Type of Sickle Cell Disease May Affect Risk of Neurodevelopmental Disorders

Children with sickle cell disease and a history of asthma have an increased risk of behavioral problems.

COLUMBUS, OHIO—Among children with sickle cell disease, type of disease and presence of comorbidities may increase the risk for attentional or behavioral problems, according to research presented at the 43rd Annual Meeting of the Child Neurology Society. Demographics and disease complications also may influence the risk of neurodevelopmental disorders among these children.

"Earlier identification of pediatric patients with sickle cell disease and attention deficit hyperactivity disorder (ADHD), intellectual disability, and specific learning disabilities will allow faster treatment of these disorders and may improve academic performance and quality of life," said Eboni I. Lance, MD, Co-Medical Director of the Sickle Cell Neurodevelopmental Clinic at Kennedy Krieger Institute in Baltimore.

Receiving AUBAGIO® (teriflunomide) tablets, for oral use

Intestinal lung disease may be fatal. Intestinal lung disease may occur acutely at any time during therapy and has a variable clinical presentation. New onset or worsening pulmonary symptoms, such as cough and dyspnea, with or without associated fever, may be a reason for discontinuation of the therapy and for further investigation as appropriate. If discontinuation of the drug is necessary, consider initiation of an accelerated elimination procedure [see Warnings and Precautions (5.3)].

5.9 Concomitant Use with Immunosuppressive or Immunomodulating Therapies

Co-administration with antineoplastic, or immunosuppressive therapies used for treatment of multiple sclerosis has not been evaluated. Safety studies in which AUBAGIO was concomitantly administered with other immune modulating therapies for up to one year (interferon beta, glatiramer acetate) did not reveal any specific safety concerns. The long term safety of these combinations in the treatment of multiple sclerosis has not been established.

In any situation in which the decision is made to switch from AUBAGIO to another agent with a known potential for hematologic suppression, it would be prudent to monitor for hematologic toxicity, because there will be overlap of systemic exposure to both compounds. Use of an accelerated elimination procedure may decrease this risk, but may also potentially result in return of disease activity if the patient had been responding to AUBAGIO treatment [see Warnings and Precautions (5.3)].

6.1 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 clinical practice.

A total of 2047 patients receiving AUBAGIO (7 mg or 14 mg once daily) constituted the safety population in the pooled analysis of placebo controlled studies in patients with relapsing forms of multiple sclerosis; of these, 71% were female. The average age was 37 years.

Table 1 lists adverse reactions in placebo-controlled trials with rates that were at least 2% for AUBAGIO patients and at least 2% above the rate in placebo patients. The most common were headache, an increase in ALT, diarrhea, alopecia, and nausea. The adverse reaction most commonly associated with discontinuation was an increase in ALT (3.2%, 2.6%, and 2.3% of all patients in the AUBAGIO 7 mg, AUBAGIO 14 mg, and placebo treatment arms, respectively).

Table 1. Adverse Reactions in Pooled Placebo-Controlled Studies in Patients with Relapsing Forms of Multiple Sclerosis

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>AUBAGIO 7 mg (N=1045)</th>
<th>AUBAGIO 14 mg (N=1099)</th>
<th>Placebo (N=1097)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16%</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td>Increase in ALT</td>
<td>13%</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13%</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>10%</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>8%</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3%</td>
<td>4%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Cardiovascular deaths

Four cardiovascular deaths, including three sudden deaths, and one myocardial infarction in a patient with a history of hypertension were reported among approximately 2600 patients exposed to AUBAGIO in the premarketing database. These cardiovascular deaths occurred during uncontrolled extensions of these studies, one to nine years after initiation of AUBAGIO therapy. No specific relationship between AUBAGIO and cardiovascular death has not been established.

Acute Renal Failure

In placebo-controlled studies, creatinine values increased more than 100% over baseline in 8/1045 (0.8%) patients in the 7 mg AUBAGIO group and 6/1092 (0.6%) patients in the 14 mg AUBAGIO group. The 14 mg AUBAGIO group had a higher rate of acute renal failure (0.4%) than the placebo group. These elevations were transient. Some elevations were accompanied by hyperkalemia. AUBAGIO may cause acute renal acid nephropathy with transient acute renal failure because AUBAGIO increases renal acid clearance.

Hypophosphatemia

In clinical trials, 10% of AUBAGIO-treated patients had hypophosphatemia with serum phosphorus levels of at least 0.6 mmol/L, compared to 7% of placebo-treated patients taking AUBAGIO. Vaccination with live vaccines is not recommended. The long half-life of AUBAGIO should be considered when contemplating administration of a live vaccine after stopping AUBAGIO.

In any situation in which the decision is made to switch from AUBAGIO to another agent with a known potential for hematologic suppression, it would be prudent to monitor for hematologic toxicity, because there will be overlap of systemic exposure to both compounds. Use of an accelerated elimination procedure may decrease this risk, but may also potentially result in return of disease activity if the patient had been responding to AUBAGIO treatment [see Warnings and Precautions (5.3)].

5.5 Peripheral Neuropathy

In placebo-controlled studies, peripheral neuropathy, including both polyneuropathy and mononeuropathy (e.g., carpal tunnel syndrome), occurred more frequently in patients taking AUBAGIO than in patients taking placebo. The incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.4% (13 patients) and 1.9% (17 patients) of patients receiving 7 mg and 14 mg of AUBAGIO, respectively, compared with 0.4% receiving placebo (4 patients). Treatment was discontinued in 0.7% (8 patients) with confirmed peripheral neuropathy (3 patients receiving AUBAGIO 7 mg and 5 patients receiving AUBAGIO 14 mg). Five of them recovered following treatment discontinuation. Not all cases of peripheral neuropathy resolved with continued treatment. Peripheral neuropathy also occurred in patients receiving leflunomide.

Age older than 66 years, concomitant neurotoxic medications, and diabetes may increase the risk for peripheral neuropathy. If a patient taking AUBAGIO develops symptoms consistent with peripheral neuropathy, such as bilateral numbness or tingling of hands or feet, consider discontinuing AUBAGIO therapy and performing an accelerated elimination procedure [see Warnings and Precautions (5.3)].

5.6 Skin Reactions

Necrotic ulcers of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients with rheumatoid arthritis receiving leflunomide. A similar risk would be expected for AUBAGIO [see Clinical Pharmacology (12.3) in the full prescribing information].
Hemoglobin S-Beta Thalassemia Was Associated With Increased Odds of Attention Problems

ADHD Was Common Among Participants

From May 2012 to March 2014, Dr. Lance and colleagues conducted a retrospective chart review of children with sickle cell disease who presented to Kennedy Krieger Institute or Johns Hopkins Hospital. The investigators reviewed the charts for documentation of neuropsychological diagnoses such as ADHD; attentional problems; behavioral problems; executive dysfunction; learning disabilities in math, reading, and reading comprehension; intellectual disabilities; developmental delay; fine motor disorders; language disorders; and autism spectrum disorders. The researchers also extracted from the charts data about age, genotype of sickle cell disease, disease complication history, treatments, and school services.

A total of 59 children met inclusion criteria, including 18 who presented to Kennedy Krieger Institute and 41 who presented to Johns Hopkins Hospital. Patients' average age was 17, and 38% of participants were male. Nearly all (97%) of the children were African American.

About 63% of the children had hemoglobin SS type sickle cell disease, 20% had hemoglobin SC, and 10% had hemoglobin S-Beta thalassemia.

When the researchers reviewed participants' neurodevelopmental diagnoses, they found that 19% of patients had ADHD, 19% had developmental delay, 12% had attention problems, 12% had learning disabilities in math, and 12% had learning disabilities in reading comprehension. Also, 10% of participants had a language disorder, 8% had anxiety, and 8% had behavioral problems.

Associations and Risks for Neurodevelopmental Disorders

Children with hemoglobin S-Beta thalassemia plus or null had significantly higher odds of attention problems than children with the hemoglobin SS type of sickle cell disease. Children with sickle cell disease and a history of asthma had significantly greater odds of behavioral problems than children with sickle cell disease without a history of asthma, even after adjustment for gender and sickle cell disease type. The investigators found no other significant relationships between other neurodevelopmental disorders and demographic characteristics or disease-related complications. They noted that stroke was not associated with significantly increased risk of a specific neurodevelopmental diagnosis, in comparison with other neurodevelopmental disorders.

“There may be differences in the disease phenotype, demographics, and prevalence of certain neurodevelopmental disorders within the pediatric sickle cell disease population,” said Dr. Lance. “Children with sickle cell disease should be screened for neurodevelopmental disorders, with emphasis on specific disease-related characteristics and complications as potential risk factors,” added Dr. Lance. “Specifically, evaluations should include a detailed sickle cell disease history of disease characteristics and complications, as well the typical history of neurologic complications and neurodevelopmental symptoms.”

——Erik Greb

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