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 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 in this 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. At the time, it was only known as BG-12, is said to be associated with malignancy.

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 with severe 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 1-year control 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 II trial. At week 52, the open-treatment analysis showed 61% of patients had a PASI 75 response, and a per-protocol analysis found that 71% maintained that level of response. Infliximab-treated patients also had significant improvements in nail psoriasis and in quality of life parameters at weeks 10 and 24.

"We have actually found a number of serious control antago-

nists, 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, infusions reactions, he said.

Analysis of the 1-year treatment trial 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 patient died. There had also been three cases of lupuslike syndrome, two of which were serious, but no cases of congestive heart failure, tuberculosis, or dermatitis.

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.

**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 90% improvement compared to baseline," Dr. Smith said.

It generally takes 4-6 weeks for 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 malignancy.

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 with severe 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.

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All patients subsequently entered the open phase II trial. At week 52, the open-treatment analysis showed 61% of patients had a PASI 75 response, and a per-protocol analysis found that 71% maintained that level of response. 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, infusions reactions, he said.

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**Infliximab Benefits Lasting in Plaque Psoriasis**

**BY NANCY WALSH**
New York Bureau

**Glasgow, Scotland — In the first phase II 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, 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 1-year control 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 II trial. At week 52, the open-treatment analysis showed 61% of patients had a PASI 75 response, and a per-protocol analysis found that 71% maintained that level of response. Infliximab-treated patients also had significant improvements in nail psoriasis and in quality of life parameters at weeks 10 and 24.

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