of achieving disease control and remission.

Tocilizumab: a new biologic for RA

- Tocilizumab is the first agent developed to target IL-6 specifically.
- Tocilizumab is an intravenously administered monoclonal antibody that acts as an IL-6 receptor antagonist.
- IL-6 plays a pivotal role in the pathogenesis of RA.
- Tocilizumab has shown efficacy in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs and in patients who have an inadequate response to anti-TNF agents or who were intolerant to them.
- Clinical trials demonstrated that tocilizumab is generally well tolerated.
- The safety profile reported in clinical trials is likely to be manageable in clinical practice.

Tocilizumab in clinical practice

- Tocilizumab is likely to be used as a first-line biologic in RA patients where anti-TNF agents are contraindicated or as a second-line biologic in RA patients who have failed to respond to anti-TNF agents.
- Tocilizumab may be used as first-line treatment in RA patients where methotrexate is contraindicated, but this will depend on local guidelines and reimbursement policies.

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▪ **Proof-of-concept study that was the first randomized, controlled trial to demonstrate that inhibition of IL-6 significantly improved the signs and symptoms of RA.**

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17 Maini RN, Taylor PC, Szechinski J *et al.*: Double-blind randomised controlled clinical trial of the interleukin-6 receptor antagonist tocilizumab in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum.* 54, 2817–2829 (2006).

▪ **Provides further indication that targeted blockade of IL-6 was an efficacious means of decreasing disease activity in patients with RA (as monotherapy or in combination with methotrexate [MTX]), confirming the Japanese monotherapy data.**

18 Nishimoto N, Hashimoto J, Miyasaka N *et al.*: Study of Active Controlled Monotherapy Used for Rheumatoid Arthritis, an IL-6 Inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x-ray reader-blinded randomised controlled trial of tocilizumab. *Ann. Rheum. Dis.* 66, 1162–1167 (2007).

▪▪ **Phase III study investigating the radiographic benefit of tocilizumab (TCZ) monotherapy in Japanese patients with active RA between 6 months and 5 years and an inadequate response to at least one disease-modifying antirheumatic drug or immunosuppressant.**

19 Nishimoto N, Miyasaka N, Yamamoto K *et al.*: Study of Active Controlled Tocilizumab Monotherapy for Rheumatoid Arthritis Patients with an Inadequate Response to Methotrexate (SATORI). *Mod. Rheumatol.* 19, 12–19 (2009).

20 Jones G, Sebba A, Gu J *et al.*: Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann. Rheum. Dis.* (2009) (Epub ahead of print).

▪▪ **Phase III study demonstrating that TCZ monotherapy was superior to MTX monotherapy in improving RA signs and symptoms in patients who had not previously failed MTX or biologics treatment.**

21 Smolen JS, Beaulieu A, Rubbert-Roth A *et al.*: Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION) study: a double-blind, placebo-controlled, randomised trial. *Lancet* 371, 987–997 (2008).

▪▪ **A 6-month, double-blind, randomized, controlled trial involving 622 patients with moderate-to-severe active RA who were on MTX therapy. It established that TCZ could be an effective therapeutic approach in these patients.**

22 Genovese MC, McKay JD, Nasonov EL *et al.*: Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequte response to disease-modifying antirheumatic drugs: the Tocilizumab in Combination With Traditional Disease-Modifying Antirheumatic Drug Therapy study. *Arthritis Rheum.* 58, 2968–2980 (2008).

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23 Emery P, Keystone E, Tony HP *et al.*: IL-6 receptor inhibition with tocilizumab improved treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biological: results from a 24-week multicentre randomised placebo-controlled trial. *Ann. Rheum. Dis.* 67, 1516–1523 (2008).

▪▪ **First study to demonstrate the efficacy of TCZ plus MTX in patients with an inadequate response to TNF-antagonist treatment.**

24 Kremer J, Fleischmann R, Brzezicki J *et al.*: Tocilizumab inhibits structural damage, improves physical function, and decreases DAS28 remission rates in RTA patients who respond inadequately to methotrexate: the LITHE study. OP-0157. Presented at: *EULAR – Annual European Congress of Rheumatology*. Copenhagen, Denmark, 10–13 June 2009.

25 Fleischmann R, Ambs P, Alecock E *et al.*: Tocilizumab inhibits radiographic progression and improves physical function in rheumatoid arthritis patients at 2 years with increasing clinical efficacy over time. Presented at: *The 73rd annual meeting of the American College of Rheumatology*. PA, USA, 16–21 October 2009 (Abstract 637).

▪▪ **Demonstrates that long-term treatment with TCZ and MTX can inhibit joint damage.**

Website

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