Infliximab Benefits Lasting in Plaque Psoriasis

Visible psoriasis was absent in 26% of patients; 47% had no significant impact on social life or activities.

BY NANCY WALSH
New York Bureau

GLASGOW, SCOTLAND — In the first phase III trial evaluating infliximab for plaque psoriasis, substantial improvements were achieved by week 10 and sustained through week 50 in the majority of patients, Kristian Reich, M.D., reported at the annual meeting of the British Association of Dermatologists.

The 281 patients who were randomized to receive either placebo or infusions of infliximab, 5 mg/kg at week 0, 2, and 6 and every 8 weeks thereafter all had severe, recalcitrant disease. Most patients had approximately 30% skin surface involvement, one-third had concomitant arthritis, and the median psoriasis activity and severity index (PASI) score was 20, said Dr. Reich of Georg-August-University, Göttingen, Germany.

At week 10, 80% of patients receiving infliximab had achieved a PASI 75 score, indicating a 75% improvement in symptoms, and 57% had achieved a PASI 90 score. In comparison, only 2.6% and 1.3% of those in the placebo group had achieved PASI 75 and 90 scores, he said.

Moreover, 26% had a PASI 100, meaning there were no visible remaining signs of psoriasis, and 47% had a score of 0 on the Dermatology Life Quality Index, indicating that the disease was having no significant impact on social life or activities, he said.

At week 24, which was the conclusion of the placebo-controlled phase of the trial, 82% of patients had a PASI 75 response, and 58% had a PASI 90 response, compared with 3.9% and 1.3% of placebo-treated patients, respectively.

All patients subsequently entered the open phase of the trial. At week 50, intent-to-treat analysis showed that 61% of patients had a PASI 75 response, and a per-protocol analysis found that 71% maintained this level of response, he said.

Infliximab-treated patients also had significant improvements in nail psoriasis and in quality of life parameters at weeks 10 and 24.

"With [tumor necrosis factor] antagonists, of course, we have to take a close look at the safety profile," Dr. Reich said. During the blinded phase of the trial, 6% and 3% of patients in the infliximab and placebo groups, respectively, experienced serious adverse events. These were primarily infections or infusion reactions, he said.

Analysis of the 1-year safety data has identified four serious infusion reactions, with angioedema, hypertension, and dizziness. There have been eight serious infections, four of which were abscesses, three were infections in the rectal area, and one was in the throat. There also have been three cases of lupuslike syndrome, two of which were serious, but no cases of congestive heart failure, tuberculosis, or demyelinating disorders.

Six malignancies have occurred, four squamous cell carcinomas, and two basal cell carcinomas. "With the skin cancers, it's hard to say if these were really related to infliximab. It could well be that the clearance of the psoriasis lesions allowed detection of the skin cancers, but this is an issue we have to follow closely," he said.

"I think we can say that this is one of the most effective drugs we have in psoriasis," he said, noting that the onset of effect is rapid, usually occurring between weeks 2 and 4 of treatment.

The study was funded by Centocor. ■

Development Pipeline Filled With Oral Psoriasis Therapies

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — The future of psoriasis therapy lies in oral therapies now in development, Neil J. Korman, M.D., reported at the 11th International Psoriasis Symposium sponsored by the Skin Disease Education Foundation.

"Biologics have made an enormous difference in people's lives, but if you ask a patient if they want a shot or a pill, we all know the answer to that question," Dr. Korman said.

The new drugs in development fall into two categories: drugs that target interleukin-12 and interleukin-23, and orally available small-molecule therapies.

In humans, IL-12 mRNA has been detected in psoriatic plaques but not in normal skin. Immunoreactivity for IL-12 is also increased in psoriatic plaques.

Investigators at Centocor have developed a fully human monoclonal IL-12 antibody, CNTO 1275, that demonstrated "a low placebo response and a very beautiful dose-response curve" in an ongoing phase II trial, said Dr. Korman of Case Western Reserve University, Cleveland.

A total of 252 patients were treated with a single dose of 50 mg or 100 mg, or a weekly dosage of 50 mg or 100 mg for 4 weeks. The primary end point of a 75% or greater improvement in the Psoriasis Area and Severity Index (PASI 75) at week 12 was achieved by 52%, 59%, 67%, and 81% of patients in the four treatment groups, respectively. In contrast, only 1.6% of the 67 placebo-treated patients achieved a PASI 75.

At week 20, there was no significant difference in safety data between any of the groups, he said.

Two phase II psoriasis studies are now underway to evaluate STA-5326, an orally available small molecule that inhibits production of IL-12 and IL-23. The molecule was discovered and is being developed by Synta Pharmaceuticals.

An oral formulation of pimecrolimus has been developed by Novartis and studied in 143 patients with moderate to severe chronic plaque psoriasis in a randomized, double-blind phase II trial.

At week 13, the median change in PASI scores from baseline was about 85% in patients treated with 30 mg twice daily for 12 weeks.

One safety finding is that patients reported a warm sensation when taking oral pimecrolimus and increased GI disorders, including diarrhea and nausea, which appear to be dose dependent, he said.

In the same category is ISA 247, a novel calcineurin inhibitor developed by Isotechnika, which is structurally similar to cyclosporine and is three times more potent than cyclosporine in vitro. In a phase II study, about 74% of patients given 0.75 mg/kg twice daily for 12 weeks achieved a PASI 75 response. The incidence of hypertension was lower than in previously reported trials of cyclosporine.

Early data from an ongoing phase III study in Canada showed that only 4.4% of 453 patients treated with ISA 247 had more than a 30% increase in creatinine. This compares very favorably with creatinine elevations reported with cyclosporine, suggesting that ISA 247 is safer than cyclosporine, he said.

Finally, Biogen Idec Inc. has developed BG-12, a more efficacious and tolerable oral formulation of fumaric acid esters that will be entering phase III trials in the United States. Fumaric acid esters have been used successfully for decades in Germany to treat psoriasis, but GI side effects have limited their use.

Dr. Korman has received funding from Centocor, Novartis, and Synta.

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Fumaric Acid Esters Appear to Help Some Patients With Severe Psoriasis

BY NANCY WALSH
New York Bureau

GLASGOW, SCOTLAND — A proprietary formulation of fumaric acid esters has proved, during decades of use in Germany, to be a useful option for some patients with severe, recalcitrant psoriasis.

Although the therapy is less than perfect—with gastrointestinal side effects, slow onset of effect, and a 10% incidence of lymphocytopenia—it can be very effective in some patients, Catherine Smith, M.D., said at the annual meeting of the British Association of Dermatologists.

Since 2002, Dr. Smith and her colleagues at the St. John's Institute of Dermatology, London, have enrolled 62 patients with severe psoriasis that did not respond to standard therapies into an open study of Fumaderm, the German formulation of fumaric acid esters.

For this group of patients, treatment duration ranged from 4 weeks to 3 years, and 24 patients discontinued treatment, generally because of lack of efficacy. Although results at 16 weeks' follow-up for the remaining patients have been mixed, with 38% showing no improvement or worsening, a small subset (8%) had substantial improvement. "Importantly, these patients with very severe disease had a greater than 50% improvement compared to baseline," Dr. Smith said.

It generally takes 4-6 weeks before clinical effects are seen, and many patients have difficulty tolerating the drug. Gastrointestinal side effects, most commonly diarrhea, are seen in more than two-thirds. The reason for these gastrointestinal disturbances is not clear but may be related to the current formulation, which is a mixture of several different fumaric acid esters and is licensed only in Germany, Dr. Smith said. A new microtablet formulation that consists solely of dimethyl fumarate has now been through phase II studies and is expected to be licensed in the United Kingdom, she said. This formulation, currently known as BG-12, is said to be associated with fewer adverse effects.

The other most common side effect of fumarates is flushing or redness, described by some patients as tingling or skin pain. Lymphocytopenia is also fairly common but resolves on cessation of treatment. Eosinophilia is seen in 50% of patients between weeks 4 and 8 of treatment, but this has not been associated with any clinical allergic responses.

Case reports of renal failure were published during the early 1980s, but these incidents were in patients on very high dosages of the drug, and no subsequent cases have been reported, Dr. Smith said.

No notable long-term toxicities have been seen. Unlike with other systemic therapies for psoriasis, there has been no association with malignancy, she said.

While Fumaderm is more costly than some older therapies, its price tag is half that of infliximab.

Fumaric acid esters were first used in 1959 by German chemist Walter Schweckendiek, who undertook an "n of one" study on himself because his severe psoriasis had not responded to the available therapies. At the time, it was thought that psoriasis resulted from a defect in metabolism. He postulated that because fumaric acid is involved in the tricarboxylic acid cycle and is therefore fundamental to cellular respiration, exogenous administration of the drug would be beneficial. He reported that his skin began to improve within 12 hours and cleared completely in 10 days (Med. Monatschr. 1959;13:103-4).

"As a consequence, use of fumaric acid esters mushroomed in Germany, and today accounts for 66% of prescriptions for severe psoriasis in that country," Dr. Smith said. ■