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TARGETING IL-6 IN RHEUMATOID ARTHRITIS

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ABSTRACT:

Interleukin-6 (IL-6) is a potent pro-inflammatory agent which plays a crucial role in the pathogenesis of systemic inflammatory disease. Targeting this pathway in rheumatoid arthritis (RA) seems an attractive option as IL-6 is important for both joint destruction and systemic manifestations. Currently, tocilizumab which binds the IL-6 receptor is licensed for treatment in active, moderate to severe disease in RA and systemic juvenile idiopathic arthritis (JIA). Several other promising IL-6 blocking agents as well as a subcutaneous form of tocilizumab are currently undergoing Phase III clinical trials. The aim of this article is to provide an up-to-date analysis of clinical efficacy and tolerability data concerning the use of IL-6 inhibitors. Data from clinical trials demonstrated that clinical efficacy for tocilizumab, which included improvement in physical function and halting radiographic progression, were comparable to other biologics licensed for use in RA. Patients who should gain most are RA patients with systemic features such as high inflammatory markers and anaemia. Perhaps, the strongest selling point lies in its effectiveness as a monotherapy. This is particularly useful in those who are not tolerating combination treatment with methotrexate. Tocilizumab is one of few biologics that has been shown to be superior to methotrexate in head-to-head studies. The safety profile of tocilizumab also is comparable to other currently available biologics. There is a small but significant increase in adverse events including infections in patients treated with tocilizumab compared to the placebo, particularly in patients who are elderly and those with multiple comorbidities. Elevated lipid profiles are frequent but have not been associated with major cardiovascular events. IL-6 blockade is a major advancement in the treatment of RA as it targets a unique molecule. Over the next

few years, evidence will be available on the long-term cardiovascular safety and efficacy of subcutaneous IL-6 blocking agents.

1. Introduction:

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterised by symmetrical persistent synovitis affecting multiple predominantly small joints. The disease also leads to fatigue, pain and other extra-articular manifestations. It is a common disease with a prevalence of 1% worldwide [1]. If left untreated, it will lead to significant joint destruction, reduced mobility and increases the health care burden.

Since the introduction of early intervention concept in the early 1990s [2], the management of our rheumatoid patients has shifted to a new paradigm. Rheumatologists have become more proactive in identifying patients presenting with early inflammatory arthritis symptoms and now treat them aggressively with the aim of rendering the disease into remission at the earliest opportunity. Thus fewer RA patients are seen with significant deformity these days.

Our understanding of the pathophysiology of RA has also improved with an understanding of the various pathways of the cytokines that drive the inflammatory cascades. These include the role of tumour necrosis factor, interleukins-1 and 6, as well as the role of B and T-cells. As a result, we have various options in treating our patients from the use of conventional synthetic Disease Modifying Anti-Rheumatic Drugs (DMARDS) to the different biologics, which include TNF-inhibitors such as infliximab, etanercept, adalimumab, golimumab and certolizumab, rituximab (monoclonal anti-CD-20 providing B-cell depletion), anankira (Interleukin-1 inhibitor) and abatacept (T-cell co-stimulatory inhibitor).

Despite the wealth of the different biologics, combination treatment using DMARDs and biologics often raises safety issues. More importantly, there is a

lack head-to-head success in regards to superiority of the biologics given as monotherapy against methotrexate [3-5]. Even when a TNF-inhibitor is given in combination with DMARDs, the rate of inadequate response has been quoted about 20-40% in various populations studied [6], prompting the clinician to switch to different form of biologics. One novel treatment that shows promising results is targeting Interleukin-6 (IL-6) which plays a pivotal role in the inflammatory cascade and also halts radiographic structural progression. The aim of this article is to provide a detailed critical analysis of clinical efficacy and tolerability data concerning the use of IL-6 inhibitors. We will conclude with our expert opinion on the place of IL-6 inhibitors in the treatment of RA.

To achieve these objectives, a literature review of the published literature in English language concerning the clinical efficacy and safety of IL-6 inhibitors in RA was first undertaken using PubMed, Embase and Cochrane Library databases up to November 2012. The keywords searched include 'biologics,' 'interleukin-6,' 'tocilizumab' and 'rheumatoid arthritis.' Abstracts presented from 2008 to 2012 at the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) conferences were searched. Lastly, clinical trials that were registered in the national registries were also sought.

2. The role of Interleukin-6 in the pathogenesis of Rheumatoid Arthritis

IL-6 is a pleiotropic cytokine, a 26-kDa glycopeptide encoded on chromosome 7. It is produced by various cell types such as T cells, B cells, monocytes, fibroblasts, osteoblasts, keratinocytes, endothelial cells, mesangial cells and some tumour cells [7]. IL-6 can activate cells through 2 signalling pathways; the

first is the membrane-bound (mIL-6R) via activation of glycoprotein 130 and the second is via proteolytic cleavage of the mIL-6R that leads to the generation of a soluble receptor for IL-6 (sIL-6R) [8, 9]. The binding of IL-6 to sIL-6R enables the stimulation of cells that lack endogenous soluble receptors (sIL-6R), thus widening the number of cell types responsive to this cytokine [10, 11].

In relation to the pathogenesis of rheumatoid arthritis, IL-6 plays a role in adaptive immunity. IL-6 stimulates B cells to differentiate into plasma cells which produce immunoglobulin [12]. It also influences T-cell development by stimulating the proliferation and differentiation of T lymphocytes into TH-17 cells which produce IL-17. In vitro studies in mice have shown that the co-stimulation of IL-6 and TGF-*β* is essential for the differentiation of Th17 cells from naive CD4+ T cells [13, 14].

Excess production of IL-6 has been found in the synovial fluid and blood of RA patients and correlates with the disease activity and joint destruction [15, 16]. IL-6 promotes synovitis by inducing neovascularisation via vascular endothelial growth factor (VEGF)-stimulated pannus proliferation, resulting in infiltration of inflammatory cells and synovial hyperplasia [17]. In terms of joint erosion, IL-6 causes bone resorption by inducing osteoclast formation via the induction of RANKL in synovial cells [18, 19], and cartilage degeneration by producing matrix metalloproteinases (MMPs) in synovial cells and chondrocytes [20, 21].

In addition, this cytokine is responsible for mediating many of the systemic manifestations of RA. It induces the acute-phase response particularly the development of C-reactive protein (CRP), fatigue via the hypothalamic-pituitary-adrenal (HPA) axis [22] and osteoporosis from its effect on osteoclasts. IL-6 also affects a change in lipid concentrations in blood. Furthermore it induces the

production of hepcidin which is responsible for anaemia of chronic inflammation [23]. Thus IL-6 is a pleiotropic cytokine and a suitable target in the treatment of RA.

3. Tocilizumab and other IL-6 agents currently under development

Tocilizumab, a humanised anti-IL-6R antibody prevents IL-6 from binding to both mIL-6R and sIL- 6R, thereby blocking the pro-inflammatory effects of IL-6. Its molecular weight is ~ 150 Kd [24] and it binds to sIL-6R in a dose-dependent manner and saturates the receptor at ~ 0.1µg/ml. It also competitively inhibits IL-6 binding to sIL-6R, with complete inhibition seen at ~ 4µg/ml [10].

Tocilizumab was initially developed by a collaborative effort between the Osaka University and the Chugai Pharmaceutical Company (Ltd) Japan, a subsidiary of Hoffman-LaRoche [25]. In Europe and the rest of the world it is given intravenously at a dose of 8 mg/kg every 4 weeks. The subcutaneous form (162mg weekly) is now entering the Phase III trial and the preliminary data showed comparable efficacy and safety profiles to the established intravenous form [26]. In the United States, the recommended starting dose for RA is 4 mg/kg, followed by an increase to 8 mg/kg based on the clinical response. Starting at the lower dose may not be ideal because of its insufficient efficacy in delaying remission, a higher risk of anaphylactic reactions and increased risk of immunogenicity [27].

Currently, the use of tocilizumab is licenced for the treatment of RA and systemic juvenile idiopathic arthritis (JIA). A recent Consensus indicated that tocilizumab may be used in adult patients with active RA, normally with at least moderate disease activity according to a validated composite measure, who have

had an inadequate response to, or intolerance of at least one synthetic DMARD and/or a TNF-inhibitor [28]. In 2012, both the National Institute for Health and Clinical Excellence (NICE) of the United Kingdom and the Food and Drug Administration (FDA) agency of the United States have expanded the approved indication of tocilizumab to be used as a “first-line biological agent” in RA patients who have had an inadequate response to one or more synthetic DMARDs.

In Japan, it is also licensed for use in the treatment of Castleman’s disease [29]. There are also case reports in regards to the use of tocilizumab in other auto-immune conditions such as giant cell arteritis [30, 31], adult onset Still’s disease [32] , systemic lupus erythematosus [33], ANCA-associated vasculitis [34], Behcet’s disease [35, 36], systemic sclerosis [37] and polymyositis [38]. These reports showed that tocilizumab was the salvage therapy used after disease resistance to various former drugs. More open-labelled or randomised controlled trials are needed to explore these in the future.

There are 4 other IL-6 agents that are currently under development, 3 of which are now entering the Phase III studies as summarized in Table 1. All but one of these agents are administered as subcutaneous forms. Sarilumab is the first fully human monoclonal antibody directed against IL-6Rα. The MOBILITY study, a Phase II double-blind, multi-national trial recruited 306 adults with active, moderate-to-severe RA who did not respond adequately to methotrexate (MTX-IR) [39]. Patients were randomised into 6 groups: sarilumab 100 mg 2-weekly, 150 mg 2-weekly, 100 mg weekly, 200 mg 2-weekly, 150 mg 2-weekly or placebo (all in combination with methotrexate). The results showed that the primary outcome, American College of Rheumatology (ACR20 response) was met at 12 weeks and was significant against the placebo (p=0.02) in the 150 mg every 2-weekly sarilumab

arm, 72.0% and 46.2% respectively. The types and incidence of adverse events were comparable to other IL-6 inhibitors.

BMS945429, a humanised monoclonal antibody that potently binds IL-6 completed a phase II double blind randomised placebo-controlled trial [40]. 127 patients who were MTX-IR were randomised to 1:1:1:1 to BMS945429 (80, 160 or 320 mg; administered intravenously) or placebo plus methotrexate. At week 12, the primary end point in the form of ACR20 response was achieved in 81% (80 mg; $p < 0.0001$ vs placebo), 71% (160 mg; $p = 0.0005$ vs placebo), 82% (320 mg; $p < 0.0001$ vs placebo) and 27% (placebo), respectively. Disease activity score in 28 joints remission criteria (DAS-28 < 2.6) was also achieved at week 16 in 14% (80 mg), 28% (160 mg) and 44% (320 mg) of the BMS945429 groups. The other secondary end point, clinical improvements in health-related quality of life (HRQoL), was also statistically significant in the treatment groups.

Sirukumab is a humanised monoclonal antibody against the soluble IL-6 receptor. It is administered subcutaneously. In the second part of the proof of concept Phase II randomised controlled study, the investigators recruited 151 RA patients who were MTX-IR. The patients were randomised equally to 5 treatment arms; (i) placebo from week 0-10 followed by sirukumab 100mg every 2-weekly from week 12–24, (ii) sirukumab 100mg every 2-weekly from week 0–24, (iii) sirukumab 100mg every 4-weekly from week 0–24, (iv) sirukumab 50mg every 4-weekly from week 0–24 and (v) sirukumab 25mg every 4-weekly from week 0–24 [41]. At week 12, all of the sirukumab arms (in combination) significantly improved ACR50 response (overall $p=0.010$) and significantly reduced the DAS-28 scores from baseline ($p<0.001$) compared to placebo. The patients who received sirukumab 100

mg every 2-weekly achieved the highest remission rates based on DAS-28 and simplified disease activity index (SDAI) criteria throughout the study up to week 24.

The other novel IL-6 blocking agent which is currently under development is olokizumab. It selectively blocks the final assembly of the IL-6 signaling complex (gp80 + gp130 + IL-6) [42]. A recent double-blind, placebo-controlled pilot study, recruited 40 RA patients who were on a stable dose of methotrexate but with a high CRP. They were randomised to a single dose of olokizumab; either (0.1 or 1.0 mg/kg intravenously) or (1.0 or 3.0 mg/kg subcutaneously), or a placebo. At 12 weeks, the results showed that regardless the dose or route of administration, a single dose of olokizumab demonstrated prolonged suppression of CRP. However, the CRP level in the 0.1 mg/kg intravenous group showed some recovery after 28 days. Importantly, all doses were well tolerated. The clinical efficacy and long-term tolerability of olokizumab will be explored further in phase II trials that are currently recruiting patients.

Clinical Efficacy

The use of IL6-inhibitor has been tested in multiple large randomised controlled trials. So far, only tocilizumab is licensed and will be the focus for discussion below. 10 pivotal trials are elaborated here and summarised in Table 2. Although the study protocols are different, majority of the studies used the same clinical end-points; American College of Rheumatology (ACR) improvement response, disease activity score in 28 joints (DAS-28), Health Assessment Questionnaire of Disease Activity (HAQ-DI) from baseline and the Genant-Modified Sharp score (GSS) in assessing the radiographic structural progression.

4.1 Tocilizumab Monotherapy

The earliest Phase II double-blind placebo-controlled study was conducted by Nishimoto and his colleagues in 2004. At that time, tocilizumab was known as MRA. In this multi-centre study conducted in Japan, 164 patients with refractory RA were randomised to receive either MRA (4 mg/kg body weight or 8 mg/kg body weight) or placebo [43]. MRA was given as monotherapy as all DMARDs were withdrawn prior to the study. The primary end point was the ACR20 response while secondary end points include the ACR50 & ACR70 responses, the DAS-28 responses and the safety profiles at 18 weeks. The results showed that at 3 months, 78% of patients in the 8 mg/kg group, 57% in the 4 mg/kg group and 11% in the placebo group achieved at least a 20% improvement in disease activity according to the ACR criteria ($p < 0.001$ for 8 mg/kg group versus placebo). The secondary end points were all met with significant results versus the placebo particularly in the 8mg/kg monotherapy group. Most importantly, MRA was well tolerated; the incidence of adverse events (mostly were mild) was 56%, 59%, and 51% in the placebo, 4 mg/kg and 8 mg/kg groups respectively and these were not dose dependent. An increment in blood cholesterol was observed in 44.0% of the patients treated with MRA although no cardiovascular complication was observed. These positive findings in terms of clinical efficacy and tolerability have stimulated other phase III studies examining the use of tocilizumab monotherapy.

The AMBITION (**A**ctemra versus **M**ethotrexate double-**B**lind **I**nvestigative **T**rial **I**n m**ON**otherapy) study recruited 673 patients with different selection criteria. 67% of the patients were methotrexate-naïve at baseline whereas patients who had previously failed either methotrexate or a TNF-inhibitor were excluded [44]. There were 3 arms in which patients were randomised to either an

escalating dose of methotrexate or tocilizumab 8 mg/kg, with a separate sub-study (n = 101) recruiting patients to placebo for 8 weeks followed by active treatment. The primary endpoint was the ACR20 response at 24 weeks. The results showed non-inferiority and in fact superiority of toclizumab versus methotrexate. The weighted difference for ACR20 response at week 24 was 0.19 (95% CI 0.11 to 0.27, $p<0.001$). Significant difference was evident as early as week 2. The superiority was also true in the methotrexate-naïve patients in the sub-analysis. Other secondary end points include the ACR50 & ACR70 responses, remission in the form of DAS-28<2.6, achievement of moderate EULAR response and HAQ-DI from baseline also demonstrated superiority of tocilizumab against methotrexate. Fungal infections were more common in the methotrexate group. Four deaths occurred during the study, three in the tocilizumab arm, of which one was thought remotely related to treatment (gastrointestinal haemorrhage).

The SATORI study recruited 127 patients with an inadequate response to methotrexate (MTX-IR) [45]. This double-blind Japanese study randomised patients to either tocilizumab 8 mg/kg or to methotrexate 8 mg per week. The dose of methotrexate is notably low in this study, in keeping with current practice then in Japan. Nearly half of the participants from the control group (48%) withdrew from the study mainly due to a poor response to the treatment. The primary outcome was achieved in which with 80% tocilizumab-treated patients compared to 25% control patients achieving the ACR20 response at week 24. Serum vascular endothelial growth factor (VEGF) levels decreased significantly more in the tocilizumab group than the control group. No significant difference was seen in the number of patients discontinuing the study due to AEs. Nasopharyngitis was seen slightly more frequently in the tocilizumab group.

The ACT-RAY is the only double-blind Phase III study that assessed the efficacy and safety profile by either adding tocilizumab to methotrexate strategy or switching methotrexate to tocilizumab monotherapy. This was done over a 2 year period in patients who had an inadequate response to methotrexate (MTX-IR). The results are now available at 52 weeks [46]. 556 patients were randomly assigned either to continue methotrexate with the addition of tocilizumab 8 mg/kg 4-weekly or switch to tocilizumab monotherapy. The primary endpoint was clinical remission rate in the form of DAS-28 at week 52 while the secondary end points included other symptomatic outcomes such as ACR responses, HAQ-DI and progression of structural damage using GSS. The results showed that the DAS28–(ESR) remission rate was significant in the add-on group compared to the switch to monotherapy group, 45.5% and 36.6% respectively (p=0.03). Although all other secondary end points showed improvements in both groups which was maintained throughout up to week 52, there was no statistically significant superiority of the add-on strategy against the switch to monotherapy strategy in all other composite measures. The majority of the structural progression from baseline was arrested. However, significantly more switch patient experienced radiographic progression than in the add-on group. The rates of adverse events and serious infections were also comparable. The only different but important safety issue was that treatment with combination with methotrexate resulted in higher rate of deranged liver transaminases (greater than 3 times of the upper normal limits) than the monotherapy group, 11% and 3% respectively. This laboratory abnormality has been a consistent finding from week 28 up to week 52.

The SAMURAI (**S**tudy of **A**ctive controlled **M**onotherapy **U**sed for **R**heumatoid **A**rthritis, an **I**L-6 inhibitor) study was a Japanese open-label but x-ray

reader-blinded study to examine primarily the effect of tocilizumab monotherapy on radiographic progression based on van der Heijde-modified Sharp score (vdH-Sharp score) at 52 weeks [47]. 306 patients were randomised to either 8mg/kg dose of tocilizumab monotherapy group or DMARDs group (mostly combination DMARD therapy including low-dose methotrexate). In terms of clinical efficacy, the secondary end points showed superiority of tocilizumab monotherapy against the conventional DMARDs therapy ($p<0.001$) for each of the ACR response component although this was assessed unblinded. Clinical remission defined as DAS28<2.6 was achieved in 59% of patients receiving tocilizumab compared to only 3% of patients receiving DMARDs ($p<0.001$).

In terms of long-term clinical efficacy, the STREAM (Long-term **S**afety and efficacy of **T**ocilizumab, an anti-IL-6 **RE**ceptor monoclonal **A**ntibody, **M**onotherapy, in patients with rheumatoid arthritis) study is the longest study to-date, with 5 years follow-up duration that assessed the safety and clinical efficacy [48]. This is an extension trial that was carried out by Nishimoto and his colleague described earlier in this article [43] although the difference is that it is an open label study after the initial double-blind trial. 66% of the 143 patients completed the 5 years study. Notably, the response rate according to the ACR improvement criteria increased during the initial year and subsequently remained constant throughout the study period. At 5 years, 84.0%, 69.1% and 43.6% of the tocilizumab group achieved the ACR20, ACR50 and ACR70 responses respectively. In fact, improvement in all other parameters including tender joint counts, swollen joint counts, CRP levels, HAQ score and clinical remission (DAS28<2.6) from the earlier Phase II study was sustained throughout the 5 year follow-up. Only one patient withdrew due to lack of response while 22% withdrew due to adverse events.

4.2 Tocilizumab with Combination Therapy (Methotrexate / DMARDs)

The earliest phase II study was CHARISMA (the **C**hugai **H**umanised **A**nti-Human **R**ecombinant **I**nterleukin-**6** **M**onoclonal **A**ntibody). This was a multicentre double-blind randomised controlled trial which recruited 359 European patients who did not respond adequately to methotrexate (MTX-IR) [27]. The primary clinical end-point was the ACR20 response at 16 weeks. The secondary end points included the ACR50 and ACR 70 responses at 16 weeks, the DAS-28 response and safety assessment up to the 20th week. The patients were assigned to either receiving a placebo + methotrexate or tocilizumab at doses of 2 mg/kg, 4 mg/kg or 8 mg/kg, each with or without methotrexate. The results showed that at 16 weeks, the ACR20 response was achieved by 61% and 63% in the 4 mg/kg and 8 mg/kg dose of tocilizumab monotherapy groups respectively while 64% and 74% patients also achieved this primary end point in those similar doses but with a combination with methotrexate respectively. There were no significant differences in ACR20 response rates between the placebo and 2 mg/kg dose groups. The only significant ACR50 & ACR70 responses against the placebo + methotrexate group were seen in patients on 8 mg/kg dose of tocilizumab plus methotrexate. Other secondary end point showed that remission in the form of DAS-28 score was achieved by 34%, 17% and 8% in the 8 mg/kg dose of tocilizumab + methotrexate, 8 mg/kg dose of tocilizumab monotherapy and placebo + methotrexate groups respectively. The study also showed that responses to tocilizumab treatment were seen as early as week 4 and were still improving at the study endpoint.

The OPTION (T**O**cilizumab **P**ivotal **T**rial in Methotrexate **I**nadequate Resp**ON**ders) study, a large double-blind placebo-controlled study, recruited 623 patients worldwide who had not responded to methotrexate adequately (MTX-IR)

[49]. All other DMARDs and Biologics were discontinued prior to the start of the study. The primary end point was the ACR20 response at 24 weeks. The secondary end points include ACR50 & ACR70 responses at 24 weeks, the DAS-28 response and HAQ-DI to assess physical functionality. The patients were randomised to tocilizumab 4 mg/kg, 8 mg/kg or placebo each with methotrexate at a stable dose. The results showed that at 24 weeks, the ACR20 was achieved by 48% patients allocated to tocilizumab 4 mg/kg, 59% patients receiving 8 mg/kg dose tocilizumab and 26% patients in the placebo group ($p < 0.0001$). Significantly greater number of patients receiving tocilizumab showed ACR50 and ACR70 responses and DAS-28 remission (DAS-28 < 2.6) at week 24 than those did in the placebo groups.

The ROSE (**R**apid **O**nset and **S**ystemic **E**fficacy) study was the first Phase IIIb study which recruited 619 patients from various centres only in the United States, who had an inadequate response to DMARDs (DMARDs-IR) [50]. Prior use of other biologics was permitted and subsequently withdrawn before the randomisation. Patients were randomised in a 2:1 basis to tocilizumab 8 mg/kg or placebo while continuing a stable background DMARDs therapy. The primary endpoint was the ACR50 response at week 24. The secondary end points include the ACR20 & ACR70 responses, the DAS-28 response and the European League Against Rheumatism (EULAR) response at 24 weeks. The results showed that the ACR50 response at week 24 was significantly higher in the tocilizumab group than in the placebo group (30.1% vs11.2%; $p<0.0001$). Significantly greater number of patients receiving tocilizumab achieved the ACR20 and ACR70 responses and the EULAR good response at all time points starting from week 4 and clinical remission (DAS-28 < 2.6) at week 24 compared to the placebo group. A sub-study examining early response to therapy was also undertaken and showed improved patient's

global assessment of disease activity, pain, CRP and ESR in tocilizumab group compared to placebo as early as day 7 but not in the swollen or tender joint counts and physician's global assessment.

Of all the Phase III studies, TOWARD (**TO**cilizumab **W**ith traditional DM**ARD**) recruited the largest patient population, 1,220 patients worldwide [51]. The patients were randomised in a 2:1 manner to either tocilizumab 8 mg/kg or placebo along with stable doses of DMARD therapy throughout. It is the only study which exclusively excluded prior treatment with biologics. The primary endpoint was the ACR20 response at 24 weeks. The results showed that in the tocilizumab group, 61% patients met the primary end point compared to 25% in the placebo group. The improvement in the ACR response was consistent across the various types and numbers of DMARDs used with the exception of patients receiving at least three DMARDs in combination. All other secondary end points were also achieved notably the ACR50 & ACR70 responses, which were apparent from Week 4 and continued to Week 24. Adverse events (AEs) were reported more in the tocilizumab group than the control group (73 vs. 61%) although withdrawals from study due to AEs were infrequent. There was not a clear difference in serious infections. As the participant numbers are large, this study adds the evidence of the efficacy and relative safety of tocilizumab in combination with any other DMARDs available.

The RADIATE (**R**esearch on **A**ctemra **D**etermining Eff**I**cacy after **A**nti-**T**NF Failur**E**s) study is the only phase III multi-centre placebo-controlled trial which recruited only patients who had previously failed TNF inhibitors (TNF-IR) [6]. 499 patients from North America and Europe were randomised to tocilizumab at a dose of 8 mg/kg, 4 mg/kg or placebo along with a combination of methotrexate. Nearly half the patients had failed one TNF inhibitor, 38% had failed two agents and 14% had

failed at least three. The primary end point was the ACR20 response at week 24 while the secondary end points include the ACR50 & ACR70 responses, the DAS-28 response and also the EULAR response. The results showed that both the 8 mg/kg (50.0%) and 4 mg/kg (30.4%) groups exhibited superior ACR20 responses compared with control (10.1%; $p<0.001$). Significant ACR50 & ACR70 responses, EULAR responses were met in both groups receiving tocilizumab. However, the 8 mg/kg tocilizumab was more superior compared to the 4 mg/kg group notably in terms of clinical DAS-28 remission. Interestingly, there was no definite relationship between the ACR response rates and the number or type of prior TNF inhibitors.

The LITHE study was a double-blind randomised controlled trial with the longest follow-up, 52 weeks [52]. 1,196 patients from 15 countries were recruited and randomised to 3 arms; tocilizumab 8 mg/kg, 4 mg/kg or placebo, all in combination with methotrexate. Prior TNF inhibitor therapy was allowed. A rescue therapy of tocilizumab 4mg/kg was offered to the patients who did not receive 20% improvement in terms of tender and swollen joint counts by week 16. The two primary end points were the change from baseline in the radiographic score using GSS and change in physical function using HAQ-DI at week 52. By the end of the study period, half of the control group had received rescue treatment. Both primary outcomes were met, with a 74% and 70% reduction in radiographic progression in the tocilizumab 8 mg/kg and 4 mg/kg groups respectively. HAQ-DI improvement was also significant in the treatment groups compared to the placebo groups. Other efficacy analysis also showed that the ACR responses were greatest in the tocilizumab 8 mg/kg group. No apparent differences were seen in exposure adjusted rates of serious AEs between the tocilizumab and placebo groups.

4.3 Composite index without using acute phase reactants as measurement of clinical efficacy

Most composite indexes such as ACR improvement criteria, DAS-28 and Simplified Disease Activity Index (SDAI) include either CRP or ESR in the formula. Although it has been reported that the degree to which acute phase reactants (APR) contribute to the constituent elements of the DAS28 is no more than 15% [53], there is always a theoretical assumption that these composite indexes may overestimate the clinical response in patients treated with an IL-6 inhibitor particularly in terms of the definition of remission [54]. This is particularly true as the CRP production is induced mainly or not exclusively by the IL-6 cytokine although the TNF and IL-1 cytokines have also indirect roles in the mediation [55, 56].

In order to tackle this, Clinical Disease Activity Index (CDAI), an index that has been validated previously in assessing severity of RA was studied as it does not include APRs [57, 58]. The formula for calculation is CDAI = TJC + SJC + GH + EGA; where TJC = tender joint count (0–28), SJC = swollen joint count (0–28), GH = patient's assessment of general health (cm) and EGA = physician's global assessment (cm). The cut off points are: Remission (CDAI ≤2.8), Low Disease Activity (CDAI between 2.8 and 10), Moderate Disease Activity (CDAI between 10 and 22) and High Disease Activity (CDAI > 22).

Kaneko and colleagues recruited 31 patients who were DMARD-IR or TNF-IR, treated with tocilizumab 8mg/kg dose [59]. The length of follow-up was 52 weeks. The results showed that mean baseline of DAS28-ESR was 5.96, decreasing to 2.89 at week 52 with a remission rate (DAS28-ESR<2.6) of 35.5%. On the other hand, the mean baseline of CDAI was 28.4, falling to 10.2 at week 52 with a

remission rate (CDAI≤ 2.8) of 22.6%. Further analysis also showed that of patients whose CRP levels were not detected by week 12, 65.2% achieved remission or low disease activity as assessed by CDAI at week 52.

On a larger scale, Smolen and his colleagues obtained results from a random sample of 80% patients from the 3 randomised clinical trials (LITHE, OPTION & TOWARD) and pooled the results [60]. The patients were mainly DMARD-IR and not methotrexate-naïve or TNF-IR. The results showed that in patients treated with tocilizumab, the reduction in disease activity is statistically significant against the placebo irrespective of the type of composite measures used to evaluate disease activity. The remission rates in tocilizumab groups were much higher using the DAS-28 compared to SDAI and CDAI, 30% against 7.7% & 6.4% respectively. This can be explained by the high weight of the ESR in the DAS-28 calculation and the effect of tocilizumab on repressing the acute phase reactants. Using the CDAI index, the remission rates in patients treated with tocilizumab were in similar magnitude than those treated with tumour necrosis factor inhibitors.

4.4 Effect on Radiographic Progression

Osteoclasts are the key cells involved in mediating erosions in inflammatory arthritis. Osteoclastogenesis occurs from the interaction between receptor activator of NF-κB (RANK) and its ligand (RANKL) [61, 62]. In neonatal mouse calvaria experiment, IL-6 in the presence of sIL-6R, enhanced the expression of RANKL and osteoprotegerin (OPG) thus inducing bone resorption [19]. However the RANK expression was also found decreased, suggesting that sIL-6R trans-signalling influences osteoclastogenesis through osteoblast and osteoclast interaction.

Applying this animal study finding to the human trials, both the LITHE and ACT-RAY trials showed that tocilizumab retarded the structural disease progression using Genant-modified Sharp score (GSS). In LITHE study, progression of structural damage from baseline to week 52 was reduced by 74% and 70% with tocilizumab 8mg/kg and 4 mg/kg both in combination with methotrexate, respectively, as compared with controls (P<0.0001) [52]. The ACT-RAY study compared the effect on radiographic progression between 2 groups; tocilizumab monotherapy and tocilizumab + methotrexate. The radiographic progression was defined as any change in GSS > the smallest detectable change (SDC) computed based on the difference between the x-ray readers. The results showed that the overall radiographic progression was small in both groups although it was statistically significant (add-on therapy versus switch to monotherapy); 8% and 14% respectively [46].

The SAMURAI study assessed the radiographic progression between tocilizumab 8mg/kg monotherapy and DMARDS only groups based on a different scoring system, van der Heijde-modified Sharp score (vdH-Sharp score) at 52 weeks. The results showed 56% of patients receiving tocilizumab had no radiographic progression (i.e change from baseline in the total Sharp Score (TSS) ≤0.5 compared with 39% of patients receiving conventional DMARDs (p<0.01) [47]. In addition, the erosion scores and joint space narrowing scores also showed significantly less change in the tocilizumab group than in the DMARD group.

Recently, studies exploring the structural progression using magnetic resonance imaging (MRI) are under way. Results from 12 weeks study showed that treatment with tocilizumab is associated with early suppression of synovitis and

osteitis, with no mean increase in the erosion score [63]. There was no statistically different between tocilizumab monotherapy and in combination with methotrexate.

4.5 Other Clinical Efficacy

Treatment with tocilizumab also increases the haemoglobin level in various phase III studies whether it is administered as a monotherapy or in combination with other conventional DMARDs. In STREAM study, most patients exhibited anaemia at baseline and the mean haemoglobin level was 11.3 ± 1.4 mg/dl (SD 1.4) [48]. After 5 years follow-up, treatment with tocilizumab significantly improved anaemia in these patients and the mean haemoglobin level increased to 13.2 ± 1.5 mg/dl (SD 1.5). The AMBITION study also indicated that the improvement in haemoglobin levels was seen as early as week 2 with normalisation of mean haemoglobin by week 6 and subsequently maintained through to week 24 [44].

The HAQ-DI is designed to assess the patient's usual abilities and physical function. It is composed of 20 items from 8 different categories. The HAQ-DI is sensitive to change and is a good predictor of future disability and costs [64, 65]. Again, various tocilizumab trials showed improvement of HAQ-DI from baseline. In LITHE study, at 52 weeks, ANOVA of the adjusted mean area under curve (AUC) of the change in the HAQ-DI score from baseline showed a significantly greater decrease in the tocilizumab 8-mg/kg and 4-mg/kg plus MTX groups (–144.1 and -128.4 units, respectively) than in the control group taking placebo plus MTX (–58.1 units; $P < 0.0001$ for both comparisons) [52].

5. Safety Profile

In an analysis of cumulative safety data from five pivotal phase III trials and two extension trials, two populations were studied. The first group is the patients randomised to the different treatment arms during the controlled portions of the studies, followed until the first change in treatment regimen or until 2 years of treatment (n = 4,199, controlled population). The second group comprised those who were exposed to at least one dose of tocilizumab (n = 4,009, all-exposed population) [66]. The analysis which consisted of mean treatment duration of 2.4 years, confirmed that the long-term safety profile of tocilizumab was comparable with that observed in the phase 3 studies (duration up to 1 year).

The overall rate of adverse events (AEs) was 339.0/100 patient years (PY) in the control group, 358.0/100 PY in the tocilizumab 4-mg/kg group and 381.6/100 PY in the tocilizumab 8-mg/kg group in the all-controlled population group. In the all-exposed groups, the rate of AEs was 278.2/100 PY in which elevated transaminases levels and infections were the commonest AEs reported. The rate of serious adverse events (SAEs) was not different between the groups and did not increase with prolonged exposure. In fact, the rates of SAEs, including deaths, were similar to those observed in other biologics clinical trials in RA although direct comparison as always may not be accurate as different study protocol and designs were employed.

5.1 Infections

In the all exposed population, the rates of serious infections were the highest in the tocilizumab 8-mg/kg group compared to the tocilizumab 4-mg/kg group and the control group; 4.9/100 PY, 3.5/100 PY and 3.5/100 PY respectively.

Regardless of the different exposed groups, serious infection cases were attributed to other confounding factors such as patient's pre-existing pulmonary disease, diabetes, older age, high body mass index, concomitant steroids or prior treatment with a TNF inhibitor [66]. Skin and respiratory tract infections were commonly reported. Seven cases of tuberculosis were reported in the all-exposed group although it was uncertain whether these were new cases or cases in which the initial screening for latent tuberculosis was inadequate. One report of leucoencephalopathy [67] was associated with tocilizumab while one fatal case of reactivation of HBV was reported by Nishimoto [43]. Notably, similar to serious adverse events, the rate of serious infections was stable over time.

In another meta-analysis of 6 randomised controlled trials, 4 of which were again included in the analysis (RADIATE, OPTION, TOWARD and AMBITION), after excluding CHARISMA study due to small number of subjects, the authors found that combination treatment with tocilizumab 8mg/kg and methotrexate resulted in greater risk of serious infection when compared with controls (OR = 1.78; 95% CI 0.98, 3.23) [68]. This however is a lesser risk compared to TNF-inhibitor as a meta-analysis of harmful effects in RCTs involving anti-TNF inhibitor therapy concluded that the pooled OR for serious infection in comparison with controls was 2.0 (95% CI 1.3, 3.1) [69]. Direct comparison should be carefully interpreted though. The TOWARD trial reported opportunistic infection as one patient was diagnosed with *Mycobacterium avium intracellulare* after found to have an abnormality on a chest x-ray [51]. The main safety profiles are summarised in Table 3.

5.2 Laboratory Abnormalities

Elevated levels of hepatic transaminases (ALT and AST) were observed in about one third of the tocilizumab-treated patients. The increment was generally mild and reversible. Increment in ALT particularly more than 3 x upper limit of normal value (ULN) in patients treated with tocilizumab were less common with tocilizumab monotherapy [66]. Importantly, no association between liver enzyme elevation and clinically apparent drug-induced liver injury was demonstrated. Of the 11 liver biopsy samples that were done, only 9 steatohepatitis cases were present in which the patients also have other risk factors such as obesity and diabetes [44, 66].

Neutropenia largely due to migration of neutrophils [70] was commonly reported in patients treated with tocilizumab. Generally, this was not associated with an increased risk of infections. In the all-exposed population, 32 patients had thrombocytopenia with either a Grade 3 or Grade 4 in which one reported to have a serious bleeding event (haemorrhagic stomatitis) [66]. The infusion was maintained and the event subsequently resolved without further complication. Temporary thrombocytopenia resulted from the decrease in IL-6 after starting tocilizumab as thrombocytosis is mediated by IL-6 [28].

Alteration in lipid profiles was also linked to treatment with tocilizumab. A possible explanation is that active RA is associated with lowering of the serum cholesterol and LDL levels thus treatment with tocilizumab returns these levels to what would be 'normal' for that patients [71-73]. On a positive note, the STREAM study found no evidence of an increased risk of cardiovascular disease at 5-year follow-up [48]. Furthermore, the rates of myocardial infarctions and strokes were

similar in the tocilizumab treatment groups as in the control group and did not increase over time. The main laboratory abnormalities are summarized in Table 4.

5.3 Malignancy

The overall rate of solid malignancy in the all-exposed group was 1.1/100 PY and was stable even after prolonged exposure [66]. This is comparable to other biologic treatments. For instance, in a large contemporary United States cohort of RA patients, the rate of malignancy was 1.3/100 PY of which 62% were treated with TNF inhibitors [74]. Interestingly, in animal studies, IL-6 appears to have tumour promoting activity and targeting IL-6 pathways may be effective in some cancers [75, 76]. However, this needs to be translated into human observational studies.

5.4 Other Safety Profile

Clinically significant hypersensitivity reactions were reported in about 1% of patients and occurred mainly within the first four infusions [66]. Anaphylactic reaction was more common in the toclizumab 4mg/kg group than the 8mg/kg group [28]. Antibodies to tocilizumab occurred in about 2-4% of the patients although this did not seem to predispose the hypersensitivity reactions [28].

The rate of gastrointestinal perforations was 0.28/100 PY in the all-exposed group [66]. The majority of these patients had a history of diverticulitis and concurrent use of NSAIDs or steroid which put them at further risk.

Recent evidence has suggested that TNF inhibitors are associated with the development of demyelinating disease [77, 78] . It is still uncertain whether this is also the case with tocilizumab treatment. Until data are widely available, caution

needs to be taken in prescribing tocilizumab particularly in patients with pre-existing disease and in patients with a positive family history of demyelinating disease [28].

6. Expert Opinion

The value of blocking IL-6 lies in its versatility in neutralising various cytokine pathways responsible for immune regulation, haematopoiesis and inflammation. IL-6 is a potent pro-inflammatory agent that induces fever, fatigue and many other clinical attributes associated with inflammation. Thus blocking IL-6 pathway has proven popular in recent times in treating systemic inflammatory disease like RA and systemic JIA.

In terms of RA, anti-IL-6 receptor monoclonal antibody, tocilizumab, is licensed for use in patients with moderate to severe active disease, who has shown inadequate response to at least one sDMARD including methotrexate or after failure to an anti-TNF. In terms of selection choice, the patients that would gain most are the ones with high inflammatory markers and who are symptomatic with fatigue secondary to anaemia.

The success of treatment with tocilizumab is evidenced by ample phase II and III randomised controlled trials and open-label extension studies. Primary end points were achieved comparable to other biologics like TNF inhibitors, abatacept and rituximab. Importantly, deterioration in structural progression was also halted. Combination therapy with methotrexate at least at the start of the treatment, is still the preferred choice of administration to the patients due to better numerical values in the study results in terms of clinical efficacy. Combination with other sDMARDs such as hydroxychloroquine, sulfasalazine and leflunomide was also effective without notable differences [51, 79]. Combination therapy however is

associated with an increased risk of elevated transaminases. Hence studies concerning at which point methotrexate can be tapered down or remission-type studies at which point the treatment dose of tocilizumab can be spread out are of interest.

The ACT-RAY trial showed that switching to monotherapy was non-inferior to combination therapy with methotrexate despite achieving meaningful clinical efficacy and halted structural progression. This is particularly of benefit in patient who has intolerance or experiences side effects from methotrexate. The recommended dose as monotherapy is 8mg/kg given every 4 weeks. Various national registries have revealed that about one third of the patients worldwide are on biologic monotherapy [80, 81]. Perhaps this is the strongest selling point of tocilizumab as to date, it is one of the few biologics given as a monotherapy that have shown superiority against methotrexate in head-to-head studies [44]. In fact the ADACTA trial recently revealed clinical superiority of tocilizumab therapy against adalimumab monotherapy although comparison was not done against combination treatment of adalimumab + methotrexate [82].

In terms of feasibility, patient's preference remains the priority. As it is administered intravenously every 4 weeks, it suits patients adverse to subcutaneous injections of biologic treatment or those who are able to travel to hospital. An advantage of IV administration is that blood tests particularly fasting lipid profiles at intervals can be monitored more carefully. On the other hand, this also increases the cost of treatment further in terms of staffing resources. Hence, the development of subcutaneous tocilizumab and other IL-6 agents that are currently in the Phase III trials are eagerly anticipated.

Tolerability and safety data will always be the top priority in a novel treatment of a chronic condition. Although tocilizumab does not have the long-term safety record of the TNF inhibitors, which have been licensed for 13 years, the overall safety data appears comparable [71]. A meta-analysis of the risk of adverse events has revealed a small but significant increase in AEs and infections in patients treated with 8 mg/kg of tocilizumab compared with controls. Hence, vigilance is needed particularly when treatment is offered to patients with multiple comorbidities and the elderly population. The rate of SAEs and death were comparable to other biologics that are currently available. It is still uncertain whether treatment with tocilizumab can lead to re-activation of tuberculosis and induces demyelinating disease. Until then, the patients should be screened for these 2 conditions as per other biologics prior to starting treatment.

Long-term cardiovascular safety is of major concern in systemic inflammatory disease and patients with rheumatoid arthritis are more likely to have macrovascular complications compared to the general population [83, 84]. Elevations in liver function tests which followed the 'saw-tooth' pattern between the infusions were frequent in patients receiving tocilizumab in a dose-dependent manner, particularly in combination with methotrexate. So far, data from a 5-year study has shown that the elevated lipid profiles were not associated with an increased risk of major cardiovascular events [48].

7. Conclusion

Data from clinical trials and meta-analysis have shown that both clinical efficacy (even when using a composite index that exclude acute phase reactant in the formula like CDAI) and safety profile of IL-6 blocking agents, notably tocilizumab,

are comparable to that of other biologics that are available for use in RA. More longer term studies exploring the macrovascular complications, assessment of structural progression using modality like ultrasound and MRI together with the development of IL-6 agents administered using subcutaneous form over the next few years, should make targeting IL-6, a mainstay in the treatment of RA.

Conflicts of Interest

Md Yuzaiful Md Yusof – no conflicts of interest

Paul Emery – Consulting fees for Pfizer, Merck, Abbott, BMS, UCB

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Table 1: Interleukin-6 blocking agents other than intravenous tocilizumab currently under development

Drugs	Tocilizumab [26]	Sarilumab [39]	BMS945429 [40]	Sirukumab [41]	Olokizumab [42]
Pharmacology description	IL-6 receptor monoclonal antibody that binds to both soluble & membrane-bound receptor	IL-6 receptor monoclonal antibody that binds to the alpha subunit of the IL-6 receptor complex	An aglycosylated, humanised, anti–IL-6 monoclonal antibody that binds directly to IL-6	Humanised monoclonal antibody against soluble IL-6 receptor	Selectively blocks the final assembly of the IL-6 signaling complex (gp80 + gp130 + IL-6)
Method of administration	Subcutaneous	Subcutaneous	Intravenous	Subcutaneous	Subcutaneous / Intravenous
Study phase completion	Phase III	Phase II	Phase II	Phase II (Proof of concept)	Pilot Studies
Trials Duration	2 years (results at Week 24)	12 weeks	12 weeks	24 weeks	12 weeks

Dosing / Comparator	S/c TCZ 162mg + DMARDs vs IV TCZ 8mg/kg + DMARDs	S/c SRL 100mg q2W vs SRL 150mg q2W vs SRL 100mg qW vs SRL 200mg q2W vs SRL 150mg qW vs Placebo*	S/c BMS 80mg vs BMS 160mg vs BMS 320mg vs Placebo*	Placebo + S/c SRK 100mg q2W vs SRK 100mg q2W vs SRK q4W vs SRK 50mg q4W vs SRK 25mg q4W*	Single dose either IV (0.1 or 1mg/kg) or S/c (1 or 3mg/kg) vs placebo
Number of patient	1262	306	127	151	40
ACR 20	69/73	49/66/52/65/72/46	81/71/82/27	N/A	N/A
ACR 50	N/A	22/35/40/40/30/15	34/27/50/9	37/60/50/30/36	N/A
ACR 70	N/A	6/12/16/17/16/2	13/12/25/3	N/A	N/A

* Each treatment arm is in combination with methotrexate; ACR20, 50 & 70: American College of Rheumatology responses (20%, 50% and 70% improvement from baseline in terms of both tender and swollen joint counts along with 3 out of the 5 other core data set measures), BMS: BMS945429, DMARDs: Disease Modifying Anti-Rheumatic Drugs, IL-6: Interleukin 6, IV: Intravenous, qW: every week, q2W: every 2-week, q4W: every 4-week, S/c: subcutaneous, SRL: Sarilumab, SRK: Sirukumab

Table 2: Percentage of patients who met the American College of Rheumatology (ACR) 20, 50 and 70 improvement criteria based on the randomised controlled trials of tocilizumab monotherapy and in combination treatment with methotrexate / DMARDs.

Follow Up (Weeks)	Study	Number of patients	Criteria	Dosing Schedule	% who met ACR20 according to dose	% who met ACR50 according to dose	% who met ACR70 according to dose
	Tocilizumab Monotherapy						
12	Nishimoto [43]	164	DMARD-IR	Placebo vs TCZ 4mg/kg vs TCZ 8mg/kg	11/ 57/ 78	2/ 26/ 40	0/ 20/ 16
16	CHARISMA [27]	359	MTX-IR	MTX vs TCZ 2mg/kg vs TCZ 4mg/kg vs TCZ 8mg/kg	41/ 31/ 61/ 63	29/ 6/ 28/ 41	16/ 2/ 6/ 16
24	AMBITION [44]	673	MTX-Naïve (67%)	MTX vs TCZ 8mg/kg	53/ 70	34/ 44	15/ 28
24	SATORI [45]	127	MTX-IR	MTX vs TCZ 8mg/kg	25/ 80	11/ 49	6/ 30
52	ACT-RAY [46]	556	MTX-IR	MTX + TCZ 8mg/kg vs TCZ + Placebo	71/ 69	50/ 55	31/ 31
52	SAMURAI [47]	306	DMARD-IR	DMARDs vs TCZ 8mg/kg	34/ 78	13/ 64	6/ 44

	Combination Therapy (Tocilizumab + Methotrexate / Other DMARDs)						
16	CHARISMA [27]	359	MTX-IR	MTX vs TCZ 2mg/kg vs TCZ 4mg/kg vs TCZ 8mg/kg	41/ 64/ 63/ 74	29/ 32/ 37/ 53	16/ 14/ 12/ 37
24	OPTION [49]	623	MTX-IR	Placebo vs TCZ 4mg/kg vs TCZ 8mg/kg	26/ 48/ 59	11/ 31/ 44	2/ 12/ 22
24	ROSE [50]	619	DMARD-IR	Placebo vs TCZ 8mg/kg	N/A	11/ 30	N/A
24	TOWARD [51]	1220	MTX / DMARD-IR	Placebo vs TCZ 8mg/kg	25/ 61	9/ 38	3/ 21
24	RADIATE [6]	499	TNF-IR	Placebo vs TCZ 4mg/kg vs TCZ 8mg/kg	10/ 30/ 50	4/ 17/ 29	1/ 5/ 12
52	LITHE [52]	1196	MTX-IR	Placebo vs TCZ 4mg/kg vs TCZ 8mg/kg	25/ 47/ 56	10/ 29/ 36	4/ 16/ 20

ACR20: American College of Rheumatology 20 response (20% improvement from baseline in terms of both tender and swollen joint counts along with 3 out of the 5 other core data set measures), DMARD-IR: Inadequate Response to Disease Modifying Anti-Rheumatic Drugs, MTX-IR: Inadequate Response to Methotrexate, N/A: Data not available, TCZ: Tocilizumab.

Table 3: The main safety profiles of tocilizumab as reported in phase III randomised controlled trials. Figures are in numbers (%).

Study	Number of patient	Dosing Schedule	Withdrawals due to AEs	Number of AEs	Number of SAEs	Serious Infection	Deaths	Malignancy
	Tocilizumab Monotherapy							
ACT-RAY [46]	556	TCZ 8mg/kg + MTX	21 (7.6)	227 (81.9)	24 (8.7)	10 (3.6)	2 (0.7)*	N/A
		TCZ 8mg/kg + Placebo	17 (6.2)	228 (82.6)	26 (9.4)	9 (3.3)	2 (0.7)*	N/A
AMBITION [44]	673	TCZ 8mg/kg	11 (3.8)	230 (79.9)	11 (3.8)	4 (1.4)	3 (1.0)*	1 (0.3)
		MTX	15 (5.3)	220 (77.5)	8 (2.8)	2 (0.7)	1 (0.4)	3 (0.1)
	Combination Therapy (Tocilizumab + Methotrexate / DMARDs)							
LITHE [52]	1196	TCZ 4mg/kg	28 (7)	324**	12.8**	3.7**	0 (0)	5 (1.3)***
		TCZ 8mg/kg	33 (8)	325.4**	11.5**	4.0**	4 (1)*	2 (0.5)***
		Placebo	11 (3)	279.6**	10.2**	2.3**	2 (0.5)	1 (0.3)***

OPTION [49]	623	TCZ 4mg/kg	14 (6.5)	151 (71)	13 (6)	3 (1)	N/A	0
		TCZ 8mg/kg	12 (5.9)	143 (69)	13 (6)	6 (3)	N/A	0
		Placebo	6 (2.9)	129 (63)*	12 (6)	2 (1)	N/A	2 (1)
RADIATE [6]	499	TCZ 4mg/kg	10 (6.1)	147 (84.0)	12 (7.4)	3 (1.8)	0	N/A
		TCZ 8mg/kg	10 (6.1)	142 (87.1)	11 (6.3)	8 (4.6)	0	N/A
		Placebo	8 (5.0)	129 (80.6)	18 (11.3)	5 (3.1)	0	N/A
ROSE [50]	619	TCZ 8mg/kg	27 (6.6)	290 (70.9)	30 (7.3)	12 (2.9)	3 (0.7)*	4 (1.0)
		Placebo	8 (3.9)	122 (59.5)	11 (5.4)	1 (0.5)	0	3 (1.5)
TOWARD [51]	1220	TCZ 8mg/kg	31 (3.9)	584 (72.8)	54 (6.7)	22 (2.7)	2 (0.2)*	N/A
		Placebo	8 (1.9)	253 (61.1)	18 (4.3)	8 (1.9)	2 (0.5)	N/A

* Of the 16 total of deaths, 6 were considered probably related to drug treatment (1 from AMBITION: gastrointestinal haemorrhage, 1 from ACT-RAY: Sepsis, 2 from LITHE: pulmonary embolism and gastrointestinal infection & 2 from ROSE: Sepsis and haemorrhagic stroke), the author did not disclose the relation of treatment to death in TOWARD, the death cases for ACT-RAY was from the preliminary 24 weeks data; ** Data reported per 100 patient-years, *** Data for solid malignancies only, AEs: Adverse events; SAEs: Serious adverse events, MTX: Methotrexate, N/A: Not available, TCZ: Tocilizumab.

Table 4: Laboratory abnormalities secondary to tocilizumab treatment as reported in Phase III randomised controlled trials. Figures are in numbers (%)

Study	Number of patient	Dosing Schedule	Raised ALT > 3 x ULN	Raised Bilirubin > 3 x ULN	Neutropenia Grade 3	Neutropenia Grade 4	Raised Total Cholesterol ≥ 240mg/dL	Raised LDL Cholesterol ≥ 160 mg/dL
	Tocilizumab Monotherapy							
ACT-RAY [46]	556	TCZ 8mg/kg + MTX MTX + Placebo	3 (7) 1 (2)	N/A N/A	N/A N/A	N/A N/A	N/A N/A	N/A N/A
AMBITION [44]	673	TCZ 8mg/kg MTX	(1.7) (3.6)	(7.6) (0.7)	(3.1) (0.4)	0 0	(13.2) (0.4)	(3.1) (0)
	Combination Therapy (Tocilizumab + Methotrexate / DMARDs)							
LITHE [52]	1196	TCZ 4mg/kg TCZ 8mg/kg	28 (7) 36 (9)	24 (6) 40 (10)	7 (1.8) 17 (4.3)	2 (0.5) 1 (0.3)	56 (14) 102 (26)	53 (14) 70 (18)

		Placebo	3 (0.8)	5 (1.3)	0 (0)	0 (0)	31 (8)	15 (3.8)
OPTION [49]	623	TCZ 4mg/kg	15 (7)	N/A	N/A	N/A	55 (26)*	N/A
		TCZ 8mg/kg	28 (14)	N/A	N/A	N/A	43 (21)*	N/A
		Placebo	9 (4)	N/A	N/A	N/A	7 (3)*	N/A
RADIATE [6]	499	TCZ 4mg/kg	4 (2.5)	N/A	1 (0.6)	1 (0.6)	N/A	25 (15.3)
		TCZ 8mg/kg	4 (2.2)	N/A	4 (2.2)	4 (2.2)	N/A	21 (12)
		Placebo	1 (0.6)	N/A	0 (0)	0 (0)	N/A	6 (3.8)
ROSE [50]	619	TCZ 8mg/kg	12 (3.1)	N/A	12 (2.9)	0	78 (21.9)	97 (32.3)
		Placebo	2 (1.2)	N/A	0 (0)	0	13 (7.7)	12 (9.2)
TOWARD [51]	1220	TCZ 8mg/kg	(4.1)	(8.9)	(3.7)	0	(23)	(16.1)
		Placebo	(0.7)	(0.7)	(0)	0	(5.5)	(3.4)

* The author used 6.2 mmol/l as the cut-off points which are equivalent to 250 mg/dL; ALT: Alanine aminotransferase, DMARDs: Disease Modifying Anti-Rheumatic Drugs, LDL: Low density lipoprotein, MTX: Methotrexate, N/A: Not available, ULN: Upper limit of the normal value.

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