Efalizumab: What Went Wrong?

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ABSTRACT

Efalizumab was approved for psoriasis in 2003. In 2008, two cases of progressive multifocal leukoenecephalopathy (PML) were reported, and in 2009, a third case was confirmed in patients on efalizumab monotherapy for psoriasis. As a result, in Europe, efalizumab's marketing authorization was suspended by the European Medicines Agency. Shortly thereafter, Genentech announced plans to withdraw the drug from the U.S. The withdrawal, which was completed in June 2009, was the result of the risk of an infection that is often fatal, with three confirmed PML cases out of the approximately 2,000 patients treated with efalizumab for more than three years.

Efalizumab was one of the first biologics approved by the U.S. Food and Drug Administration for the treatment of moderate to severe plaque psoriasis. With the later approval of additional biologic agents for plaque psoriasis, prescribers had additional treatment options with improved efficacy and safety. The risks associated with efalizumab for its relatively low efficacy made it unattractive compared to other biologic product treatment options, ultimately leading to its withdrawal.

DISCUSSION

On April 8, 2009, Genentech announced that it would withdraw the drug efalizumab (Raptiva®) from the U.S market. The withdrawal was the result of the risk of progressive multifocal leukoencephalopathy (PML), an infection that is often fatal.[1] In Europe, efalizumab's marketing authorization had previously been suspended by the European Medicines Agency (EMEA).

Efalizumab is a recombinant humanized IgG1 antibody that was approved by the U.S Food and Drug Administration (FDA) in 2003. It was indicated for the treatment of adult patients with chronic moderate to severe plaque psoriasis. Approximately 2% to 3% of the general population suffers from psoriasis,[2] a chronic inflammatory disease. The most common form of psoriasis is plaque psoriasis, which is characterized by raised, inflamed lesions that occur on the body, typically in areas such as the elbows, knees, scalp and lower back. The lesions are covered with silvery white scales and are often embarrassing for the patient. The detrimental psychological effect of these lesions often leads people to seek treatment.

Treatment options for psoriasis include topical products, phototherapy and systemic products, such as the biologics. For patients with mild to moderate plaque

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Table 1. Biologics Used in the Treatment of Moderate to Severe Plaque Psoriasis

Drug Name	Approval Date*	Dosage	Efficacy (% achieved PASI 75)	Black Box Warning Re infection
Alefacept[3]	January 2003	IM- 15 mg/wk	15 mg/wk- 21% at 14wks	No
Efalizumab[3,5]	October 2003	0.7 mg/kg SC conditioning followed by 1 mg/kg weekly	27% at 12 wks	PML, meningitis, serious infection
Etanercept[3,4]	May 2004	50 mg SC biw x 12 weeks, followed by 50 mg SC weekly	50 mg biw- 49% at 12 wks	tuberculosis, serious infection
Infliximab[3,6]	September 2006	5 mg/kg IV three infusions during first 6 weeks, then at intervals of 8 wks	64% at 14 wks,	tuberculosis, serious infection
Adalimumab[3,7]	January 2008	80 mg SC initial followed by 40 mg every other wk starting 1 wk after initial	71% at 16 wks	serious infection

**indication for treatment of plaque psoriasis*

psoriasis, the first step in the treatment involves the use of topical products. Most topical products work by slowing the production of new skin cells and reducing inflammation. These products range from active ingredients, such as coal tar that can be purchased over the counter, to prescription drugs such as steroids and vitamin D analogs.

If a patient does not respond to the initial treatment, other options such as systemic drugs may be utilized for treatment. Biologics are systemic drugs derived from living organisms. The drugs are administered by injection or intravenous transfusion. Some of the biologic agents—etanercept (Enbrel®), infliximab (Remicade®), and adalimumab (Humira®)—block the action of tumor necrosis factor-α (TNF-α), a molecule involved in systemic inflammation. Efalizumab and alefacept (Amevive®) prevent the activation of T cells. In addition, efalizumab blocks trafficking of activated lymphocytes into affected skin. As immunosuppressants, all biologics have the potential to increase the risk of opportunistic infections. Table 1illustrates how efalizumab compared with other biologics available for psoriasis at the time of its withdrawal.

There are many new products in development for the treatment of psoriasis. One important biologic, approved in September 2009 for the treatment of plaque psoriasis, is ustekinumab (Stelara®), made by Centocor Ortho Biotech, Inc. Ustekinumab works by blocking the p40 component of IL-12 and IL-238. The safety and efficacy of ustekinumab have been studied in several trials. In a phase III, parallel, double-blind, placebo-controlled study by Leonardi et al,9 ustekinumab was administered in both 45 mg and 90 mg doses subcutaneously at baseline, week 4 and every 12 weeks thereafter. At the end of the 12-week period, 67.1% and 66.4% of patients receiving 45 mg and 90 mg respectively achieved a Psoriasis Area and Severity Index (PASI) 75 score vs. 3.1% for patients receiving a placebo. Adverse events occurred in 6.3% more patients receiving ustekinumab than in those receiving a placebo. Serious adverse events occurred in 1.2% of patients receiving ustekinumab. There are theoretical concerns regarding the possibility that blocking IL-12/-23 might result in an increase the risk of cancer.10,11 Another biologic agent recently approved for psoriatic arthritis, golimumab (Simponi®), works by blocking TNF-α.[12]

Efalizumab works by preventing the activation of T cells and the migration of T cells to the skin, thereby reducing the area and severity of the inflamed lesions as measured by the PASI score. T cells also play a crucial role in cell-mediated immunity. By reducing the functionality of T cells in the body, efalizumab exposes patients to the risk of opportunistic infections, most notably PML, a rare, usually fatal disease caused by the John Cunningham virus (JCV) that results in neurological impairment.[13] JCV is found in 70% to 90% of humans and causes an infection in children that is innocuous for those with healthy immune systems.[14] When the immune system is weakened by certain immunosuppressants, such as efalizumab, the virus can reactivate and infect the brain, resulting in PML. Once PML spreads, victims experience impairment of

higher cortical functions, visual problems, hemiparesis and cerebellar dysfunction. While therapy is available to mitigate these symptoms, there is currently no known cure, and most PML infections are fatal.

Prior to being withdrawn from the market, efalizumab was given a "black box" warning label on October 16, 2008, to provide a warning of the risk of life-threatening infections. At the time, the FDA had received reports of efalizumab patients being hospitalized due to serious infection. Doctors were advised to warn patients of the risks of serious infection and to weigh the potential risks of treatment with efalizumab. In March 2009, efalizumab's prescribing information was further updated with additional information about PML.

In its letter to health care professionals dated April 8, 2009,[15] Genentech said it was not possible to identify patients at increased risk of PML. The company provided instructions for prescribers to cautiously manage the transition to other forms of treatment and to monitor for signs of PML. Genentech continued to provide the product to allow sufficient time for prescribers to plan a transition to alternative therapies. Efalizumab was withdrawn from the market June 9, 2009.

More than 48,000 patients had been treated with efalizumab.With three confirmed PML cases out of the approximately 2,000 patients taking efalizumab for more than three years,[15] the apparent risks associated with efalizumab became a significant concern to prescribers.

CONCLUSION

Efalizumab was one of the first biologics approved by the FDA for the treatment of moderate to severe plaque psoriasis. With the later approval of additional drugs, such as infliximab and adalimumab for plaque psoriasis, prescribers had additional options for treatment with improved efficacy and safety. The risks associated with efalizumab for its relatively low efficacy made it unattractive compared to other biologic product treatment options. The risk of serious infections such as PML led Genentech to initiate the phased withdrawal of efalizumab.

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