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# ADALIMUMAB MOSTLY PREFERABLE FOR TREATMENT OF CROHN'S DISEASE

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## ABSTARCT

Crohn's disease is a serious chronic, inflammatory disease of the gastrointestinal (GI) tract that affects more than one million people in North America and Europe. It affects people of all ages but it is primarily a disease of young adults, with onset typically before age 40.The ADALIMUMAB commonly treatment on Ulcerative colitis, polyarticular juvenile idiopathic arthritis, chronic Plaque Psoriasis, ankylosing spondylitis, psoriatics arthritis and also Rheumatoid arthritis by FDA approval but mostly preferable the by FDA approval in Crohn's disease extends the reach of ADALIMUMAB beyond rheumatology and dermatology to an underserved patient population in gastroenterology. ADALIMUMAB in more than 1,400 adult patients with moderately to severely active Crohn's disease ADALIMUMAB has been approved in 67 countries and more than 180,000 people worldwide are currently being treated with ADALIMUMAB. Onset of response was noted after 1 week of treatment. The proportions of patients attaining an ACR20 response at week 1 in the 20-mg, 40-mg, and 80-mg ADALIMUMAB dosage plus MTX groups were 26.1%, 25.4%, 31.5%, respectively.

**Kew word**: ADALIMUMAB, Monoclonal antibody, crohn's disease, TNF, GIT.

## INTRODUCTION

Crohn's disease is a serious chronic, inflammatory disease of the gastrointestinal (GI) tract that affects more than one million people in North America and Europe. It affects people of all ages but it is primarily a disease of young adults, with onset typically before age 40. There is no medical or surgical cure for Crohn's disease and few options exist for patients suffering

with this chronic condition. This approval establishes ADALIMUMAB as the first and only self-administered biologic for the treatment of Crohn's disease. Crohn's disease is the fourth FDA approval in immune- mediated diseases for ADALIMUMAB. [1]

**ADALIMUMAB for Crohn' disease**

In addition to approval in the U.S. to treat Crohn's disease, ADALIMUMAB is the only fully human monoclonal antibody approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) in the U.S. and Europe. ADALIMUMAB resembles antibodies normally found in the body. It works by blocking TNF-alpha, a protein that when produced in excess, plays a central role in the inflammatory responses of many immune-mediated diseases. To date, ADALIMUMAB has been approved in 67 countries and more than 180,000 people worldwide are currently being treated with ADALIMUMAB. Clinical trials are currently under way evaluating the potential of ADALIMUMAB in other immune-mediated diseases. In the U.S., ADALIMUMAB is also approved by the FDA for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of joint structural damage, and improving physical function in adult patients with moderately to severely active RA. ADALIMUMAB is indicated for reducing the signs and symptoms of active arthritis, inhibiting the progression of structural damage and improving physical function in patients with psoriatic arthritis. ADALIMUMAB can be used alone or in combination with methotrexate or other disease-modifying anti-rheumatic drugs (DMARDs). ADALIMUMAB was also approved on July 28, 2006 for reducing signs and symptoms in patients with active.[2.3]

ADALIMUMAB is also indicated for reducing the signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab, the only other approved biologic for treatment of Crohn's disease. The approval was based on data from three pivotal trials of ADALIMUMAB in more than 1,400 adult patients with moderately to severely active Crohn's disease. The CLASSIC I, CHARM and GAIN trials supporting the indication for Crohn's disease evaluated the efficacy and safety of ADALIMUMAB in a diverse group of moderate to severe adult Crohn's disease patients, from those who were naive to anti-tumor necrosis factor alpha (TNF-alpha), therapy to patients who had previously lost response or were unable to tolerate infliximab, a biologic for treatment of Crohn's disease that is delivered by infusion. The safety profile of ADALIMUMAB in the Crohn's clinical trials was similar to that seen in ADALIMUMAB

clinical trials for rheumatoid arthritis (RA). Adverse events reported by >5 percent of ADALIMUMAB 160 mg/80 mg treated patients during the CLASSIC I and GAIN induction trials with a greater incidence than patients taking placebo include injection site irritation (8 percent versus 6 percent), nausea (6 percent versus 4 percent), and joint pain (6 percent versus 3 percent). Adverse events reported by >5 percent of ADALIMUMAB 40 mg treated patients during the CHARM maintenance trial with a greater incidence than patients taking placebo include nasopharyngitis (9 percent versus 7 percent), abdominal pain (7 percent versus 7 percent), headache (7 percent versus 6 percent), and nausea (7 percent versus 6 percent).The recommended dosing of ADALIMUMAB for Crohn's disease is an induction dose of 160 mg with an 80 mg dose at week two, followed by maintenance dose of 40 mg every other week beginning at week four. The initial dose may be given as four injections on one day, or divided over two days. This approval marks the first indication to launch with the ADALIMUMAB Pen, which was approved by the FDA in June 2006. The Touch trial found patients preferred the ADALIMUMAB Pen over the ADALIMUMAB pre-filled syringe, and that it offered improved ease of use and less pain compared to the ADALIMUMAB pre-filled syringe. ADALIMUMAB is the first and only biologic treatment for Crohn's disease to offer adult patients, many who are young and active, the convenience of self-injection in the comfort of their own home. Serious infections, sepsis, tuberculosis (TB) and opportunistic infections, including fatalities, have been reported with the use of TNF- blocking agents, including ADALIMUMAB. Many of these serious infections have occurred in patients also taking other immunosuppressive agents that in addition to their underlying disease could predispose them to infections. Infections have also been reported in patients receiving ADALIMUMAB alone. Treatment with ADALIMUMAB should not be initiated in patients with active infections. TNF-blocking agents, including ADALIMUMAB, have been associated with reactivation of hepatitis B (HBV) in patients who are chronic carriers of this virus. Some cases have been fatal. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating ADALIMUMAB. The combination of ADALIMUMAB and anakinra is not recommended and patients using ADALIMUMAB should not receive live vaccines.[3,4,5]

More cases of malignancies have been observed among patients receiving TNF blockers, including ADALIMUMAB, compared to control patients in clinical trials. These malignancies, other than lymphoma and non-melanoma skin cancer, were similar in type and number to what would be expected in the general population. There was an approximately 3.5

fold higher rate of lymphoma in combined controlled and uncontrolled open label portions of ADALIMUMAB clinical trials. The potential role of TNF-blocking therapy in the development of malignancies is not known. TNF-blocking agents, including ADALIMUMAB, have been associated in rare cases with demyelinating disease and severe allergic reactions. Infrequent reports of serious blood disorders have been reported with TNF-blocking agents. Worsening congestive heart failure (CHF) has been observed with TNF-blocking agents, including ADALIMUMAB, and new onset CHF has been reported with TNF-blocking agents. Treatment with ADALIMUMAB may result in the formation of auto antibodies and rarely, in development of a lupus-like syndrome. The most frequent adverse events seen in the placebo-controlled clinical trials in rheumatoid arthritis (ADALIMUMAB vs. placebo) were injection site reactions (20 percent vs. 14 percent), upper respiratory infection (17 percent vs. 13 percent), injection site pain (12 percent vs. 12 percent), headache (12 percent vs. 8 percent), rash (12 percent vs. 6 percent) and sinusitis (11 percent vs. 9 percent). Discontinuations due to adverse events were 7 percent for ADALIMUMAB and 4 percent for placebo. As with any treatment program, the benefits and risks of ADALIMUMAB should be carefully considered before initiating therapy.[ 6,7,8,9,10]

**PATIENTS AND METHODS**

Eligible patients were 18 years of age or older and had RA that was diagnosed according to the 1987 revised criteria of the American College of Rheumatology (ACR; formerly, the American Rheumatism Association). Active disease was defined as the presence of at least 9 tender joints (of 68 joints evaluated) and 6 swollen joints (of 66 joints evaluated). Additionally, participants must have been treated with MTX for a minimum of 6 months and must have been taking a stable weekly dose (12.5–25 mg, or 10 mg if intolerant to higher doses) for at least 4 weeks before entering the study. All participants must have failed treatment with at least 1 DMARD besides MTX, but no more than 4 DMARDs. Exclusion criteria consisted of standard exclusion criteria used in trials of other biologics in patients with RA. In addition, patients who had received treatment with anti-CD4 therapy or TNF antagonists, had a history of active listeriosis or mycobacterial infection, and had a major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days prior to screening were also excluded.[1]

In Monoclonal antibody, ADALIMUMAB is an IgG1 made by phage display technology with amino acid sequences only from the human germline, making it indistinguishable in

structure and function from natural human IgG1. ADALIMUMAB has high specificity and affinity for TNF and not TNF (lymphotoxin). ADALIMUMAB has a terminal half-life comparable to that of human IgG1 (2 weeks). Study protocol. This study was a 24-week, randomized, double-blind, placebo-controlled trial of ADALIMUMAB with concomitant MTX therapy and was performed at 35 sites throughout the US and Canada. All patients gave their written informed consent, and the Institutional Review Board at each study site approved the trial. After screening and baseline assessments, which included chest radiographs and tuberculin skin testing, study visits were conducted weekly during the first month, every other week during the second month, and monthly thereafter. Patients were randomized to receive placebo or ADALIMUMAB at a dosage of 20 mg, 40 mg, or 80 mg subcutaneously every other week as 2 injections of 1.6 ml per injection. Patients were instructed in self-injection techniques. All DMARDs, except MTX, were discontinued 4 weeks before the study. In addition to MTX, concomitant RA therapies permitted during the study included salicylates, nonsteroidal anti-inflammatory drugs, and corticosteroids (maximum daily dose of 10 mg of oral prednisone or equivalent). Dosage tapering or changes in the route of administration of the concomitant medications were not permitted during the study. Folic acid or leucovorin was permitted. High potency opioid analgesics (e.g., methadone, hydromorphone, or morphine) were prohibited; other analgesics were allowed, although not within 12 hours of study visits. Efficacy assessments. The primary efficacy end point was the ACR20 response. Secondary efficacy end points included the ACR50 and the ACR70 response rates and improvements in ACR core set of disease activity measures for RA clinical trials, as follows: tender joint count, swollen joint count, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, the Disability Index of the Health Assessment Questionnaire (HAQ) and serum levels of C-reactive protein. Other secondary efficacy end points were the score on the Short Form 36 (SF-36), which is a 36-item health survey, and the fatigue scale of the Functional Assessment of Chronic Illness Therapy (FACIT). Serum concentrations of the cartilage destruction markers pro–matrix metalloproteinase 1 (proMMP-1) and proMMP-3 were obtained during the study. Patients who failed to meet or to maintain an ACR20 response but had received study drug (ADALIMUMAB or placebo) for at least 16 weeks were eligible to remain in the study or to roll over to an open-label continuation study with ADALIMUMAB. Patients who rolled over into the open-label continuation study after 16 weeks were considered completers. All patients who did not complete 24 weeks of the study were considered ACR nonresponders in the primary and secondary analyses of week 24 data.

Patients who achieved and maintained an ACR20 response for 16 weeks continued in the study until they had completed 24 weeks of treatment, at which time they were eligible to enter the open-label continuation study. [1, 2]

## RESULT AND DISCUSSION

Disposition of the patients. A total of 336 RA patients were screened, and 271 patients met the entry criteria and were randomized to 4 treatment groups: 62 (22.9%) in the placebo group, 69 (25.5%) in the 20-mg ADALIMUMAB group, 67 (24.7%) in the 40-mg ADALIMUMAB group and 73 (26.9%) in the 80-mg ADALIMUMAB group. Among the 271 patients that entered the study, 161 completed the 24 weeks. Ninety-two patients who did not achieve an ACR20 response elected to enter the open-label continuation study between weeks 16 and 24 of these 92 rollover patients, 23, 27, and 27 were in the ADALIMUMAB 20 mg, 40 mg, and 80 mg groups, respectively, and 35 were in the placebo group. In addition, 18 patients withdrew from the study prematurely because of adverse events (n 7), withdrawal of consent (n 5), lack of efficacy (n 3), protocol violation (n 1), or loss to follow up (n 2). All of the 18 patients who withdrew from the study did so before week 16 and were not eligible to roll over into the open-label extension trial. ACR20 responses. Patients receiving ADALIMUMAB plus MTX demonstrated significant and rapid improvement in disease activity compared with those receiving placebo plus MTX. At week 16, the point at which nonresponders could roll over into the continuation study, ACR20 responders consisted of 21% of the patients treated with placebo, 52% of those treated with 20 mg of ADALIMUMAB, 70% of those treated with 40 mg of ADALIMUMAB, and 62% of those treated with 80 mg of ADALIMUMAB. In the primary analysis, patients who did not complete the 24 weeks were classified as nonresponders, irrespective of clinical response. Treatment with ADALIMUMAB given every other week plus MTX given weekly was found to be statistically superior to placebo plus MTX in terms of the ACR20 response rates at week 24 (P 0.001 for each ADALIMUMAB dosage group versus the placebo group). The ACR20 response rate at week 24 was comparable between the 40-mg (67.2%) and 80-mg (65.8%) dosages of ADALIMUMAB, but slightly lower for the 20-mg dosage (47.8%), as compared with the placebo group (14.5%). The sample size did not allow statistically meaningful comparisons between ADALIMUMAB doses. ACR50 and ACR70 responses. Each ADALIMUMAB dosage plus MTX group was statistically superior to the placebo plus MTX group for ACR50 response rates at week 24.The 40-mg and 80-mg ADALIMUMAB dosages were associated with ACR70 response rates (26.9% and 19.2%, respectively) that

were significantly greater than the response associated with placebo (4.8%) Onset and maintenance of response. Onset of response was noted after 1 week of treatment. The proportions of patients attaining an ACR20 response at week 1 in the 20-mg, 40-mg, and 80-mg ADALIMUMAB dosage plus MTX groups were 26.1%, 25.4%, 31.5%, respectively, compared with 6.5% in the placebo plus MTX group. The proportion of ADALIMUMAB-treated patients achieving a first-time ACR20 response was greatest at week 1, the first scheduled visit. In each ADALIMUMAB dosage group, the percentage of patients achieving an ACR20 response increased from week 1 through week 12 and continued at that level through week 24.

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