

Promising Treatments, Markers Target Lupus

BY DIANA MAHONEY

A number of groundbreaking developments in systemic lupus erythematosus have injected a much-needed boost into the lupus community, which has been repeatedly disappointed by setbacks and failures in clinical trials of “promising” new agents.

Clinicians are optimistic about two positive late-stage clinical trials, the vali-

dated of an evidence-based responder index to measure disease activity, the discovery of genetic markers that may help predict the clinical outcome of patients who are treated with existing therapies, and the introduction of new guidelines to facilitate and better control clinical trials, according to Dr. Richard Furie, chief of rheumatology and allergy-clinical immunology at North Shore-Long Island Jewish Health System in New York.

In fact, the announcement in July that the monoclonal antibody belimumab showed effectiveness against lupus in the first of two phase III clinical trials—the first drug to ever do so, according to a statement from Human Genome Sciences, which codveloped the biologic with Glaxo SmithKline—was in some ways a surprise. The drug, which inhibits the biological activity of B-lymphocyte stimulator (BLyS), had nearly been count-

ed out after it failed to meet its primary efficacy end point in a phase II clinical trial, except in a subgroup of patients who experienced a statistically significant improvement in lupus signs and symptoms, according to Dr. Daniel J. Wallace of the University of California, Los Angeles.

Based on extensive post hoc analysis of the phase II data, investigators identified factors that could have contributed to the negative trial and redesigned the study accordingly. The revised trial excluded the 28% of patients in the phase II study who were not seropositive for antinuclear antibodies or anti-double-stranded DNA antibodies; it extended the response time to 52 weeks, and it utilized a new composite end point, called the SLE Responder Index, to measure an in-

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INDICATIONS AND USAGE

Monotherapy and Combination Therapy

ONGLYZA (saxagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [See *Clinical Studies* (14).]

Important Limitations of Use

ONGLYZA should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

ONGLYZA has not been studied in combination with insulin.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Use with Medications Known to Cause Hypoglycemia

Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with ONGLYZA. [See *Adverse Reactions* (6.1).]

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug.

ADVERSE REACTIONS

Clinical Trials Experience

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

Monotherapy and Add-On Combination Therapy

In two placebo-controlled monotherapy trials of 24-weeks duration, patients were treated with ONGLYZA 2.5 mg daily, ONGLYZA 5 mg daily, and placebo. Three 24-week, placebo-controlled, add-on combination therapy trials were also conducted: one with metformin, one with a thiazolidinedione (pioglitazone or rosiglitazone), and one with glyburide. In these three trials, patients were randomized to add-on therapy with ONGLYZA 2.5 mg daily, ONGLYZA 5 mg daily, or placebo. A saxagliptin 10 mg treatment arm was included in one of the monotherapy trials and in the add-on combination trial with metformin.

In a prespecified pooled analysis of the 24-week data (regardless of glycemic rescue) from the two monotherapy trials, the add-on to thiazolidinedione (TZD) trial, and the add-on to glyburide trial, the overall incidence of adverse events in patients treated with ONGLYZA 2.5 mg and ONGLYZA 5 mg was similar to placebo (72.0% and 72.2% versus 70.6%, respectively). Discontinuation of therapy due to adverse events occurred in 2.2%, 3.3%, and 1.8% of patients receiving ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. The most common adverse events reported in at least 2 patients treated with ONGLYZA 2.5 mg or at least 2 patients treated with ONGLYZA 5 mg associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0.3%), blood creatinine increased (0.3% and 0% versus 0%), and blood creatinine phosphokinase increased (0.1% and 0.2% versus 0%). The adverse reactions in this pooled analysis reported (regardless of investigator assessment of causality) in ≥5% of patients treated with ONGLYZA 5 mg, and more commonly than in patients treated with placebo are shown in Table 1.

Table 1. Adverse Reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Trials* Reported in ≥5% of Patients Treated with ONGLYZA 5 mg and More Commonly than in Patients Treated with Placebo

| | Number (%) of Patients | |
|-----------------------------------|------------------------|------------------|
| | ONGLYZA 5 mg N=882 | Placebo N=799 |
| Upper respiratory tract infection | 68 (7.7) | 61 (7.6) |
| Urinary tract infection | 60 (6.8) | 49 (6.1) |
| Headache | 57 (6.5) | 47 (5.9) |

* The 5 placebo-controlled trials include two monotherapy trials and one add-on combination therapy trial with each of the following: metformin, thiazolidinedione, or glyburide. Table shows 24-week data regardless of glycemic rescue.

In patients treated with ONGLYZA 2.5 mg, headache (6.5%) was the only adverse reaction reported at a rate ≥5% and more commonly than in patients treated with placebo.

In this pooled analysis, adverse reactions that were reported in ≥2% of patients treated with ONGLYZA 2.5 mg or ONGLYZA 5 mg and ≥1% more frequently compared to placebo included: sinusitis (2.9% and 2.6% versus 1.6%, respectively), abdominal pain (2.4% and 1.7% versus 0.5%), gastroenteritis (1.9% and 2.3% versus 0.9%), and vomiting (2.2% and 2.3% versus 1.3%).

In the add-on to TZD trial, the incidence of peripheral edema was higher for ONGLYZA 5 mg versus placebo (8.1% and 4.3%, respectively). The incidence of peripheral edema for ONGLYZA 2.5 mg was 3.1%. None of the reported adverse reactions of peripheral edema resulted in study drug discontinuation. Rates of peripheral edema for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo were 3.6% and 2% versus 3% given as monotherapy, 2.1% and 2.1% versus 2.2% given as add-on therapy to metformin, and 2.4% and 1.2% versus 2.2% given as add-on therapy to glyburide.

The incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for ONGLYZA (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The incidence rate of fracture events in patients who received ONGLYZA did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of saxagliptin on bone.

An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura, was observed in the clinical program. The relationship of this event to ONGLYZA is not known.

Adverse Reactions Associated with ONGLYZA (saxagliptin) Coadministered with Metformin in Treatment-Naïve Patients with Type 2 Diabetes

Table 2 shows the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients participating in an additional 24-week, active-controlled trial of coadministered ONGLYZA and metformin in treatment-naïve patients.

Table 2. Initial Therapy with Combination of ONGLYZA and Metformin in Treatment-Naïve Patients: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Treated with Combination Therapy of ONGLYZA 5 mg Plus Metformin (and More Commonly than in Patients Treated with Metformin Alone)

| | Number (%) of Patients | |
|-----------------|------------------------------------|---------------------|
| | ONGLYZA 5 mg + Metformin* N=320 | Metformin* N=328 |
| Headache | 24 (7.5) | 17 (5.2) |
| Nasopharyngitis | 22 (6.9) | 13 (4.0) |

* Metformin was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2000 mg daily.

Hypoglycemia

Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. In the add-on to glyburide study, the overall incidence of reported hypoglycemia was higher for ONGLYZA 2.5 mg and ONGLYZA 5 mg (13.3% and 14.6% versus placebo (10.1%). The incidence of confirmed hypoglycemia in this study, defined as symptoms of hypoglycemia accompanied by a fingerstick glucose value of ≤50 mg/dL, was 2.4% and 0.8% for ONGLYZA 2.5 mg and ONGLYZA 5 mg and 0.7% for placebo. The incidence of reported hypoglycemia for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo given as monotherapy was 4.0% and 5.6% versus 4.1%, respectively, 7.8% and 5.8% versus 5% given as add-on therapy to metformin, and 4.1% and 2.7% versus 3.8% given as add-on therapy to TZD. The incidence of reported hypoglycemia was 3.4% in treatment-naïve patients given ONGLYZA 5 mg plus metformin and 4.0% in patients given metformin alone.

Hypersensitivity Reactions

Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5%, and 0.4% of patients who received ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. None of these events in patients who received ONGLYZA required hospitalization or were reported as life-threatening by the investigators. One saxagliptin-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.

Vital Signs

No clinically meaningful changes in vital signs have been observed in patients treated with ONGLYZA.

Laboratory Tests

Absolute Lymphocyte Counts

There was a dose-related mean decrease in absolute lymphocyte count observed with ONGLYZA. From a baseline mean absolute lymphocyte count of approximately 2200 cells/microl, mean decreases of approximately 100 and 120 cells/microl with ONGLYZA 5 mg and 10 mg, respectively, relative to placebo were observed at 24 weeks in a pooled analysis of five placebo-controlled clinical studies. Similar effects were observed when ONGLYZA 5 mg was given in initial combination with metformin compared to metformin alone. There was no difference observed for ONGLYZA 2.5 mg relative to placebo. The proportion of patients who were reported to have a lymphocyte count ≤750 cells/microl was 0.5%, 1.5%, 1.4%, and 0.4% in the saxagliptin 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. In most patients, recurrence was not observed with repeated exposure to ONGLYZA although some patients had recurrent decreases upon rechallenge that led to discontinuation of ONGLYZA. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions.

The clinical significance of this decrease in lymphocyte count relative to placebo is not known. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of ONGLYZA on lymphocyte counts in patients with lymphocyte abnormalities (e.g., human immunodeficiency virus) is unknown.

Platelets

ONGLYZA did not demonstrate a clinically meaningful or consistent effect on platelet count in the six, double-blind, controlled clinical safety and efficacy trials.

DRUG INTERACTIONS

Inducers of CYP3A4/5 Enzymes

Rifampin significantly decreased saxagliptin exposure with no change in the area under the time-concentration curve (AUC) of its active metabolite, 5-hydroxy saxagliptin. The plasma dipeptidyl peptidase-4 (DPP4) activity inhibition over a 24-hour dose interval was not affected by rifampin. Therefore, dosage adjustment of ONGLYZA is not recommended. [See *Clinical Pharmacology* (12.3).]

Inhibitors of CYP3A4/5 Enzymes

Moderate Inhibitors of CYP3A4/5

Diitiazem increased the exposure of saxagliptin. Similar increases in plasma concentrations of saxagliptin are anticipated in the presence of other moderate CYP3A4/5 inhibitors (e.g., amprenavir, aprepitant, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil); however, dosage adjustment of ONGLYZA is not recommended. [See *Clinical Pharmacology* (12.3).]

Strong Inhibitors of CYP3A4/5

Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). The dose of ONGLYZA should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor. [See *Dosage and Administration* (2.3) and *Clinical Pharmacology* (12.3).]

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ONGLYZA (saxagliptin), like other antidiabetic medications, should be used during pregnancy only if clearly needed.

Saxagliptin was not teratogenic at any dose tested when administered to pregnant rats and rabbits during periods of organogenesis. Incomplete ossification of the pelvis, a form of developmental delay, occurred in rats at a dose of 240 mg/kg, or approximately 1503 and 66 times human exposure to saxagliptin and the active metabolite, respectively, at the maximum recommended human dose (MRHD) of 5 mg. Maternal toxicity and reduced fetal body weights were observed at 7986 and 328 times the human exposure at the MRHD for saxagliptin and the active metabolite, respectively. Minor skeletal variations in rabbits occurred at a maternally toxic dose of 200 mg/kg, or approximately 1432 and 992 times the MRHD. When administered to rats in combination with metformin, saxagliptin was not teratogenic nor embryolethal at exposures 21 times the saxagliptin MRHD. Combination administration of metformin with a higher dose of saxagliptin (109 times the saxagliptin MRHD) was associated with craniorachischisis (a rare neural tube defect characterized by incomplete closure of the skull and spinal column) in two fetuses from a single dam. Metformin exposures in each combination were 4 times the human exposure of 2000 mg daily.

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (exposures ≥1629 and 53 times saxagliptin and its active metabolite at the MRHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.

Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

Nursing Mothers

Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations. It is not known whether saxagliptin is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ONGLYZA in pediatric patients have not been established.

Geriatric Use

In the six, double-blind, controlled clinical safety and efficacy trials of ONGLYZA, 634 (15.3%) of the 4148 randomized patients were 65 years and over, and 59 (1.4%) patients were 75 years and over. No overall differences in safety or effectiveness were observed between patients ≥65 years old and the younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Saxagliptin and its active metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function. [See *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.3).]

OVERDOSAGE

In a controlled clinical trial, once-daily, orally-administered ONGLYZA in healthy subjects at doses up to 400 mg daily for 2 weeks (80 times the MRHD) had no dose-related clinical adverse reactions and no clinically meaningful effect on QTc interval or heart rate.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours).

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

Instructions

Patients should be informed of the potential risks and benefits of ONGLYZA and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Physicians should instruct their patients to read the Patient Package Insert before starting ONGLYZA therapy and to reread it each time the prescription is renewed. Patients should be instructed to inform their doctor or pharmacist if they develop any unusual symptom or if any existing symptom persists or worsens.

Laboratory Tests

Patients should be informed that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C, with a goal of decreasing these levels toward the normal range. A1C is especially useful for evaluating long-term glycemic control. Patients should be informed of the potential need to adjust their dose based on changes in renal function tests over time.

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The SLE Responder Index 'represents a breakthrough' in detecting disease improvement.

DR. WALLACE

dividual patient's improvement from baseline, Dr. Wallace explained.

“The new index looks at whether the patient feels better, whether the doctor thinks the patient feels better, and whether there are any new disease manifestations,” Dr. Wallace said. Given the heterogeneous nature of lupus and the longstanding difficulty of assessing disease activity in clinical trials, the responder index “represents a breakthrough for finally utilizing a methodology that enables researchers to demonstrate disease improvement,” he said.

And although the success of the SLE Responder Index is limited to just one data set, “the fact that it worked prospectively and not just post hoc should be encouraging to drug developers,” Dr. Furie said. “Perhaps it will become the standard or at least serve as the foundation for further refinements.”

On the heels of the belimumab announcement was the news that another experimental lupus drug, epratuzumab, performed well in a phase IIB clinical trial. In a 12-week, dose- and regimen-ranging, placebo-controlled study of 227 patients with moderately to severely active lupus, epratuzumab (a humanized anti-CD22 monoclonal antibody) showed a “clinically meaningful” effect over placebo, according to a statement by Belgium's UCB SA, which bought rights to epratuzumab from Immunomedics. Specifically, at week 12, the treatment effect of epratuzumab was nearly 25%, compared with placebo, the report noted.

If one or both of these new drugs ultimately receive Food and Drug Administration approval for the treatment of lupus, they most likely will be used initially in patients who have chronically active disease despite treatment with steroids or other immunosuppressive therapies,

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according to Dr. Wallace. "Belimumab in particular does not work fast. It is not a replacement for corticosteroids in the treatment of acute disease."

If approved, belimumab will be a major advance for those with moderate or inadequately controlled disease activity who require prednisone, because it may enable lower corticosteroid doses, said Dr. Michelle Petri, professor of rheumatology at Johns Hopkins University, Baltimore.

"The reality is prednisone is not going away. Approximately 80% of our lupus patients are on it—and for good reason, as it remains the most effective immunosuppressive therapy we have for the disease, and it works fast. The problem is that nearly 80% of organ damage in lupus is directly or indirectly due to steroids," Dr. Petri said at the annual meeting of the European Congress of Rheumatology this year in Copenhagen.

The risk for prednisone-associated organ damage increases by an order of magnitude as the cumulative dose increases, said Dr. Petri, referring to a recent study in which she and Mae Thamer, Ph.D., from the Medical Technology and Practice Patterns Institute in Bethesda, Md., evaluated the effect of corticosteroid use in 525 patients with incident SLE who were enrolled in the Hopkins Lupus Cohort. Using a marginal structural model to adjust for time-dependent confounding associated with disease activity, the investigators determined that patients who received cumulative doses of prednisone in the lowest range (0-180 mg/month) had only a small increased risk of irreversible organ damage, compared with nonprednisone use (hazard ratio 1.16), whereas the risk among those receiving cumulative doses in the highest range (more than 540 mg/month) was more than doubled (HR 2.51). The hazard ratios for the middle-range doses (180-360 mg/month and 360-540 mg/month) were 1.50 and 1.64, respectively (J. Rheumatol. 2009; 36:560-64).

"When you look at the models, it's pretty clear that when the prednisone gets above 11 mg daily, there is a huge increase in the hazard ratio for organ damage," Dr. Petri said. "That is when to start to think about adding other therapies, if you haven't already, to achieve better control of disease activity and to limit the prednisone dose." It is at this point, she noted, that the expansion of treatment options is needed.

With respect to other steroid-sparing options, however, the "ideal" immunomodulatory therapy in lupus continues to be the antimalarial hydroxychloroquine (Plaquenil), Dr. Petri said. Hydroxychloroquine "has been shown to prevent severe flares in lupus. It also reduces the risk of lupus nephritis, organ damage, cardiovascular risk factors, and thrombosis, and it improves survival." In reality, she added, "if we could just convince our patients to stay on Plaquenil, I don't think we would need as much immunosuppressive therapy."

In fact, hydroxychloroquine is undergoing a rebirth of sorts, according to Dr. Furie. "Many people believe that all SLE patients should be on this drug. It's ef-

fective and fairly benign, and we are learning that it has pleiotropic effects," he said, including protection against thrombotic events and a beneficial effect on lipid profiles, which could potentially help reduce SLE patients' high risk of cardiovascular disease.

The recent finding by Spanish investigators that antimalarial drugs are more effective in SLE patients with polymorphisms on the tumor necrosis factor- α (TNF- α) and interleukin-10 (IL-10) genes associated with unusually high TNF- α levels and unusually low IL-10 levels may eventually allow the identifi-

cation of lupus patients who are the most likely to benefit from antimalarial therapy (J. Rheumatol. 2008;35:1559-66).

Finally, the lupus research community is encouraged by the development of new recommendations for monitoring SLE in clinical practice, which were introduced at the annual European Congress of Rheumatology this year by Dr. Marta Mosca of the University of Pisa (Italy), the lead author of the recommendation paper, which is slated for publication in the *Annals of the Rheumatic Diseases* later this year. The guidelines are intended to provide a "road map" for clin-

icians in terms of assessing disease activity, kidney and other organ involvement, comorbidities, and the various cardiovascular, ophthalmologic, neuropsychiatric, and other risks associated with SLE and its treatment.

"The guidelines will be an important tool for helping rheumatologists make clinical management decisions," Dr. Mosca said. "As new therapies are developed, the guidelines will help ensure the quality control of patient care and will allow us to better standardize the collection and comparison of data in observational studies." ■



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