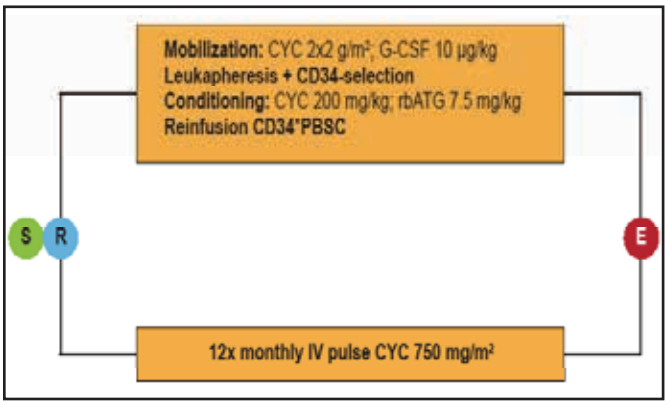
The ASTIS Trial: First Results

Written by Maria Vinall

Jacob M. van Laar, MD, Newcastle University, Newcastle, United Kingdom, presented the first results from the Autologous Stem Cell Transplantation International Scleroderma trial [ASTIS; ISRCTN54371254], an international, investigator-initiated, open-label Phase 3 trial that suggests that hematopoietic stem cell transplantation (HSCT) results in better long-term event-free and overall survival compared with conventional treatment for patients with poor prognosis, early diffuse, cutaneous systemic sclerosis.

To be eligible for inclusion in the study, patients were required to be aged 16 to 65 years and have early, poor prognosis, diffuse, cutaneous systemic sclerosis, defined as a disease duration ≤4 years with a skin score ≥15 and evidence of heart, lung, or kidney involvement; or a disease duration ≤2 years with a skin score ≥20 and evidence of an acute-phase response. Patients with pulmonary hypertension >50 mm Hg or serious organ dysfunction were excluded, as were those with previous extensive (>5 gr IV; >3 months oral) treatment with cyclophosphamide (CYC). A total of 156 patients (mean age 43.7 years, 59% women, mean disease duration 1.4 years) were enrolled from 27 centers in 10 countries. Subjects were randomized to the HSCT arm (n=79) or to intravenous pulse CYC 750 mg/m^2 (CYC-treated group; n=77; Figure 1) and monitored every 3 months up to 24 months and annually thereafter. The primary endpoint of the trial was event-free survival, defined as overall survival or survival until development of major organ failure.

Figure 1. Randomization.



CYC=cyclophosphamide; G-CSF=granulocyte colony-stimulating factor; rbATG=rabbit antithymoglobulin; PBSC=peripheral blood stem cell.

Sixty-one transplant patients and 54 CYC patients completed 24 months of follow-up. As of the time of this presentation, 15 patients in the treatment arm and 12 CYC patients had completed 84 months of follow-up, and 43 transplant subjects and 33 controls were still being followed. As of May 1, 2012, 46 events had occurred (19 in the transplant arm ,and 27 in the CYC arm). Sixteen subjects in the transplant arm died compared with 26 deaths in the CYC arm. Half of the deaths in the HSCT group occurred early and were deemed to be treatment-related, according to an independent data-monitoring committee. In the conventional treatment group, none of the deaths was deemed to be treatment-related, but more deaths occurred later, and most were related to disease progression, cancer, and major organ failure.

Long-term (≥2 years) event-free and overall survival were significantly improved with HSCT treatment (HR, 0.30; 95% CI, 0.12 to 0.76; p=0.011 and HR, 0.22; 95% CI, 0.08 to 0.58; p=0.002, respectively).

Preliminary results of an exploratory analysis showed that smoking status appeared to be a determinant of event-free survival, with nonsmokers benefiting most from transplantation.

24-Week Results From the RAPID-PsA Study

Written by Maria Vinall

Philip J. Mease, MD, University of Washington, Seattle, Washington, USA, presented key results from the first Phase 3 trial of certolizumab pegol (CZP) in patients with active psoriatic arthritis (PsA). In the Phase 3, Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Certolizumab Pegol in Subjects With Adult Onset Active and PsA study [RAPID-PsA; NCT01087788], patients who were treated with CZP were twice as likely to meet the primary study endpoint of ACR20 response at Week 12 compared with those who were taking placebo.

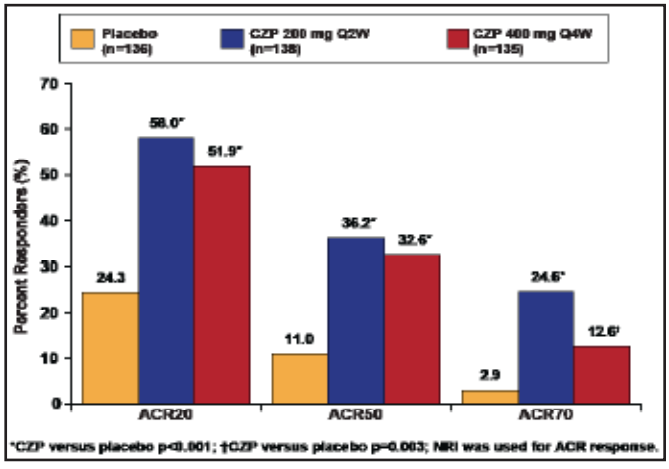
Dr. Mease presented the 24-week results from an ongoing 158-week randomized, placebo-controlled study that included 409 patients with active PsA who had failed 1 or more disease-modifying antirheumatic drugs, including a maximum of 1 anti-tumor necrosis factor (anti-TNF). Patients were randomized to placebo (n=136) or started on a loading dose of 400 mg CZP every 2 weeks for the first 4 weeks and then continued with either 200 mg CZP administered subcutaneously every 2 weeks (n=138) or 400 mg CZP administered subcutaneously every 4 weeks (n=135). Patients in the placebo group who failed to achieve a ≥10% improvement in tender joint count (TJC) and swollen joint count (SJC) at Weeks 14 and 16 were

randomized to 1 of the CZP arms, following a loading dose. The primary efficacy endpoints were ACR20 response at Week 12 and change from baseline in the modified Total Sharp Score (mTSS) at Week 24 (mTSS results were not reported at the meeting). Key secondary endpoints included: ACR20 response and change from baseline in Health Assessment Questionnaire-Disease Index (HAQ-DI) at Week 24, the Psoriasis Area and Severity Index (PASI) 75 response at Week 24 in the subgroup of subjects with psoriasis involving ≥ 3% body surface affected (BSA) at baseline, and change from baseline in mTSS at Week 48.

Subjects were aged 47 to 48 years, evenly divided between men and women, and overweight (body mass index 29.2 to 30.5 kg/m^2). Approximately 20% of patients had prior anti-TNF exposure. Subjects had significant disease, as evidenced by the SJC (mean 10.4 to 11.0/66), TJC (mean 19.6 to 21.5/68) the presence of enthesitis in >60% of subjects and dactylitis in approximately one-third of subjects. The median baseline PASI score for subjects was 7.0 to 8.1.

At Week 12, 58% of patients who received CZP 200 mg every 2 weeks and 51.9% of those who received CZP 400 mg every 4 weeks achieved an ACR20 response compared with 24.3% of patients who were receiving placebo (p<0.001). More CZP-treated patients in both groups also achieved ACR50 and ACR70 response compared with placebo (Figure 1). Results were observed as early as Week 1. Functional improvement was significant (p<0.001) for subjects who received CZP, with both groups reporting changes in HAQ-DI scores at Week 24 that exceeded the minimally important difference of 0.35 [Mease P et al. *J Rheumatol* 2011]. Although the response was slightly slower, treatment with CZP was associated with a robust skin response (Table 1).

Figure 1. ACR Response at Week 12.



The safety profile of CZP was similar to that observed in patients with rheumatoid arthritis. Adverse events occurred at rates of 68% for the placebo group versus 69% for the combined CZP group, and serious adverse events occurred at 4% for the placebo group versus 7% for the combined CZP group. Two deaths occurred during this phase of the study, but neither was considered to be related to the study drug.

Table 1. PASI 75 and 90 Response.

	CZP 200 mg Q2W (n=90)		CZP 400 mg Q4W (n=76)		Placebo (n=86)	
	Week 12	Week 24	Week 12	Week 24	Week 12	Week 24
PASI75	46.7*	62.2*	47.4*	60.5*	14.0	15.1
PASI90	22.2*	46.7	19.7**	35.5*	4.7	5.8

*p<0.001 vs placebo; **p=0.004 vs placebo; PASI=Psoriasis Area and Severity Index; CZP=certolizumab pegol; Q2W=every 2 weeks; Q4W=every 4 weeks.

Efficacy and Safety of NNC0109-0012 (anti-IL-20 mAb) in Patients with RA: Results from a Phase 2a Trial

Written by Maria Vinall

Elevated expression of interleukin-20 (IL-20) and its receptors has been demonstrated in synovium from patients with rheumatoid arthritis (RA) and is thought to be implicated in the pathogenesis of RA. NNC0109-0012 is a novel human monoclonal IgG4 antibody that binds to and neutralizes the activity of IL-20. Results of a Phase 2 study, presented by Ladislav Šenolt, MD, PhD, Institute of Rheumatology, Prague, Czech Republic, suggest that IL-20 is a potential target for RA therapy.

The primary objective of this randomized multicenter, double-blind, multiple-dose, placebo-controlled Phase 2a trial was to evaluate the change in disease activity (DAS28-CRP) following 12 weeks of treatment with NNC0109-0012 in patients with active RA. Secondary objectives included EULAR and ACR20/50/70 responses and safety, pharmacokinetics (PK), pharmacodynamics (PD), safety, tolerability, and immunogenicity. Subjects were required to be aged 18 to 75 years with active RA (DAS28-CRP ≥4.5; ≥5 swollen and ≥5 tender joints of the 28-joint count), have a disease duration ≥3 months, and have been on stable methotrexate therapy (≥7.5 to ≤25 mg/week) for at least 4 weeks prior to randomization.

A total of 67 patients (mostly women, two-thirds rheumatoid factor [RF]- and anticitrullinated protein antibody [ACPA]-positive, mean DAS28-CRP score of 6.0; Table 1) with active RA were randomized to subcutaneous NNC0109-0012 3 mg/kg once weekly for 12 weeks (n=45) or placebo (n=22) along with standard methotrexate treatment and followed for an additional 13 weeks.