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Research Article

SIDE EFFECTS OF DIFFERENT TREATMENTS IN LEBANESE IBD PATIENTS

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A R T I C L E I N F O

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A B S T R A C T

IBDs (inflammatory bowel diseases) remain a complex issue, and the therapeutic approach is constantly changing and will continue to evolve during the future. Thus, descriptive and comparative studies based on real life experience of different therapeutic agents used in the treatments of IBDs are important in order to have a global assessment of the safety and side effects of those therapies. A retrospective analysis was conducted in this study and has included 112 patients with IBD, retrieved from a single center in Lebanon, in orderto assess the side effects in Lebanese IBD patients treated with different treatment regimens: biologic, immunosuppressors, or a combination of both drug classes. Side effects were mainly observed among IBD patients treated with azathioprines (31%) compared to 9% with the biologic treatment and 10% with the combination therapy. Side effects were mainly observed among smokers with Crohn's disease as well as nonsmoker patients having Ulcerative Colitis. The side effects described in our study were mainly: Leucopenia, anemia, thrombocytopenia, hepatotoxicity, acute pancreatitis, Hodgkin Lymphoma, Non Hodgkin Lymphoma, cutaneous reaction, myalgia, infections and alopecia.

INTRODUCTION

IBDs are a group of inflammatory conditions with an unknown or unclear etiology. The two major IBDs are Crohn's disease and Ulcerative colitis[1]. Treatments and therapeutic approaches in IBDs are constantly evolving, and emerging treatments, such as biologic treatments, are constantly being studied in many recent clinical trials to evaluate and compare the effectiveness and outcomes of each one of them, and to determine the risks versus the benefits that physicians face when using such therapy.Treatments of IBDs includes: Anti-inflammatory drugs, Immunomodulators such as Azathioprine as well as Biologic treatment which includes Infliximab, Adalimumab. Some other biologic therapies that may be used are Certolizumab, Natalizumab, Vedolizumab and Ustekinumab.

Immunosuppressors

The immune response in Inflammatory bowel diseases releases inflammation-inducing chemicals in the intestinal lining. Thus, the goal of this treatment is to suppress this response. Some examples of immunosuppressors include Azathioprine (Imuran), Mercaptopurine, Methotrexate and Cyclosporine. In the liver, Azathioprine is converted to 6-thioguanine which impairs the Synthesis of the DNA by inhibiting the proliferation of lymphocytes.

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In fact, immunosuppressors are usually used in the maintenance therapy because they require two to four months to achieve their maximal effect. Azathioprine is given at doses of 1 to 2.5 mg/Kg per day P.O with a maximum of 200mg/day. The dose of the 6MP is generally 1 to 1.5 mg/kg P.O per day with a maximum of 150mg/day. The adequate dose varies since there is a genetic variation in the metabolism of thiopurine that involves the TPTM (thiopurine methyltranferase genotype). This enzyme is essential in the metabolism of thiopurines, hence, the patient who lacks TPMT is at risk for pancytopenia, and thus, should not be treated with thiopurines. Azathioprine is generally well tolerated and has no external cosmetics side effects, but on the other hand it has increased the risk of bacterial, fungal and viral infections. Pancreatitis, myelosuppression, photosensitivity, elevated transaminases and hepatotoxicity are the main side effects that explain the necessity of frequent monitoring while being treated with Azathioprine. The treatment should be stopped or adequate changing of doses should be done when some significant side effects appears such as severe leukopenia (WBC less than 3000). Adjustment of drug dosage can also rely on the monitoring of blood levels of 6MMP (6-methylmercaptopurine), which can be helpful in assessing compliance and drug metabolism. Thiopurines are also linked to a mild increased risk of development of certain types of cancer, such as cervix/vulva cancer and skin cancer, in addition to lymphoma, which might be associated with an increased risk of EBV infections in patients receiving thiopurines.[2]The side effects of Azathioprine are either dose-dependent or dose independent. The dose dependent side

effects are bone marrow depression (1 to 2%) and liver dysfunction (0.3%). On the other hand, the dose independent side effects are ~~as~~ pancreatitis (1.4 %), allergic reactions, such as drug fever, arthritis or rash (2.3%), nausea and pneumonitis. Individuals on Azathioprine are also at higher risk for infections and cancer. A meta-analysis of six studies ~~has~~ concluded that IBD patients treated with Azathioprine have a four times higher risk of lymphoma when compared to the general population[3]. This risk seems to increase gradually over the years, and a significant reduction in the risk was noted with the discontinuation of therapy. Moreover, a retrospective study states that the risk of neoplasia was mainly increased in patients who developed sustained leukopenia [4-5]. In addition, in one series of 396 patients with Crohn disease or ulcerative colitis, malignancy (a diffuse histiocytic lymphoma of the brain) was seen in only one patient and was likely related to the treatment with Azathioprine. On the other hand, despite the presence of the risk of lymphoma, the study concludes that treatment with Azathioprine to preserve remission was associated with an increase in quality of life [6-7].

Many reports have also stated an association between treatment with Azathioprine and lymphoproliferative disorders[3-8]. In a prospective cohort study of 19,486 patients with IBD, patients treated with Azathioprine had an increased risk of developing lymphoproliferative disorders [7]. The incidence rates of lymphoproliferative disorder were:

- 0.9 per 1000 patient-years in patients under treatment
- 0.2 per 1000 patient-years in patients who had discontinued therapy
- 0.26 per 1000 patient-years in patients who had never received therapy

It was also shown that overall IBD patients treated with Azathioprine have more risk of developing lymphoproliferative disorders when compared to those who had never received this treatment. In the study of Fraser AG, *et al*, in which a 30-year review of an IBD patient attending oxford clinic, showed the efficacy of Azathioprine in UC (Ulcerative colitis) and Crohn's disease and its efficacy was sustained over five years[9]. Moreover, an overview of the evidence based indication of Azathioprine was done in the study of Herrlinger *et al*, in which the optimal dose of Azathioprine in Crohn's disease was 2.5mg/Kg body weight, and the treatment should be maintained for 4 years or more. Also, the study of Caprilli R *et al* has shown that among the immunosuppressors, only Azathioprine and Methotrexate are appropriate in the treatment of IBDs.[10]In addition, in the study of sandborn WJ and in the retrospective study of Leite S *et al* it was shown that Azathioprine is safe in ~~a~~ long term treatment and its efficacy was observed in induction as well as in maintaining remission at 12 months.[11] Some studies have evaluated and showed the importance of thiopurines in patients who are newly diagnosed with Crohn's disease as part of the initial treatment strategy. This approach provides a possible decrease of relapse, but is linked to a small rate of complications (infections, leukopenia, and pancreatitis) and a mild increased risk of lymphoma.

Biologic treatment

Over the last decade, the biologic treatment has revolutionized the treatment approach in IBD. This category of drugs includes tumor necrosis factor (TNF)-alpha inhibitors, also called biologics, which work by neutralizing a protein produced by the immune system. TNF alpha was known as cachexin and was recognized for its ability to lyse tumors. It is difficult to assess the risk of malignancy conferred by this therapy from the baseline risk that already exists because of the disease by itself. For example, patients with UC are already at increased risk of colon cancer. Hence, the inhibition of TNF alpha might potentiate the risk of malignancy, even though many studies have shown that the risk is not significantly increased. Furthermore, there has been a reported association between the use of biologic therapy and higher risk of opportunistic infections. Consequently, more studies and data need to be conducted to attain a better assessment of this side effect and safety of those drugs. Thus, the risk of malignancy conferred by this therapy is not very well assessed, and the side effects and the necessity of any monitoring are still an issue that needs to be considered and compared to the older treatment regimens of IBDs. Therefore, the administration of such therapy always needs to take into consideration the benefits versus the risks and further studies are needed to evaluate this point. The side effects that are described in this class of treatment are: reaction at the injection site, leukopenia (neutropenia), infections infusion reactions, demyelinating disease, heart failure, cutaneous reactions including psoriasis, malignancy and induction of autoimmunity.

Examples of anti TNF alpha include Infliximab (Remicade), Golimumab (Simponi) and Adalimumab (Humira). Infliximab is a chimeric (mouse/human) anti TNF alpha antibody. Some patients who do not respond or losethe response to one anti-TNF agent may tolerate a different anti TNF agent. Side effects described with infliximab are mainly Infusion reactions (acute or delayed), neutropenia, infections and demyelination. Infusion reactions are classified as one of two types: acute, which lasts less than 24 hours, and delayed, which lasts more than 24 hours. True anaphylactic reactions can occur in some patients treated with Infliximab.[12] However, the majority of acute infusion reactions that occur with Infliximab treatment are more characterized by nonspecific symptoms and are classified more accurately as anaphylactoid (nonallergic) reactions[13]. These reactions are not mediated by IgE. The frequency and severity of acute infusion reactions were evaluated in a study of 165 consecutive patients who received a total of 479 infliximab infusions.

[14]The following observations were made

10% experienced at least one infusion reaction

Mild, moderate, or severe reactions occurred in 3.1, 1.2, and 1.0 percent of infusions, respectively. Also, the use of Infliximab in patients with fistulizing disease was approved based on 2 trials where closure of all fistulas was noted in 68% of cases.

Neutropenia and infection may occur and are usually mild. Neutropenia is defined as neutrophils less than 2 x 10^9 cells/L. It occurred under the treatment with anti TNF alpha in 19 percent of 367 patients with IBD[15]. Levels of less than 1.5 x 10^9/L were seen in 9 percent. The underlying mechanism of neutropenia is not clearly understood. In addition, patients who developed neutropenia had significantly lower baseline neutrophil counts compared with those who did not (4.2 x 10^9/L versus 6.2 x 10^9/L). A decrease in neutrophils was seen in 74 percent of patients after two weeks of therapy (mean decrease in neutrophil counts of 1.1 x 10^9/L). On the other hand, a mild increase in the other white cell subsets

(lymphocytes, monocytes, and basophils) was noticed. No discontinuation of therapy was necessary in most of the patients who developed neutropenia, but persistence or recurrence of this side effect was often seen in those switched to another TNF-alpha inhibitor. Among patients who developed neutropenia, serious infections occurred in only 6% (4 of 69). Less than 1 % of all patients in the cohort developed a severe neutrophilia with a neutrophilic count less than 0.5 x10^9/L. Other cytopenias are uncommon. Pancytopenia and aplastic anemia are rare.

Demyelination: concerning the demyelination effect: a 2001 review of cases of demyelinating disease in the FDA database only showed 2 cases that are associated with Infliximab .[16]

A retrospective study of Ioanna parisi *et al* has shown the safety of Infliximab in terms of liver impairment. In addition, the safety of infliximab has been demonstrated in the study of Friese that focused on the safety of this drug in the pediatric population: no serious infection was noted but some mild reactions and infusions reactions were noted with this drug. Furthermore, a long term cohort study of H Fidder *et al* has demonstrated the safety profile of infliximab. Moreover, the study of Lichtenstein *et al*[17] has shown that infliximab does not significantly increase the risk of infections, malignancies and mortality.

Adalimumab is a human anti TNF alpha monoclonal antibody that was reviewed in some recent studies and showed that it can effectively induce and maintain remission in patients with Crohn's disease, and more recent published data has also shown its efficacy in UC. A single center cohort study reflecting real life experience with Adalimumab and Infliximab treatment in patients with UC has shown that both are effective in generating induction and maintenance of response among these patients. Adalimumab has been associated with some side effects which mainly are:

- Dermatologic: Skin rash (5% to 11%), injection site reactions (5% to 21%) that include erythema, pain, itching, hemorrhage and swelling
- Central nervous system: Headache (12%)
- Immunologic: Antibody development (3% to 26%)
- Neuromuscular and skeletal: Increased creatine phosphokinase (15%)
- Infection, mainly in the upper respiratory tract infection (17%), sinusitis (11%)

Also, a higher frequency of nonmelanoma skin cancers was noted in patients treated with Adalimumab (0.7% patient years), when compared to the control group (0.2%patient years).

Combination therapy

The use of concomitant immunosuppressive therapy has also shown additional benefits compared to Infliximab alone. In fact, a metanalyses of 24 studies concluded that adding an immunomodulator such as Azathioprine to the biologic drug (Infliximab) has lowered the frequency of formation of antibodies to Infliximab, which was reflected in higher response and remission rates. However, a large cohort study has shown that such combination is likely to have a higher potential of malignancy (especially lymphoma) compared to the monotherapy (Infliximab). Thus, administering the combination therapy may be appropriate mainly for patients having moderate to severe active Crohn's disease. Furthermore, hepatosplenic T-cell lymphoma, is a rare T-cell lymphoma that has occurred mainly in adolescent and young adult males with Crohn's disease or Ulcerative Colitis treated with Adalimumab, and who received concomitant Azathioprine or Mercaptopurine. The underlying mechanism of the development of malignancy is not fully understood but when compared to the general population, an increased risk of lymphoma has been revealed in clinical trials. The safety and efficacy profile of Adalimumab and Infliximab have both been proved but a comparison between their respective efficacy and safety profiles needs further assessment. In addition, the further benefits versus risks taken while adding Azathioprine to Adalimumab or Infliximab also need to be evaluated in further studies.Moreover, in a trial of 133 patients with new onset of Crohn's diseasewho received a combination therapy (Infliximab and Azathioprine) or glucocorticoids followed by a treatment with Azathioprine and Infliximab as needed, it was noticed that significant side effects were similar in both groups (31% versus 25%)[16].

The main side effects of different class of drugs and the necessity and frequency of any monitoring are also an issue that needs to be discussed in further studies. Few studies have compared the outcomes and side effects of combination therapy to the classical treatment with Azathioprine alone, or to the treatment with one biologic drug alone. Our study will focus on side effects observed among Lebanese IBD patients treated with an immunomodulator (Azathioprine) alone, with a biologic (Infliximab or Adalimumab) alone, or with a combination of Azathioprine and a biologic treatment.

METHODOLOGY

A retrospective systematic review was done based on of the records of IBD patients. The primary outcomesbehind the research is to assess and describe the side effects observed in IBD patients under different treatment regimens: Azathioprine, Biologic (Infliximab or Adalimumab) or a combination of Azathioprine with Adalimumab. Side effects of the biologic treatment and immunosuprresors in the Lebanese IBD patients were the main outcomes in this study. The statistical analysis was performed using SPSS statistics. characteristics of patients were described along with each side effect observed in the study.

Data Collection

The data wascollected from a single center in Lebanon: CHUNDS Hospital. The data spans over a period of 1 year to include 112 patients with IBD (Crohn's or Ulcerative Colitis).The data was collected after approval of the CHUNDS hospital committee. Medical files of all patients with IBD in the center were collected and data was obtained from the medical files that respond to the inclusion criteria of this study. Ethics and privacy of all patients included in the study were totally preserved. The data collected included: Gender, Disease type, smoking, treatment class and side effects observed under the treatment. The confidentiality of patients and all the ethical principles of the world medical association were preserved while collecting data.

Inclusion and Exclusion Criteria

The inclusion criteria for this research includes having Crohn's disease or Ulcerative colitis, being a Lebanese

patientsTreated with Azathioprine, Infliximab, Adalimumab, and Azathioprine + Adalimumab. Inclusion criteria also entailed being on an outpatient basis. Only patients with adequate follow up were included in the study. The Exclusioncriteria included were: any discontinuation of treatment, cross overs from one treatment regimen to another, patients with prior surgical procedures such as bowel resections and anastomoses.

RESULTS

112 patients were included in the study: 66 males and 46 females. The patients were followed for a duration of 12 months for the monotherapy (immunosuppresors or Biological) and 6 months for the combination therapy. 59 patients had Crohn's Disease and 53 had Ulcerative Colitis. Among the sample population, 21.5% of patients were smokers, and 78.5% were nonsmokers. (Table1)

It was observed that the majority of patients (62.5%) received immunosuppressive treatment, while 28.5% received biological treatment, and only 8.9% received a combination of immunosuppressive and biological treatment. In more detail, patients receiving Azathioprine were 70 patients while 32 patients received either Adalimumab (22 patients) or Infliximab(10 patients), and only 10 patients received a combination of Azathioprine and Adalimumab. The side effects were stratified between smokers and nonsmokers since smoking is known to have an impact on side effects and to flare up the rate in IBD patients. Higher side effects rate was noticed inpatients treated with Azathioprine (31%) when compared to the biological treatment (9%) or the combination treatment (10%). During the 12 months of follow up treatment with AZT, 10 patients have shown a decrease in the white blood cell count, 4 developed mild anemia, ???? had mild decrease in the number of platelets, 1 patient has suffered from pyrosis and mild myalgia, 1patient had asthenia, 1 patient had sore throat, 1 patient had anemia alopecia and decrease in WBC and 1 patient had mild elevation in the transaminases level. Four patients had discontinued azathioprine after 1month of treatment due to a significant leukopenia (WBC count less than 3000). One patient had discontinued the treatment with azathioprine after 4 months of treatment due to anemia and leukopenia. Hepatotoxicity, anemia and leukopenia have been reported in 1 patient. One patient treated with azathioprine has suffered from severe thrombopenia (platelet less than 15000). Also 1 Patient developed a non Hodgkin lymphoma under azathioprine treatment. 1 patients followed during the 12 months with Biological treatmentdeveloped cutaneous allergy and 1 patient had a mild decrease in WBC count. Concerning the patients treated with the combination therapy for 6 months, there were no side effects noted among those patients during that period. It was seen that the largest number of patients exhibiting side effects had been receiving azathioprine (22 patients), while only 3 patients had side effects with Infliximab or Adalimumab, and only 1 patient with the combination treatment. This, however, did not reveal a statistically significant relationship showing that azathioprine is associated with the highest incidence of side effects because the significance level was weak. (Table 2)

Table 1 Baseline characteristics of the patients included in the study

Independent Variables		Number	Percentage
Sex	Male	66	58.9
	Female	46	41.1
Disease	Crohn	59	52.7
	Ulcerative Colitis	53	47.3
Smokers	Crohn	15	13.4
	Ulcerative Colitis	9	8
Other autoimmune disease	Crohn	2	1.7
	Ulcerative Colitis	1	0.8

Table 2 Side Effects rate observed with the different treatment regimen

Independent variable (side effects)		Immunos uppressors	Biolo gic	I+B	p-value
Total Side effects	Side effects	22/70 31%	3/32 9%	1/10 10%	
Side effects in crohn	CD Smoker	10/12 83%	1/3 33%	0/0Non applicable	0.154
	CD Non smoker	2/22 9%	0/12 0%	0/9 0%	0.698
Side effects in UC	UC smoker	1/6 17%	0/3 0%	0/0Non applicable	0.453
	UC non smoker	9/30 30%	2/13 15%	1/1 100%	0.224

Table 3 side effects of the different treatments in our study compared to the literature

Leucopenia	18.5% vs 30% (literature)	10% vs 9%
Anemia	7.4% vs 10%	none
Thrombocytopenia	3.7% vs 10%	none
Hepatotoxicity	1.8% vs 1.4%	none
Acute Pancreatitis	4.6% vs unclear	none
Hodgkin Lymphoma	none	2.7% vs <1%
Non Hodgkin Lymphoma	1.8% vs < 1%	none
Cutaneous reaction	1.8% vs unclear	10% vs 10%
Myalgia	1.8% vs unclear	none
Infections	8% vs 10%	none
Alopecia	1.8% vs 1%	none

DISCUSSION

There were more side effect rates noted among patients treated with the Immunosuppressor treatement in all groups (smoker and non-smokers) when compared to the Biological or combination treatment. The observed side effects of azathioprine in our study are leukopenia 18.6% compared to 30% in the literature. Anemia and thrombocytopenia have a frequency that is not well defined in the literature and was observed in our study at a rate of 7.1% for anemia and 2.8% for thrombocytopenia. Liver dysfunction is described at a rate of 1.4% in the literature compared to 1.8% observed in our study. (Table 3) Side effects described with infliximab are mainly Infusion reactions (acute or delayed), neutropenia infections demyelination. The frequency and severity of acute infusion reactions were evaluated in a study of 165 consecutive patients who received a total of 479 infliximab infusions.[14] The following observations were made:

10 % experienced at least one infusion reaction compared to 10% cutaneous reaction with infliximab observed in our study.

Neutropenia in patients treated with infliximab was seen in 9% compared to 10% that was observed in our study.

A retrospective study of Ioanna parisi *et al* has shown the safety of infliximab in terms of liver impairment. This was also compatible with the result of our study that has showed no hepatic problems seen in patients treated with Infliximab. Although infliximab is an episodic treatment that predisposes to the formation of antibodies against TNF alpha inhibitors, no

severe side effects occurred with infliximab, therefore no discontinuation of this treatment was noted in our study. Also the study of Lichtenstein *et AL*[17] has shown that infliximab doesnot significantly increase infections, malignancies and mortality which was compatible with our study since the lymphoproliferative disorder was not noted among patients treated with the biological treatment. However, despite the high rate of side effects noted among patients treated with immunosppressors in our study, there were no statistical significance that has provenit. This might be due to the fact that the proportion of patients receiving azathioprine was the largest among all treatment groups. Also, larger sample size followed over a longer period of time is still necessary in order to assess short and long term side effects of the different treatment modalities while treating IBD patients. Furthermore, the low number of patients treated with the combination therapy and the short duration of the combination therapy (6 months) as opposed to the follow up for 12 months of the monotherapy might explain the lower side effects rates in this treatment group. The presence of serious side effects noted such as pancreatitis, pancytopenia and lymphoma shows the necessity of frequent monitoring of IBD patients especially when treated with azathioprine.

In this study, a real-life experience was described and has targeted the side effects of different IBD treatments in Lebanese patients with IBD. A highest rate of side effects was noted among patients treated with Azathioprine and the prevalence of dangerous side effects such as pancytopenia, pancreatitis and lymphoma were mainly noted in patients treated with Immunosuppresors (Azathioprine). The incidence of those side effects as well as the other milder side effects obtained and discussed previously, indicates that monitoring and effective follow up are essential in IBD patients treated with the Biological treatment and especially the IBD patients treated with Azathioprine. In our study, the absence of serious side effects with the combination therapy may be due to the low number of patients treated with this regimen and it may be also due to the time of treatment which was only for 6months in this category. This may indicate a relative safety of such combination for a short time, but longer exposure and longer follow up with a larger sample size are still mandatory in order to effectively evaluate the short and long term side effects of the combination therapy. Larger sample size and further studies conducted over a longer period are still necessary to significantly evaluate the side effects and the safety profile after a long term use of the different treatment regimens in order to statistically prove the difference in side effects and flare up rates between the different treatment modalities. In conclusion, IBDs remain a complex issue, and the therapeutic approach will continue to evolve during the future. Thus, descriptive and comparative studies of real life experience of new drugs that have already proven their efficacy are still a must in order to have a global assessment of safety, remission and benefits provided over older treatments.

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