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

higher (p=0.01) remission rates compared with those with GPA (73%). Patients at study entry who were considered to be in relapse (67%) had significantly lower (p=0.01) remission rates compared with those who entered with a new diagnosis (81%). In all disease types, time to disease flare was longer for those patients with higher remission rates. Disease flares in the two treatment arms did not differ in number or severity.

The investigators noted that an increasing rise in ANCA titer or B-cell count was not an accurate predictor of disease flare. B-cell depletion occurred with cyclophosphamide-azathioprine, as well as rituximab, but was more prolonged with cyclophosphamide-azathioprine. Among rituximab-treated patients who achieved complete remission, flares occurred only after reconstitution of detectable B-cells. Dr. Stone noted that although flares occur in the absence of both B-cells and ANCA, as long as B-cells remain depleted and ANCA remains negative, the risk of a severe flare is low.

There were no clinically significant differences in overall or serious adverse events, deaths, infections, or malignancies. In particular, no additional malignancies occurred beyond those reported in the original study.

These results demonstrate that a single course of rituximab is as effective up to 18 months as standard therapy (cyclophosphamide-azathioprine) for remission induction and maintenance in severe ANCA-associated vasculitis. Relapses are more common in those with PR3-ANCA, GPA, and relapsing disease at baseline. Additional mechanistic studies are needed to define the immunological events that surround relapses more precisely.

JAK2 Reduces Basal Synthesis of Collagen in SSc Fibroblasts

Written by Maria Vinall

A study that explored the potential role of Janus kinase 2 (JAK2) as a molecular target for the treatment of fibrotic disease was presented by Clara Dees, PhD, University of Erlangen-Nuremberg, Erlangen, Germany. In this study, inhibition of JAK2 reduced the basal synthesis of collagen selectively in systemic sclerosis (SSc) fibroblasts but not in control fibroblasts. The profibrotic effects of transforming growth factor beta (TGFβ) were nullified with inhibition of JAK2. Inhibition of JAK2 also prevented fibrosis in inflammatory and noninflammatory fibrosis models.

SSc is characterized by an uncontrolled activation of fibroblasts, resulting in the release of excessive amounts of extracellular matrix components, leading to thickening and tightening of the skin. This study evaluated the role of JAK2 in the pathogenesis of SSc and analyzed the potential role of JAK2 inhibition as a novel antifibrotic.

Activation of JAK2 was determined by immunohistochemistry for phospho-JAK2 and phospho-signal transducers and activators of transcription 3 (STAT3; a major STAT protein that is activated by JAK2). Dermal fibroblasts were stimulated with TGFβ (a key factor in fibroblast activation in SSc) and incubated with the specific JAK2 inhibitor TG101209 at different concentrations. Fibroblast activation was determined by staining for α-smooth muscle actin (αSMA) and stress fibers. Bleomycin-induced dermal fibrosis and tight-skin 1 (Tsk-1) mice were used to evaluate the antifibrotic potential of a specific JAK2 inhibition *in vivo*.

Increased activation of JAK2 with prominent accumulation of phospho-JAK2, particularly in fibroblasts, was observed in the skin of SSc mice. JAK2 signaling persisted in cultured SSc fibroblasts, and stimulation of healthy fibroblasts with TGFβ increased the levels of phospho-JAK2, similar to those seen in SSc fibroblasts. Inhibition of JAK2 with TG101209 prevented the activation of SSc fibroblasts in the presence of TGFβ stimulation and decreased αSMA almost back to baseline levels. TGFβ-induced collagen synthesis (collagen type 1, alpha 1 [col1A1] mRNA, and collagen protein) was also reduced.

Furthermore, inhibition of JAK2 by the selective JAK2 inhibitor TG101209 abrogated the activated phenotype of SSc fibroblasts by decreasing the formation of stress fibers, the expression of αSMA, and the basal mRNA and protein levels of collagen. These inhibitory effects in the absence of exogenous stimulation were only observed in SSc fibroblasts, not in resting dermal fibroblasts from healthy individuals.

Inhibition of JAK2 consistently exerted potent antifibrotic effects in experimental fibrosis. In the model of bleomycin-induced fibrosis, treatment with TG101209 decreased dermal thickening by 95%±5% (p=0.007), collagen content by 76%±7% (p<0.001), and myofibroblast counts completely back to baseline levels (p=0.001). Potent antifibrotic effects were also observed in the Tsk-1 model. Application of TG101209 reduced hypodermal thickening, collagen content, and myofibroblast counts (p=0.01). These results suggest that JAK2 might be a promising molecular target for the treatment of SSc and other fibrotic diseases.