Initial Triple Therapy Superior to Monotherapy on Measures of Disease Activity in RA

Written by Wayne Kuznar

Triple disease-modifying antirheumatic drug (DMARD) therapy is superior to methotrexate (MTX) monotherapy on measures of disease activity as initial treatment for rheumatoid arthritis (RA).

The design and results of the multicenter stratified single-blind Treatment in the Rotterdam Early Arthritis Cohort trial [tREACH] comparing treatment strategies, including different glucocorticoid bridging therapies, in adults with early RA were discussed by Pascal H.P. de Jong, MD, Erasmus University Medical Center, Rotterdam, The Netherlands.

In 2010, the European League Against Rheumatology recommended MTX monotherapy rather than a combination of DMARDs as an initial treatment strategy for RA [Smolen Js et al. *Ann Rheum Dis* 2010], although several clinical trials concluded that initial combination therapy had superior clinical efficacy over monotherapy. The principal motive for disregarding combination therapy were the fact that trials were biased by glucocorticoids and there were safety concerns. There is also not much data on the optimal glucocorticoid dosage and/or tapering scheme, noted Prof. de Jong.

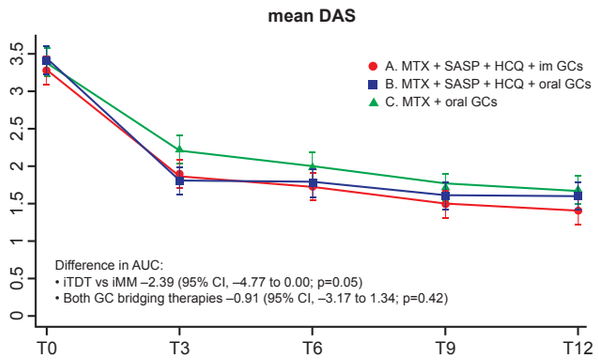
The tREACH trial compared three treat-to-target strategies in 281 adults who had a high probability of progressing to persistent arthritis based on the Visser prediction model. Interestingly, the Visser algorithm and 2010 criteria for RA have similar discriminative abilities to identify patients at risk of persistent arthritis. Patients were randomized to one of three strategies:

- Arm A (n=91): Triple DMARD therapy (MTX, sulfasalazine, and hydroxychloroquine) with one-time administration of intramuscular glucocorticoids
- Arm B (n=93): Triple DMARD therapy with an oral glucocorticoid tapering scheme, starting at 15 mg/day
- Arm C (n=97): MTX with oral glucocorticoids as in Arm B

Patients were followed every 3 months, with treatment decisions designed to maintain a disease activity score (DAS) <2.4. In the event of treatment failure, defined as DAS ≥2.4, the medication regimen was intensified to include biologic agents. In cases of sustained remission, defined as DAS <1.6 at two consecutive visits, medication was tapered. The mean symptom duration of participants was 166 days and the mean DAS at baseline ranged from 3.28 to 3.40. Women comprised 68% of the study populationw.

The difference in disease activity over time, as measured by area under the curve (AUC) for mean DAS score, was –2.39 in favor of the triple DMARD strategy (p=0.05; Figure 1). The largest difference in disease activity between groups occurred at 3 months indicating that treatment goals were achieved faster with triple DMARD therapy. The difference after 3 months diminished because of the treat-to-target approach in all groups, necessitating intensification of treatment in Arm C, explained Prof. de Jong. There was no difference on this outcome between the two glucocorticoid bridging strategies. Functional ability, as measured by the AUC for mean scores on the Health Assessment Questionnaire, was again superior with triple DMARD therapy versus MTX monotherapy (difference: 1.67; p=0.05), again with no difference on this measure between the two glucocorticoid strategies.

Figure 1. Change in Disease Activity



AUC=area under the curve; DAS=disease activity score; GC=glucocorticoid; HCQ=hydroxychloroquine; im=intramuscular; iMM=initial MTX monotherapy; iTDT=initial triple disease-modifying antirheumatic drug therapy; MTX=methotrexate; SASP=sulfasalazine.

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Radiographic progression after 1 year occurred in 19%, 23%, and 21% of patients in Arms A, B, and C, respectively.

At 3 months, there were fewer treatment failures in the triple DMARD therapy groups, resulting in the prescription of ~40% fewer biological medications, and this difference remained over time.

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.