EXTENDED REPORT

Humoral immune response to vaccines in patients with rheumatoid arthritis treated with tocilizumab: results of a randomised controlled trial (VISARA)

Clifton O Bingham III,1 Warren Rizzo,2 Alan Kivitz,3 Azra Hassanali,4 Ruchi Upmanyu,5 Micki Klearman6

ABSTRACT

Objective To evaluate the effect of tocilizumab (TCZ), an interleukin 6 receptor inhibitor, on humoral immune responses to immunisations in patients with rheumatoid arthritis (RA).

Methods Patients with RA with inadequate response/intolerance to one or more anti-tumour necrosis factor-α agents were randomly assigned (2:1) to TCZ 8 mg/kg intravenously every 4 weeks plus methotrexate (MTX) or MTX alone up until week 8. Serum was collected before vaccination at week 3, antibody titres were evaluated at week 8, and then all patients received TCZ+MTX through week 20. End points included proportion of patients responding to ≥6/12 pneumococcal polysaccharide vaccine (PPV23) serotypes (primary) and proportions responding to tetanus toxoid vaccine (TTV; secondary) at week 8.

Results 91 patients were randomised. At week 8, 60.0% of TCZ+MTX and 70.8% of MTX patients responded to ≥6/12 PPV23 serotypes, with insufficient evidence for any difference in treatments (10.8% (95% CI —33.7 to 12.0)), and 42.0% and 39.1%, respectively, responded to TTV. Two of three TCZ+MTX patients with non-protective baseline TTV antibody titres achieved protective levels by week 8. The safety profile of TCZ was consistent with previous reports.

Conclusions Short-term TCZ treatment does not significantly attenuate humoral responses to PPV23 or TTV. To maximise vaccine response, patients should be up to date with immunisations before starting TCZ treatment.

ClinicalTrials.gov identifier NCT01163747.

INTRODUCTION

Patients with rheumatoid arthritis (RA) have increased risk of infection because of underlying disease and immunomodulatory therapies. Therefore, routine immunisations are important to reduce morbidity and mortality.1–3 However, RA treatments may reduce primary immune responses to vaccines and diminish anamnestic responses.4–6

Tocilizumab (TCZ), a humanised monoclonal antibody directed against soluble and membrane-bound interleukin 6 (IL-6) receptors,7 is widely approved for treating moderate-to-severe RA. Because TCZ may affect how IL-6 regulates T-cell activation and B-cell differentiation,8–13 understanding the influence of TCZ on vaccine responses is important for this vulnerable population.

In previous studies, TCZ treatment did not impair antibody response to the trivalent-inactivated influenza vaccine14 or the 23-valent pneumococcal polysaccharide vaccine (PPV23).15 VISARA is the first randomised controlled trial evaluating humoral immune responses to T-cell-dependent and T-cell-independent antigens, tetanus toxoid vaccine (TTV) and PPV23, respectively, in patients with moderate-to-severe RA treated with TCZ.

METHODS

This two-arm, randomised, parallel-group, open-label, multicentre, phase IV study in patients with active RA receiving background methotrexate (MTX) treatment was conducted by 33 investigators at 35 centres in the USA. Patients were randomly assigned 2:1 to receive TCZ 8 mg/kg intravenously every 4 weeks plus MTX (7.5–25 mg/week; TCZ+MTX) or MTX alone through week 8 (figure 1). At week 3, serum was collected for measurement of pre-vaccination antibody levels, after which PPV23 (Pneumovax; Merck & Co) was administered as an intramuscular or a subcutaneous injection in the deltoid, and TTV (Adsorbed; Aventis Pasteur) was administered as an intramuscular injection in the opposite deltoid. At week 8 (5 weeks after vaccination), serum was collected for measurement of post-immunisation levels of antibodies against pneumococcal polysaccharide and tetanus toxoid. All patients then received TCZ+MTX through week 20.

Men and non-pregnant women aged 18–64 years with RA according to revised 1987 American College of Rheumatology criteria16 for >6 months were enrolled. Patients had to have inadequate clinical response to antirheumatic therapies, including MTX, and inadequate clinical response or intolerance to ≥1 anti-tumour necrosis factor-α therapies. See online supplementary text for additional inclusion and exclusion criteria.

The primary endpoint was proportion of patients in each treatment group responsive to ≥6 of 12 anti-pneumococcal antibody serotypes at week 8 (5 weeks after vaccination and after two TCZ infusions in the TCZ+MTX group). A positive response to PPV23 was defined as a twofold or >1 mg/L increase from baseline at week 8. Secondary end points, safety assessments, analysis populations and antibody measurement methods are described in online supplementary text. No formal hypothesis testing was conducted.
Descriptive statistics by treatment group and summaries of differences between treatment groups are presented along with 95% CIs for vaccine response only. A sample size of 91 patients was based on similar studies conducted with other RA treatments and assuming an 80% difference between treatment groups.

RESULTS

Of 112 patients screened, 91 were randomly assigned to receive TCZ+MTX (n=60) or MTX alone (n=31). See online supplementary text for screening failures. The per-protocol (PP) population (figure 1) comprised 81 patients (54 in the TCZ+MTX group, 27 in the MTX group); 10 patients were excluded because of protocol violations. Baseline demographics and disease characteristics were generally well balanced between treatment groups, and mean baseline oral corticosteroid and MTX doses were comparable (see online supplementary table S1).

At week 8, the proportion of responders to PPV23 (primary end point) was numerically greater in the MTX group than in the TCZ+MTX group (70.8% vs 60.0%, respectively), with insufficient evidence for any difference between treatments (10.8% (95% CI −33.7 to 12.0); table 1). Overall, a greater proportion of MTX-treated than TCZ+MTX-treated patients responded to a combination of PPV23 serotypes (>1 up to 12). However, the 95% CIs for the proportion of responders were wide in both treatment groups for all combinations (figure 2A). Proportions of patients responding to individual anti-pneumococcal antibody serotypes were comparable between treatment groups (<10% difference between groups) for serotypes 3, 4, 7f, 12f, 14 and 23f, whereas the proportion of responders to serotypes 1, 6b, 8, 9n, 18c and 19f was lower (>10% difference) in the TCZ+MTX than in the MTX group (figure 2B).

When stratified by age, groups aged 51–64 years had ~10% fewer responders regardless of treatment (table 1). Consistent with the primary end point, the proportion of patients in both

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**Figure 1** Study flow for patients included in intention-to-treat (ITT) analysis. MTX, methotrexate; PnP, pneumococcal polysaccharide vaccine; PP, per-protocol; SF, safety follow-up; TCZ, tocilizumab; TT, tetanus toxoid.

*Before randomisation, did not discontinue etanercept for ≥2 weeks; infliximab, adalimumab, certolizumab or golimumab for ≥8 weeks; or anakinra for ≥1 week.
age groups who responded to ≥6 of 12 anti-pneumococcal antibody serotypes was numerically lower in the TCZ+MTX than the MTX group, with overlapping CIs. At week 8, similar proportions of patients in the TCZ+MTX (42.0%) and MTX (39.1%) groups responded to TTV (between-group difference 2.9% (95% CI –21.4% to 27.1%)); 95% CIs for the treatment groups were overlapping (table 1). In the TCZ+MTX group, three patients had non-protective anti-tetanus antibody titres at baseline (<0.1 IU/mL); two subsequently achieved protective levels by week 8. The proportion of patients achieving ≥2-fold and ≥4-fold increases in anti-tetanus toxoid antibody levels was greater in the TCZ+MTX group than in the MTX group (table 1). Concomitant treatment with oral corticosteroids did not appear to attenuate responsiveness to PPV23 or TTV (data not shown); however, this should be confirmed in larger studies.

The pharmacodynamic effect of TCZ was demonstrated by a marked and sustained reduction in C-reactive protein (CRP) levels from baseline through week 8 (see online supplementary table S2).

During the first 8 weeks of the study, differences in the safety profile between treatment groups were consistent with prescribing information for each drug. The incidence of adverse events (AEs) was higher in the TCZ+MTX group, driven primarily by events of sinusitis, nausea and headache. Most AEs were considered mild or moderate in intensity. Serious AEs (SAEs) were
experienced by one patient in the MTX group and two patients in the TCZ+MTX group (see online supplementary table S3). During the first 8 weeks, no patients in the MTX group discontinued treatment because of an AE or disease flare. One patient in the TCZ+MTX group experienced 116 AEs (upper respiratory tract infection, sinusitis, nausea, headache, nasopharyngitis and urinary tract infection were the most commonly reported), and five SAEs were reported in four patients. Five patients in the TCZ+MTX group discontinued treatment because of AEs. No malignancies or deaths were reported.

**DISCUSSION**

IL-6 is a driver of B-cell maturation and plasma cell differentiation; therefore, clinicians need to understand the impact of IL-6 blockade on immune response. Results of this study indicate that immune responses to PPV23 after TCZ+MTX treatment were slightly attenuated compared with MTX alone; 60.0% and 70.8% of patients, respectively, responded to ≥ 6 of 12 anti-pneumococcal antibody serotypes. Response to this T-cell-independent vaccine after TCZ treatment gave an evaluation of the impact of TCZ on specific immunoglobulin production to pneumococcal polysaccharide antigens. Similarly, numerically greater proportions of MTX-treated than TCZ +MTX-treated patients responded to multiple combinations (≥1–12) of pneumococcal antigen serotypes. The response to individual pneumococcal serotypes varied among patients in each treatment group. Numerically, the proportion of responders to serotypes 1, 6b, 8, 9n, 18c and 19f (generally associated with invasive pneumococcal disease and multidrug resistance) was greater in the MTX group, although these differences are of unknown clinical significance and the protective titre against each subtype is unclear. As expected, the immune response to PPV23 was attenuated in older patients. However, the difference in proportions of responders between older and younger sub-populations was similar in the two treatment groups.

Because most patients had detectable baseline anti-tetanus antibody titres, response to this T-cell-dependent vaccine after TCZ treatment gave an evaluation of the effect of TCZ on immunoglobulin G production by memory T-helper cells (anamnestic or recall response to TTV). The immune response to TTV after TCZ+MTX treatment was similar to that after treatment with MTX alone (42.0% vs 39.1%, respectively). The reduction in response rates observed with MTX was consistent with previous reports. Small differences were observed between treatment groups in the proportion of patients with ≥2- and ≥4-fold increases from baseline in TTV antibody levels at week 8 for patients with baseline antibody levels ≥0.1 IU/mL.

The rapid and sustained reduction in CRP levels from baseline confirmed that TCZ was pharmacologically active. Overall, the vaccines and randomised treatments were well tolerated. As expected, most AEs reported by patients randomly assigned to MTX occurred after week 8, when TCZ was added. The AE profile was consistent with the known TCZ safety profile.

While most patients with RA treated with TCZ 8 mg/kg—the highest approved dose—mounted a detectable immune response to PPV23 and TTV, levels of protective antibodies were poorly defined. A limitation is that vaccine response was measured after only two TCZ infusions; whether results would be similar with longer-term TCZ treatment is unknown. Although no specific safety concerns were identified after vaccination in patients treated with TCZ, data from this study do not change the current prescribing recommendations that patients be brought up to date with immunisations in accordance with current guidelines if possible before TCZ treatment is initiated.

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**Contributors**

COB designed the study, recruited participants, collected, analysed and interpreted data, wrote the report, and approved the final draft. WR recruited participants, reviewed the report, and approved the final draft. AK recruited participants, reviewed the report, and approved the final draft. AH designed the study, analysed and interpreted data, reviewed the manuscript, and approved the final draft. RU analysed and interpreted data, wrote the report, and approved the final draft. MK designed the study, analysed and interpreted data, reviewed the manuscript, and approved the final draft.

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**Competing interests**

COB has served as a consultant to Genentech/Roche and has received travel support in that capacity. WR has served as a consultant to UCB, BMS, Roche/Genentech/Savient, Takeda and Crescendo; he has also received speakers’ bureau fees for AbbV, UCB, Roche/Genentech, Takeda and Amgen. AK has served as a consultant to Genentech and has received grant support from Genentech. AH is an employee of Genentech. RU is an employee of Roche. Nicki Klearman is an employee of and owns stock in Roche/Genentech.

**Patient consent**

Obtained.

**Ethics approval**

The investigator at each site assured that the study was conducted in accordance with the principles of the Declaration of Helsinki and with Good Clinical Practice according to the regulations and procedures described in the protocol. Signed informed consent was obtained from all patients before any study-specific assessments or procedures were performed.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

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**REFERENCES**


7 Milana M, Kasutani K, Okazaki M, et al. T celllicumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of the IL-6 cytokine family. Int Immunopharmacol 2005;5:1731–40.


**Clinical and epidemiological research**

Clinical and epidemiological research


19 RoActemra 20 mg/mL concentrate for solution for infusion. Hertfordshire, UK: Roche Registration Ltd, 2010.
Humoral immune response to vaccines in rheumatoid arthritis patients treated with
tocilizumab: results of a randomized controlled trial (VISARA)

Online Supplementary Materials

Additional enrollment criteria

All patients were on stable background methotrexate (MTX) treatment for \( \geq 8 \) weeks before baseline; a stable dose of 7.5-25 mg/week had to have been achieved by baseline. Patients were excluded if they had recently undergone major surgery, had functional class IV rheumatoid arthritis (RA), had current or previous inflammatory joint disease or rheumatic autoimmune disease other than RA, or had significant systemic involvement secondary to RA. Patients were also excluded if they had been treated previously with tocilizumab (TCZ), alkylating agents, rituximab, or cyclosporine; treated with intra-articular or parenteral corticosteroids within 4 weeks before baseline; or treated with abatacept within 24 weeks before baseline. Concomitant use of oral corticosteroids (\( \leq 10 \) mg/day prednisone or equivalent) was allowed; however, patients must have been on a stable dose for \( \geq 4 \) weeks before baseline and maintained this dose through week 8 of the study, the immunization endpoint.

Secondary endpoints

Secondary endpoints included proportion of patients in each treatment group who responded to each of the 12 pneumococcal serotypes and to combinations of the 12 serotypes measured (ie, \( \geq 2/12, \geq 3/12 \) through 12/12); proportion of patients in each treatment group responsive to tetanus
toxoid vaccine (TTV), defined as antibody levels $\geq 0.2$ IU/mL (if baseline levels were $<0.1$ IU/mL) or a $\geq 4$-fold increase from baseline (if baseline levels were $\geq 0.1$ IU/mL) at week 8; and level of anti-pneumococcal and anti-tetanus antibodies at week 8. The pharmacodynamic activity of TCZ was evaluated by the change from baseline in C-reactive protein (CRP) level at week 8.

Safety assessments

Safety assessments included evaluation of frequency and severity of adverse events (AEs), serious AEs (SAEs), clinical laboratory results, vital signs, concomitant medications, and immunogenicity assessments. Safety assessments were conducted at specified visits, and post-treatment safety follow-up assessments were conducted at weeks 24 and 28. The end of the patient’s participation in the study occurred on completion of the week-28 safety follow-up visit. Patients withdrawn before week 20 were asked to return to the clinic for safety assessments at 4 and 8 weeks after the last TCZ infusion. The overall safety of 20 weeks of TCZ+MTX treatment across the entire 20-week treatment period was evaluated through an examination of pre– and post–week-8 data for patients randomly assigned to the TCZ+MTX group.

Analysis populations

The primary population was the per-protocol (PP) population, which included all randomly assigned patients who received $\geq 1$ dose of study medication and had no major protocol violations deemed to compromise the integrity of the study. The PP population was used to evaluate the primary and all secondary endpoints at week 8. Any patient who met PP criteria, received $\geq 1$ of the vaccines (23-valent pneumococcal polysaccharide vaccine [PPV23] or TTV), and had both
pre-vaccination and post-vaccination assessments (weeks 3 and 8, respectively) of immune response to the respective vaccine was included in the primary analysis. Pre-specified analysis of the effect of age was assessed in a PP subgroup analysis of the primary endpoint for patients aged 18-50 versus 51-64 years. The population analyzed for safety included all randomly assigned patients who received ≥1 dose of study medication and had ≥1 safety assessment, including an AE assessment.

**Measurement of serum antibody levels**

For evaluation of anti-pneumococcal and anti-tetanus antibody levels, serum was collected and sent to a central laboratory. Batch analysis for anti-pneumococcal and anti-tetanus antibody levels was performed throughout the study, with individual patient pre-immunization and post-immunization samples analyzed at the same time. The 12 pneumococcal polysaccharide serotypes evaluated were 1, 3, 4, 6b, 8, 9n, 12f, 14, 19f, 23f, 7f, and 18c.

**Screening failures**

Of 112 patients screened, 91 were randomized to study treatment. Reasons for screening failure included age restriction (6 patients), laboratory values (5 patients), restricted medications (2 patients), no prior treatment with ≥1 anti-tumor necrosis factor agent-α (2 patients), and 1 patient each because of active infection, not meeting swollen joint criteria, history of diverticulitis, latent tuberculosis that was diagnosed but not properly treated, MTX dose not stable for ≥8 weeks before baseline, and previous immunization with pneumococcal vaccine.
**Supplementary Table S1.** Baseline demographics and disease characteristics (per-protocol population)

<table>
<thead>
<tr>
<th></th>
<th>MTX n=27</th>
<th>TCZ (8 mg/kg) + MTX n=54</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (18.5)</td>
<td>13 (24.1)</td>
</tr>
<tr>
<td>Female</td>
<td>22 (81.5)</td>
<td>41 (75.9)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>24 (88.9)</td>
<td>50 (92.6)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (7.4)</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (3.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>American Indian/Alaskan Native</td>
<td>0 (0)</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>51.4 (9.5)</td>
<td>51.1 (8.9)</td>
</tr>
<tr>
<td><strong>Weight, kg, mean (SD)</strong></td>
<td>90.0 (22.9)</td>
<td>86.0 (22.8)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (3.7)</td>
<td>7 (13.0)</td>
</tr>
<tr>
<td>Not Hispanic</td>
<td>26 (96.3)</td>
<td>45 (83.3)</td>
</tr>
<tr>
<td>NA</td>
<td>0 (0)</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td><strong>Duration of RA, years, mean (SD)</strong></td>
<td>8.4 (7.0)</td>
<td>13.2 (11.5)</td>
</tr>
<tr>
<td><strong>Baseline oral corticosteroid use, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18 (66.7)</td>
<td>30 (55.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>9 (33.3)</td>
<td>24 (44.4)</td>
</tr>
<tr>
<td><strong>Baseline oral corticosteroid dose, mg/day, mean (SD)</strong></td>
<td>7.0 (2.9)</td>
<td>7.2 (3.0)</td>
</tr>
<tr>
<td><strong>Baseline methotrexate dose, mg/week, mean (SD)</strong></td>
<td>15.3 (5.0)</td>
<td>17.0 (5.2)</td>
</tr>
<tr>
<td><strong>Baseline RF positivity (positive &gt;15), n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10 (37.0)</td>
<td>22 (40.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>17 (63.0)</td>
<td>32 (59.3)</td>
</tr>
<tr>
<td><strong>Baseline anti-CCP positivity, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12 (44.4)</td>
<td>23 (43.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>15 (55.6)</td>
<td>30 (56.6)</td>
</tr>
<tr>
<td><strong>Baseline anti-pneumococcal antibody, mg/L, mean (SD)</strong></td>
<td>85.9 (116.9)</td>
<td>72.3 (61.8)</td>
</tr>
<tr>
<td><strong>Baseline anti-tetanus, IU/mL, mean (SD)</strong></td>
<td>2.7 (2.6)</td>
<td>2.1 (1.9)</td>
</tr>
</tbody>
</table>

CCP, cyclic citrullinated protein; MTX, methotrexate; NA, not available; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; TCZ, tocilizumab.

^a_n=25, ^b_n=53.
**Supplementary Table S2. C-Reactive protein levels**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 3</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MTX n=27</td>
<td>TCZ (8 mg/kg) + MTX n=54</td>
<td>MTX n=25</td>
</tr>
<tr>
<td>CRP, mg/dL, mean (SD)</td>
<td>0.90 (1.04)</td>
<td>0.84 (0.98)</td>
<td>1.24 (1.32)</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; MTX, methotrexate; SD, standard deviation; TCZ, tocilizumab.
**Supplementary Table S3.** Safety profile (safety population)

<table>
<thead>
<tr>
<th></th>
<th>Through Week 8</th>
<th></th>
<th>After Week 8</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MTX n=31</td>
<td>TCZ (8 mg/kg) + MTX n=60</td>
<td>MTX n=31</td>
<td>TCZ (8 mg/kg) + MTX n=60</td>
</tr>
<tr>
<td>Total AEs, n</td>
<td>6</td>
<td>49</td>
<td>36</td>
<td>72</td>
</tr>
<tr>
<td>Any AE, n (%)</td>
<td>3 (9.7)</td>
<td>23 (38.3)</td>
<td>14 (45.2)</td>
<td>33 (55.0)</td>
</tr>
<tr>
<td>SAE, a n (%)</td>
<td>1 (3.2)</td>
<td>2 (3.3)</td>
<td>0 (0)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Deaths, n</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawals due to AE, n (%)</td>
<td>0 (0)</td>
<td>1 (1.7)</td>
<td>0 (0)</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>Pregnancy, n</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AE, adverse event; MTX, methotrexate; SAE, serious adverse event; TCZ, tocilizumab.

*aFive SAEs reported in 4 patients; cellulitis, hypertensive crisis, intraspinal abscess requiring surgical drainage, acute dehydration, and staphylococcal (methicillin resistant) sepsis.*
Short-term biologic treatment does not affect immune response to vaccination

Patients with rheumatoid arthritis should be up to date with routine vaccinations before beginning treatment with biologic medicines.

INTRODUCTION
Rheumatoid arthritis is a chronic inflammatory disease that affects a person’s joints, causing pain and disability. Patients with rheumatoid arthritis naturally have an increased risk of developing infections due to the underlying disease, as well as some of the medicines that are used to treat it. Making sure that patients receive vaccinations to prevent against infections is very important. But some medicines called biologic disease-modifying antirheumatic drugs (bDMARDs) that are used to treat rheumatoid arthritis may affect how a person’s immune system responds to vaccination (their immune response), and may mean that people are not properly protected by the vaccine.

Vaccines may be live or non-live. Live vaccines are made from living organisms or viruses that have been altered so they cannot cause illness, but they can still replicate. Non-live vaccines used killed organisms or viruses, or certain parts of their structure.

WHAT DID THE AUTHORS HOPE TO FIND?
Before this study there was limited information available about the use of vaccines in people with rheumatoid arthritis who were receiving tocilizumab, a bDMARD that blocks the inflammatory effects of a molecule called interleukin-6. The authors hoped to improve understanding by comparing the immune responses to vaccines in people receiving tocilizumab plus another drug called methotrexate compared to those who were treated with only methotrexate on its own.

WHO WAS STUDIED?
The study included 91 people with rheumatoid arthritis. All patients were aged between 18–64 years, had been diagnosed with rheumatoid arthritis for at least 6 months and had not seen an improvement with another group of bDMARDs called TNF inhibitors. All patients were already taking methotrexate.

HOW WAS THE STUDY CONDUCTED?
This was an open-label, randomised clinical trial, which means that patients were assigned by chance to one of two treatment groups to receive either tocilizumab plus methotrexate or methotrexate on its own. Using chance in this way means that the groups will be similar and will allow the variable or treatment under investigation to be compared objectively. During the treatment both patients and their doctors knew which group they were in.

After 3 weeks, the participants in each group were given two non-live vaccines: one against pneumococcal pneumonia and one against tetanus. Blood samples were taken before the vaccinations and 5 weeks later to measure how well the immune system had responded.

WHAT WERE THE MAIN FINDINGS OF THE STUDY?
The study found that overall there were no differences between the two groups in their response to either the pneumonia vaccine or the tetanus vaccine.

ARE THESE FINDINGS NEW?
Yes, this is the first controlled study to evaluate the effect of tocilizumab on patients’ immune responses to routine vaccines.

HOW RELIABLE ARE THE FINDINGS?
When patients on tocilizumab were vaccinated, they had only received one dose of the tocilizumab beforehand. It is possible that longer treatment would have shown different results. These studies were done using non-living vaccines, and the results cannot be expanded to live vaccines. Live organism vaccines have not been studied and should not be given to people who are receiving bDMARDs, including tocilizumab.
WHAT DO THE AUTHORS PLAN ON DOING WITH THIS INFORMATION?
These studies suggest that short-term exposure to tocilizumab does not affect vaccine responses, but the authors recommend that vaccines are given before the biologic therapy is started according to local guidelines. No additional studies are planned.

WHAT DOES THIS MEAN FOR ME?
If possible, people with rheumatoid arthritis should receive routine vaccines before starting treatment with a bDMARD. It is important to tell your doctor that you are receiving a bDMARD if you go for any vaccinations. People with rheumatoid arthritis can continue to receive non-live vaccinations even when they are taking tocilizumab, but live vaccines should be avoided.

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