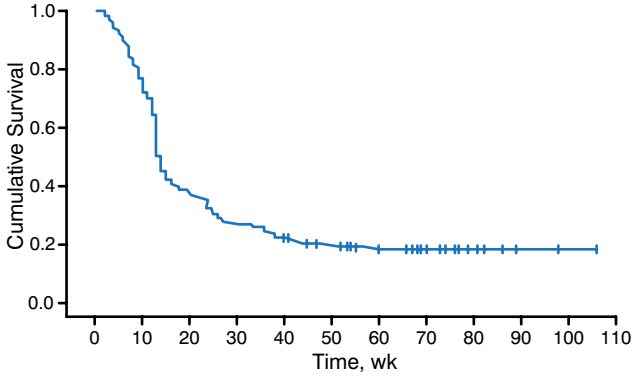
Figure 1. Time to Regained Low Disease Activity After Flare in Patients Who Stopped TNFi Therapy



TNFi, tumor necrosis factor inhibitor.

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also received a stable dose of disease-modifying antirheumatic drug(s) and had ≥ 2 Disease Activity Score in 28 joints (DAS28) scores < 3.2 in this period. Patients were randomized 2:1 to either stop (65%) or continue (35%) their TNFi therapy (DAS28 flare; defined as DAS28 ≥ 3.2 with an increase ≥ 0.6 compared with the previous DAS28).

At 12 months, the data showed that 46.9% of patients who stopped their TNFi experienced a DAS28 flare, compared with 16.6% of those who continued their TNFi ($P < .001$). The median time to first flare was 24 weeks in patients who stopped taking their TNFi. However, most patients in the group who stopped their TNFi regained low disease activity quickly after a flare, at a median time of 14 weeks (Figure 1).

During the 12-month study period, flare-free discontinuation of TNFi was possible in 53% of patients with stable low RA disease activity.

Overall, these data demonstrate that abrupt discontinuation of TNFi can be safely and effectively implemented in this patient population. Additionally, if a disease flare is going to occur after TNFi withdrawal, it will occur soon, and patients can effectively restart their therapy with restoration of low disease activity, on average, by 14 weeks.

APR Improves PsA Symptoms Out to Week 104

Written by Maria Vinall

Alvin F. Wells, MD, PhD, Rheumatology and Immunotherapy Center, Franklin, Wisconsin, USA, reported results from the Efficacy and Safety Study of Apremilast to Treat Active Psoriatic Arthritis (PsA) [PALACE4; NCT01307423]. Up to week 104, apremilast (APR) monotherapy produced clinically relevant improvements in the symptoms, physical function, and skin manifestations of PsA in patients who had not taken disease-modifying antirheumatic drugs (DMARDs).

PsA occurs in about 30% of patients with psoriasis and is prevalent in an estimated 0.3% to 1.0% of the general population [Gladman DD et al. *Ann Rheum Dis.* 2005]. The manifestations of PsA, including enthesitis, dactylitis, swollen and tender joints, and psoriasis, are associated with impaired physical function and health-related quality of life [Carneiro S et al. *J Rheumatol.* 2013; Sakkas LI et al. *Semin Arthritis Rheum.* 2013; Strand V et al. *Health Qual Life Outcomes.* 2013; Gladman DD et al. *Ann Rheum Dis.* 2005].

APR is an oral phosphodiesterase 4 inhibitor that regulates inflammatory mediators associated with the pathogenesis of PsA [Schafer PH et al. *Br J Pharmacol.* 2010]. PALACE4 was a phase 3, double-blind, randomized, placebo-controlled, parallel-group study designed to evaluate the long-term efficacy and safety of APR treatment compared with placebo over 104 weeks. The study consisted of 3 treatment phases with a planned overall study duration of up to 5 years.

To be eligible, patients were required to be DMARD-naïve adults with documented PsA with a duration ≥ 3 months and with ≥ 3 swollen joints and ≥ 3 tender joints. Patients with active tuberculosis or a history of incompletely treated tuberculosis, malignancy, or joint disease other than PsA were excluded. Participants were randomized (1:1:1) to receive placebo (n = 176), APR 20 mg BID (n = 175), or APR 30 mg BID (n = 176).

Efficacy assessments included the American College of Rheumatology 20%/50%/70% improvement response criteria (ACR20/50/70) and the Health Assessment Questionnaire Disability Index (HAQ-DI). Safety assessments included adverse events (AEs) and clinical laboratory parameters at scheduled visits during each treatment phase (weeks 0, 4, 16, and 24 during the placebo-controlled phase; weeks 28, 40, and 52 during the blinded active treatment phase; and weeks 65, 78, 91, and 104 during the long-term open-label phase). There were no significant differences in baseline

demographics and clinical characteristic among the groups.

At week 52, patients receiving APR 20 mg BID had ACR20/50/70 responses of 55.4%, 28.3%, and 12.0%, respectively. Patients receiving APR 30 mg BID had ACR20/50/70 responses of 58.0%, 29.8%, and 15.5%, respectively. The modified ACR20/50/70 responses were sustained through week 104.

Mean reductions from baseline in swollen tender joint count at week 104 for APR 20 mg and APR 30 mg were –8.7 and –9.5, respectively, and for tender joint count for APR 20 mg and APR 30 mg, –12.4 and –13.0, respectively. HAQ-DI scores improved for both doses of APR and at week 52 and week 104. The mean change from baseline to week 104 was –0.33 for APR 20 mg and –0.38 for APR 30 mg. The manifestations of PsA, including enthesitis, dactylitis, and psoriasis, were improved with both APR doses.

Most AEs were mild or moderate in severity in both APR doses and exposure periods. Diarrhea and nausea were the most often reported AEs. Discontinuations due to AEs were low. Marked laboratory abnormalities were similar in both APR and exposure periods, were generally infrequent, and returned to baseline with discontinued treatment. APR continued to demonstrate an acceptable safety profile and was generally well tolerated for up to week 104.

Triple Therapy More Cost-effective Than Biologic First in Patients Who Fail MTX

Written by Mary Beth Nierengarten

For patients with rheumatoid arthritis (RA) who fail methotrexate (MTX), using a biologic instead of triple therapy first is not a cost-effective use of health care resources due to the large additional costs for very small benefits.

Nick Bansback, PhD, University of British Columbia, Vancouver, British Columbia, Canada, presented the results of a randomized noninferiority trial that compared the cost-effectiveness of treating patients who fail MTX with a biologic first or adding triple therapy followed by a biologic.

The analysis was based on the Rheumatoid Arthritis: Comparison of Active Therapies in Patients With Active Disease Despite Methotrexate Therapy study [RACAT; O'Dell JR et al. *N Engl J Med*. 2013], a 48-week double-blind noninferiority trial that randomized 353 patients with active RA despite MTX therapy to either a triple regimen of disease-modifying antirheumatic drugs (MTX, sulfasalazine, and hydroxychloroquine) or etanercept (ETN) plus MTX. The trial showed that triple therapy was noninferior to ETN plus MTX in these patients.

In the current study, Bansback and colleagues first conducted a within-trial incremental cost-effectiveness ratio (ICER) analysis that considered all the incremental costs between the 2 strategies, including drugs, visits, tests, surgical procedures, other hospitalizations, and work absences, as well as the benefits in terms of quality-adjusted life years (QALYs). This ratio indicated the value for money of an intervention.

Based on the assumption that we do not pay >$100 000.00 for an additional QALY in the current health care system, the study considered any number below that of reasonable value.

The results of this analysis at 24 weeks showed that the cost of ETN plus MTX was substantially higher than triple therapy, largely because of the higher cost of ETN. The ICER at 24 weeks for ETN was $2.67 million per QALY, substantially higher than the $100 000.00 cutoff benchmark (Figure 1).

In a second analysis at 48 weeks, the ICER was $0.98 million per QALY for the ETN strategy, which was also found not to be very cost-effective.

Using a lifetime model based on a previous analysis to examine the cost-effectiveness of these 2 strategies over the longer term, the study also found that the strategy of using ETN was not cost-effective even when considering the potential impact of changes in radiographic progression [Finckh A et al. *Ann Intern Med.* 2009].

A sensitivity analysis provided data as well to provide confidence that using ETN first would not be cost-effective, said Dr Bansback. As shown in Figure 2, no lines cross the green line that would indicate good value with ETN as first therapy after MTX failure.

Interpreting the data, Dr Bansback noted that the use of biologics over the past 10 years has increased health care expenditures by tens of billions of dollars and that a considerable amount of money has been wasted by using biologics first instead of triple therapy. Biologics only appear to be cost-effective, he emphasized, after failure of triple therapy.

Figure 1. Within-Trial Analysis at 24 Weeks: ICER for Etanercept

$$\text{ICER} = 24\ \text{wk}\ \frac{\$12\ 002 - \$1225}{0.358 - 0.353} = \$2.67\ \text{M/QALY}$$

ICER, incremental cost-effectiveness ratio; M, million; QALY, quality-adjusted life year.

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