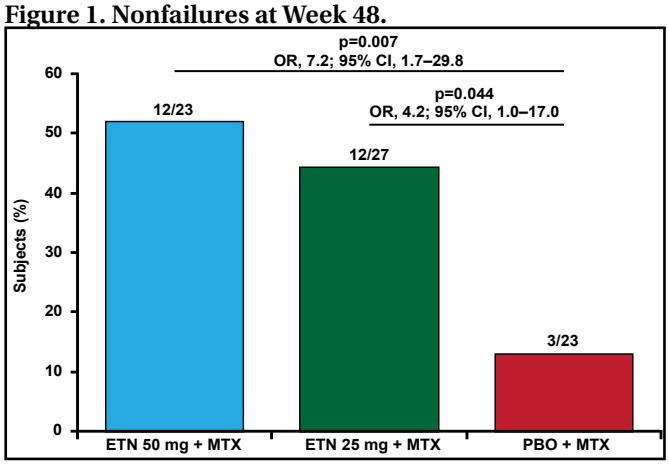
activity. Mean DAS28 score at the start of etanercept treatment was 5.0.

After 48 weeks, the proportion of nonfailures was 52% for etanercept50 (OR, 7.2; 95% CI, 1.7 to 29.8; p=0.007 vs placebo) and 44% for etanercept25 (OR, 4.2; 95% CI, 1.0 to 17.0; p=0.044 vs placebo; Figure 1). Median time to failure was 6 weeks from randomization for placebo, and 48 and 36 weeks for etanercept50 and etanercept25, respectively. Adverse events were similar between the groups and no unexpected safety signals were noted.

The data suggest that induction-maintenance may be possible with etanercept for some RA patients, even in established disease.

Figure 1. Nonfailures at Week 48.



ETN=etanercept; MTX=methotrexate; PBO=placebo.
Adapted from RF van Vollenhoven, MD.

IMPROVED: Final Study Results of Combination Treatment in Patients with Early RA and UA

Written by Maria Vinall

Final results of the Induction Therapy with Methotrexate and Prednisone in Rheumatoid or Very Early Arthritis Disease [IMPROVED] study, reported by Lotte Heimans, MD, Leiden University Medical Center, Leiden, The Netherlands, showed that patients with rheumatoid arthritis (RA) and undifferentiated arthritis (UA) achieved similarly greater rates of remission after early initial treatment with combination therapy (methotrexate [MTX] and prednisone). Patients who failed to achieve early remission benefited more when switched to a treatment strategy with adalimumab than with multiple disease modifying antirheumatic drugs (DMARDs), with virtually no radiographic damage progression in all patients.

The objectives of the IMPROVED trial were to assess if induction of remission and drug-free remission is possible with initial combination therapy in early RA and UA, to determine which strategy results in more remission if the initial combination fails, and to compare results in RA and UA patients. The study included adult patients with RA (2010 criteria; n=479) of <2 years duration or rheumatologist-determined UA (n=122). The goal was remission (Disease Activity Score [DAS] <1.6).

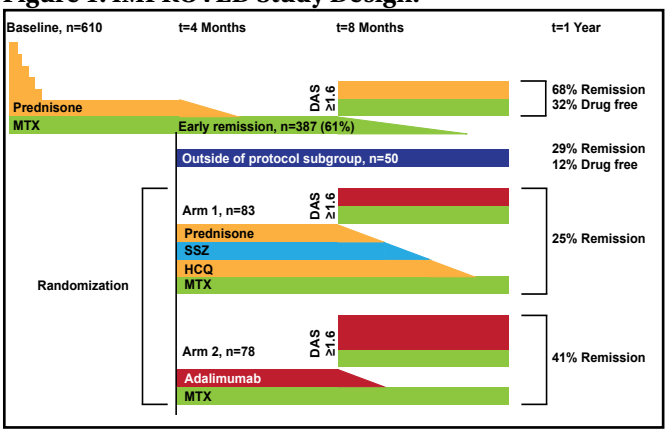
All patients were initially treated with MTX (25 mg QW) and prednisone (60 mg QD tapered to 7.5 mg QD over 7 weeks). Prednisone was tapered then discontinued for patients with a DAS <1.6 at 4 months. MTX was tapered for patients with a DAS <1.6 at 8 months. If remission was lost after 8 months, prednisone was restarted at 7.5 mg QD. Patients not in remission at 4 months were randomized to Arm 1 (MTX + prednisone + sulfhasalazine 2000 mg QD + hydroxychloroquine 400 mg QD [poly DMARDs + prednisone]; n=83) or Arm 2 (MTX + adalimumab [ADA] 40 mg every 2 weeks; n=78). Patients in either arm achieving remission at 8 months had their treatments tapered to MTX monotherapy. If not in remission after 8 months, patients in Arm 1 switched to ADA plus MTX and patients in Arm 2 increased ADA to 40 mg QW.

At baseline, RA patients had significantly (p≤0.02) higher DAS and Health Assessment Questionnaire scores compared with UA patients; 68% of RA patients were positive for anticitrullinated protein antibody plus (ACPA+) compared with 3% of UA patients (p<0.001). Mean age was 52 years; 70% of RA and 61% of UA patients were women; mean symptom duration was ~17 weeks. Proportions of remission and radiographic progression measured by Sharp/van der Heijde score (SHS) after 1-year follow-up were compared between the different treatment strategies.

Early remission (4 months) was achieved by 61% of all patients (Figure 1). At 1 year, 68% of those 61% were in remission and 32% were in drug-free remission. Significantly more patients in arm 2 (MTX + ADA, 41%) achieved remission at 1 year compared with those in arm 1 (poly DMARDs + prednisone, 25%; p=0.01). There was no difference between RA (62%) and UA (65%) patients who achieved early remission (p=0.46) or 1 year remission (53% vs 58%, respectively; p=0.1). Damage progression was minimal. Only 33 patients showed a 1-point progression on SHS. Toxicity was comparable between the 2 randomized arms.

In this treat-to-remission cohort, early remission more often led to remission at 1 year (radiological damage progression after 1 year and drug-free remission). Also, remission-steered therapies led to minimal radiographic damage in UA and RA patients regardless of the treatment employed.

Figure 1. IMPROVED Study Design.



DAS=Disease Activity Score; HCQ=hydroxychloroquine; MTX=methotrexate; SSZ=sulfasalazine. Reproduced with permission from L Heimans, MD.

Short- and Long-Term Efficacy of Tofacitinib in the Treatment of Patients with RA and an Inadequate Response to TNF Inhibitors

Written by Maria Vinall

Treatment with the oral Janus kinase (JAK) inhibitor tofacitinib was associated with an improvement in the signs and symptoms of rheumatoid arthritis (RA), physical function, and patient reported outcomes in RA patients with an inadequate response to tumor necrosis factor inhibitors (TNFi). The improved response was maintained over 24 months. Data from 11 studies [Monotherapy: NCT00550446, NCT00687193, NCT00814307; background DMARD: NCT00413660, NCT00603512, NCT00960440, NCT00847613, NCT00856544, NCT00853385; LTE: NCT00413699, NCT00661661] were pooled and Gerd R. Burmester, MD, Charité University Hospital, Berlin, Germany, presented the results.

In a prior study, tofacitinib improved the signs and symptoms of RA in 399 TNFi treatment refractory patients over 6 months [Burmester G-R et al. *Arthritis Rheum* 2011]. The purpose of this analysis was to provide additional short- and long-term data concerning the effect of tofacitinib on the signs and symptoms of RA, physical function, pain, and fatigue compared with placebo in this patient population and to further characterize the activity of tofacitinib by number of failed TNFi, by reason for failure (adverse event vs lack of efficacy). In the newer study, data from 9 randomized Phase 2 and 3 studies (n=614) and 2 open-label long-term extension studies (n=510) were analyzed. Patients were treated with tofacitinib (5 or 10 mg BID) either as monotherapy or on a background of nonbiologic disease-modifying antirheumatic drugs (DMARDs), or, in Phase 2 and 3 studies, with placebo.

Efficacy in reducing the signs and symptoms of RA was assessed by changes in American College of Rheumatology improvement response criteria (ACR20/50/70) and 28-joint Disease Activity Score (DAS28)-4 erythrocyte sedimentation rate (ESR) scores. Physical function was assessed by mean change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI). Pain and fatigue were assessed using change from baseline on the Short Form-36 Bodily Pain item and the Functional Assessment of Chronic Illness Therapy-Fatigue item. More than 60% of the patients had failed at least one TNFi in all groups.

At Month 3, significantly greater ACR20/50/70 responder rates were seen with tofacitinib compared with placebo ($p<0.0001$, $p<0.0001$, $p<0.05$, respectively). This pattern was consistent regardless of 1 or 2 prior TNFi failures. Tofacitinib also improved mean DAS28-4 ESR scores, values for HAQ-DI, and body pain and fatigue at 3 months and over 24 months. No new safety signals were detected in the previously presented randomized controlled trial in TNFi inadequate response patients treated with tofacitinib [Burmester GR et al. *Arthritis Rheum* 2011].

The investigators concluded that tofacitinib may offer a benefit in difficult-to-treat patients resistant to standard DMARDs.

SC Tocilizumab Reduces RA Disease Activity When Used with DMARDs

Written by Wayne Kuznar

When used in combination with traditional disease-modifying antirheumatic drugs (DMARDs), response rates were significantly superior with a subcutaneous (SC) form of tocilizumab compared with placebo in a 24-week Phase 3 study of patients with moderate to severe rheumatoid arthritis (RA).

A SC form of tocilizumab gives patients the opportunity to self-administer treatment, reported Alan Kivitz, MD, Altoona Center for Clinical Research, Duncansville, Pennsylvania, USA. 656 patients with moderately to severely active RA of at least 6 months duration and an inadequate response to 1 or more DMARDs (20% had prior treatment with anti-TNF) were randomized in a 2:1 ratio to treatment with SC tocilizumab (n=437; 162 mg every 2 weeks) or SC placebo (n=219) with continuation of DMARDs [Kivitz AJ et al. ACR 2012 Poster L8]. Oral corticosteroids and nonsteroidal anti-inflammatory drugs were permitted if patients were on stable dosages for at least 4 weeks prior to baseline.