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TNF-α Inhibitor Treatment for Crohn's Disease: Comparative Review of Post Therapy Malignancy between Infliximab and Adalimumab

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Authors' contributions

This work was carried out in collaboration between all authors. Author DH designed the study and made corrections to manuscript, authors NN and JK wrote the first draft of the manuscript and managed the literature searches and analyses of the study, authors AS and AA contributed to the professional content of the manuscript, made corrections to manuscript and prepared final draft for submission. All authors read and approved the final manuscript.

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ABSTRACT

The association between chronic inflammatory disease and cancer has been well established through years of research. In corollary, progressive resistance to chimeric monoclonal antibodies has been reported in literature. The purpose of this investigation was to establish the overall trend of the chimeric monoclonal antibody (Infliximab) failure compared with human monoclonal antibody (Adalimumab). It was opined that this failure may result in subclinical yet cancer-inducing inflammation that could be measurable in patient populations undergoing the therapy by examining cancer prevalence. An overall trend of increased incidence of new malignancy in patient

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populations on Infliximab compared with Adalimumab was confirmed from the literature reviewed. There was also a significant trend of developing Gastrointestinal (GI) related cancer in patients on Infliximab, which corresponds with the majority of the progression process in Crohn's disease. It was opined that future observations in clinical practice will lead to the phasing out of Infliximab as a front-line monoclonal antibody in the treatment of Crohn's disease in favor of less immunogenic monoclonal antibodies. In conclusion an increased incidence of both general and GI malignancies has been widely reported in patient populations undergoing Infliximab therapy than with Adalimumab.

Keywords: Crohn's disease; inflammatory bowel disease; infliximab; adalimumab; TNF-α inhibitor; risk of malignancy; inflammation; oncogenesis.

1. INTRODUCTION

Crohn's disease (CD) which emerged in Europe and North America in the mid-20th century and increased to become a major healthcare problem, is a chronic, relapsing, idiopathic inflammatory bowel disease (IIBD), which causes severe inflammation in the full layer of the Gastrointestinal (GI) mucosa [1]. It falls into the group of diseases under inflammatory bowel diseases (IBD). This disease has been researched for several decades now, but still the etiology remains elusive. However scientists and researchers have done far-reaching advancements in understanding the pathogenesis and the treatment of the disease. There are several factors such as genetic polymorphisms that lead to overly aggressive T-cell responses to a subset of commensal enteric bacteria and some environmental factors like infection i.e. facultative intracellular bacterium, and *Mycobacterium avium*, subspecies paratuberculosis (MAP) [1,2,3] as well as diet which contribute to the development of inflammation in the GI mucosa [4]. The characteristic presentation in Crohn disease is abdominal pain and diarrhea, which may be complicated by intestinal fistulization or obstruction. Unpredictable flares and remissions characterize the long-term course [5,6,7,8]. Ulcerative colitis is a chronic, relapsing, idiopathic inflammatory bowel disease (IIBD) which is similar, and in the same category of condition as Crohn's disease. CD is always considered in the differential diagnosis of Ulcerative colitis. Several differences are seen between them; among which are clinical and pathological including their location in the GI, i.e. anywhere for Crohn's, more of large intestine for Ulcerative colitis, type of inflammation is patchy for Crohn's and continuous for Ulcerative colitis, bleeding is not common with bowel movement in Crohn's while a frequent rectal bleeding is seen in Ulcerative colitis. The ulcerations in Crohn disease look mostly linear giving the classic cobblestone appearance of the mucosa. Histologically a non caseous granuloma and transmural involvement are very characteristic for Crohn's disease, whereas a non granuloma with mucosal and submucosal involvement is seen in Ulcerative condition.

The inflammation usually predates the disease, functioning as a tumour initiator and promoter and as a key determinant of tumour stroma. It leads to the production of several biomarkers. Certain cytokines, especially tumour necrosis factor (TNF), are generated in this process. TNF and other cytokines start the chain reaction, which produces a large of array of pro-inflammatory immune cells. Overtime this inflammatory process produces radical oxygen species, proteinases and other pro-inflammatory and tissue damaging toxic substances.

Literature is replete with increasing evidence suggesting that TNF is responsible for several highly regulated processes in the body such as monitoring the immune response, initiating apoptosis and regulation of molecular adhesion and communication. Studies have shown that there is direct correlation between increased amount of TNF in the serum and stool of patient suffering from Crohn's disease. Inhibition of TNF production in the GI mucosa can stop the inflammation and keep the Crohn's disease in remission [9,10,11].

Initially, Crohn's disease was treated with corticosteroids with limited success due to inability of the drugs to achieve and sustain the inhibition of pro-inflammatory cytokines and numerous side effects in long-term use. TNF inhibition treatment mainly consists of monoclonal antibody drugs, which directly bind to the TNF produced during the disease process, preventing them from binding to their mucosal and immune cell receptors [9]. It should be noted

though, that TNF-α is also a crucial component of the immune surveillance, promoting the activation of NK cells, T cells, B cells, macrophages and dendritic cells. It has been described as a powerful anti-cancer effector cytokine produced by the immune cells, with ability to kill tumour cells mainly by apoptosis [12]. Since TNF-α can enhance or inhibit cancer progression, it is rational to suggest that its inhibition may result in potential increase in cancer incidence [13]. Other side effects include infections, skin reactions and general events such as fatigue, oedema, dizziness, arthralgia, myalgia dyspnoea, migraine etc. Although clinical data available on TNF therapy do not provide clear evidence for a causal relationship between anti TNF-α therapy and malignancy, the long term side effects of these therapies in promoting carcinogenesis remain unresolved. These studies may be associated with a different molecular basis of the monoclonal antibody drug rather than their mechanism of action, which in this case is blocking TNF-alpha [13].

Nonetheless, TNF-α inhibitors have become the primary and the most beneficial treatment of several chronic inflammatory diseases. Several drugs function in this manner such as Infliximab, Adalimumab, Certolizumab and Golimumab which work with the same mechanism of TNF blockade in chronic inflammatory diseases. Although these drugs have similar mechanism of action, their production and derivation is very different. Infliximab, one of the first TNF monoclonal antibody antagonists, is derived from chimeric human-mouse recombinant DNA-produced IgG, whereas Adalimumab is derived from pure human IgG antibodies against TNF-α. TNF therapy has been shown to be very effective in treating patients who do not respond to other conventional treatment [14].

It has been well documented that infliximab and adalimumab have excellent efficacy and have tremendously enriched the treatment of Crohn's disease and other immune mediated diseases. However there have been increasing reports on various safety issues in some recent publications of which the incidence of malignancies had the lowest percentage occurrence. Some of these reports were not consistent with practice experience. Therefore in this review, the risk of developing malignancy through long-term usage of Infliximab and Adalimumab has been evaluated from a number of publications. The purpose was to condense the vast amount of information and make it available for a safe use of anti-TNF agents.

2. METHODOLOGY

This study is a narrative literature review. Several databases of scholarly articles have been used to investigate both Adalimumab and Infliximab. Evidence based knowledge about post therapy malignancy effect of the two drugs during the treatment of Crohn's disease was derived. The inclusion criteria for this study were based on specific number of patients that developed new cases of malignancy during the study. A subset of our research targeted GI malignancies specifically. Those studies that used patient populations that were already predisposed to certain types of malignancies due to age or gender bias were not used. Although some studies used were traditional research, meta-analyses have also been cited.

3. RESULTS

The rate of malignancy in the reviewed articles was significantly lower for adalimumab (5.0 – 5.4 / 1000 patients) than those reported for infliximab (4.2 – 27.7 / 1000 patients) as shown in Table 1. However both Infliximab and Adalimumab patients exhibited decreased rates of malignancy in CD with increasing follow-up years. Regarding our main focus, new malignancy and especially new GI malignancies, there was a noticeable trend of patients on Infliximab who displayed higher rates of oncogenesis (Table 1, Fig. 1).

GI related malignancies in many Infliximab studies were found to have a significantly higher rate of oncogenesis than reported in clinical trials. Adalimumab oncogenesis rates were relatively closer in both clinical trials and research studies (Table 2).

4. DISCUSSION

Crohn's disease, a severe form of inflammatory bowel disease, has been studied extensively due to both its prevalence in the United States and the poor long term quality of life of patient populations. It is a T-helper 1 (Th1) mediated disease characterized by increased production of interferon-γ (IFN-γ) and interleukin 12 (IL-12) [27].

Table 1. Oncogenesis (GI) rate comparative studies with infliximab and adalimumab

Study	No. of patients	Treatment	No. of patients w/cancer (%)
Long et al. <90d	1935	Both or either TNF 1	14(0.72)
Long et al. <90d		TNF 1 + ISS	22(1.14)
Long et al. >365d	1141	Both or either TNF 1	7(0.61)
Long et al. >365d		TNF 1 + ISS	11(0.96)
Biancone et al.	591	Infliximab	12(2.03)
Lichtenstein et al.	1427	Infliximab	6(0.42)
Lichtenstein et al.	7774	Infliximab	139(1.79)
Eshuis et al.	469	Infliximab	13(2.77)
Burmester et al.	3606	Adalimumab	18(0.50)
Burmester et al.	2228	Adalimumab	12(0.54)

References in Table 1: Long et al. [15], Biancone et al. [16], Lichtenstein et al. [17], Eshuis et al. [18], Burmester et al. [19]. Legend: TNF 1(Tumor necrotic factor 1); ISS (Immune system suppressors)

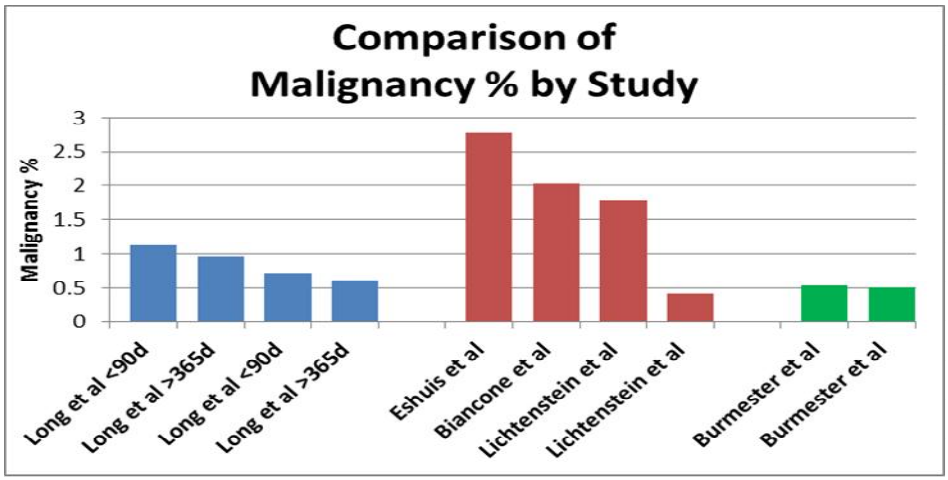

Fig. 1. Comparison of malignancy percentage (%) by study

Legend (Reference to table 1): Blue bar (Both or either TNF 1 & TNF1+ISS), Red bar (Infliximab), Green bar (Adalimumab)

Table 2. Comparative linkage of Inflammation and GI Cancer with or without treatment

Study	Number of patients	Treatment	Number of patients with GI cancer (%)
Freeman et al.	449	None or non-biologic	8 (1.78)
Kamiya et al.	130	None or non-biologic	2(1.54)
Mizushima et al.	294	None or non-biologic	12(4.08)
Gyde et al.	513	None or non-biologic	9(1.75)
Gillen et al.	125	None or non-biologic	8(6.40)
Hanauer et al.	573	Infliximab	6(1.05)
de Vries et al.	147	Infliximab	5(3.40)
Burmester et al.	2228	Adalimumab	10(0.45)
Burmester et al.	3606	Adalimumab	21(0.58)

References in Table 2. Freeman et al. [20], Kamiya et al. [21], Mizushima et al. [22], Gyde et al. [23], Gillen et al. [24], Hanauer et al. [25], deVries et al. [26], Burmester et al. [19]

Presently, management of Crohn's disease involves long-term drug regimens including treatment of the acute phase of the disease through anti-inflammatory drugs and corticosteroids. Corticosteroid use is not recommended in the long-term management of these patients, so during maintenance many providers turn to immunomodulatory drugs. It follows that Crohn's disease presents a unique opportunity for the investigation of malignancy and its relationship with different monoclonal antibodies.

Unlike Ulcerative Colitis and other similar GI issues where surgery can be curative, bowel resection in Crohn's disease may not prevent a relapse of symptoms. In a prospective two year single-centre, open label pilot study, Papamichael et al. [28], reported 23 patients who had undergone ileocecal resection for CD and treated with adalimumab from the 14th post-operative day for prevention of recurrence. Another group of fifteen patients started adalimumab therapy when endoscopic recurrence was confirmed at 6 months post operation despite being treated with infliximab, azathioprine or mesalazine. After two years of follow-up, the authors reported that 9 patients (60%) achieved complete (n = 3) or near complete (n = 6) mucosal healing while 5 of the 9 patients (56%) achieved clinical remission. They concluded that adalimumab therapy may be useful for the prevention of recurrence and maintaining remission after ileocecal resection for CD. In a similar randomized controlled trial, Regueiro et al. reported that infliximab therapy initiated soon after surgery was useful in preventing post-operative recurrence in CD [29]. From the foregoing further large RCTs would be necessary in order to evaluate the effectiveness of adalimumab and infliximab for the prevention and treatment of post-operative recurrence in CD.

4.1 Infliximab and Adalimumab in the Management of Crohn's Disease

TNF-α inhibitors, especially Infliximab, are considered to be the most effective treatment in both initial and maintenance treatment for CD patients when other therapies fail to achieve remission. Infliximab (Remicade) is a chimeric monoclonal antibody directed against TNF-α that is used in a variety of inflammatory diseases. It first came on the market in 1998 and is one of the few monoclonal antibodies that has been in clinical use long enough for meaningful data to be gathered on its potential for malignancy. Because it is a chimeric monoclonal antibody as opposed to a fully humanized one, it is more prone to antibodies being formed against the non-humanized portions of its structure. This in turn can lead to Infliximab becoming less effective over time.

Because of this, most treatments that involve the use of Infliximab also include immunosuppressant agents. The theory behind this is that it will take longer for the host immune system to recognize the foreign segments of the Infliximab structure, prolonging the length of time Infliximab can be administered. Some studies have suggested that infliximab instead be used as an agent during the acute treatment of Crohn's disease rather than the maintenance phase for this reason. However, Infliximab remains a front-line agent for the long-term treatment of Crohn's disease.

Adalimumab (Humira) is a fully humanized monoclonal antibody that is directed against TNF-α as well. It came onto the market much later than Infliximab in 2008. In the treatment of Crohn's disease, Adalimumab has for the most part been used in cases where patients become refractory to treatment with Infliximab. Because it is fully humanized, there is not as strong an incidence of antibody formation against it as is the case with Infliximab. This is best reflected by the dosing regimen of the two drugs: Adalimumab involves injections on a monthly basis while Infliximab requires weekly dosing. Adalimumab can also be administered on an outpatient basis whereas Infliximab administration can require close monitoring, an important distinction between the two drugs for clinicians and pharmacists.

Adalimumab has been found to be very effective in replacing Infliximab in patients developing resistance. Adalimumab has also been found to be equally effective in treatment of CD as an initial/inductive and maintenance treatment. Table 2 shows that Adalimumab causes relatively fewer adverse reactions than Infliximab and the incidence of malignancies has been considerably lower in Adalimumab treated patients [30].

There are two key differences between Infliximab and Adalimumab: Infliximab is a chimeric antibody and blocks the TNF-β as well TNF-α and Adalimumab is a fully human antibody that does not neutralize the TNF-β lymphotoxin. One

study suggests that although Adalimumab is as effective in treatment for CD as Infliximab in the inductive and maintenance phases of CD it is still not widely used a first drug of choice. It is primarily used in CD patients after failure of treatment from Infliximab. Although Adalimumab has the advantage of subcutaneous administration which is superior to the IV administration of Infliximab in terms of cost to the patient and provider, it is suspected that due to lack of enough clinical trials clinicians consider it as a secondary drug of choice [31]. A follow up studies carried out by García-López S et al. [32], in 2014 show that results with both Infliximab, and Adalimumab were very consistent.

4.2 Chronic Inflammation and Cancer Risk in Anti-TNF therapy

Patients with chronic inflammatory disease like Crohn's disease always have a slightly increased risk of malignancy over healthy populations. Risk decreases with patients getting treated with anti-TNF therapy, which is often used in combination with thioprines and other immunosuppressants; however this risk of malignancy in combination therapy has been reported to be higher than in healthy populations. This combination treatment makes patients very susceptible in developing lymphoma or a solid tumor. The link between chronic usage of TNF-α blockade and cancer risk is still under research. Many studies have shown that patients treated with higher doses of anti-TNF-α therapy are at significantly higher risks of malignancy than lower doses [33]. It should be noted, however, that to date no study has been able to determine the malignancy risk of TNF-α binding monoclonal antibodies as a solitary treatment in Crohn's disease. This is because it would be less than optimal for management of the disease and severely unethical.

The Therapy, Resource, Evaluation and Assessment Tool (TREAT) registry for Crohn's disease has extensive data for the disease process and the analysis showing no increased risk of developing cancer from treatment with Anti-TNF-α drugs [34]. In the same vein it was found from animal models that TNF–α blockade prevents the growth of colitis associated colon cancer by blocking the TNF receptors 1 and 2 [18]. Further research in this blockade has shown that continuing maintenance therapy with TNF-α inhibitors rather than symptomatic use may also help prevent the development of colitis associated cancer in chronic patients.

In a recent study of Crohn's disease patients on Infliximab, result showed that there is increased incidence of malignancy in patients aged 40 to 70 years when compared with 10 to 40 years. However, the same could be said of healthy populations. The role of Infliximab or any other TNF-α inhibitor in the carcinogenesis of any neoplasia during Crohn's disease process is very difficult to analyze. The effects of TNF and other pro-inflammatory cytokines may also play an additive role in the risk of oncogenesis when combined with immunosuppressants. Only long term studies with specific treatment regimens and controlled disease processes would aid in finding the exact neoplastic factors associated with Crohn's disease [35].

One other study suggests that the risk of developing malignancy varies with different doses of TNF alpha inhibitors. The risk of developing cancer was no different than placebo group in the patients receiving low doses of infliximab or adalimumab, whereas it increased 4-fold, when treated with high doses of the same drugs [17].

Several studies have linked Crohn's disease to an increased risk of GI malignancy, particularly colorectal cancer. Recurrence of inflammation in Crohn's disease begins slowly as drug resistance sets in. This inflammation will typically be sub-clinical early on, though non-specific inflammatory markers have been used in the monitoring of these conditions. As a result, there are periods during the long-term maintenance of this disease where inflammation reduction is less than optimal. Although inflammation has long been implicated in oncogenesis, more recently it has been directly linked. Table 2 and Fig. 2 show the reported incidence of inflammation and gastrointestinal cancer during treatment with or without adalimumab and infliximab respectively. The incidence of malignancy was low with adalimumab monotherapy (4.5–5.8 / 1000 patients) compared with infliximab monotherapy (10.5–34.0 / 1000 patients) while those untreated or treated with non-biologics exhibited relatively higher rate of incidence (15.4–64.0 / 1000 patient population). Bressier and Siegel compared the monotherapy and combination therapy of anti TNF drugs and determined the relative risks of malignancy as well as the expected rate of malignancy from the patients with CD and general population respectively. They reported that patients who received combination of adalimumab or infliximab with immunomodulator exhibited increased risk of malignancy (Relative

Risk 2.82, CI 95%) and greater than expected incidence of malignancies compared with those on monotherapy (standard incident ratio 3.04, CI 95%). They however concluded that the incidence of malignancy with adalimumab monotherapy was not significantly greater than the general population while co-administration with immunomodulators increased the risk significantly [36]. It suffices to state that though post-therapy risk of malignancy was evident in treatment of CD with adalimumab and infliximab, there have been no better alternatives to date. Therefore monotherapy of these biologics are still of great value.

4.3 Correlation between Chronic Inflammation and Cancer Risk

There are several different mechanisms through which inflammation occurs and in some cases triggers oncogenesis. Tumor cells have high concentrations of certain types of inflammatory cells and some signaling molecules. The clinical markers which pathologists look for in an invasive cancer are tissue remodeling, angiogenesis and other wound healing characteristics. These cues are fundamental in cancer development and also closely resemble features of chronic inflammatory process in post-destruction of tissue.

In some cases certain inflammatory mechanisms are aimed concomitantly by some oncogenes which activate the production of pro-inflammatory cytokines. In a few other cases, these activated oncogenes lead to necrotic cell death by inhibiting apoptosis. Both cases lead to inflammation which eventually promotes tumor growth and development. This could be seen when there is mutation in the RAS gene family, where it triggers the transcription of the interleukin-8, a chemotactic factor for neutrophils. Another example is seen when mutations in the N-myc and blc-2 genes inhibit apoptotic cell death, leading to cell necrosis and consequently activating the NF-KB pathway.

Macrophages are considered a key factor in healing due to chronic inflammation. Macrophages are also considered to be the tumor makers. Macrophages are normally associated with both primary and secondary tumors, these macrophages are called tumor-associated macrophages (TAM). There are several chemo-attractants, which show evidence of promoting macrophage deposition through the dense vascularization in the tumor. Some of these key markers for macrophages are CSF-1, CCL2-5, CCL-8 and VEGF. According to some studies, it can be concluded that there is a positive relationship between the number of macrophages in a solid tumor with its micro-vessel density, invasion and metastasis [37]. Mast cells and eosinophils show inconclusive results about tumor genesis. Although their presence in high levels in a tumor is inevitable, their effects have pro or anti-tumor development which is based on their location in the tumor and the type of tumor. Dendritic cells have been found to have beneficial effects in destroying

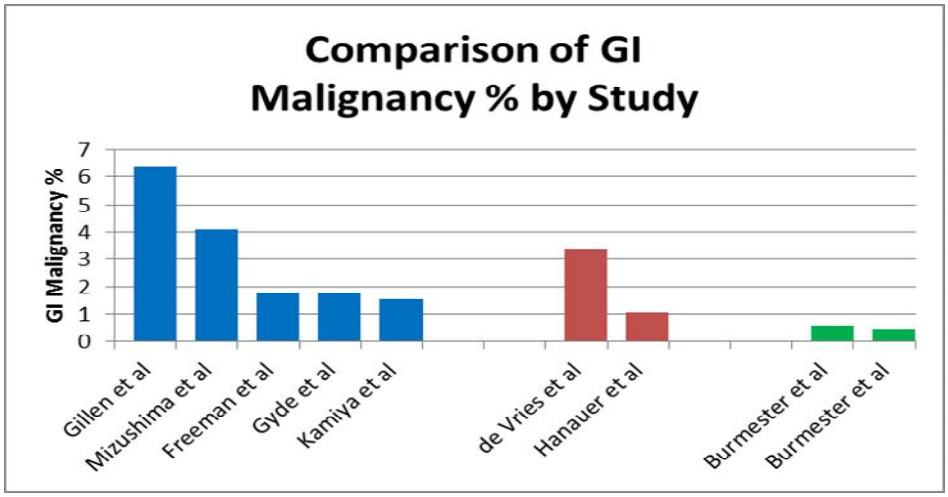

Fig. 2. Comparison of GI malignancy percentage (%) by study

Legend (Reference to table 2): Blue bar (None or non biologic), Red bar (Infliximab), Green bar (Adalimumab)

tumor cells, prolong survival and reduce incidence of metastasis in some cancers, especially for lung and stomach cancer patients. B cell immunity or instantaneous humoral response in chronic inflammatory disease patients has been shown to provide poor prognosis [38].

The transition of chronic inflammatory process to development of cancer could be explained either by overcompensation of healing or the traditional mutation of so called “gatekeeper genes” or tumor suppressor genes, like p53, APC, Rb. Under chronic inflammatory conditions, proliferation of the mutated cells occurs due to high mitotic activity. These inflammatory marker cells with dangerous reactive oxygen species possess the potential to proliferate and give rise to neoplastic cell growth. These neoplastic cells when in contact with growth factors stimulate angiogenesis and metastatic invasion. Some of the common inflammatory biomarkers for Crohn’s Disease are anti-ompc, anti-I2 and ASCA [39].

The first disease these drugs were targeted on was Rheumatoid arthritis (RA) which has been studied more extensively than any other disease process treated by TNF-α inhibitors. Studies on RA patients have shown that this therapy is associated in development and reactivation of Non-Melanoma Skin Cancer (NMSC) [40]. There is a relatively large amount of data available for the RA patients treated with different TNF-α inhibitors in comparison to Crohn’s disease.

4.4 Other Risks Associated with TNF-α Inhibitors

It has been found that TNF-α plays a critical role in restricting the development of infection and malignancy in inflammatory bowel disease. The new generation of TNF-α inhibitors are very potent in binding to both forms of TNF-α (soluble and transmembrane). These drugs, Infliximab and Adalimumab, have been used to treat patients with Crohn’s disease as well as Rheumatoid Arthritis, Psoriasis, Psoriatic arthritis and Ulcerative colitis. With this treatment there are also some serious side effects. Infections such as tuberculosis [41], lymphomas and other malignancies have been observed in numerous studies. Some studies have found that TNF-α inhibitors can reactivate latent infections and cancers as well [42].

It is very important to keep in mind that the disease process of CD produces an aggressive systemic inflammatory reaction which produces several tumor promoting agents like reactive oxygen species. This fact makes it very difficult for researchers to segregate adverse reactions caused by drugs alone. Several studies show that CD patients who are immunosuppressed are at high risk for opportunistic infection like EBV, which makes patients highly susceptible to developing malignancy. Higher presence of infections and lymphomas were found in patients on a combination treatment of Infliximab with Azathioprine and 6-mercaptopurine than Infliximab monotherapy [40]. Data obtained from one study showed that patients who developed malignancy while on TNF-alpha inhibitors could possibly have asymptomatic neoplasia at enrolment of clinical trial and highly suggest the need of thorough screening tests before induction [16].

4.5 Limitation of the Study

A major limitation of this study is that it was not designed as a systematic review but rather as a narrative review; perhaps a systematic review with meta-analysis would have given a better outcome and minimize perceived bias and omission in the study. Since more studies are still ongoing in treating this condition with these drugs, it is imperative that the result of this study should be interpreted cautiously.

5. CONCLUSION

In conclusion, the choice of therapy is like any other condition, but because of the failure of many therapeutic options, as well as the pain and suffering of this patient together with the economic effect, it is imperative that physicians decide on what risk to take in order to achieve a good outcome. The therapy with Infliximab may have an increased risk of oncogenesis in comparison to Adalimumab. Although the risk for cancer developing with either monoclonal antibody is lower than the incidence in untreated Crohn’s disease, clinicians must weigh the difference in malignancy between the two drugs when choosing which treatment to use. Currently Infliximab is the front line monoclonal antibody used in most treatment protocols, but perhaps when weighing the risk of malignancy future protocols may lead with Adalimumab. Adalimumab induces remissions more frequently than placebo in adult patients with Crohn disease specifically for those patients with intolerance to

many actual treatments including infliximab. It is a fact that further long-term controlled clinical trials are required to investigate this potential change in protocol or even an alternative with new therapeutics.

CONSENT

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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