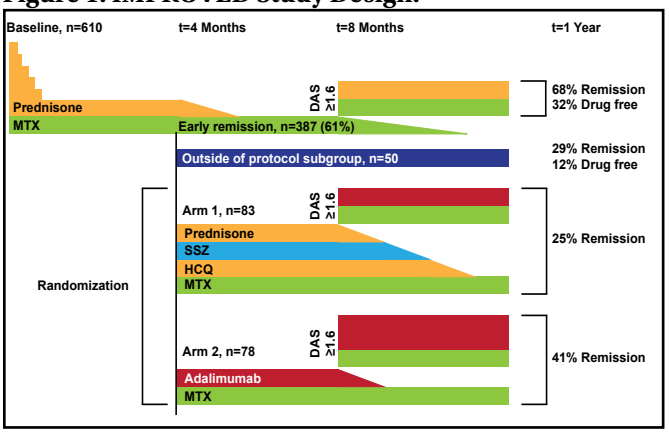
Figure 1. IMPROVED Study Design.



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.

Significantly more patients treated with SC tocilizumab compared with placebo achieved an American College of Rheumatology 20% improvement response (ACR20) at Week 24, the primary endpoint of the study (61% vs 31.5%, respectively; p<0.0001).

Achievement of secondary endpoints also favored SC tocilizumab.

- An ACR50 response was achieved by 40% assigned to SC tocilizumab compared with 12% assigned to placebo (p<0.0001), and an ACR70 response occurred in 20% versus 5%, respectively (p<0.0001)
- The adjusted mean change in the 28-joint Disease Activity Score was −3.1 in the tocilizumab group and −1.7 in the placebo group (p<0.0001)
- The adjusted mean change in the Health Assessment Questionnaire Disability Index from baseline to Week 24 was −0.40 in the tocilizumab group versus −0.30 in the placebo group (p=0.0054)
- The change in the modified Total Sharp Score from baseline to Week 24 was 0.62 in the tocilizumab group versus 1.23 in the placebo group (p=0.0149), reflecting less progression of joint damage in the tocilizumab group

Neutropenia occurred more often in patients receiving SC tocilizumab compared with placebo (20.5% vs 3.7%); however, the proportion of patients experiencing infections or serious infections was similar in both groups. There were no cases of thrombocytopenia in patients assigned to placebo; Grade 1 thrombocytopenia occurred in 6.7% and Grade 2 thrombocytopenia occurred in 0.5% of the patients assigned to SC tocilizumab, with no instances of either Grade 3 or 4 thrombocytopenia. Elevated transaminases were more common in patients who received SC tocilizumab; few alanine and aspartate aminotransferase elevations were >3 times the upper limit of normal in SC tocilizumab-treated patients (3.7% and 0.7%, respectively).

The authors concluded that the superior efficacy responses and similar safety profile of SC tocilizumab compared with placebo offers patients an alternate route of administration for tozilizumab therapy in RA.

Apremilastin Patients with Psoriatic Arthritis: Results of the PALACE-1 Trial

Written by Maria Vinall

In a late-breaking clinical trial reported by Arthur Kavanaugh, MD, University of California, San Diego, California, USA, apremilast, an oral phosphodiesterase 4 inhibitor, was shown to be safe and effective in treating psoriatic arthritis (PsA) in subjects previously exposed to disease-modifying antirheumatic drugs (DMARDs). Apremilast modulates the production of pro- (tumor necrosis factor [TNF]-α, natural killer [NK] cells, and epidermal keratinocytes) and anti-inflammatory mediators (interleukin [IL]-10), including those implicated in the etiopathogenesis of PsA.

The Efficacy and Safety Study of Apremilast to Treat Active Psoriatic Arthritis [PALACE-1; NCT01172938] was a randomized, placebo-controlled study in subjects with a documented PsA diagnosis for ≥6 months who were previously or currently being treated with DMARDs or biologics. Participants could not have failed >3 DMARDs or >1 TNF inhibitors. Concurrent treatment with stable doses of methotrexate (MTX), sulfasalazine, or leflunomide was allowed. A total of 504 subjects were randomized (1:1:1) to placebo, 20 mg BID apremilast, or 30 mg BID apremilast and stratified by baseline DMARD use. Placebo subjects in whom the tender and swollen joint counts had not improved by at least 20% at Week 16 were re-randomized to apremilast 20 or 30 mg BID. At Week 24, all remaining placebo subjects were re-randomized to apremilast 20 or 30 mg BID.

At baseline, the mean age of the subjects was ~50 years, mean duration of PsA and psoriasis was ~7.5 years and 16 years, respectively, and mean 28-joint Disease Activity Score was ~4.9. Seventy-two percent of patients had prior use of DMARDs (54.2% MTX), 22% had prior use of TNF inhibitors, and 9% had failed treatment with a TNF inhibitor.

The percentage of subjects achieving an American College of Rheumatology 20% improvement criteria (ACR20) response at Week 16 was significantly greater for subjects treated with 20 mg (31%; p<0.02) and 30 mg (41%; p<0.0001) apremilast compared with placebo (19%). Higher ACR responses were seen in subjects receiving apremilast 30 mg plus monotherapy and in biologic-naïve subjects compared with the overall population response. At Week 24, apremilast was associated with significant (p<0.05) differences compared with placebo on the ACR50, ACR70, HAQ-DI, and visual analog scale pain scores, as well as on the DAS28 and European League Against Rheumatism response.

In general, response rates were higher with apremilast 30 mg BID. Apremilast was generally well tolerated. There were no significant differences as to number of adverse events (AEs), serious AEs, or AEs leading to withdrawal between groups; 95% of AEs were mild or moderate in severity. The most common AEs were diarrhea, nausea, headache, and upper respiratory tract infection.

Inhibition of TNF-α and IL production, as well as NK and keratinocyte responses by this phosphodiesterase-4 inhibitor suggests a novel approach to the treatment of psoriasis [Schafer P et al. *Br J Pharmacol* 2010].