

Belimumab Shows Effectiveness in Phase III Trial

BY ROBERT FINN

The monoclonal antibody belimumab appears to be effective for the treatment of systemic lupus erythematosus, according to the results of a randomized, placebo-controlled trial involving 865 patients.

Human Genome Sciences and Glaxo SmithKline, which codeveloped the biologic, announced the results during a conference call for security analysts. The results have not yet undergone peer review. The trial, BLISS-52, was conducted at 90 clinical sites in 13 countries, primarily in Asia, South America, and Eastern Europe. A second phase III trial, BLISS-76, is in its final stages with 826 patients at 133 clinical sites in 19 countries, primarily in North America and Europe. Patients in BLISS-52 were followed for 52 weeks, while patients in BLISS-76 will be followed for 76 weeks.

H. Thomas Watkins, president and chief executive officer of Human Genome Sciences, said that results from BLISS-76 will be announced in November. If the results are positive, the companies will submit marketing applications in the United States, Europe, and other regions during the first half of 2010, he said.

The two trials have similar designs. Pa-

tients were randomized to receive either standard of care plus placebo or standard of care plus 1 mg/kg or 10 mg/kg of belimumab. The drug (or placebo) was delivered intravenously on days 0, 14, 28, and every 28 days thereafter.

The primary end point of BLISS-52 was "patient response," defined as an improvement in SELENA-SLEDAI instrument scores of 4 or more at week 52 with no clinically significant flare in the BILAG index or worsening of the Physician's Global Assessment score. SELENA SLEDAI refers to the Safety of Estrogen in Lupus Erythematosus National Assessment trial version of the Systemic Lupus Erythematosus Disease Activity Index. BILAG is an index developed by the British Isles Lupus Assessment Group.

Dr. Joan T. Merrill, head of clinical pharmacology at the Oklahoma Medical Research Foundation, Oklahoma City, said in an interview: "The use of these two instruments in the trial design was very clever. The two major weaknesses of the SLEDAI have been overcome in this trial. It is not as sensitive to change as the BILAG, so if you do see a 4-point drop you are impressed. However, the 4-point drop in the overall score could happen while there is significant worsening in some organs, and this was ad-

ressed using the BILAG and the Physician's Global Assessment to eliminate such patients from the responder group."

At week 52, 44% of the patients taking placebo met the primary efficacy end point, compared with 52% of the patients taking 1 mg/kg belimumab, and 58% of the patients taking 10 mg/kg belimumab.

Both doses of belimumab proved superior to placebo with a high degree of statistical significance.

There were also significant improvements in several secondary end points. For example, investigators observed improvement in Physician's Global Assessment scores in 4-8 weeks. A significantly higher proportion of patients in both belimumab groups were able to reduce their average prednisone dose by at least 25% from baseline to 7.5 mg/day or less during the final 12 weeks of the study. Health-related quality of life at week 52, as measured by the SF-36 Physical Component Summary score, was significantly better in both belimumab treatment groups.

"This is an outstanding result," according to Dr. Merrill, who is also the medical director of the Lupus Foundation of America. "By showing an effect on both the efficacy end point and the steroid taper, the treatment impact is more robust than it might seem just looking at the primary outcome."

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Rates of adverse events, serious adverse events, infections, and fatalities were similar in the belimumab and placebo groups. The most common

adverse events were headache, arthralgia, upper respiratory tract infection, urinary tract infection, and influenza.

Dr. Merrill is a consultant for Genentech Inc., Bristol-Myers Squibb Co., MedImmune Inc., and other companies that develop products for lupus. She was not an investigator in the study being discussed but is involved in the ongoing phase III trial that includes sites in the United States and Western Europe. The companies plan to market belimumab under the trade name Benlysta. ■

BRIEF SUMMARY

(see package insert for full prescribing information)

Atralin™ (tretinoin) gel 0.05%

For topical use only

INDICATIONS AND USAGE
Atralin Gel is a retinoid indicated for topical treatment of acne vulgaris.

Important Limitations of Use

The safety and efficacy of the use of this product in the treatment of any other disorders have not been evaluated.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Skin Irritation

The skin of certain individuals may become dry, red, or exfoliated while using Atralin Gel. If the degree of irritation warrants, patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use altogether. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued. Mild to moderate skin dryness may also be experienced if so, use of an appropriate moisturizer during the day may be helpful.

Tretinoin has been reported to cause severe irritation on eczematous or sunburned skin and should be used with caution in patients with these conditions.

Topical over-the-counter acne preparations, concomitant topical medication, medicated cleansers, topical products with alcohol or astringents, when used with Atralin Gel, should be used with caution. [See Drug Interactions (7)]

Ultraviolet Light and Environmental Exposure

Unprotected exposure to sunlight, including sunlamps, should be minimized during the use of Atralin Gel. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products of at least SPF 15 and protective clothing over treated areas is recommended when exposure cannot be avoided.

Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.

Fish Allergies

Atralin Gel contains soluble fish proteins and should be used with caution in patients with known sensitivity or allergy to fish. Patients who develop pruritus or urticaria should contact their health care provider.

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two randomized, controlled trials, 674 subjects received treatment for up to 12 weeks with Atralin Gel [see Clinical Studies (14)]. In these studies, 50% of the subjects who were treated with Atralin Gel reported one or more adverse reactions; 30% of the subjects reported treatment-related adverse reactions. In the vehicle group, 29% of the 487 randomized subjects reported at least one adverse reaction; 5% of the subjects reported events that were treatment-related.

There were no serious, treatment-related adverse reactions reported by subjects in any of the treatment groups.

Selected adverse reactions that occurred in at least 1% of subjects in the two studies combined, are shown in Table 1 (below). Most skin-related adverse reactions first appear during the first two weeks of treatment with Atralin Gel, and the incidence rate for skin-related reactions peaks around the second and third week of treatment. In some subjects the skin-related adverse reactions persist throughout the treatment period.

Table 1. Number of Subjects with Selected Adverse Reactions (Occurring in At Least 1% of Subjects)

Event	Atralin Gel (n = 674)	Vehicle Gel (n = 487)
Dry Skin	109 (16%)	8 (2%)
Peeling/Scaling/Flaking Skin	76 (12%)	7 (1%)
Skin Burning/Sensation	53 (8%)	8 (2%)
Erythema	47 (7%)	1 (<1%)
Pruritus	11 (2%)	3 (1%)
Pain of Skin	7 (1%)	0 (0%)
Sunburn	7 (1%)	3 (1%)

DRUG INTERACTIONS

When treating with Atralin Gel, caution should be exercised with the use of concomitant topical medication, medicated or abrasive soaps and cleansers, products that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices, or lime. Particular caution should be exercised with the concomitant use of topical over-the-counter acne preparations containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid. Allow the effects of such preparations to subside before use of Atralin Gel is begun.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with Atralin Gel. Atralin Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Atralin Gel at doses of 0.1, 0.3 and 1 g/kg/day was tested for maternal and developmental toxicity in pregnant Sprague-Dawley rats by dermal application. The dose of 1 g/kg/day was approximately 4 times the clinical dose assuming 100% absorption and based on body surface area comparison. Possible tretinoin-associated teratogenic effects (craniofacial abnormalities [hydrocephaly], asymmetrical thyroid variations in ossification, and increased supernumerary ribs) were noted in the fetuses of Atralin Gel treated animals. These findings were not observed in control animals. Other maternal and reproductive parameters in the Atralin Gel treated animals were not different from control. For purposes of comparison of the animal exposure to human exposure, the clinical dose is defined as 2 g of Atralin Gel applied daily to a 50-kg person.

Oral tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters and nonhuman primates. Tretinoin was teratogenic in Wistar rats when given orally in doses greater than 1 mg/kg/day (approximately 8 times the clinical dose based on body surface area comparison). In the cynomolgus monkey, fetal malformations were reported for doses of 10 mg/kg/day, but none were observed at 5 mg/kg/day (approximately 80 times the clinical dose based on body surface area comparison), although increased skeletal variations were observed at all doses.

Dose-related increases in embryolethality and abortion were reported. Similar results have also been reported in pigtail macaques.

Topical tretinoin in a different formulation has generated equivocal results in animal teratogenicity tests. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (approximately 8 times the clinical dose assuming 100% absorption and based on body surface area comparison). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day (approximately 160 times the clinical dose assuming 100% absorption and based on body surface area comparison) was topically applied. Supernumerary ribs have been a consistent finding in rats when dams were treated topically or orally with retinoids.

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Cases of temporally associated congenital malformations have been reported with use of other topical tretinoin products. The significance of these spontaneous reports in terms of risk to the fetus is not known.

Nonteratogenic effects on fetuses: Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 20 times the clinical dose based on a body surface area comparison.

Topical tretinoin has been shown to be fetotoxic in rabbits when administered in doses 8 times the clinical dose based on a body surface area comparison.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Atralin Gel is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children below the age of 10 have not been established.

A total of 381 pediatric subjects (aged 10 to 16 years), treated with Atralin Gel were enrolled into the two clinical studies. Across these two studies, comparable safety and efficacy were observed between pediatric and adult subjects.

Geriatric Use

Safety and effectiveness in a geriatric population have not been established. Clinical studies of Atralin Gel did not include any subjects over age 65 to determine whether they respond differently than younger subjects.

Marketed by:

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Wait Time for New Pediatric Derm Patients Is 6-8 Weeks

BY KERRI WACHTER

PHILADELPHIA — A quarter of pediatric dermatologists report that new patients have to wait more than 12 weeks to get an appointment, and the average overall wait time for pediatric dermatologists is 6-8 weeks, according to a recent survey of 243 pediatricians, general dermatologists, and pediatric dermatologists.

In comparison, the reported median wait time for a new-patient visit is less than 2 weeks to see a pediatrician and less than 5 weeks for a general/adult dermatologist, Dr. Kristen Cam reported in a poster presented at the annual meeting of the Society for Pediatric Dermatology.

"A significant shortage of pediatric dermatologists is perceived by pediatricians, dermatologists, and pediatric dermatologists," wrote Dr. Cam, a dermatology resident at the Children's Hospital of Philadelphia, and her colleagues.

They conducted the survey to assess anecdotal evidence that patients experience long wait times to see a pediatric dermatologist.

The researchers asked approximately 800 physicians from the American Academy of Pediatrics, the American Academy of Dermatology, and the Society for Pediatric Dermatology to complete a 45-question online survey. In all, 243 completed the survey. Of

these, 19% identified themselves as pediatricians, 28% as general or adult dermatologists, and 53% as pediatric dermatologists.

More than 90% of the survey respondents perceived a shortage of available pediatric dermatology services. Almost half of the pediatric dermatologists reported that their practices are actively recruiting additional pediatric dermatologists. A quarter of them reported actively recruiting for more than a year, the investigators reported.

Almost two-thirds of pediatric dermatologists practiced in urban areas. More pediatric dermatologists practiced in academic and hybrid academic/private practice settings than in private practice.

Slightly more than half of the pediatric dermatologists had completed a categorical pediatrics residency and almost half had completed fellowship training.

Median salary ranges were comparable for pediatric dermatologists and general/adult dermatologists—\$200,000 to \$250,000—despite additional subspecialty training.

In comparison, the median salary range for pediatricians was \$100,000 to \$150,000.

"Salary was perceived to be the strongest factor deterring physicians from entering pediatric dermatology," Dr. Cam and her associates wrote. ■