**LILLY’S IXEKIZUMAB FOUND TO BE EFFECTIVE IN PHASE III PSORIASIS STUDIES**

Eli Lilly and Company’s ixekizumab was found to be statistically superior to etanercept and placebo on all skin clearance measures in pivotal, Phase III UNCOVER studies in moderate-to-severe plaque psoriasis.

In the three studies, patients were assigned to receive placebo or ixekizumab (80mg every two or four weeks) for 12 weeks, following a 160mg starting dose. In the two active comparator studies (UNCOVER-2 and 3), patients could be assigned to receive etanercept 50mg twice weekly for 12 weeks. In UNCOVER-1, responders to treatment were assigned to continue treatment on placebo or ixekizumab (80mg every four or 12 weeks) for up to 60 weeks. Patients treated with both dosing regimens of ixekizumab had significantly greater levels of skin clearance compared to placebo and etanercept at the 12-week endpoint. Skin clearance was measured by the Psoriasis Area and Severity Index (PASI) and the Static Physician Global Assessment (sPGA).

For patients treated with ixekizumab every four weeks or every two weeks, 78-90 percent of patients achieved at least PASI 75 at 12 weeks, and 31-41 percent of these patients achieved PASI 100. For comparison, five to seven percent of patients treated with etanercept in the UNCOVER-2 and three studies achieved PASI 100.

Statistically significant improvements for patients treated with ixekizumab were observed as early as the first week when compared to either placebo or etanercept, and continued through week 12. In the UNCOVER-1 study, high levels of response were maintained through 60 weeks of treatment.

Adverse events were comparable for patients receiving ixekizumab in the 12-week, randomized control portion across all three studies. The overall rates and severities of adverse events observed were comparable to those for etanercept in the two active comparator trials. The most frequently reported events were nasopharyngitis and injection site reaction. Most patients who experienced an injection site reaction continued treatment with ixekizumab.

Lilly says it intends to submit ixekizumab to regulatory authorities in the first half of 2015.

**UPDATED APPROACHES TO PSORIASIS AND PSORIATIC DISEASE**

Steven Cohen, MD, MPH sat down with DermTube Journal Club host Joshua Zeichner, MD to discuss emerging data on biologics and address their use to manage psoriasis and psoriatic arthritis. He offered strategies for long-term safe and effective use and a look at therapeutics in the pipeline and discussed why dermatologists can and should be involved in treating psoriatic arthritis. Since most dermatologists are prescribing systemic therapies and are well trained in doing so, there is no reason dermatologists can’t treat psoriatic arthritis, he says.

Watch the full episode at DermTube.com. Search key: psoriatic disease.

**STUDY EVALUATES EFFICACY OF CALCITRIOL OINTMENT FOR NAIL PSORIASIS**

A single-center, double-blind study enrolled 10 adult male and female subjects with psoriasis of the fingernails and/or toenails to demonstrate the efficacy and safety of calcitriol ointment 3mcg/g (Vectical) compared to betamethasone dipropionate ointment in the treatment of nail psoriasis.

Patients treated with betamethasone dipropionate ointment or calcitriol ointment demonstrated a similar reduction of nail thickness of the selected target nail. The difference between the two groups was not statistically significant (P=0.42).

The study concluded that calcitriol ointment for nail psoriasis should be further investigated in a subsequent larger trial.

By Pnina Fishman, PhD

Plaque psoriasis, the most common of the five varieties of psoriasis and affecting two to three percent of the population, typically appears in red patches covered in dead skin or scale that looks like a white, silvery build up. These patches tend to be itchy and often bleed. As a result, dermatology has traditionally focused on topical treatments such as corticosteroids or salicylic acid and coal tar-based substances—an improvement over the recommendation of Hippocrates, which was arsenic. We have had enough success with these treatments that they remain the first line of defense in dealing with plaque psoriasis. Alternatively or in addition, phototherapy has shown some positive effect on the condition as well.

However, the last decade or so has demonstrated that this disease is much more systemic and that systemic treatments show great promise in treating plaque psoriasis, especially when topical treatment and phototherapies have failed. These include acitretin (Soriatane), cyclosporine, and methotrexate, as well as off-label systemic treatments. Each has shown some efficacy, but each also has side effects and may not be tolerated well by certain individuals.

A NOVEL ORAL ANTI-INFLAMMATORY TREATMENT

CF101 (Can-Fite BioPharma) is an oral anti-inflammatory agent that binds with high affinity and selectivity to the A3 adenosine receptor (A3AR), a G protein-associated cell surface receptor. The company’s technology platform is based on the finding that A3AR is highly expressed in inflammatory and cancer cells whereas low expression is found in normal body cells. High A3AR expression levels are also found in peripheral blood mononuclear cells (PBMCs) of patients with inflammatory and cancer diseases, including psoriasis, rheumatoid arthritis, Crohn’s Disease, and liver cancer, reflecting A3AR expression in remote sites.

Targeting the receptor with synthetic and highly selective A3AR agonists induces anti-inflammatory and anti-cancer effects. In addition, the receptor is suggested as a biological marker based on human clinical data showing that high receptor expression at baseline predicts patients’ response to drug treatment.

A Phase II clinical study to assess the safety and efficacy of CF101 for the treatment of patients with moderate to severe plaque psoriasis was conducted after we already had data from Phase II studies conducted in patients with rheumatoid arthritis showing that CF101 is very safe and has a marked anti-inflammatory effect. This first psoriasis study was a Phase II, multicenter, randomized, double-blind, dose-ranging, placebo-controlled study. Eligible patients were assigned to one of three sequential dosing cohorts with planned sample sizes of approximately 15 patients each. A total of 84 patients with moderate to severe plaque psoriasis were screened. Patients who met the inclusion criteria (n = 75) were randomized to placebo (n = 19), CF101 1mg q12 hours (n = 25), CF101 2mg q12 hours (n = 17) or CF101 4mg q 12 hours (n = 15). Patients were permitted to use emollients throughout the study period. Most patients completed the study (n = 64, 84.2%)

The study end points were: change from baseline (CFB) in the Psoriasis Area Severity Index (PASI) Scores; proportion of patients achieving 50 percent and 75 percent improvement in PASI scores (PASI 50 and PASI 75, respectively); and static Physicians’ Global Assessment (PGA (graded on a 0–5 scale with 0 to 1 representing no clinical signs and 5 representing more severe cases).

Study data demonstrated that CF101 in all dosages was found to be safe and well tolerated with a safety profile similar to that seen in the placebo treated group. Efficacy was found in the patients treated with the 2mg group. Analysis of mean change from baseline in PASI score at Week 12 revealed a statistically significant difference between the 2mg CF101-treated group and the placebo group (p <0.001 vs. baseline and p = 0.031 vs. placebo). Furthermore, a progressive improvement in the mean change from baseline in the PASI score throughout the study period was observed. In addition, 35.3 percent (6 out of 17) of the patients achieved PASI ≥50 response. Among this group, one showed improvement of PASI 73 and one reached PASI 90. In this group 23.5 percent achieved a PGA score of 0 or 1, in comparison with 0 percent in the placebo group (p <0.05). The percentage of patients presenting only slight or no clinical signs (PGA score 0-1) increased throughout the study period in the 2mg CF101-treated group.

Based on these positive Phase II results, a Phase II/III study was initiated. The Phase II/III study is a randomized, double-blind, placebo-controlled, dose-finding study of the efficacy and safety of daily CF101 administered orally in patients with moderate to severe plaque psoriasis in 300 patients. The first study cohort was comprised of three arms with planned sample sizes of approximately 100 patients each. A total of 300 patients with moderate to severe plaque psoriasis were screened. Patients who met the inclusion criteria (n = 275) were randomized to placebo (n = 75), CF101 1mg q12 hours (n = 75), CF101 2mg q12 hours (n = 75) or CF101 4mg q 12 hours (n = 70). Patients were permitted to use emollients throughout the study period. Most patients completed the study (n = 230, 83.5%)

The study end points were: change from baseline (CFB) in the PASI score; proportion of patients achieving 50 percent and 75 percent improvement in PASI scores (PASI 50 and PASI 75, respectively); and static Physicians’ Global Assessment (PGA (graded on a 0–5 scale with 0 to 1 representing no clinical signs and 5 representing more severe cases).

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Physicians’ Global Assessment (PGA (graded on a 0–5 scale with 0 to 1 representing no clinical signs and 5 representing more severe cases).
and the PGA score as well as various safety parameters. Enrollment in this study, which is being conducted in 17 clinical centers in the US, Israel, and Europe, has been finalized. Top line results from the trial are expected in the first quarter of 2015.

This Phase II/III study entailed an interim safety and efficacy analysis of the first 103 patients who completed 24 weeks of treatment in the trial. The positive clinical effects of CF101 at the 2mg dose relative to placebo were observed through PASI and PGA scores, with the responses accumulating steadily over the 24-week treatment period. To allow the trial to meet its full objectives, the study protocol has been amended to enroll patients for the 2mg dose and placebo administration for an extended study period of 32 weeks. The placebo period was extended to 16 weeks. Due to the linear effect of the drug, it is assumed patients will benefit from this extension. Patients who took the placebo 12 weeks and then switched to active drug showed the same results and benefits from taking the drug as patients who were taking the drug from the beginning of the study. Therefore the longer time of 16 weeks on placebo will not harm patients and it will give a better understanding of the drug in the end of the study.

CF101 offers a novel therapeutic option in treating plaque psoriasis because of its anti-inflammatory effect, its well-defined mechanism of action, and its excellent safety profile. Moreover, because CF101 has shown utility in other treatments, further investigation of its uses for other indications makes sound scientific sense. CF101 is also currently being developed for the treatment of rheumatoid arthritis (Phase IIb) and ophthalmic indications including glaucoma (Phase II) and uveitis by OphthaliX, a subsidiary of Can-Fite.

Prof. Pnina Fishman is the scientific founder of Can-Fite Biopharma Ltd. and was previously a professor of Life Sciences and headed the Laboratory of Clinical and Tumor Immunology at the Felsenstein Medical Research Institute, Rabin Medical Center. Prof. Fishman is an accomplished scientist and has authored or co-authored more than 150 publications and presented the findings of her research at many major scientific meetings. Her scientific work was the foundation on which Can-Fite was built. This scientific work has gained recognition as one of the leading approaches for next generation therapies for cancer and other diseases.

EXPERTS CALL FOR ACTION ON PSA

A panel of rheumatologists, dermatologists, and patient representatives from Europe and North America this summer published recommendations to address gaps in the diagnosis and treatment of Psoriatic Arthritis (PsA). Writing in Arthritis Care and Research, the 16 participants in the 2013 Psoriatic Arthritis Forum outlined three priority actions:

- Improve the burden of PsA by raising awareness, educating physicians and patients, and improving communication.
- Increase screening, diagnosis, and referrals of appropriate patients by developing and validating a screening tool for dermatologists and primary care physicians.
- Develop and validate an updated PsA treatment algorithm by defining treatment response and indicators for treatment change (including defining success from the perspective of the patient, physician, and regulatory agencies).

The full consensus statement is available at: http://onlinelibrary.wiley.com/doi/10.1002/acr.22404/abstract

OTEZLA MONOTHERAPY SHOWS LONG-TERM CLINICAL BENEFITS

Celgene International Sarl, a wholly-owned subsidiary of Celgene Corporation, announced results from a long-term (52-week) phase III trial of Otezla, its selective inhibitor of phosphodiesterase 4 (PDE4), in psoriatic arthritis patients who have not had prior treatment with systemic or biologic disease-modifying antirheumatic drugs (DMARDs).

Results demonstrated that treatment with Otezla monotherapy in patients with pre-existing enthesitis or dactylitis resulted in long-term improvements. Results were sustained over 52 weeks in patients initially randomized to Otezla monotherapy and completing 52 weeks of the study. At week 52, median Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) decreased by 75 percent and 45.9 percent of patients receiving Otezla 30mg BID achieved a score of 0, indicating no pain at any of the enthesitis sites. Otezla 30mg BID also resulted in a median 100 percent decrease in dactylitis count—68.8 percent achieved a dactylitis count of 0, indicating no signs of dactylitis.

In patients treated with Otezla monotherapy through 52 weeks, clinically meaningful improvements were seen at week 16 in the Health Assessment Questionnaire-Disability Index (HAQ-DI), and sustained for up to 52 weeks. HAQ-DI measures the difficulty patients have performing activities of daily life.

Long-term safety findings from PALACE 4 identified no new safety findings compared with the previously reported 24-week safety results. Otezla is FDA approved for the treatment of adults with active psoriatic arthritis.

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