SAGES

South African Gastroenterology Society

P O Box 13241
Mowbray 7705
South Africa
Tel: +27-21-4043062
Fax: +27-21-4470582
karin.fenton@uct.ac.za
www.sages.co.za

SAGES INFLAMMATORY BOWEL DISEASE REGISTRY STUDY

PROTOCOL

A Non-interventional Registry Study for Treatment with Biologic agents in patients with Moderate to Severe Active Inflammatory Bowel Disease (Ulcerative colitis and Crohn's disease): Long term outcome and Surveillance of adverse events.

1. INTRODUCTION

Crohn's disease (CD) and Ulcerative colitis (UC) are the two main forms of Inflammatory Bowel Disease (IBD). Ulcerative colitis is characterized by intestinal inflammation which is usually confined to the colon and rectum and affects the mucosa and submucosa, whereas Crohn's disease is characterized by transmural inflammation which extends to deeper longitudinal layers, serosa and lymph nodes and can affect any part of the gastrointestinal (GI) tract[1].

UC is slightly more frequent than CD with a global incidence for UC at 37-246 cases/100 000 persons, while for CD the incidence is 26-199 cases/100 000 persons. The incidence in developing counties is lower, although there is a steady increase. UC is more common in males and CD more frequent in females. IBD can affect any person at any age, but onset is most common in the second and third decades[2].

The exact aetiology of inflammatory bowel disease is still unknown however several studies have implicated a combination of infectious, genetic, environmental, and immunological factors. Smoking is strongly associated with IBD. The widely accepted theory of IBD pathogenesis is based on dysfunctional interaction between the gut microflora and mucosal immune system. The aberrant immunologic defects resulting from this can lead to excessive type 1 T helper (Th1) T-cell response in CD and Th2 response in UC. These responses result in exaggerated cytokine (interleukin) and transcription factor release, ultimately raising the level of circulating tumour necrosis factor-alpha (TNF-α)[3, 4].

The conventional therapeutic approach to IBD involves the use of pro- and antibiotics, corticosteroids, anti-inflammatories (5-ASA), immunosuppressive agents like the thiopurines (azathioprine and 6-mercaptopurine), biological agents (anti-TNFα) and surgical intervention[5]. These treatments are used either as monotherapy or a combination therapy in acute flare-ups and to maintain remission; nevertheless, whether these agents are able to modify the long-term course of the disease is unknown at present. Both UC and CD is neither medically nor surgically curable, thus requiring therapeutic approaches to maintain symptom control, improve quality of life, and minimize short and long-term toxicity and complications. The emergence of the anti-TNF-α agents in the late 1990s has been a major clinical advancement in IBD treatment strategies[6]. Unfortunately, issues such as adverse effects and cost are among the pressing set-backs associated with the use of these agents[7].
TNF-α is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Pathologic inflammation, as seen in UC and CD, is associated with elevated levels of TNF-α[8]. There is considerable evidence for the efficacy of anti-TNF agents in CD and to a lesser extent UC.

Fatalities, serious infections and sepsis have been reported with the use of TNF antagonists. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying immune disorder, could predispose them to infections. Tuberculosis (TB) has been observed in these patients on TNF antagonists with increased frequency. TNF antagonists have also been associated with demyelinating disease[9].

In the randomized studies involving TNF antagonists, more cases of malignancies including lymphoma and non-melanoma skin cancer have been observed among patients receiving a TNF antagonist compared with the control group. However, the occurrence was rare. Patients with UC and CD involving the colon have a substantially increased risk of developing colorectal cancer (CRC) compared to the general population. Small bowel cancer occurs at an increased rate in patients with small bowel CD, but the absolute risk remains small. Extra-intestinal malignancies are uncommon in IBD, but lymphomas, biliary tract cancers and squamous cell cancers of the skin may occur at an increased rate in IBD patients[10, 11].
It appears therefore that, although anti-TNF agents offer superior symptom resolution and maintenance of remission in IBD patients with complex, severe disease, it comes at a cost of side-effects as noted above. However, no data is currently available in South Africa on anti-TNF use. As a developing country, South Africa has a high TB burden and Deetlefs *et al* observing a high 12% TB infection rate in a Cape Town IBD cohort[12]. 55% of these infections were prior to their IBD diagnosis. Thus, close surveillance of these patients are important so that long-term complications not noted in clinical trials are systematically documented. This will strengthen the body of evidence for the case of anti-TNF agents leading to a more informed health care provider and ultimately better patient care.

2. RATIONALE

This protocol describes a non-interventional Registry study that will evaluate the long-term safety and efficacy of Biologic agents as used in routine clinical practice in all patients (adults >18 years only) with UC and CD, who qualify for anti-TNF therapy according to the local product label.
The management of the patients in this study reflects current practice. The participating gastroenterologist is free to determine appropriate therapy for each patient and to decide of interventions and investigations as part of routine clinical practice. All study patients will be followed indefinitely or until discontinuation of anti-TNF therapy.

3. STUDY OBJECTIVES

Primary objective: Long-term safety of anti-TNF agents in routine clinical use as recommended in the product label.
Secondary objective: Long-term effectiveness of anti-TNF agents in routine clinical practice as recommended in the product label.

4. INVESTIGATIONAL/TREATMENT PLAN

The treating physician, which must be a gastroenterologist, must sign a consent form with SAGES (see physician consent form). This agreement will be a binding document which will ensure the treating physician adheres to timeous submission of patient clinical detail and the SAGES Biologic committee ensures data capturing and patient confidentiality.

The treating gastroenterologist remain the principle physician in the overall care of the patient. All investigations and treatments offered to the patient will be at the discretion of the treating physician.

Once the decision to treat the patient with an anti-TNF agent has been reached and informed consent (see patient informed consent) has been obtained, the gastroenterologist will complete the SAGES Biologic application form (initial form) and submit this the SAGES IBD committee. Separate initial applications forms exist for CD and UC and the appropriate form should be filled out (see attachment).
The SAGES IBD committee will capture the patient data on a database, where after a panel of SAGES appointed reviewers will decide on the appropriateness of treatment on an anonymous basis. Details of the submitting physician, the patient involved and the reviewers will all be anonymized. The final decision on the submission will be communicated to the treating physician.

The SAGES IBD committee will consist of at least six (3) members. Membership will be on a rotational basis and will be decided by SAGES council. A decision to treat with a Biologic agent will be granted on an agreement of at least three (3) committee members. A treatment decision will be rejected on disagreement of at least two (2) committee members.

Once an agreement to treat with a biologic has been reached, the application together with the council decision will be forwarded to the medical aid fund. The decision taken by the medical aid will be communicated directly to the treating physician.
The patient will start treatment as per local treatment guide lines and product label. Very little interaction is envisaged during this phase, unless obviously if adverse event occurs. As most medical aid funds presently grant Biologic treatment for between three (3) and Six (6) months, repeat applications will be made to the SAGES Biologic committee before the expiration of the current approval. A follow-up application form will be filled out this time and separate forms exist for CD and UC (see attachments). Thus, multiple changes at data capturing will be created in this way.

In addition to the routine clinical data and laboratory data requested on the application form, at least one health related quality of life (HRQoL) questionnaires will be filled out. The Short Quality of Life in Inflammatory Bowel Disease Questionnaire (SIBDQ) (SIBDQ attachment) will be used at the completion of a treatment cycle, or at least once a year. Efficacy data will also be obtained using the Harvey-Bradshaw Index for CD and Mayo score for UC (included in initial application forms) which will be completed by the gastroenterologist with every application and re-application.
Serious adverse events defined as serious infections, opportunistic infections (TB), new malignancies, lupus/lupus-like illness, demyelinating disorders and congestive heart failure will be recorded throughout the study or anytime thereafter.
Information on concomitant medication will be captured at the time of enrolment. Information on medication for recurrence of disease and or any other medication to treat serious adverse events.

5. INCLUSION CRITERIA

All patients deemed eligible for anti-TNF therapy by their treating gastroenterologist.

6. EXCLUSION CRITERIA

Patients unable or unwilling to provide informed consent.

7. STUDY PROCEDURES

(i) Informed Consent:
All patients will provide informed consent. Prior to signing the informed consent, the treating gastroenterologist or designee will explain to the patient the nature and purpose of the study and the data to be provided to SAGES. A copy of the signed consent form will be placed in the patient medical record and a copy given to the patient. The consent will allow the treating physician to release their information to SAGES.

(ii) Demographic Detail:
On enrolment, the treating physician will obtain demographic detail for all patients. Demographic details are set out in the application forms for UC and CD (appendix 3 and 4).

(iii) Medical History:
A complete medical and surgery history as well as history of tobacco and alcohol use will be obtained for each patient at enrolment. In addition, information about IBD specific medical and surgical history will be recorded. History should include disease location as well as duration of disease and/or history of disease related complications.

(iv) Safety Data Collection:
Adverse and serious adverse events will be captured. The description of the event, the date of onset, severity, time course, duration and outcome will be collected. Information about medication taken for the SAE or adverse event of interest will be captured.

(v) Concomitant Medication:
All previous IBD related medications (corticosteroids, aminosalicylates, immunosuppressants and Biologic agents) used to treat the disease will be captured at enrolment. Information on the highest maintained dose, date of last administration, length of time on the medication and reason for stopping the medication will be collected and captured. Any changes made to the IBD medications must be documented.
All other medication the patient is receiving at study enrolment should be recorded along with the reason for use, duration of use and dosages. Any changes made to the medications must be documented.

(vi) Physician Global Assessment:
A physician global assessment will be calculated at study entry and at other time-points deemed necessary by the treating physician. For patient on ongoing therapy, Mayo score will be used and for CD the Harvey-Bradshaw Index.

(vii) Outcomes and Questionnaires:
All patients will complete the SIBDQ after the completion of a treating cycle. For patients on ongoing treatment, the SIBDQ will be completed at least once or twice a year.

(viii) Withdrawal of Patients from the Study:
A patient may withdraw from the study at any time without prejudice. If the treating physician, for any reason, decides to permanently discontinue treatment with a Biologic agent in the best interest of the patient, active data collection will cease but adverse events will continue to be monitored. The reason for withdrawal or discontinuation should be documented.

(ix) Increase Dose/Change of Biologic Agent:
If, for any reason, the treating physician feels that the dose of the current biologic agent should be increased or substituted with an entire different one, a new application should be lodged with SAGES IBD committee.

(x) Adverse Events:
The treating physician will monitor each subject for adverse events and serious adverse events on a routine basis throughout the treatment phase. The physician will assess and record all events in detail including date of onset, description, severity, time course, duration and outcome. This include unplanned/unexpected pregnancy. Events will be followed until they have resolved. This information will be relayed to the SAGES IBD committee timeously.

8. USE OF INFORMATION AND PUBLICATION

All collected information remains the sole property of SAGES and its members. The information is confidential. This information may be disclosed as deemed necessary by SAGES to SAGES members, other investigators, pharmaceutical companies, medical aid funders and regulatory agencies on formal request. This request must be accompanied by a short proposal of the intended use of the data. Data given to third parties may be anonymized.
All potential publications using the database should give recognition to SAGES as owner of the data. SAGES may from time to time, appoint some its members to interrogate the data and use this for publication purposes. This will be at SAGES discretion.

9. REFERENCES

1. Viscido A, Aratari A, Maccioni F, et al. Inflammatory bowel diseases: clinical update of practical guidelines. Nucl Med Commun 2005;26:649-55.
2. Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. Scand J Gastroenterol 2015;50:942-51.
3. Qin X. Etiology of inflammatory bowel disease: a unified hypothesis. World J Gastroenterol 2012;18:1708-22.
4. Lakatos PL, Szamosi T, Lakatos L. Smoking in inflammatory bowel diseases: good, bad or ugly? World J Gastroenterol 2007;13:6134-9.

5. Ko JK, Auyeung KK. Inflammatory bowel disease: etiology, pathogenesis and current therapy. Curr Pharm Des 2014;20:1082-96.
6. Owczarek D, Cibor D, Szczepanek M, et al. Biological therapy of inflammatory bowel disease. Pol Arch Med Wewn 2009;119:84-8.
7. Nielsen OH. New strategies for treatment of inflammatory bowel disease. Front Med (Lausanne) 2014;1:3.
8. Slebioda TJ, Kmiec Z. Tumour necrosis factor superfamily members in the pathogenesis of inflammatory bowel disease. Mediators Inflamm 2014;2014:325129.
9. Fellermann K. Adverse events of tumor necrosis factor inhibitors. Dig Dis 2013;31:374-8.
10. Barral M, Dohan A, Allez M, et al. Gastrointestinal cancers in inflammatory bowel disease: An update with emphasis on imaging findings. Crit Rev Oncol Hematol 2016;97:30-46.
11. Dohan A, Faraoun SA, Barral M, et al. Extra-intestinal malignancies in inflammatory bowel diseases: An update with emphasis on MDCT and MR imaging features. Diagn Interv Imaging 2015;96:871-83.
12. Deetlefs E, Epstein D, Watermeyer GA, et al. Tuberculosis in an inflammatory bowel disease cohort from South Africa. S Afr Med J 2012;102:802-4.