for 1718 adult RA patients with at least 2 outpatient encounters and no prevalent CVD for their analysis to assess the impact of medication exposure over time. The primary outcome was CVD defined as CAD, any cardiac revascularization procedure, stroke or transient ischemic attack (TIA), peripheral artery disease (PAD), abdominal aortic aneurysm (AAA), or cardiac revascularization procedures.

Median follow-up was 3.4 years, and the median age was 57 years. One-third of participants had used an anti TNF-α (n=588); 62% (n=1119) had used MTX.

The researchers identified 127 cases of incident CVD, confirmed by chart review: 48 cases of CAD, primarily myocardial infarction, unstable angina, or revascularization; 45 strokes or TIAs; and 34 cases of PAD or AAA.

Among patients who were taking MTX, the case rate for CAD per 1000 patient-years was 14.6 (10.6 to 20.1) versus 23.2 (18.8 to 28.5) in nonusers, translating into a 37% risk reduction (incidence rate ratio=0.63; 0.42 to 0.93). The median exposure to MTX was 22 months, with the risk of CVD falling as the duration of MTX use increased. Patients with 23 months or more of exposure experienced a 72% reduction in risk (p<0.001).

The incidence rate for CAD per 1000 person-years was 37.5 for nonusers versus 17.6 for users of MTX. The hazard for incident CAD in MTX users was 0.54 (95% CI, 0.37 to 0.77; p=0.001) compared with nonusers. For patients who were taking MTX for more than 24 months, the hazard for incident CAD was 0.33 (95% CI, 0.22 to 0.50; p<0.001). The incident rate for CAD per 1000 person-years was 32.1 in TNF-α inhibitor users versus 11.8 for nonusers. Among the TNF-α inhibitor users, the hazard for incident CAD was 0.54 (95% CI, 0.30 to 0.95; p=0.03) compared with nonusers. In patients who were taking TNF-α inhibitors for more than 24 months, the hazard was 0.24 (95% CI, 0.12 to 0.51; p<0.001). Patients who took the drugs for more than 35 months had a 93% reduced risk of CAD (0.01 to 0.52; p=0.010). Median TNF-α exposure was 17 months.

Study limitations included the observational design and limited information on smoking status, family history of CVD, level of physical activity, and use of aspirin. The study presenters concluded that the use of MTX or TNF-α inhibitors can provide some protection against CVD in patients with RA.

TENDER Trial 2-Year Outcomes Show Long-Term Benefits of Tocilizumab in sJIA

Written by Rita Buckley

Fabrizio De Benedetti, MD, PhD, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, presented efficacy and safety results from A Randomized, Placebo-Controlled Study to Evaluate the Effect of Tocilizumab (TCZ) on Disease Response in Patients With Active Systemic Juvenile Idiopathic Arthritis (sJIA), With an Open-Label Extension to Examine the Long-Term Use of Tocilizumab [TENDER; NCT00642460].

In the TENDER trial, 112 patients aged 2 to 17 years with active, refractory sJIA (≥ 6 months; inadequate response to previous anti-inflammatory drugs [NSAIDs] and oral corticosteroids [oral CS]) were randomly assigned 2:1 to TCZ (n=75; 8 mg/kg if body weight ≥30 kg; 12 mg/kg if body weight <30 kg) or placebo (n=37) every 2 weeks for 12 weeks in Part 1. All patients received open-label TCZ in Part 2 (to 104 weeks). Stable doses of NSAIDs and methotrexate were continued, with oral CS tapering permitted according to predefined criteria.

The data were cut for each ongoing patient at the Week 104 infusion, based on date of randomization, with baseline in the longer-term extension considered the first dose of TCZ.

At the data cutoff (May 31, 2011), 61 patients had received at least 104 weeks of treatment; 32 of the ongoing patients had not yet reached 104 weeks of TCZ treatment; and 20 withdrew, including 1 at Week 104 (safety, 9; insufficient therapeutic response, 5; other nonsafety issues, 6).

Main baseline characteristics included mean disease duration of 5.2 years, mean active joint count of 19.8, and presence of fever (temperature ≥37.5°C in the past 7 days) in 43% of patients. High proportions of those who were treated with TCZ achieved JIA ACR 70/90 responses and maintained these responses over time (Table 1). Mean joint counts decreased over time. By Week 104, 55% of patients had 0 active joints and 31% had inactive disease status. In those patients who were taking oral CS at baseline, 60% was able to discontinue the drugs by Week 104 (Table 1); mean oral CS dose decreased from 0.30 mg/kg/day at baseline to 0.04 mg/kg/day at Week 104.

Table 1. Efficacy Endpoints (ITT Population).

	Week 12[a]		Week 52[b]	Week 78[b]	Week 104[b]
	Placebo (n=37)	TCZ (n=75)	TCZ (n=106)	TCZ (n=101)	TCZ (n=65)
JIA ACR70, n (%)	3 (8)[e]	53 (71)[e]	92 (87)[g]	88 (87)[g]	57 (88)[g]
JIA ACR90, n (%)	2 (5)[e]	28 (37)[e]	67 (63)[g]	72 (71)[g]	46 (71)[g]
Active joints, mean (SD)	9.5 (9.0)[f]	7.3 (11.9)[f]	2.8 (6.4)[c]	1.9 (4.1)[c]	1.9 (3.6)[c]
No active joints, n (%)	2 (5)	12 (16)	50 (47)[g]	53 (52)[g]	36 (55)[g]
Inactive disease, n (%)	NA	NA	28 (26)[g]	36 (36)[g]	20 (31)[g]
CHAQ-DI, mean (SD)	1.30 (0.98)[f]	0.94 (0.77)[f]	0.67 (0.75)[c]	0.63 (0.72)[c]	0.55 (0.71)[c]
Oral CS cessation, n (%)[c,d]	NA	NA	48 (52)	54 (61)	25 (60)

JIA=juvenile idiopathic arthritis; ACR=American College of Rheumatology; CS=corticosteroids; TCZ=tocilizumab; NA=not applicable; CHAQ-DI=Childhood Health Assessment Questionnaire-Disability Index; [a]Baseline was date of randomization; [b]Baseline was f rst dose of TCZ; [c]Patients who withdrew have been excluded at postwithdrawal visits; [d]Percentage is based on only those patients who were on oral CS at baseline and reached a nominal visit day on which dose was calculated; [e]Percentage is based on all patients; those who withdrew (for any reason) or escaped are assumed to have been nonresponders; [f]Patients who withdrew or escaped have been excluded; [g]Percentage is based on number of patients who reached time point+patients who withdrew because of insuf cient therapeutic response and are assumed to have been nonresponders.

Forty-seven serious adverse events (SAEs) occurred in 35 patients (Table 2); 15 SAEs were considered by the investigator to be related (remotely, possibly, or probably) to TCZ. Twenty-two serious infection AEs were reported in 20 patients; 8 were reported as being related to TCZ (gastroenteritis, otitis media, pharyngotonsillitis, septic arthritis, streptococcal sepsis, tonsillitis, upper respiratory infection, varicella), and all but 1 resolved (patient death). At the data cutoff, 3 patients died (1, suspected tension pneumothorax; 1, road traffic accident [both reported as unrelated]; 1 suspected streptococcal sepsis [possibly treatment-related]).

Table 2. Cumulative Safety (Safety Population; n=112).

	Prior Safety Update[a]	Week 104[b]
Exposure to TCZ, y	157.46	202.03
Rate of SAEs/100 PY (n)	24.8 (39)	23.3 (47)
Rate of serious infection AEs/100 PY (n)	11.4 (18)	10.9 (22)
SAEs related (remotely, possibly, probably) to TCZ/100 PY (n)	8.3 (13)	7.4 (15)
Macrophage activation syndrome/ 100 PY (n)	1.9 (3)	1.5 (3)
AEs leading to withdrawal/100 PY (n)	3.8 (6)[c]	3.0 (6)[c]
Deaths/100 PY (n)	0.6 (1)	1.5 (3)

TCZ=tocilizumab; PY=patient years; AE=adverse event; [a]Includes all safety data in the database up to and including August 10, 2010; [b]Includes all safety data in the database up to the Week 104 infusion (based on date of randomization) for each patient. T e last date for this was May 31, 2011; [c]Includes 2 withdrawals due to transaminase increases that were protocol-mandated.

Excessive interleukin-6 (IL-6) production has been implicated in the pathogenesis of sJIA. TENDER study data show that treatment up to 104 weeks with the IL-6 inhibitor TCZ is highly effective, with a favorable risk-benefit ratio in patients with severe, refractory, persistent sJIA.

Long-Term Results of the RAVE Trial

Written by Maria Vinall

John H. Stone, MD, Massachusetts General Hospital, Boston, Massachusetts, USA, presented the results of the 18-month follow-up from the Rituximab in ANCA-Associated Vasculitis trial [RAVE; ISRCTN28528813; Stone JH et al. *N Engl J Med* 2010], which found that one course of treatment with rituximab was noninferior to standard course of therapy (cyclophosphamide followed by azathioprine) for remission-induction of severe antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Patients who were at highest risk for flare had relapsing disease at baseline, proteinase 3(PR3)-ANCA positivity, or granulomatosis with polyangiitis (GPA).

The RAVE trial was a randomized, double-blind, placebo-controlled, noninferiority study. Patients from the original 6-month study were switched from cyclophosphamide to azathioprine or from rituximab to placebo between 3 and 6 months if remission was achieved [Birmingham Vasculitis Activity Score/Wegener's Granulomatosis (BVAS/WG)=0 and complete remission if BVAS/WG=0 off prednisone] and followed for 18 months. Remission rates were compared for the following subsets using log-rank tests: new diagnosis versus relapsing disease at baseline; myeloperoxidase (MPO)- versus PR3-ANCA; and microscopic polyangiitis (MPA) versus GPA.

After 18 months, more than 60% of patients from the original groups remained in the study. There was no significant difference in the cumulative number of severe or limited disease flares between the rituximab and cyclophosphamide-azathioprine treatment groups. By the end of the study, 39% of patients in the rituximab group versus 33% in the cyclophosphamide-azathioprine group met the definition of complete remission (p=NS). In the rituximab group, 77% of the originally treated patients achieved complete remission versus 71% for cyclophosphamide-azathioprine at any time during the study (p=0.69).

When analyzed by disease subsets, patients who were MPO-ANCA-positive (79%) had significantly (p=0.01) higher remission rates compared with PR3-ANCA-positive patients (72%). Patients with MPA (79%) had significantly