Biologic's Benefits for Psoriasis Outweigh Risks

BY BRUCE JANCIN

BUDAPEST, HUNGARY — More than 100 psoriasis patients treated with adalimumab, etanercept, or infliximab experienced marked clinical improvement for every patient who developed a serious adverse event, according to a risk-benefit analysis of the major randomized trials of the tumor necrosis factor antagonists.

In the resultant rank ordering of TNF blockers in terms of efficacy, infliximab came out on top. The number of patients with moderate to severe chronic plaque psoriasis who needed to be treated (NNT) with infliximab instead of placebo in order for one additional patient to achieve at least a 75% reduction in their Psoriasis Area and Severity Index (PASI 75) score was 1.4, Dr. Stephen J. Rozzo said at the annual meeting of the European Society for Dermatological Research.

The NNT for a PASI 75 with adalimumab at 40 mg every other week was 1.6. Etanercept was least efficacious, with a NNT of 2.3 when dosed at 50 mg twice weekly and 3.2 with 50 mg once weekly. Infliximab was dosed at 5 mg/kg at weeks 0, 2, and 6, and then every 8 weeks.

Viewing the efficacy data from the trials and their open-label extensions from another angle, 74% of infliximab-treated patients achieved PASI 75, as did 64% on adalimumab, 44% on twice-weekly etanercept, and 31% on once-weekly etanercept, according to Dr. Rozzo of Abbott Laboratories in Abbott Park, Ill.

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The safety analysis was more complex. Each biologic agent had its own side effect profile. No agent had a consistently better safety profile, and there was a good deal of overlap in terms of adverse event rates.

As a generalization, however, the numbers needed to harm (NNH) were more than 100-fold greater than the NNTs for all three TNF antagonists.

Infliximab had the highest associated risk of nonmelanoma skin cancer, with an NNH of 99 for this end point in the placebo-controlled trials. In contrast, the NNH for nonmelanoma skin cancer was 270 with once-weekly etanercept, 324 with twice-weekly etanercept, and 470 with adalimumab. The NNH for one additional serious infectious adverse event was 99 for infliximab, 148 for once-weekly etanercept, 183 for twice-weekly etanercept, and 291 for adalimumab, he said.

There were no cases of tuberculosis, other opportunistic infections, or demyelinating disorders for any of the TNF antagonists during the placebo-controlled portion of the clinical trials.

The long-term safety analysis was based upon nearly 7,400 psoriasis patients who were exposed to one of the TNF antagonists for an average duration of almost 11 months. This analysis concluded that the risk of serious infections was 0.015 cases per patient-year of exposure to adalimumab, 0.014 per patient-year for various dosages of etanercept, and 0.018 per patient-year for infliximab. The risk of nonmelanoma skin cancer was 0.007 per patient-year for adalimumab, 0.010 per patient-year for etanercept, and 0.017 per patient-year for infliximab.

Mean baseline body weights of study participants ranged from 88.9 kg to 92.7 kg, suggesting a high prevalence of obesity.

Dr. Rozzo indicated that the NNTs and NNHs generated in this evidence-based assessment need to be taken with a grain of salt, as they were obtained from clinical trials that did not involve head-to-head comparisons among biologics. Moreover, the duration of the placebo-controlled portions varied from study to study. For these reasons, he did not perform any tests of statistical significance for the differences in results. The take-away message from this analysis, according to Dr. Rozzo, is that this class of medications has an extremely favorable benefit-risk ratio. The assessment was sponsored by Abbott. ■

Ustekinumab Lessens Sexual Problems in Psoriasis Patients

BY BRUCE JANCIN

BERLIN — Impaired sexual function is common in the setting of moderate to severe psoriasis, and ustekinumab therapy reduces these problems by 10-fold.

That's a key quality-of-life finding from the ongoing randomized double-blind phase III PHOENIX-1 and -2 clinical trials of this human monoclonal antibody directed against the proinflammatory cytokines interkeukin-12 and -23, Dr. Lyn Guenther reported at the annual congress of the European Academy of Dermatology and Venereology.

The marked reduction in sexual difficulties was paralleled by a sharp improvement in overall quality of life in the ustekinumab-treated patients in the PHOENIX studies. Their mean baseline score on the Dermatology Life Quality Index (DLQI) was 12, reflecting a very large negative impact on quality of life. Twelve weeks into the studies, the average DLQI had dropped by 9.13 points for ustekinumab patients, compared with a 0.53-point dip in the placebo arm, according to Dr. Guenther, medical director of the Guenther Dermatology Research Centre and professor of dermatology at the University of Western Ontario, London.

The DLQI is scored on a 0-30 scale. A 5-point or greater improvement is considered clinically significant.

The PHOENIX trials include 1,996 adults with moderate to severe psoriasis who were randomized 2:1 to ustekinumab (Stelara) at 45 mg or 90 mg at weeks 0, 4, 12, and every 12 weeks thereafter or to placebo. After 12 weeks, subjects in the placebo group were crossed over to ustekinumab.

The mean age of participants at entry was 46 years. Sixty-nine percent are men. Their average baseline Psoriasis Area and Severity Index (PASI) score was 20, with 26% of their body surface area being affected and an average disease duration of 20 years. Twenty-eight percent had psoriatic arthritis.

Question 9 on the DLQI is designed to explore sexual problems. Here's the phrasing: "Over the last week, how much has your skin caused any sexual difficulties?"

The response options are "not at all," "a little," "a lot," "very much," or "not relevant." A reply of "a lot" or "very much" was interpreted as indicating sexual difficulties.

The prevalence of impaired sexual function by this measure went from 22% at baseline—27% in women and 29% in men—to 3% after 12 weeks on ustekinumab. There was no change at 12 weeks in the placebo group, but they showed markedly improved overall quality of life and sexual function upon repeat DLQI testing at 24-28 weeks—3 months after having been switched to ustekinumab.

DLQI scores did not differ between 90 mg as opposed to 45 mg of ustekinumab.

Sexual dysfunction is an aspect of psoriasis that doesn't get enough attention, Dr. Guenther commented.

Based upon the PHOENIX findings, further studies of ustekinumab's impact in this domain are warranted using more detailed tools for assessing sexual dysfunction, she said. The studies are funded by Centocor. Dr. Guenther is a consultant to the company. ■

U.S. and U.K. Data Flesh Out Anti-TNFs, Skin Cancer Link

BY DENISE NAPOLI

PHILADELPHIA — Two studies showed an increased risk for nonmelanoma skin cancer in rheumatoid arthritis patients who take anti–tumor necrosis factor therapies, and should prompt rheumatologists to evaluate the use of these drugs in patients who are at risk for skin cancer, according to the researchers.

Previous studies have been too small to show a definitive link between biologic therapy for RA and skin malignancy, although RA previously has been well established as a risk factor for skin cancer, according to Dr. Prahba Ranganathan, who presented the results of her retrospective cohort study of RA patients in the Department of Veterans Affairs national database at the annual meeting of the American College of Rheumatology.

Among 16,829 patients with RA, 3,096 were treated with anti-TNFs at the VA between Oct. 1, 1998 and Sept. 30, 2006, she said. The incidence of nonmelanoma skin cancer was 25.9 per 1,000 patient-years in this cohort, compared with 19.6 per 1,000 patient-years in the biologic-naive cohort, a 34% increased risk. The melanoma incidence was increased as well, with 3.7 cases per 1,000 patient-years seen in the anti-TNF–treated group, vs. 2.6 cases per 1,000 patient-years in the biologic-naive cohort. The differences were significant.

A second study presented at the press conference confirmed these findings. Dr. Kimme Hyrich of the University of Manchester (England) looked at RA patients from the British Society for Rheumatology's biologics register, a prospective cohort study begun in 2001 to monitor the long-term safety of anti-TNFs.

Dr. Hyrich found that among 11,598 RA patients who were treated with anti-TNFs and had no prior nonmelanoma skin cancer, the incidence of a malignancy was 3.5 per 1,000 patient-years. In contrast, among 8,975 similar patients who were treated with nonbiologic therapies, the incidence of new nonmelanoma skin cancers was 2.4.

That was a 70% increased risk for the anti-TNF–treated patients, although the data were not significant, Dr. Hyrich reported, pointing out that patients treated with anti-TNF drugs typically have more contact with their physicians, which could have introduced a surveillance bias.

Dr. Ranganathan cautioned that even in patients with multiple skin cancer risks—including being male and older, and having a history of skin cancer—anti-TNFs are still a good choice for patients who've failed other treatments.

While patients at risk may need periodic skin exams, "I don't think [having risk factors] would be an absolute contraindication," she said.

Dr. Ranganathan, Dr. Hyrich, and their respective research teams did not report having any financial disclosures relative to their studies. ■