FirstWord℠
Medical Conference Round-up Report

The American College of Rheumatology/Association of Rheumatology Health Professionals (ACR/ARHP) Annual Meeting

Boston, Massachusetts, from November 14th – 19th, 2014
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Introduction

The American College of Rheumatology/Association of Rheumatology Health Professionals (ACR/ARHP) Annual Meeting

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Rheumatic diseases cover a broad range of over 100 conditions, from degenerative diseases, such as osteoarthritis, to those associated with inflammation and autoimmunity, including rheumatoid arthritis and lupus. The American College of Rheumatology/Association of Rheumatology Health Professionals (ACR/ARHP) Annual Meeting, held in Boston, Massachusetts from November 14 to 19, is one of the leading forums for highlighting the latest discoveries and research that is transforming rheumatic disease care.

The meeting was attended by more than 15,000 rheumatologists and rheumatology health professionals, and FirstWord’s journalists were on-hand to report the latest developments and thinking to its clients within hours of presentations and sessions ending. This report provides a round-up of essential information including data on the anti-IL-17A monoclonal antibody secukinumab in patients with psoriatic arthritis and a study of a novel DAGR drug in patients with rheumatoid arthritis.
Certolizumab Pegol Plus Methotrexate Effective for Early Rheumatoid Arthritis

By Brian Hoyle

Certolizumab pegol plus methotrexate is significantly more effective than methotrexate alone in inhibiting disease progression in patients with early rheumatoid arthritis (RA), according to a study.

The efficacy and safety of certolizumab pegol plus methotrexate, compared to methotrexate alone in methotrexate-naïve patients with early RA and poor prognostic factors have not been previously reported.

Tatsuya Atsumi, MD, Hokkaido University Graduate School of Medicine, Sapporo, Japan, and colleagues randomised 306 patients with early RA who had not been treated previously with methotrexate to receive at least 1 dose of certolizumab pegol plus methotrexate (n = 159) or placebo plus methotrexate (n = 157). The dose of methotrexate was ramped up to 16 mg by week 8 in those who could tolerate the dose.

The patients had experienced symptoms of RA for less than 1 year or up to 1 year. They fulfilled the 2010 American College of Rheumatology / European League Against Rheumatism (ACR / EULAR) criteria for rheumatoid arthritis.

The primary endpoint of the study was change from baseline in van der Heijde modified total Sharp score of radiographic-evident erosion and joint narrowing at week 52. Secondary endpoints were the change from baseline of the modified total Sharp score at week 24 and clinical remission rates at weeks 24 and 52.

The percentage of patients who displayed non-progression at week 52 was significantly higher in the certolizumab pegol plus methotrexate group versus the methotrexate monotherapy group (82.9% vs 70.7%; P = 0.011).

At 52 weeks, compared with baseline, greater improvements were seen among patients in the combination therapy group for DAS28 >5.1 (P < .001), modified total Sharp score (P = .002), patient self-assessment according to the HAQ-DI questionnaire (P = .004), and matrix metalloproteinase-3 (P < .001).

At week 52, ACR/EULAR-defined remission, in which active disease is nearly or completely absent, was evident in 45.3% of patients who received certolizumab pegol plus methotrexate, compared with 28.0% of those receiving only methotrexate (P = .002).

No new or unexpected safety signals were observed.
These data have prompted a global, multicentre, randomised, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of the certolizumab pegol plus methotrexate regimen in the treatment of adults with early active rheumatoid arthritis who have not received prior treatment with disease modifying anti-rheumatic drugs.

Those results are expected in 2016.

[Presentation title: The First, Multicenter, Double-Blind, Randomized, Parallel-Group Study of Certolizumab Pegol in Early Rheumatoid Arthritis Demonstrates Inhibition of Joint Damage Progression. Abstract 2472]

Chondroitin Sulfate Plus Glucosamine Comparable to Celecoxib for Knee Osteoarthritis Pain

By Brian Hoyle

Chondroitin sulfate plus glucosamine is comparable to celecoxib in reducing pain in patients with knee osteoarthritis and is a safe alternative for patients with cardiovascular or gastrointestinal conditions who have contraindications to celecoxib.

The findings were presented by Marc Hichberg, MD, University of Maryland School of Medicine, Baltimore, Maryland.

The Multicentre Osteoarthritis Intervention Trial With Sysadoa (MOVES) compared the efficacy and safety of a fixed-dose chondroitin sulfate plus glucosamine hydrochloride combination with celecoxib in patients with knee osteoarthritis and moderate-to-severe knee pain among 606 patients from 42 medical centres in France, Germany, Poland, and Spain.

Patients with knee osteoarthritis (Kellgren-Lawrence grade 2 or 3) and moderate-to-severe pain according to the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain score were randomised to an oral daily dose of chondroitin sulfate 400 mg plus glucosamine hydrochloride 500 mg or to celecoxib 200 mg for 6 months.

Patients with a history of cardiovascular or gastrointestinal disease were excluded.

The primary outcome was a decrease in the WOMAC pain score from baseline to 6 months.

The mean age of the patients at baseline was 62.7 years. Most (83.9%) were women. The mean WOMAC pain score was 371.3 ± 41.6. The majority of patients (62.6%) had Kellgren-Lawrence grade 2 osteoarthritic knee pain. The two groups were comparable at baseline.
Absolute WOMAC pain scale scores for the combination group and the celecoxib group at baseline were 372.0 and 370.6, respectively. The respective scores at 1 month (267.7 and 236.4), 2 months (231.0 and 206.0), and 4 months (209.9 and 183.5) significantly favoured celecoxib (P < .001, P = .008, and P = .007, respectively). However, the WOMAC scores at 6 months were comparable (185.8 and 184.7, respectively; P = .917).

The adjusted mean change (95% confidence interval [CI]) from baseline to 6 months in WOMAC pain was -185.7 (-200.3 to -171.1), representing a 50.1% decrease in patients receiving the chondroitin sulfate plus glucosamine hydrochloride combination, and -186.8 (-201.7 to -171.9), representing a 50.2% decrease, in the celecoxib group. The mean difference at 6 months met the non-inferiority margin (-1.11, 95% CI, -22.0 to -19.8).

At 6 months, WOMAC-rated stiffness decreased by 46.9% in the chondroitin sulfate plus glucosamine hydrochloride group and 49.2% in the celecoxib group (P = .434). WOMAC function score improved in 45.5% and 46.0% of patients, respectively (P = .530). Visual analogue scale (VAS) rated pain declined in 48.0% and 48.8% of patients, respectively (P = .924).

There were no significant differences in patient and physician global assessments of disease activity or response to therapy were evident.

Over 70% of patients in both groups fulfilled the Outcome Measures in Rheumatology- Osteoarthritis Research Society International (OMERACT-OARSI) criteria for treatment response at 120 days, with 6-month response rates of about 80% in both groups.

Joint swelling decreased by over 50% from baseline in both groups: 12.5% to 5.9% for the combination group, and from 14.0% to 4.5% for the celecoxib group.

Use of rescue medication was low and similar in both groups. The type and pattern of adverse events was also similar between the 2 groups.

[Presentation title: Combined Chondroitin Sulfate and Glucosamine Is Comparable to Celecoxib for Painful Knee Osteoarthritis. Results From a Multicenter, Randomized, Double-Blind, Phase IV Non-Inferiority Trial. Abstract 1679]
Baseline Sharp-van der Heijde Score Significantly Predicts Radiologic Progression of RA

By Nicola Parry

In patients with rheumatoid arthritis (RA), radiologic progression of disease is most significantly correlated with baseline radiographic damage, as measured by the Sharp-van der Heijde score (SHS), according to a study.

Numerous factors are associated with progressive radiographic damage, and data from clinical trials have suggested that choice of therapy can influence the course of disease, including the development of rapid radiographic progression (RRP; defined as ≥ 5 units change in SHS score per year).

With this in mind, Alan Erickson, MD, University of Nebraska Medical Center, Omaha, Nebraska, and colleagues set out to investigate the associations of treatment strategy and baseline factors with SHS progression. In order to accomplish this, they evaluated data from the 48-week, double-blind Rheumatoid Arthritis: Comparison of Active Therapies in Patients with Active Disease Despite Methotrexate Therapy (RACAT) trial.

In RACAT, 304 patients RA who had experienced inadequate methotrexate response were randomised to sulfasalazine and hydroxychloroquine or etanercept. After 24 weeks of treatment, those who failed to achieve a Disease Activity Score in 28 joints (DAS28) improvement of 1.2 were then switched to the other therapy.

Results showed that baseline SHS was the only factor that consistently predicted disease progression. SHS changes were defined as increases ≤0.5 or >0.5 units (U). Two expert readers determined SHS scores at baseline and 48 weeks, and the mean was used for each patient at each time point. Baseline SHS values differed significantly between the ≤0.5 U and >0.5 U categories of SHS change (15.3 vs 26.4; P = .002).

At week 48, only 4.3% of patients experienced ≥5 U increase in SHS, and 23% experienced increases >0.5 U that were evenly spread over the 4 treatment groups. About 60% of patients showed changes of -0.5, 0, or 0.5 units, and 17% demonstrated improvement (<-0.5 change).

Although there was a weak correlation with rheumatoid factor-positive status, the researchers determined this was not statistically significant.

"Other measures, including treatment strategy, were not predictive of radiographic progression," the researchers concluded.

[Presentation title: Predictors of Radiologic Disease Progression During the Rheumatoid Arthritis Comparison of Active Therapies Trial: Abstract 2139]
Methotrexate/Etanercept Combination More Effective Than Monotherapy in Recent-Onset Juvenile Idiopathic Arthritis

By Nicola Parry

In patients with recent-onset juvenile idiopathic arthritis (JIA), the initial combination of methotrexate and etanercept resulted in more clinical improvement than methotrexate or sulfasalazine alone, researchers said.

“JIA is a chronic disorder leading to functional disability and possibly damage due to prolonged inflammation,” stated lead investigator Petra C.E. Hissink Muller, MD, Leiden University Medical Center, Leiden, the Netherlands. Although recent clinical trials have shown that early aggressive treatment is important in JIA, many questions remain about the optimal treatment of these patients, she added.

Dr. Hissink Muller and colleagues designed a study to compare the effect of 3 disease-modifying antirheumatic drug (DMARD) strategies on time to inactive disease, time to flare after DMARD discontinuation, American College of Rheumatology (ACR) criteria for paediatric patients (ACR Pedi), functional ability, safety, and radiological damage.

The researchers shared the 3-month clinical outcome data from this ongoing BeSt for Kids trial in patients with JIA.

Ninety-five DMARD-naïve children (age range 2 to 16 years at enrollment) with recent-onset JIA were enrolled in the study and randomly, evenly assigned to receive sequential DMARD monotherapy (starting with sulfasalazine 50 mg/kg/day or methotrexate 10 mg/m2/week, based on physician’s preference), or 2 arms of combination therapy, with the first being methotrexate 10 mg/m2/week and 4 weeks of prednisone bridging at 0.5 mg/kg/day, tapered to nothing over 2 weeks, and the second being methotrexate 10 mg/m2/week and etanercept 0.8 mg/kg/week.

Primary endpoints were the time to inactive disease and time to flare.

Secondary endpoints included adjusted ACR Pedi scores, expressed as 30% (ACR Pedi 30), 50% (ACR Pedi 50) and 70% (ACR Pedi 70%) improvements from baseline.

Although there was no significant difference between treatment arms with respect to the percentage of patients with inactive disease at 3 months, Dr. Hissink Muller and colleagues found that significantly more children (P = .04) who initially received a combination of methotrexate and etanercept achieved ACR Pedi 70 (47%) response, compared with those treated with DMARD monotherapy or combination methotrexate and prednisone therapy (25% vs 19%).
Although more children who were treated with a combination of methotrexate and etanercept also achieved ACR 30 and 50 responses, the differences were not statistically significant.

Toxicity was similar in the 3 treatment arms (33% vs 46% vs 39%), consisting mainly of gastrointestinal events (7% vs 14% vs 9%), with few serious adverse events reported (2% vs 1% vs 0%).

This trial is ongoing, and additional data remain pending a follow-up of up to 2 years, Dr. Hissink Muller concluded.

[Presentation title: A Comparison of Three Treatment Strategies in Recent Onset DMARD Naïve Juvenile Idiopathic Arthritis: 3-Months Results of the BeSt for Kids-Study. Abstract L2]

Secukinumab Fast and Effective in Treating Psoriatic Arthritis

By Nicola Parry

The human anti–interleukin (IL)-17A monoclonal antibody secukinumab provides rapid-onset, significant improvements in the signs and symptoms of psoriatic arthritis, researchers stated.

“Despite the successes of the last decade in advancing the treatment of psoriatic arthritis, particularly with tumour necrosis factor (TNF) inhibitors, we have much still to do in terms of reaching high hurdle responses and improving quality of life,” said Iain B. McInnes, FRCP, PhD, University of Glasgow, Glasgow, United Kingdom. “New medicines and modes of action will form one part of that future progress,” he added.

According to the researchers, the phase 3 FUTURE 1 trial demonstrated efficacy of secukinumab in the treatment of both psoriasis with subcutaneous (SC) dosing, and psoriatic arthritis using an intravenous (IV) loading and SC maintenance-dose regimen.

The current study, FUTURE 2, was designed as the first double-blind, placebo-controlled phase 3 study to evaluate secukinumab SC loading and maintenance dosing in psoriatic arthritis. This included 397 adults with active psoriatic arthritis who were randomly assigned to receive SC secukinumab (300, 150, or 75 mg) or placebo at baseline, weeks 1, 2, 3, 4, and every 4 weeks thereafter.

The primary outcome was the American College of Rheumatology 20% (ACR20) response at Week 24.

At 24 weeks, the researchers found that ACR20 responses were significantly greater with secukinumab (300, 150, and 75 mg) compared with placebo (54.0%, 51.0%, and 29.3% vs 15.3%; P < 0.0001 for secukinumab 300 and 150 mg; P < 0.05 for 75 mg vs. PBO), and patients receiving secukinumab 300 and
150 mg experienced further improvements by week 3. These responses were also relatively rapid in the early phase of the study, added Dr. McInnes.

ACR50 responses also improved, particularly with the higher doses of secukinumab. A total of 35% of 300-mg recipients achieved ACR50 compared with 7.1% who received placebo (P < .01); and 35.0% of 150-mg recipients achieved ACR20 (P < .01). ACR70 response was also greater in the higher-dose recipients (300 mg: 20.0% vs 1.0%, P < .05; and 150 mg: 21.0% vs 1.0%, P < .05).

Additionally, both of the higher doses were efficacious in subgroups of patients who were anti-TNF-naïve and anti-TNF-inadequate responders (TNF-IR), although the 300-mg dose was associated with greater improvements in the anti-TNF-IR group.

The safety profile of secukinumab was also consistent with that previously reported in patients with psoriatic arthritis and psoriasis, with a similar incidence of adverse events (53.8% vs 58.2%), and serious AEs (3.3% vs 2.0%) at 16 weeks in the pooled secukinumab and placebo groups. There is no significant concern of neutropaenia in the study thus far, said Dr. McInnes.

“This is an exciting study that describes the beneficial effects of secukinumab in people with psoriatic arthritis,” Dr. McInnes concluded. “As such, it represents a potentially new approach, which, if further studies go as we hope, will expand our treatment options for this devastating disease in the future.”

[Presentation title: Secukinumab, a Human Anti-Interleukin-17A Monoclonal Antibody, Improves Active Psoriatic Arthritis: 24-Week Efficacy and Safety Data from a Phase 3 Randomized, Multicenter, Double-Blind, Placebo-Controlled Study Using Subcutaneous Dosing. Abstract L1]

**Novel Drug Shows Promise in Rheumatoid Arthritis**

*By Nancy A. Melville*

An investigational dissociated agonist of the glucocorticoid receptor (DAGR) was as effective as prednisone in patients with rheumatoid arthritis (RA), providing less undesirable effects, according to results of a phase 2 trial.

“The glucocorticoid receptor is expressed in almost every cell in the body, and it regulates genes that control development and metabolism, and the immune response,” explained lead author Vibeke Strand, MD, Stanford University School of Medicine, Stanford, California. “A dissociated agonist of the glucocorticoid receptor is a non-steroidal ligand of the glucocorticoid receptor (GR) with both partial agonist and antagonistic properties,” she added.
In preclinical and clinical trials, a DAGR called PF-04171327 demonstrated potent anti-inflammatory activity at doses that produce less undesirable effects on bone and glucose metabolism compared with prednisone.

Dr. Strand and colleagues conducted a phase 2 study in RA to determine what doses of a DAGR would provide sufficient efficacy at week 8 compared with placebo and prednisone 10 mg daily, providing effects on bone and glucose metabolism comparable with prednisone 5 mg daily.

The researchers evenly randomised 323 adults with active RA who were receiving methotrexate to receive once daily doses of the DAGR at 1, 5, 10, or 15 mg; prednisone at 5 or 10 mg; or placebo for 8 weeks, followed by a 4-week taper.

The primary endpoints at week 8 were American College of Rheumatology 20% (ACR20) response and evaluation of markers of bone formation (total procollagen type 1 N-terminal propeptide [P1NP]) and resorption (urine N-telopeptide/urine creatinine [uNTX/uCr]).

Secondary efficacy endpoints included evaluation of additional bone formation (osteocalcin) and resorption (serum C-telopeptide) biomarkers, fasting plasma glucose, and haemoglobin A1c (HbA1c).

The researchers found that the ACR20 response was met by the DAGR 10 mg and 15 mg doses compared with placebo, and that the DAGR 15 mg dose was non-inferior to prednisone 10 mg.

Compared with prednisone 5 mg, the DAGR doses of 1, 5, and 10 mg daily had similar effects on the bone formation marker P1NP. All doses of the DAGR were non-inferior to prednisone 5 mg with respect to osteocalcin.

Small negative changes in HbA1c were found at week 8 with all DAGR doses, and were comparable to those observed with prednisone 5 mg.

All DAGR doses were well tolerated and comparable to placebo and prednisone doses, with no safety signal detected.

Compared with prednisone 5 mg, DAGR doses of 1, 5, 10 and 15 mg daily had similar effects on bone-formation markers, with smaller decreases in HbA1c in these patients.

Dr. Strand emphasised that both the DAGR 10- and 15-mg daily doses were more effective than placebo, and as effective as prednisone 10 mg daily, in patients with RA, producing effects on bone and glucose metabolism that were comparable with prednisone 5 mg daily.
“Further evaluation of DAGR as an alternative to prednisone for treatment of autoimmune diseases is warranted, based on these data,” she concluded.

[Presentation title: A PHASE 2, Randomized, Double-Blind Comparison of the Efficacy and Safety of PF-04171327 (1, 5, 10, 15 mg QD) Vs 5 and 10 Mg Prednisone QD or Placebo in Subjects With Rheumatoid Arthritis (RA) over 8 Weeks Followed By a 4-Week Taper of Study Drug: Publication L6]

**Exercise Programmes Improve Outcomes in Subacromial Impingement Syndrome**

**By Nicola Parry**

In patients with subacromial impingement syndrome (SIS), exercise programmes led by physiotherapists lead to greater improvements in pain and function than providing a standard advice-and-exercise leaflet, researchers stated.

SIS is the most common cause of shoulder pain, explained lead investigator Edward Roddy, DM, Keele University, Keele, England, United Kingdom. Although SIS is frequently managed by exercise and corticosteroid injection, it is still not totally clear how to optimise the use of these therapies to best treat patients.

The Subacromial Impingement Syndrome and Pain: a Randomized Controlled Trial of Exercise and Injection (SUPPORT) trial was designed to evaluate the efficacy of exercise and corticosteroid injection in this patient population. Dr. Roddy and colleagues randomised 256 patients with SIS to receive ultrasound (US)-guided corticosteroid (methylprednisolone 40 mg, subacromial) injection and physiotherapist-led exercise; US-guided corticosteroid injection and an exercise leaflet; unguided corticosteroid injection and physiotherapist-led exercise; or unguided corticosteroid injection and an exercise leaflet. Each group comprised 64 subjects.

The researchers collected outcomes at 6 weeks, 6 months, and 12 months by postal questionnaire. The primary outcome -- the change in Shoulder Pain and Disability Index (SPADI) -- was compared between the injection groups at 6 weeks, and the exercise groups at 6 months.

The overall response rates for the primary outcome were 94% at 6 weeks, 88% at 6 months, and 80% at 12 months. According to the researchers, however, they observed a greater mean improvement in total Shoulder Pain and Disability Index score in patients who received physiotherapist-led exercise compared with an advice-and-exercise leaflet at 6 months (9.48; 95% confidence interval [CI], 3.30 to 15.65) and 12 months (6.64; 95% CI, 0.33 to 12.96).

Although SPADI total score improved in both injection groups, there were no significant differences between the groups at any of the time points.
“Our findings show that patients with SIS should have access to physiotherapist-led exercise programmes that are supervised, individualised, and progress over a number of treatment sessions, rather than be offered a standard advice-and-exercise leaflet,” Dr. Roddy concluded.

“Although ultrasound is very commonly used to guide the placement of steroid injections, this trial does not suggest any added benefit of using ultrasound-guidance over unguided injection,” he added.

[Presentation title: Clinical Effectiveness of Exercise and Corticosteroid Injection for Subacromial Impingement Syndrome: A Randomised Controlled Trial: Publication 1114]

**Oral Tadalafil Effective in the Treatment of Scleroderma-Related Interstitial Lung Disease**

**By Brian Hoyle**

Six months of oral tadalafil (20 mg) on alternate days appears to be an efficacious treatment for scleroderma-related interstitial lung disease, improving both patient- and physician-assessed condition, as well as lung function and breathing, researchers stated.

Previous trials have indicated the potential value of tadalafil in relieving the tightened connective tissue experienced by patients with scleroderma, explained lead investigator Vikas Agarwal, MD, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Dr. Agarwal and colleagues designed a small trial to assess this possibility. The team randomised 39 patients with scleroderma-related interstitial lung disease to a 6-month regimen of every-other day oral tadalafil 20 mg or matching placebo. The primary outcome measure was change in forced vital capacity (FVC) from baseline. Secondary outcomes were change in Diffusion Lung Capacity for Carbon Monoxide (DLCO), Total Lung Capacity (TLC), Health Assessment Questionnaire, Medical Outcomes Study 36-item Short-Form General Health Survey, and 6-minute walk distance at 6 months.

The completion rate for this trial was 77% (30/39), and those 30 completers were included in the analysis.

At 6 months, while not statistically significant, the change in FVC (% predicted) from baseline in the tadalafil group (49.18 ± 3.81 at baseline, 51.0 ± 4.06 at 6 months; difference 1.82 ± 2.08) exceeded that in the placebo group (57.46 ± 2.37 at baseline, 57.46 ± 3.05 at 6 months; difference 0 ± 2.41).

Of the secondary outcome measures, the only significant difference between the tadalafil and placebo groups was in the patient global assessment score, which was significantly improved in the tadalafil group (change from baseline: -26.70 ± 5.67 vs -12.69 ± 4.78; P < .05).
The tadalafil group displayed statistically nonsignificant (all P > .05) improvements relative to the placebo group in TLC (change from baseline: 2.8 ± 4.57 vs -2.71 ± 5.75), DLCO (change from baseline: -0.4 ± 2.24 vs 0.14 ± 6.97), visual analog scale (VAS) determined breathing score (change from baseline: -29.41 ± 8.03 vs -10.07 ± 6.31), and physician global assessment score (change from baseline: -26.70 ± 5.67 vs -12.69 ± 4.78). The 6-minute walk test results were comparable between the tadalafil group (47.06 ± 11.33 metres) and the placebo group (45 ± 16.93 metres). There was no significant difference in adverse events between the groups.

The findings from this small study should prompt a larger, multicentre study with the statistical power to conclusively determine the benefit of tadalafil in interstitial lung disease, the researchers concluded.

Scleroderma involves the hardening and tightening of connective tissue, potentially involving the lungs. In interstitial lung disease, the walls of the alveoli thicken due to inflammation and fibrosis, which is associated with high mortality.

[Presentation title: A Double Blind Randomized Control Trial of Oral Tadalafil in Interstitial Lung Disease of Scleroderma. Abstract 1679]

Secukinumab Fast and Effective in Treating Ankylosing Spondylitis, Regardless of Prior TNF-Inhibitor Use

By Nicola Parry

The human anti–interleukin (IL)-17A monoclonal antibody, secukinumab, provides rapid-onset and clinically significant improvements in the signs and symptoms of active ankylosing spondylitis (AS), regardless of prior use of anti-tumour necrosis factor (TNF) agents, researchers stated.

The results of a recent phase 2, proof-of-concept study demonstrated the efficacy of secukinumab in the treatment of active AS by week 6. Building on those data, the 16 Week Efficacy and 2 Year Long Term Safety and Efficacy of Secukinumab in Patients with Ankylosing Spondylitis (MEASURE 1) phase 3 trial was designed to evaluate intravenous (IV) loading and subcutaneous (SC) maintenance dosing of secukinumab in AS.

“This is the first non-TNF inhibitor biologic drug showing efficacy in phase 3 [trials] in AS, and the efficacy is seen both in TNF inhibitor-naive and TNF-inhibitor incomplete-responder patients,” stated lead author Dominique L. Baeten, MD, PhD, University of Amsterdam, Amsterdam, the Netherlands.

Dr. Baeten and colleagues randomised 371 adults with AS to either intravenous (IV) secukinumab (10 mg/kg) or placebo at baseline and weeks 2 and 4, followed by subcutaneous (SC) secukinumab (75 mg or 150 mg) or placebo every 4 weeks.
Secukinumab met the primary endpoint, Assessment of SpondyloArthritis International Society Criteria 20% (ASAS20) response at 16 weeks, with significantly greater responses achieved in the secukinumab 75 mg and 150 mg groups compared with placebo (59.7% vs 60.8% vs 28.7%; P < .01 for both secukinumab doses).

Dr. Baeten indicated that ASAS20 response rates were also maintained from week 16 through week 52 (71.3% vs 76.7% vs 28.7%; P < .01 for both secukinumab doses). Additionally, both doses of secukinumab were efficacious in subgroups of patients who were anti-TNF-naïve and anti-TNF inadequate responders (TNF-IR).

ASAS20 response rates were 60.0%, 66.3%, and 32.6% in anti-TNF-naïve subjects (P < .001 for both secukinumab doses), and 58.8%, 45.5%, and 18.2% in anti-TNF-IR subjects (P < .05 for both secukinumab doses).

The trial met all secondary endpoints at both doses of secukinumab, with responses sustained through week 52. Dr. Baeten noted the rapid onset of action of secukinumab, emphasising that significant improvements were demonstrated in ASAS20 as early as week 1.

Secukinumab was generally well tolerated over the 52-week study duration, with no unexpected safety signals. By week 52, adverse events (AEs) had occurred in 76.5% and 85.1%, and serious AEs in 10.1% and 9.4% of patients in the secukinumab 75 mg and 150 mg groups, respectively.

“Follow up research will now have to tell us how secukinumab should be used and positioned in comparison with TNF inhibitors,” Dr. Baeten concluded. “Obviously, this will also depend on the potential impact of secukinumab on new bone formation, an issue which is currently under investigation.”

Funding for this study was provided by Novartis AG, Basel, Switzerland.

[Presentation title: Secukinumab, a Monoclonal Antibody to Interleukin-17A, Significantly Improves Signs and Symptoms of Active Ankylosing Spondylitis: Results of a 52-Week Phase 3 Randomized Placebo-Controlled Trial with Intravenous Loading and Subcutaneous Maintenance Dosing. Abstract 819]

Apremilast Benefical for Psoriatic Arthritis, With No Dose Adjustment Needed for Body Weight or Body Mass Index

By Nancy A. Melville

Oral apremilast is efficacious in the treatment of psoriatic arthritis, with no adjustment of dose needed to account for body weight or body mass index (BMI), according to pooled results from three, phase 3 trials.
Lead investigator Georg Schett, MD, University of Erlangen-Nuremberg, Erlangen, Germany and colleagues analysed data from the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) 1, 2, and 3 trials to assess the effect of baseline weight and BMI on clinical response to apremilast over 24 weeks.

The researchers randomised subjects (1:1:1) to receive twice-daily oral preparations of placebo (n = 496), apremilast 20 mg (n = 500), or apremilast 30 mg (n = 497). Subjects were stratified according to whether or not they had had prior treatment with disease-modifying antirheumatic drugs. Those whose joints had not responded to treatment by week 16 were re-randomised (1:1) to either of the apremilast doses if they were receiving placebo, or were continued on their current apremilast dose. At week 24, any patients still receiving placebo were re-randomised to 1 of the 2 doses of apremilast.

The 1,493 patients in the 3 arms were comparable according to demographics, disease characteristics, and prior/concurrent therapy. The mean weight and BMI across the arms was 85.7 ± 20.6 kg and 29.9 ± 6.5 kg/m², respectively.

The primary endpoint was met in the 3 PALACE trials. A significantly greater proportion of patients receiving 20 mg or 30 mg apremilast responded to treatment as defined using the criteria of the modified American College of Rheumatology 20 scoring system, compared with those receiving placebo.

A heightened response for apremilast was noted in all weight categories (<70, 70 to <85, 85 to <100, and ≥100 kg) and BMI categories (<25, 25 to <30, 30 to <35, 35 to <40, and ≥40 kg/m²).

Both doses of apremilast were effective, with the higher dose producing the most pronounced benefit. Significant improvements in the Health Assessment Questionnaire-Disability Index (HAQ-DI) score versus placebo were evident at week 16 for the 30-mg dose of apremilast. The lower dose of apremilast also produced improved HAQ-DI scores compared with placebo. Dose-dependent benefits of apremilast noted at week 16 were generally maintained at week 24.

The researchers concluded that the observation of comparable results in patients of differing body weight and BMI indicate that the dose of apremilast does not need to be adjusted to account for baseline body weight or BMI.

[Presentation title: Apremilast, an Oral Phosphodiesterase 4 Inhibitor, and the Impact of Baseline Weight and BMI on ACR20 and HAQ-DI Response: Pooled Results from 3 Phase 3, Randomized, Controlled Trials. Abstract 1561]
Oral Salmon Calcitonin Shows No Clinical Benefit in Symptomatic Knee Osteoarthritis

By Nicola Parry

A new tablet form of salmon calcitonin (sCT) failed to produce reproducible clinical benefits in phase 3 trials in patients with symptomatic knee osteoarthritis (OA), researchers said.

According to Morten Karsdal, PhD, Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, in earlier preclinical and clinical studies, sCT has been shown to reduce the amount of bone and cartilage damage that occurs in OA.

With this in mind, Dr. Karsdal and colleagues conducted 2 randomised, double-blind, multicentre, placebo-controlled phase 3 studies to investigate its efficacy and safety in the treatment of patients with OA of the knee. For these trials, sCT was produced in tablet form with a carrier to improve its gastrointestinal absorption -- as such, it represented the first protein developed for oral administration and evaluation in phase 3 studies.

The 2 trials involved a total of 2,206 patients with OA of the knee who were experiencing pain and structural damage due to their condition. Patients were randomised to receive either oral sCT 0.8 mg twice daily or placebo.

The primary outcomes were changes in joint space width (JSW) and changes in pain and knee function.

At 24 months, the researchers found no significant difference in JSW in either of the 2 studies, as measured by x-ray. They did find that oral sCT significantly improved Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores (P < .0001), and reduced bone and joint damage as measured by biomarkers (P = .0003) in one trial. However, Dr. Karsdal noted that this beneficial effect was not repeated in the second study.

“The lessons learned from these phase 3 clinical studies may be used to design better studies for OA, by selecting subpopulations that may better match the mode of action of different interventions,” said Dr. Karsdal. “We have designed novel and more potent molecules that we currently are developing for obesity, type 2 diabetes, and osteoarthritis.”

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