

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 ≥ 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 (≤ 10 mg/day prednisone or equivalent) was allowed; however, patients must have been on a stable dose for ≥ 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 ≥ 0.2 IU/mL (if baseline levels were < 0.1 IU/mL) or a ≥ 4 -fold increase from baseline (if baseline levels were ≥ 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 Patients withdrawn before week 20 were asked to return to the clinic for safety assessments at 4 and 8 weeks after the last TCZ infusion.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 ≥ 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 ≥ 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)

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

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

^an=25; ^bn=53.

Supplementary Table S2. C-Reactive protein levels

	Baseline		Week 3		Week 8	
	MTX n=27	TCZ (8 mg/kg) + MTX n=54	MTX n=25	TCZ (8 mg/kg) + MTX n=50	MTX n=26	TCZ (8 mg/kg) + MTX n=50
CRP, mg/dL, mean (SD)	0.90 (1.04)	0.84 (0.98)	1.24 (1.32)	0.09 (0.17)	0.84 (0.86)	0.10 (0.18)

CRP, C-reactive protein; MTX, methotrexate; SD, standard deviation; TCZ, tocilizumab.

Supplementary Table S3. Safety profile (safety population)

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

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.