

Ustekinumab Bests Etanercept in Psoriasis Study

BY DOUG BRUNK

Ustekinumab at a dose of 45 or 90 mg at baseline and again at week 4 was more effective than a 50-mg dose of etanercept twice weekly in a 12-week randomized study of patients with moderate to severe psoriasis.

The findings “are generally consistent with those of previous studies,” researchers led by Dr. Christopher E.M.

Griffiths reported. “The high level of efficacy of ustekinumab treatment that we observed was achieved with only two injections during the 12-week period, as compared with twice-weekly injections of etanercept, which may be important for improved treatment compliance.”

For this phase III study, 903 patients with moderate to severe arthritis were randomly assigned to one of three treatment groups: 45 mg ustekinumab at

baseline and week 4 (209 patients), 90 mg of ustekinumab at baseline and week 4 (347 patients), or 50 mg etanercept twice weekly for 12 weeks (347 patients).

Ustekinumab (marketed as Stelara by Centocor Ortho Biotech Services) blocks interleukin-12 and interleukin-23 while etanercept (marketed as Enbrel by Amgen and Wyeth) blocks tumor necrosis factor (TNF)-alpha.

The primary end point was the pro-

portion of patients who achieved at least 75% improvement in the Psoriasis Area and Severity Index (PASI) at week 12 (N. Engl. J. Med. 2010;362:1118-28).

A total of 68% of patients in the 45-mg ustekinumab arm and 74% in the 90-mg ustekinumab arm achieved at least a 75% in the PASI score at week 12, compared with 57% of those in the etanercept arm.

Similarly, 65% of patients in the 45-mg ustekinumab arm and 71% of those in the 90-mg ustekinumab arm had cleared or minimal disease based on the physician's global assessment score, compared with 49% in the etanercept arm.

Disclosures: The study was supported by Centocor Research and Development. The investigators disclosed conflicts with a number of pharmaceutical companies, including Centocor, Amgen, and Wyeth.

Comparison Was Long Overdue

This is the first study to directly compare two biologic agents for the treatment of moderate to severe psoriasis. We have been assuming that ustekinumab was better than etanercept for patients with moderate to severe psoriasis based upon individual clinical trials, but this study now provides proof.

For situations in which insurance companies have a tiered approval process whereby etanercept failure is a condition for ustekinumab use, this study is unlikely to change that requirement. For insurance companies that do not have a tiered approval process, this study could logically lead to treatment guidelines that support initial use of ustekinumab without prior use of etanercept.

Clinicians who provide care to patients with moderate to severe psoriasis have cautious optimism for ustekinumab in terms of its long-term safety profile. However, we really don't know for sure what that long-term safety profile is going to be. Accordingly, some of my colleagues will argue for the use of etanercept over ustekinumab from a safety point of view until more is known.

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Table 3 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=652) %	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	19	25	16	5
Ataxia	1	2	5	9	5	1
Abnormal gait	0	4	4	8	4	1
Confusion	1	2	3	7	3	0
Thinking abnormal	0	2	1	6	2	0
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

* 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.

Other Adverse Reactions Observed During the Clinical Studies of LYRICA Following is a list of treatment-emergent adverse reactions reported by patients treated with LYRICA during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once or more occasions in at least 1/1000 patients; infrequent adverse reactions are those occurring in one or more occasions in at least 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the **Warnings and Precautions** section. Body as a Whole - Frequent: Abdominal pain, Allergic reaction, Fever, Infrequent: Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction; Rare: Anaphylactoid reaction, Ascites, Granuloma, Hangover effect, Intentional Injury, Retroperitoneal Fibrosis, Shock. Cardiovascular System - Infrequent: Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope; Rare: ST Depressed, Ventricular Fibrillation. Digestive System - Frequent: Gastroenteritis, Increased appetite; Infrequent: Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema; Rare: Aphthous stomatitis, Esophageal Ulcer, Periodontal abscess. Hemic and Lymphatic System - Frequent: Erythema; Infrequent: Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; Rare: Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocytopenia. Metabolic and Nutritional Disorders - Rare: Glucose Tolerance Decreased, Urate Crystalluria. Musculoskeletal System - Frequent: Arthralgia, Leg cramps, Myalgia, Myasthenia; Infrequent: Arthritis; Rare: Chondrodystrophy, Generalized Spasm. Nervous System - Frequent: Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching; Infrequent: Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia; Rare: Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Guillain-Barré syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Personality disorder, Psychotic depression, Schizophrenic reaction, Sleep disorder, Torticollis, Trismus. Respiratory System - Rare: Apnea, Atelectasis, Bronchitis, Hiccups, Laryngismus, Lung edema, Lung fibrosis, Yawn. Skin and Appendages - Frequent: Pruritus; Infrequent: Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; Rare: Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Nail Disorder, Peticial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule. Special senses - Frequent: Conjunctivitis, Diplopia, Otitis media, Tinnitus; Infrequent: Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; Rare: Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis. Urogenital System - Frequent: Anorgasmia, Impotence, Urinary frequency, Urinary incontinence; Infrequent: Abnormal ejaculation, Albuminuria, Amenorrhea, Dyspareunia, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, Urine abnormality; Rare: Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulonephritis, Ovarian disorder, Pylonephritis.

Comparison of Gender and Race The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

Post-marketing Experience The following adverse reactions have been identified during postapproval use of LYRICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Nervous System Disorders - Headache. Gastrointestinal Disorders - Nausea, Diarrhea.

DRUG INTERACTIONS

Since LYRICA is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. *In vitro* and *in vivo* studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between LYRICA and commonly used antiepileptic drugs. **Pharmacodynamics** Multiple oral doses of LYRICA were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when LYRICA was co-administered with these drugs. No clinically important effects on respiration were seen.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C. Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) \geq 5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at \geq 1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established. When pregnant rabbits were given LYRICA (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD. In a study in which female rats were dosed with LYRICA (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at \geq 100 mg/kg and offspring survival was decreased at \geq 250 mg/kg. The effect on offspring survival was pronounced at doses \geq 1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at \geq 250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental

toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD. There are no adequate and well-controlled studies in pregnant women. LYRICA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To provide information regarding the effects of *in utero* exposure to LYRICA, physicians are advised to recommend that pregnant patients taking LYRICA enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>. **Labor and Delivery** The effects of LYRICA on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures \geq 50 times the mean human exposure (AUC₀₋₂₄ of 123 μ g-hr/mL) at the maximum recommended clinical dose of 600 mg/day. **Nursing Mothers** It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and efficacy of pregabalin in pediatric patients have not been established. In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses \geq 50 mg/kg. The neurobehavioral changes of acoustic startle persisted at \geq 250 mg/kg and locomotor activity and water maze performance at \geq 500 mg/kg in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established. **Geriatric Use** In controlled clinical studies of LYRICA in neuropathic pain associated with diabetic peripheral neuropathy, 246 patients were 65 to 74 years of age, and 73 patients were 75 years of age or older. In controlled clinical studies of LYRICA in neuropathic pain associated with postherpetic neuralgia, 282 patients were 65 to 74 years of age, and 379 patients were 75 years of age or older. No overall differences in safety and efficacy were observed between these patients and younger patients. LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance LYRICA is a Schedule V controlled substance. LYRICA is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior). **Abuse** In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, LYRICA (450 mg, single dose) received subjective ratings of “good drug effect,” “high” and “liking” to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5500 patients, 4% of LYRICA-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. **Dependence** In clinical studies, following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache or diarrhea [see **Warnings and Precautions**] suggestive of physical dependence.

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans There is limited experience with overdose of LYRICA. The highest reported accidental overdose of LYRICA during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse reactions experienced by patients exposed to higher doses (\geq 900 mg) were not clinically different from those of patients administered recommended doses of LYRICA. **Treatment or Management of Overdose** There is no specific antidote for overdose with LYRICA. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with LYRICA. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility **Carcinogenesis** A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for two years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD. **Mutagenesis** Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro*, was not clastogenic in mammalian systems *in vitro* and *in vivo*, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes. **Impairment of Fertility** In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3-4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. In addition, adverse reactions on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD. In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established. **Human Data** In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo- and pregabalin-treated subjects in mean percent sperm with normal motility was 4% and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied.

Animal Toxicology and/or Pharmacology **Dermatopathy** Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies. **Ocular Lesions** Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) \geq 2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year.



Distributed by:
Parke-Davis
Division of Pfizer Inc.
New York, NY 10017

PBP00681A

Revised November 2009
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