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IXEKIZUMAB: A MONOCLONAL ANTIBODY WELL WORTH FOR PSORIASIS

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ABSTRACT

Psoriasis is a very long lasting disease affecting millions of people worldwide. In the patients affected by psoriasis, the skin cells multiply faster than normal and raised and red plaques appeared over the skin. Psoriasis also has association with psoriatic arthritis, increased risk of depression, diabetes and cardiovascular disease. It is an autoimmune disease and complete cure cannot be achieved when all the current treatment options can relieve the symptoms only for a short time. After a very long searching of more sustainably effective drugs for psoriasis, the FDA recently approved the new drug ixekizumab. Ixekizumab is a humanized IgG4 variant IL- 17A neutralizing monoclonal antibody. It has high affinity for human IL- 17A and effectively inhibits the binding of IL-17A to IL- 17A receptor. As the pathogenesis of autoimmune psoriasis is contributed by IL-17A producing pathogenic T-cells, ixekizumab can completely or almost completely clear the disease in moderate to severe psoriasis. The major drawback is that ixekizumab is an immunosuppressive agent causing increased risk of infection. Ixekizumab brings the hope to psoriatic patients but further immense research needs to be performed in the treatment of psoriasis.

KEYWORDS: Psoriasis, Ixekizumab, monoclonal antibody, autoimmune disease.

INTRODUCTION

Psoriasis is an autoimmune disease causing long-lasting red, itchy and scaly patches of skin. Five main types of psoriasis named plaque, guttate, inverse, pustular, and erythrodermic types are found in which plaque psoriasis is the most common merging about 90% of cases.[1] In psoriasis, the skin cells multiply fast which can be equal to 10 times of normal causing raised and red plaques over the skin. The typical places affected are on the knees, scalp, and elbow and to a lesser extent on palms and soles of the feet. Patients suffer from itchy and painful lesion of plaque causing irritated skin. Fingernails and toenails can become discolored and detached from nail bed. Psoriatic arthritis causing pain and swelling of the joint is a common association of psoriasis. Psoriasis is also associated with increased risk for mental health problems, diabetes and heart disease.[2]

Almost 3 percent of world's population is affected by this uncomfortable disease. The history of disease is very long that the evidence of affecting people can be found in Egyptian mummies. Therefore multiple varieties of treatment have been searched and used in all these years.[3] The treatment options are different and variable among patients. Topical treatments like application of cream and ointment containing corticosteroid, Vitamin D analogues, anthralin, retinoid, coal tar and moisturizers are used. Another treatment option is phototherapy with sunlight, UVB, photochemotherapy, excimer laser. Oral and injected treatment with retinoids, methotrexate, and cyclosporine are also used to treat psoriasis.[4] Now the latest drug which can completely clear psoriasis was approved by Food and Drug Administration (FDA) in March, 2016. This drug ixekizumab was found to completely or almost completely clear the disease in patients with moderate to severe psoriasis. It becomes an important and effective treatment option for this irritating disease.[5]

MECHANISM OF ACTION

It has been found out that interleukin (IL) - 17A stimulates the release of chemokines and cytokines which mobilize and activate the neutrophils and memory T-cells to the site of injury and inflammation.[6] Pathogenesis of autoimmune psoriasis is contributed by IL-17A producing pathogenic T-cells. Ixekizumab is a humanized IgG4 variant IL- 17A neutralizing monoclonal antibody. It has high affinity for human IL- 17A and effectively inhibits the binding of IL- 17A to IL- 17A receptor.[7]

PHARMACOKINETICS

Maximum serum concentration (C_{max}) was achieved in 4 days after single subcutaneous dose. Steady-state concentration (C_{ss}) was achieved in 8 weeks after starting dose and every 2 week dosing regimen.[8] Bioavailability ranging between 60% and 81% was found after subcutaneous injection. Half-life of ixekizumab was 13 days and dosing every 2 weeks caused accumulation. Elimination was suggested to be degradation into small peptides and amino acids via catabolic pathways.[9]

DRUG INTERACTIONS

Ixekizumab being antagonist of IL- 17A can normalize the formation of CYP450 enzymes and therefore in patients treated with drugs which are CYP450 substrates like warfarin and cyclosporine, drug concentration and effects should be monitored. [10] Live vaccines should be avoided in patients treated with ixekizumab. [11]

CLINICAL TRIALS

Ixekizumab approval was based on data by three multicenter, randomized, double-blind, placebo-controlled trials including a total of 3,866 participants. The scores of nature, extent and severity of psoriatic skin changes were assessed in these UNCOVER-1, UNCOVER-2 and UNCOVER-3 trials. [12]

UNCOVER-1

Randomly assigned 1296 patients were given subcutaneous injections of placebo (placebo group), ixekizumab 80 mg every 2 weeks after starting dose of 160mg (2-week group) or ixekizumab 80mg every 4 weeks after a starting dose of 160 mg 4-week group). Response to ixekizumab was defined by static Physicians Global Assessment (sPGA) score of 0 (clear) or 1 (minimal psoriasis) and 75% or greater reduction from baseline in Psoriasis Area and Severity Index (PASI 75). At week 12, patients responding to ixekizumab were reassigned randomly and given placebo, ixekizumab 80 mg every 4 weeks, or ixekizumab 80 mg every 12 weeks for 60 weeks duration. At week 12 assessments, better responses to ixekizumab than to placebo were seen in patients. In 2-week dosing group, 81.8% showed sPGA score of 0 or 1 and 89.1% showed PASI 75 response. In 4-week dosing group, 76.4% showed sPGA score of 0 or 1 and 82.6% showed PASI 75 response. In placebo group, only 3.2% showed sPGA score of 0 or 1 and 3.9% showed PASI 75 response. Among the patients who were reassigned randomly at week 12, sPGA scores were 73.8% for patients receiving 80mg of

ixekizumab every 4 weeks, 39.0% for patients receiving 80mg of ixekizumab every 12 weeks and only 7.0% for patients receiving placebo.[13]

UNCOVER-2

In this trial, 1224 patients were randomly assigned and given subcutaneous placebo, etanercept (50 mg twice weekly), ixekizumab (80mg) once in every 2 weeks or every 4 weeks. In patients receiving ixekizumab, initial injection of starting dose of 160 mg was given beforehand. At week 12, both dose regimens of ixekizumab showed greater efficacy than placebo and etanercept. Regarding PASI 75, 2-week and 4-week dosing group achieved 89.7% and 77.5% respectively when etanercept and placebo groups achieved only 41.6% and 2.4% respectively.[13] PASI 100% was achieved by 40.5% of 2-week dosing group and 30.8% of 4-week dosing group. Only 5.3% of etanercept group and 0.6% of placebo group achieved PASI 100%. Regarding sPGA score, 2-week dosing group and 4-week dosing group achieved 83.2% and 72.9% of sPGA 0/1 score respectively compared to 36.0% of etanercept group and 2.4% of placebo group. For sPGA 0 scoring, 41.9% of ixekizumab 2-week dosing group and 32.3% of 4-week dosing group achieved sPGA 0 when 5.9% of etanercept group and 0.6% of placebo group achieved sPGA 0.[14]

UNCOVER-3

Randomly assigned 1346 patients were given the same pattern with UNCOVER 2 trial. PASI 75 was achieved by 87.3% and 84.2% of ixekizumab 2-week and 4-week dosing group respectively when only 53.4% of etanercept group and 7.3% of placebo group achieved PASI 75. And 37.7% of 2-week dosing group and 35.0% of 4-week dosing group achieved PASI 100. 7.3% of etanercept group and 0% of placebo group achieved PASI 100. Regarding sPGA scoring, sPGA 0/1 score was found in 80.5% of 2-week group, 75.4% of 4-week group, 41.6% of etanercept group and 6.7% of placebo group. For sPGA 0 scoring, 40.3% of 2-week group and 36.0% of 4-week group achieved sPGA 0 score respectively when only 8.6% of etanercept and 0% of placebo group achieved sPGA 0.[14]

ADVERSE EFFECTS, CONTRAINDICATIONS AND SPECIAL POPULATION

The most common adverse reactions seen were increased risk of infection as ixekizumab is an immunosuppressive agent.[15] Upper respiratory tract infections, oral candidiasis, tinea infections and conjunctivitis were other adverse effects of ixekizumab. It is only contraindicated in patients with previous history of hypersensitivity reaction to ixekizumab.[16] No available data was generated regarding the use of ixekizumab in pregnant

women but the risk benefit should be outweighed to be used in pregnant women. The benefits of breastfeeding should also be considered with the mother's need for ixekizumab. Safety and efficacy differences between older and younger patients were not found.[17]

PRESENT STATUS

Ixekizumab is available in a sterile, preservative free, clear and colorless to slightly yellow solution available in a single-dose prefilled autoinjector or a single-dose prefilled syringe to deliver 80mg ixekizumab.[18] Ixekizumab is given by subcutaneous injection and the recommended dose is 160 mg (two 80 mg injections) at week 0 followed by 80 mg at weeks 2, 4, 8, 10 and 12. After 12 weeks, ixekizumab 80 mg was given every 4 weeks.[19] Patients may self-inject after being trained in subcutaneous injection technique using autoinjector or prefilled syringe. Each injection should be given at a different injection site such as upper arms, any quadrant of abdomen or thighs. If one dose is missed, another dose should be administered as soon as possible. After that, the dosing should be resumed at the regular scheduled time.[20]

CONCLUSION

Psoriasis is a prolonged autoimmune disorder affecting many people worldwide. The most significant fact is that there is no cure for psoriasis and various options of treatment have been used to relieve and control the irritating symptoms. It is also associated with psoriatic arthritis, heart disease and depression. Ixekizumab is approved by FDA as it is an effective drug which can completely or almost completely clears the patches of psoriasis and it showed the reliable efficacy during the clinical trials.

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