At 12 months, use of biological medications was 29% in Arm A, 26% in Arm B, and 43% in Arm C. There were no differences between groups in serious adverse events and no difference in dosage adjustments per drug due to adverse events.

Prof. de Jong concluded that treatment goals are attained faster and are maintained with the need for fewer biologic agents in RA patients started on triple DMARD therapy compared with MTX monotherapy.

Inhibitor of Interleukins 12 and 23 Slows Joint Destruction in Psoriatic Arthritis

Written by **Wayne Kuznar**

A prespecified integrated analysis of two Phase 3 clinical trials demonstrates that the monoclonal antibody ustekinumab reduces radiographic progression of joint disease in patients with active psoriatic arthritis. Iain B. McInnes, PhD, University of Glasgow, Glasgow, Scotland, presented the integrated analysis of the two Phase 3 Multicenter, Randomised, Double-Blind, Placebo-Controlled Trials of Ustekinumab, a Fully Human Anti-IL-12/23p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Psoriasis Arthritis [PSUMMIT I and II; NCT01009086; NCT01077362].

Ustekinumab is a human monoclonal antibody against the p40 subunit of interleukins (IL)-12 and -23. The IL-23/IL-17 axis mediates pathways that have the potential to drive inflammation and matrix destruction, said Prof. McInnes.

The 615 patients enrolled in PSUMMIT I had inadequate response to methotrexate and no exposure to tumor necrosis factor (TNF)-α inhibitors. Prior anti-TNF-α therapy was permitted in PSUMMIT II, in which 312 patients were enrolled. In PSUMMIT II, 70% of patients had discontinued TNF-α inhibitors for lack of efficacy or intolerance; 25% had received ≥3 prior anti-TNF-α therapies. Therapies at baseline are depicted in Table 1. The integrated analysis therefore included 927 patients with disease activity despite prior treatment with alternative agents.

In the trials, patients were randomized to receive ustekinumab 45 mg, 90 mg, or placebo at Weeks 0 and 4 and then every 12 weeks [McInnes JB et al. *Lancet* 2013; Ritchlin CT et al. *Arthritis Rheum* 2012 (abstr 2557)]. In each study, patients with no response to placebo (defined as <5% improvement in tender and swollen joint count from baseline) at Week 16 were crossed over to ustekinumab 45 mg. All remaining patients randomized to placebo crossed over at Week 24 to ustekinumab 45 mg. Patients randomized to ustekinumab 45 mg who had no response (as defined above) had their dose of ustekinumab increased to 90 mg, starting at Week 16. Radiographic progression was assessed in the hands and the feet by the change from baseline to Week 24 in total psoriatic arthritis modified van der Heijde-Sharp (vdHS) scores.

Table 1. Prior Use of Therapies at Baseline in PSUMMIT I and PSUMMIT II

PSUMMIT I and II				
	PBO	UST 45 mg	UST 90 mg	UST Combined
PSUMMIT I	206	205	204	409
MTX use at BL	46.6	48.3	49.5	48.9
PSUMMIT II	104	103	105	208
MTX use at BL	47.1	52.4	49.5	51.0
PSUMMIT II				
	PBO	UST 45 mg	UST 90 mg	UST Combined
Patients previously treated with biologic anti-TNFα agent(s)*	62/104 (59.6%)	60/103 (58.3%)	58/105 (55.2%)	118/208 (56.7%)
Adalimumab	37	31	33	64
Etanercept	41	42	32	74
Certolizumab	2	0	1	1
Golimumab	5	7	4	11
Infliximab	29	37	30	67

BL=baseline; MTX=methotrexate; PBO=placebo; TNF=tumor necrosis factor; UST=ustekinumab.

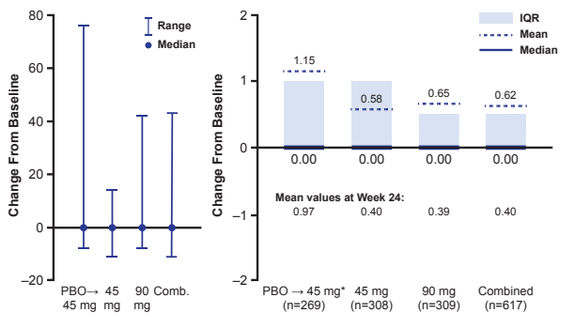
*70% discontinued anti-TNF for lack of efficacy or intolerance; 25% of patients received ≥3 prior anti-TNF.

Linear extrapolation to Week 24 was performed if there was a baseline x-ray available and a second x-ray performed before Week 24; if data were insufficient for linear extrapolation (ie, only 0 or 1 available radiographs), the median of the change in vdHS derived from all subjects within the same methotrexate stratification group at the missing visit was assigned.

In the integrated analysis, at Week 24, patients randomized to ustekinumab 45 and 90 mg had a mean change from baseline in total vdHS score of 0.40 and 0.39, respectively, compared with a mean change of 0.97 for patients receiving placebo ($p=0.017$ and $p<0.001$, respectively). The favorable effect of ustekinumab on radiographic progression continued to Week 52 (Figure 1).

When evaluated individually, results from PSUMMIT I were consistent with the prespecified integrated analysis (significant inhibition of structural damage at Week 24 for both ustekinumab doses). The effect of ustekinumab on inhibiting progression of structural damage could not be discerned in the smaller PSUMMIT II study, which had a high proportion of dropouts in the placebo group. Different rates of imputation for missing data could have disproportionately altered progression rates in PSUMMIT II, potentially obscuring any true difference in radiographic progression between groups, explained Prof. McInnes.

Figure 1. Change From Baseline in Modified Total vdHS Score at Week 52



*Patients who did not receive UST are excluded.

ITT=intention-to-treat; PBO=placebo; UST=ustekinumab; vdHS=van der Heijde-Sharp.
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Characterization of Jo1 Reactive T Cells in Patients With Myositis

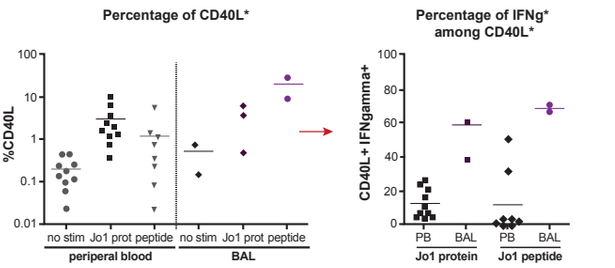
Written by **Muriel Cunningham**

Myositis is an autoimmune disease affecting skeletal muscle, skin, heart, and lungs. Types of myositis include polymyositis, dermatomyositis, inclusion body myositis, and immune mediated necrotizing myopathy. This is a rare disorder, occurring with an incidence of approximately 1 in 100,000/year. While typically treated with steroids and other immuno-suppressive drugs, the search continues for effective therapies. The autoantibody directed against histidyl tRNA synthetase (Jo1) is specific for myositis and is the most common autoantibody found in these patients. Approximately 20% [Gunawardena H et al. *Rheumatology (Oxford)* 2009] of myositis patients will have detectable Jo1 autoantibodies and its presence is associated with interstitial lung disease (ILD). Evidence suggests that the autoimmune response of myositis originates in the lungs [Chinoy H et al. *Ann Rheum Dis* 2012].

Inka Albrecht, PhD, Karolinska University Hospital, Stockholm, Sweden, presented her research in the characterization of Jo1-specific T helper cell responses in blood and bronchoalveolar lavage (BAL) samples obtained from patients with myositis. Building on earlier published research that revealed the existence of a Jo1-antigen T cell response [Ascherman DP et al. *J Immunol* 2002], Prof. Albrecht and colleagues sought to determine the frequency and phenotype of the cells, their location, and the major T cell epitope. A 13 amino-acid peptide was derived from the first 60 amino acids of the full Jo1 protein. Cells isolated from the peripheral blood mononuclear cells (PBMCs; n=9) and BAL (n=3) of patients with myositis were stimulated with the Jo1 protein and the test peptide [Chattopadhyay PK et al. *Nat Med* 2005; Frentsch M et al. *Nat Med* 2005]. CD154, also known as CD40 ligand (CD40L), is a marker that is upregulated on the cell when the antigen-specific Th cell recognizes its antigen. The expression of the pro-inflammatory cytokines interferon (IFN)-γ, interleukin (IL)-2, and IL-17A were also analyzed.

Cells from PBMCs stimulated with the full Jo1 protein had increases in CD40L, IFN-γ, IL-2, and IL-17A compared with unstimulated cells. Similar results were obtained when the cells were stimulated with the test peptide. Blocking assays determined that this reaction was specific. When the PBMC results from all tested patients were pooled, the CD40L increases were significant when stimulated with the full protein ($p<0.0001$) but not with the test peptide ($p=0.1307$; Figure 1). This suggests other epitopes that lie outside of the test peptide sequence may be involved. BAL cells also had increased CD04L, IFN-γ, IL-2, and IL-17A when stimulated with the full Jo1 protein and the test peptide, with dramatically higher increases in IFN-γ compared with PBMCs.

Figure 1. Summary of Flow Cytometry Results



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Further characterization revealed that the BAL Th cells are Th1 with high expression of chemokine receptors CCR5 and CXCR3. "In the lung the cells have a clear pro-inflammatory phenotype and we were able to identify the first major epitope within the first 60 amino acids," summarized Prof. Albrecht.

Future research will focus on analyzing cells from the blood and BAL of additional Jo1-positive patients, establishing a tetramer for the identified epitope, and searching for additional epitopes. It is hoped that further identification, isolation, and characterization of Jo1-specific CD4 T cells will ultimately lead to novel therapies for myositis.