Educational Booklet
Important Safety Information
Remicade/Infliximab

janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Introduction

1- Objectives:

- To ensure prescriber awareness of these risks and as well as guidance on the management of them
- The overall goal of the educational program is to provide appropriate and accurate educational tools designed to help optimize the benefit-to-risk profile of Remicade.

2- Approved indications:

-Rheumatoid arthritis -Ankylosing spondylitis -Psoriatic arthritis
-Plaque Psoriasis -Adult and Pediatric Crohn's disease
-Fistulizing Crohn's disease -Adult and pediatric Ulcerative colitis

3- Summary of Safety Concerns: as mentioned in the included slides.

Infusion-related Reactions/Hypersensitivity Reactions and serum sickness-like reactions

- To minimize the incidence of hypersensitivity reactions, including infusion reactions and serum sickness-like reactions, REMICADE should be administered as regular maintenance therapy after an induction regimen at weeks 0, 2 and 6 .

- REMICADE has been associated with hypersensitivity reactions that vary in their time of onset. Hypersensitivity reactions, which include urticaria, dyspnea, and/or rarely bronchospasm, laryngeal edema, pharyngeal edema, and hypotension, have occurred during or within 2 hours of REMICADE infusion. However, in some cases, serum sickness-like reactions have been observed in Crohn's disease patients 1 to 14 days after REMICADE therapy. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgia, polyarthralgia, hand and facial edema, and/or dysphagia.

- REMICADE should be discontinued for severe reactions.

Reference: REMICADE® IPI dated February 2015 - Saudi Arabia

Hepatitis B reactivation

- As also observed with the use of other immunosuppressive drugs, use of TNF-blockers, including REMICADE, has been associated with reactivation of hepatitis B virus in patients who are chronic carriers of this virus (i.e., surface antigen positive).

- Remicade is Contraindicated in all active infections, in case of Hepatitis B reactivation Remicade should be stopped

Congestive Heart Failure

- "In a phase II study aiming at evaluating REMICADE® in moderate to severe congestive heart failure (CHF), higher incidence of mortality due to worsening of heart failure was seen in patients treated with REMICADE®, especially those treated with the higher dose of 10 mg/kg." Therefore, REMICADE should only be used with extreme caution in patients with heart failure and after consideration of other treatment options for their indicated conditions; the dose of REMICADE should not exceed 5 mg/kg.

- Remicade® is contraindicated in patients with moderate or severe heart failure (NYHA class III/IV)
- If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy.

- REMICADE must not be continued if new or worsening symptoms of heart failure appear.

Opportunistic infection

- Infections Bacterial (including sepsis and pneumonia), mycobacterial [including tuberculosis (frequently disseminated or extra-pulmonary at clinical presentation)], invasive fungal, viral, and other opportunistic infections have been observed in patients receiving REMICADE. Some of these infections have been fatal. Patients should be evaluated for tuberculosis risk factors (including close contact with a person with active tuberculosis) and tested for latent tuberculosis infection prior to treatment with REMICADE. Tuberculin tests may yield false negative results, especially in patients who are severely ill or immunocompromised.

- Remicade is Contraindicated in all active infections, in case of Serious Bacterial infection Remicade should be stopped until the incidence is resolved

Reference: REMICADE® IPI dated February 2015 - Saudi Arabia

Tuberculosis

- Infections Bacterial (including sepsis and pneumonia), mycobacterial [including tuberculosis (frequently disseminated or extra-pulmonary at clinical presentation)], invasive fungal, viral, and other opportunistic infections have been observed in patients receiving REMICADE. Some of these infections have been fatal. Patients should be evaluated for tuberculosis risk factors (including close contact with a person with active tuberculosis) and tested for latent tuberculosis infection prior to treatment with REMICADE. Tuberculin tests may yield false negative results, especially in patients who are severely ill or immunocompromised.

- Treatment of latent tuberculosis infection should be initiated prior to therapy with REMICADE.

- Anti-tuberculosis therapy should be considered prior to initiation of REMICADE in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

- Anti-tuberculosis therapy prior to initiating REMICADE should also be considered in patients who have several or highly significant risk factors for tuberculosis infection and have a negative test for latent tuberculosis.

- The decision to initiate anti-tuberculosis therapy in these patients should only be made following consultation with a physician with expertise in the treatment of tuberculosis and taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy.

Lymphoma (excluding HSTCL)

- In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF-blocker compared with control patients.

- During clinical trials of REMICADE in patients with rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, the incidence of lymphoma in REMICADE-treated patients was higher than expected in the general population, but the occurrence of lymphoma was rare.

- Patients with Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy.

Hepatosplenic T-cell lymphoma

- Rare post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF-blockers including REMICADE. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal.

- Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with or immediately prior to a TNF-blocker.

- The vast majority of REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males.

- Cases of hepatosplenic T-cell lymphoma have also occurred in Crohn's disease and ulcerative colitis patients receiving azathioprine or 6-mercaptopurine who were not treated with REMICADE.

- Before initiating or continuing REMICADE therapy in a patient who is receiving an immunosuppressant such as azathioprine or 6-mercaptopurine, carefully assess the need for continuing the immunosuppressant therapy in light of the potential risks of concomitant treatment. The causal relationship of hepatosplenic T-cell lymphoma to REMICADE therapy remains unclear.

Pediatric malignancy

- Post marketing cases of malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) who received TNF-blocking agents (initiation of therapy ≤ 18 years of age), including REMICADE, to treat Juvenile Idiopathic Arthritis (JIA), Crohn's disease or other conditions. Approximately half the reports were lymphomas. The other cases represented a variety of different malignancies and included malignancies that are not usually observed in children and adolescents. Most of the patients were receiving concomitant immunosuppressant, such as methotrexate, azathioprine or 6-mercaptopurine. The role of TNF-blockers in the development of malignancies in children and adolescents remains unclear.

Merkel cell carcinoma

- Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocker therapy, including REMICADE.
- Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

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Reference: REMICADE® IPI dated February 2015 - Saudi Arabia

Malignancy

- In the controlled portions of some clinical trials of the TNF-blocking agents, more cases of non-lymphoma malignancy have been observed among patients receiving a TNF-blocker compared with control patients. The rate of non-lymphoma malignancies among REMICADE-treated patients was similar to that expected in the general population whereas the rate among control patients was lower than expected. In an exploratory clinical trial evaluating the use of REMICADE in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in REMICADE-treated patients compared with control patients. All patients had a history of heavy smoking.

- The potential role of TNF-blocking therapy in the development of malignancies is not known. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Cervical cancer

- A population-based retrospective cohort study using data from Swedish national health registries found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age. A causal relationship between infliximab and cervical cancer cannot be excluded. Periodic screening should continue in women treated with REMICADE, including those over 60 years of age.

- The potential role of TNF-blocking therapy in the development of malignancies is not known. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Live Vaccines/Therapeutic Infectious Agents

- In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines can result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with REMICADE is not recommended.

- Fatal outcome due to disseminated Bacille Calmette-Guérin (BCG) infection has been reported in an infant who received BCG vaccine after *in utero* exposure to infliximab. At least a six month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab.

- Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with REMICADE.

Non-live Vaccines

- In a subset of patients from the ASPIRE study, a similar proportion of patients in each treatment group mounted an effective two-fold increase in titers to a polyvalent pneumococcal vaccine, indicating that REMICADE did not interfere with T-cell independent humoral immune responses.

- It is recommended that pediatric patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating REMICADE therapy.

Reference: REMICADE® IPI dated February 2015 - Saudi Arabia

Post-marketing Experience:

- The most common serious adverse events reported in the postmarketing experience in children were infections (some fatal) including opportunistic infections and tuberculosis, infusion reactions and hypersensitivity reactions. Spontaneous serious adverse events in the postmarking experience with REMICADE in the pediatric population have included malignancies, transient hepatic enzyme abnormalities, lupus-like syndromes, and positive autoantibodies.

- Rare post marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with REMICADE with the vast majority of cases occurring in Crohn's disease and ulcerative colitis, and most of whom were adolescent or young adult males.

- **Overdose**
- Single doses up to 20 mg/kg have been administered without toxic effects.

Any suspected adverse events should be reported to the national spontaneous reporting system according to the national regulations.

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