Benefit of Erythropoietin for HCV Questioned

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BOSTON — Erythropoietin is quickly becoming an integral part of hepatitis C virus treatment regimens, despite a lack of firm data supporting its long-term clinical benefit, Dr. Eric Yoshida said at the annual meeting of the American Association for the Study of Liver Diseases.

Only a few studies have prospectively examined the effect of erythropoietin in these patients, and whereas the studies have shown statistically significant improvements in terms of increasing hemoglobin levels and allowing for maintenance of ribavirin dosage, opinions vary on whether these differences translate into clinical benefit.

"Does this mean there is no place for erythropoietin for these patients? No … it means we should treat the patient—not the numbers," said Dr. Yoshida, head of gastroenterology at the University of British Columbia, Vancouver.

Ribavirin, considered a mainstay of antiviral therapy for hepatitis patients, can cause a dose-dependent hemolytic anemia. Guidelines suggest decreasing the dosage of ribavirin when hemoglobin levels fall below 12 g/dL, and discontinuing the drug if levels fall below 8.5 g/dL.

But because ribavirin is so important to sustained viral response, some patients persist with it even when they develop an anemia that significantly impairs their quality of life, said Dr. Yoshida, who reviewed three studies that have examined the effect of erythropoietin in hepatitis C patients (Ann. Pharmacother. 2007;41:268-75).

The first study, a placebo-controlled trial, randomized 64 patients to either weekly erythropoietin injections for 16 weeks or placebo. At baseline, the mean hemoglobin level was 11 g/dL in both groups (Am. J. Gastroenterol. 2003;98:2491-9).

At the study's end, patients receiving erythropoietin had significantly higher mean hemoglobin levels (14 g/dL vs. 11

g/dL). Ribavirin dosage was similar in both groups, indicating that those taking the study drug were able to maintain their ribavirin dosage.

By the end of the trial, undetectable HCV RNA was seen in 69% of erythropoietin- treated patients and 60% of placebo patients. However, Dr. Yoshida noted there was a high dropout rate (42% of erythropoietin patients and 50% of placebo patients), which makes it difficult to conclude that the difference in percentage of patients with undetectable HCV RNA was related to erythropoietin therapy.

A second study randomized 185 patients to placebo or erythropoietin for 8 weeks, after which eligible patients from both groups entered into an 8-week open-label trial (Gastroenterology 2004;126:1302-11).

By the end of the first 8 weeks, significantly more erythropoietin-treated patients than placebo patients were still taking their baseline ribavirin dose (88% vs. 60%, respectively). At the end of the crossover phase, prior placebo patients had increased their ribavirin dosage significantly, from a mean of 852 mg/day to a mean of 921 mg/day.

Baseline hemoglobin levels (11 g/dL in both groups) rose to 13 g/dL in the erythropoietin group by the end of the first 8 weeks, but remained unchanged in the placebo group. By the end of the open-label phase, mean hemoglobin levels in prior placebo patients were the same as those in patients who had taken erythropoietin for the entire study (13 g/dL).

A post hoc analysis concluded that erythropoietin-treated patients also reported significant improvements in their quality of life (Hepatology 2004;40:1450-8). The importance of quality-of-life benefits should not be underestimated in hepatitis patients, Dr. Yoshida said, because quality-of-life scores of HCV patients on treatment can be lower than those of patients with diabetes and congestive heart failure.

The study found no significant differences between groups in HCV RNA levels.

These trials raise yet more questions, Dr. Yoshida said. The hemoglobin level that should trigger erythropoietin treatment is still unclear.

There are also no firm data on the duration of erythropoietin treatment that is beneficial, and the studies performed to date offer little guidance.

Still, noted Dr. Yoshida, the drug's expense along with its unproven survival benefit are enough to signal caution to many providers. "Hopefully, future trials will address these questions," he said.

Dr. Yoshida declared no financial interest in any hematopoietic agent. ■

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† Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
‡ Investigator term; summary level term is amblyopia.

Controlled Studies in Postherpetic Neuralgia *Adverse Reactions Leading to Discontinuation* In clinical trials in patients with postherpetic neuralgia, 14% of patients treated with LYRICA and 7% of patients treated with placebo discontinued prematurely due to adverse reactions. In the LYRICA treatment group, the most common reasons for discontinuation due to adverse reactions were dizziness (4%) and somnolence (3%). In comparison, less than 1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring in greater frequency in the LYRICA group than in the placebo group, were confusion (2%), as well as peripheral edema, asthenia, ataxia, and abnormal gait (1% each). *Most Common Adverse Reactions* Table 2 lists all adverse reactions, regardless of causality, occurring in ≥1% of patients with neuropathic pain associated with postherpetic neuralgia in the combined LYRICA group for which the incidence was greater in this combined LYRICA group than in the placebo group. In addition, an event is included, even if the incidence in the all LYRICA group is not greater than in the placebo group, if the incidence of the event in the 600 mg/day group is more than twice that in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse reactions with a maximum intensity of "mild" or "moderate".

Table 2 Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body System - Preferred term	75 mg/d [N=84] %	150 mg/d [N=302] %	300 mg/d [N=312] %	600 mg/d [N=154] %	All PGB* [N=852] %	Placebo [N=398] %
Body as a whole						
Infection	14	8	6	3	7	4
Headache	5	9	5	8	7	5
Pain	5	4	5	5	5	4
Accidental injury	4	3	3	5	3	2
Flu syndrome	1	2	2	1	2	1
Face edema	0	2	1	3	2	1
Digestive system						
Dry mouth	7	7	6	15	8	3
Constipation	4	5	5	5	5	2
Flatulence	2	1	2	3	2	1
Vomiting	1	1	3	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	0	8	16	16	12	4
Weight gain	1	2	5	7	4	0
Edema	0	1	2	6	2	1
Musculoskeletal system						
Myasthenia	1	1	1	1	1	0
Nervous system						
Dizziness	11	18	31	37	26	9
Somnolence	8	12	18	25	16	5
Ataxia	1	2	5	9	5	1
Abnormal gait	0	2	4	8	4	1
Confusion	1	2	3	7	3	0
Thinking abnormal†	0	2	1	6	2	2
Incoordination	2	2	1	3	2	0
Amnesia	0	1	1	4	2	0
Speech disorder	0	0	1	3	1	0
Respiratory system						
Bronchitis	0	1	1	3	1	1
Special senses						
Blurry vision‡	1	5	5	9	5	3
Diplopia	0	2	2	4	2	0
Abnormal vision	0	1	2	5	2	0
Eye disorder	0	1	1	2	1	0
Urogenital system						
Urinary incontinence	0	1	1	2	1	0
Digestive system						
Increased appetite	2	3	6	5	1	
Dry mouth	1	2	6	4	1	
Constipation	1	1	7	4	2	
Metabolic and nutritional disorders						
Weight gain	5	7	16	12	1	
Peripheral edema	3	3	6	5	2	
Nervous system						
Dizziness	18	31	38	32	11	
Somnolence	11	18	28	22	11	
Ataxia	6	10	20	15	4	
Tremor	3	7	11	8	4	
Thinking abnormal‡	4	8	9	8	2	
Amnesia	3	2	6	5	2	
Speech disorder	1	2	7	5	1	
Incoordination	1	3	6	4	1	
Abnormal gait	1	3	5	4	0	
Twitching	0	4	5	4	1	
Confusion	1	2	5	4	2	
Myoclonus	1	0	4	2	0	
Special senses						
Blurred vision§	5	8	12	10	4	
Diplopia	5	7	12	9	4	
Abnormal vision	3	1	5	4	1	

* PGB: pregabalin
† Excludes patients who received the 50 mg dose in Study E1 (included in full prescribing information).
‡ Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
§ Investigator term; summary level term is amblyopia.

Controlled Studies with Fibromyalgia *Adverse Reactions Leading to Discontinuation* In clinical trials of patients with fibromyalgia, 19% of patients treated with pregabalin (150–600 mg/day) and 10% of patients treated with placebo discontinued prematurely due to adverse reactions. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse reactions were dizziness (6%) and somnolence (3%). In comparison, <1% of placebo-treated patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin treatment group than in the placebo treatment group, were fatigue, headache, balance disorder, and weight increased. Each of these adverse reactions led to withdrawal in approximately 1% of patients. *Most Common Adverse Reactions* Table 4 lists all adverse reactions, regardless of causality, occurring in ≥2% of patients with fibromyalgia in the 'all pregabalin' treatment group for which the incidence was greater than in the placebo treatment group. A majority of pregabalin-treated patients in clinical studies experienced adverse reactions with a maximum intensity of "mild" or "moderate".

Table 4 Treatment-emergent adverse reaction incidence in controlled trials in Fibromyalgia (Events in at least 2% of all LYRICA-treated patients and occurring more frequently in the all pregabalin-group than in the placebo treatment group)

System Organ Class - Preferred term	150 mg/d [N=132] %	300 mg/d [N=502] %	450 mg/d [N=505] %	600 mg/d [N=378] %	All PGB* [N=1517] %	Placebo [N=505] %
Ear and Labyrinth Disorders						
Vertigo	2	2	2	1	2	0
Eye Disorders						
Vision blurred	8	7	7	12	8	1
Gastrointestinal Disorders						
Dry mouth	7	6	9	9	8	2
Constipation	4	4	7	10	7	2
Vomiting	2	3	3	2	3	2
Flatulence	1	1	2	2	2	1
Abdominal distension	2	2	2	2	2	1
General Disorders and Administrative Site Conditions						
Fatigue	5	7	6	8	7	4
Edema peripheral	5	5	6	9	6	2
Chest pain	2	1	1	2	2	1
Feeling abnormal	1	3	2	2	2	0
Edema	1	2	1	2	2	1
Feeling drunk	1	2	1	2	2	0
Infections and Infestations						
Sinusitis	4	5	7	5	5	4
Investigations						
Weight increased	8	10	10	14	11	2
Metabolism and Nutrition Disorders						
Increased appetite	4	3	5	7	5	1
Fluid retention	2	3	3	2	2	1
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	4	3	3	6	4	2
Muscle spasms	2	4	4	4	4	2
Back pain	2	3	4	3	3	3
Nervous System Disorders						
Dizziness	23	31	43	45	38	9
Somnolence	13	18	22	22	20	4
Headache	11	12	14	10	12	12
Disturbance in attention	4	4	6	6	5	1
Balance disorder	2	3	6	9	5	0
Memory impairment	1	3	4	4	3	0
Coordination abnormal	2	1	2	2	2	1
Hypoaesthesia	2	2	3	2	2	1
Lethargy	2	2	1	2	2	0
Tremor	0	1	3	2	2	0
Psychiatric Disorders						
Euphoric Mood	2	5	6	7	6	1
Confusional state	0	2	3	4	3	0
Anxiety	2	2	2	2	2	1
Disorientation	1	0	2	1	2	0

Controlled Add-On Studies in Adjunctive Therapy for Adult Patients with Partial Onset Seizures *Adverse Reactions Leading to Discontinuation* Approximately 15% of patients receiving LYRICA and 6% of patients receiving placebo in add-on epilepsy trials discontinued prematurely due to adverse reactions. In the LYRICA treatment group, the adverse reactions most frequently leading to discontinuation were dizziness (6%), ataxia (4%), and somnolence (3%). In comparison, <1% of patients in the placebo group withdrew due to each of these events. Other adverse reactions that led to discontinuation of at least 1% of patients in the LYRICA group and at least twice as frequently compared to the placebo group were asthenia, diplopia, blurred vision, thinking abnormal, nausea, tremor, vertigo, headache, and confusion (which each led to withdrawal in 2% or less of patients). *Most Common Adverse Reactions* Table 3 lists all dose-related adverse reactions occurring in at least 2% of all LYRICA-treated patients. Dose-relatedness was defined as the incidence of the adverse event in the 600 mg/day group was at least 2% greater than the rate in both the placebo and 150 mg/day groups. In these studies, 758 patients received LYRICA and 294 patients received placebo for up to 12 weeks. Because patients were also treated with 1 to 3 other AEDs, it is not possible to determine whether the following adverse reactions can be ascribed to LYRICA alone, or the combination of LYRICA and other AEDs. A majority of pregabalin-treated patients in clinical studies had adverse reactions with a maximum intensity of "mild" or "moderate".

Table 3 Dose-related treatment-emergent adverse reaction incidence in controlled trials in adjunctive therapy for adult patients with partial onset seizures (Events in at least 2% of all LYRICA-treated patients and the adverse reaction in the 600 mg/day group was ≥2% the rate in both the placebo and 150 mg/day groups)

Body System - Preferred term	150 mg/d [N=185] %	300 mg/d [N=90] %	600 mg/d [N=395] %	All PGB* [N=670]† %	Placebo [N=294] %
Body as a whole					
Accidental injury	7	11	10	9	5
Pain	3	2	5	4	3

* PGB: pregabalin
† Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
‡ Investigator term; summary level term is amblyopia.