Outcomes of immunosuppressors and biologic drugs in inflammatory bowel diseases: a real life experience

Treatments and therapeutic approaches in IBD are constantly evolving. The newly emerged biologic treatments are one such evolving approach, with much ongoing studies to determine the outcomes safety and side effects, in comparison to the older immunosuppressive treatment regimens. In this research, a retrospective analysis was conducted on 112 patients with IBD, retrieved from a single center in Lebanon, in aim of evaluating the outcomes of biologic, immunosuppressive, or combination of both drug classes, over one another, in the treatment of patients with IBD in the real life experience. Patient treated with Azathioprine were 58%, patients receiving Infliximab were 13%, 20% received Adalimumab, and only 8.9% of patients received a combination of Azathioprine and Adalimumab. Overall Response rates to treatment were high (92.9%), while non-responders were 7.1%. As for flare up rates, it was observed that 32.1% of patients had flare ups during treatment, while the majority (61.6%) did not. Less flare up and side effect rates were noted among patients treated with biologic treatment. In addition, the results showed that biologic drugs are superior in achieving a higher response rate compared to immunosuppressive treatment. This result was significant to the 95% confidence interval.

Keywords: immunosuppressors, biologic drugs, bowel diseases

Introduction

Crohn's disease and Ulcerative Colitis are the main constituents of Inflammatory Bowel Diseases [1] which consists of chronic inflammation and damage in the gastrointestinal tract leading to symptoms such as abdominal pain, diarrhea, rectal bleeding, weight loss, fatigue and anorexia. These disorders have both distinct and overlapping pathologic and clinical characteristics. Crohn's disease most commonly affects the ileum, but can affect any part of the GI tract, from the mouth to perianal area. In Crohn's disease, lesions may appear in patches, which mean that some parts of the GI tract are affected while leaving other sections completely normal. In addition, in Crohn's disease, the inflammation extends through the entire thickness of the bowel wall. This transmural inflammation results in sinus tracts and can result in fistulae and micro perforation. On the other hand, the Ulcerative colitis is limited to the rectum and colon and is characterized by a relapsing remitting episodes of inflammation limited to the mucosal layer the colon. It usually begins in the rectum and lower colon, but may also spread continuously to involve the entire colon [2].

The prevalence and incidence of IBDs seem to be lower in Asia and the Middle East. However, an increase in incidence has been noted in some newly industrialized countries in Asia, Africa and South America.

In USA, the number of patient suffering from IBD is around 1.32million. It is also noted that IBD affects some subpopulations more than others. A higher susceptibility of IBDs has been described between people age 15-35-year-old. Also, there is a small increase in incidence among people aged more than 5 [3-5].

Gastrointestinal manifestations of IBD including stomatitis, diarrhea associated with presence of mucus or blood in the stool, fecal incontinence and constipation, can be found as the primary symptom in ulcerative colitis. Obstipation, bowel obstruction, pain and abdominal cramps are also some important manifestations of IBD. Also, rectal bleeding and pain may be present, as well as severe urgency and tenses, nausea and vomiting, delayed growth in children, pyoderma gangrenous, erythema nodosum, episcleritis, scleritis, uveitis, non-erosive and asymmetric arthritis which is more common in Crohn's disease and affect mainly

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the large joints. Furthermore, IBD patients have higher risk of cholelithiasis, primary sclerosing cholangitis, venous thromboembolism, and kidney stones.

Symptoms do not always correlate with the degree of severity of the disease. Hence, endoscopic evaluation is the gold standard to evaluate the degree of mucosal inflammation and the disease activity.

Reducing the inflammation by inducing mucosal healing is one of the ultimate aim of IBD medical treatment. The goals of treatment are not only symptom relief, but also long-term clinical remission and reduction of complications such as decreased need for hospitalizations, time without a relapse and the need for abdominal surgery. Assessment of health-related-quality of life is another goal of medical therapy. The treatment involves drug therapy or surgery. Treatment strategies consist of an induction regimen with a rapid onset of action followed by maintenance regimen when remission is achieved. The drug of choice for induction depends on many factors such as disease severity, age of the patient, location of the disease and clinical course [6-8]

Treatment strategies follow a "treat to target" approach in which MRI, clinical assessment of the disease, labs, colonoscopy and endoscopy are all utilized to evaluate the course of the disease and help physicians adopt appropriate treatment strategy.

Treatment options include anti-inflammatory drugs; these drugs are often the first approach in the treatment of IBD. Anti-inflammatories include corticosteroids and 5ASA such as mesalamine balsalazide and olsalazine

Immunomodulators are another treatment option and include azathioprine, mercaptopurine, cyclosporine and methotrexate. The biologic class of drugs consists of the anti TNF alpha agents, which include infliximab, adalimumab and golimumab. Some other biologic therapies that may be used are certolizumab, natalizumab, vedolizumab and ustekinumab.

The efficacy and indication of Azathioprine in IBD treatment is already known. Also, The efficacy of anti TNF alpha in IBD patients is proven with different studies: One example is the single center cohort study of N. Gies et al reflecting a real life experience with Adalimumab and Infliximab treatment in patients with UC; It has shown that both treatments are effective in generating induction. Also the study of Kestens C, van Oijen MG, Mulder CL, et al [9-12] has shown that Adalimumab and infliximab are equally effective for Crohn's disease in patients not previously treated with anti-tumor necrosis factor-α agents. Furthermore, very few studies have compared side effect rates and outcomes between the different treatment options, and there were no studies that have been done in the Lebanese population concerning this issue. So, our study will not only focus on one treatment class but will compare outcomes in a real life experience of different therapeutic options (Azathioprine vs biologic treatment vs the combination therapy) in the IBD Lebanese population.

Methodology

The study adopts a retrospective systematic review of patients known to have inflammatory bowel disease. The aim of this research is to assess outcomes, remission and side effects in selected treatment regimens: Azathioprine, Infliximab, Adalimumab, or combination of Azathioprine with Infliximab or Adalimumab. In this research, remission is determined both clinically and with the aid of laboratory and endoscopic scores such as Mayo and SES, when applicable. The data collected are then subjected to statistical testing for the investigation of relationships between mainly treatment options and treatment class as well as other confounding factors, with remission. Follow up, side effects and flare up rates related to the different treatment strategies were also described in this study.

Data Collection

With all ethics and privacies preserved, and after approval of the CHU NDS hospital committee, the data collected spanned over a period of 1 year follow up of 112 patients with either Crohn's or Ulcerative Colitis from a single center in Lebanon; CHUNDS Hospital. Consent from all the patients included in the study was obtained. All the precautions were taken to protect the privacy of research subjects and the confidentiality of the personal information that was included in their medical files at CHUNDS hospital. The ethical principles of the World Medical Association (WMA) were respected.

The data collected per patient included Gender, Age, Disease type, Duration of disease in Years, duration of Treatment in Months, Smoking, Treatment Class, Treatment regimen, Response, Flare Ups, Other Autoimmune Diseases, Disease Location, WBC before and after treatment, Hemoglobin levels before and after treatment, CRP before and after treatment, AST before and after treatment, ALT before and after treatment, Simple Endoscopic Score for Crohn's Disease, Mayo Score for Ulcerative Colitis, response and side effects.

Inclusion and Exclusion Criteria

The inclusion criteria for this research is patients having either ulcerative colitis or Crohn's disease, with adequate follow up from time of flare up to remission. Treatment must have been restricted to the agents under investigation; Azathioprine, Infliximab, Adalimumab, and Azathioprine + Adalimumab. Inclusion criteria also entailed being on an outpatient basis, with strict adherence to treatment protocols. Exclusion criteria included non-adherent patients, cross overs from one treatment regimen to another, patients with prior surgical procedures such as bowel resections and anastomoses, and patients with inadequate follow up or supporting labs and endoscopic findings.

Results

The sample population in this research included 112 patients, divided as 66 males and 46 females. The distribution of disease type was 59 patients with Crohn's Disease and 53 with Ulcerative Colitis. The duration of follow up for the patients was 12 months. However, the duration adopted for the combination therapy was 6 months. Among the sample population, 21.4% of patients were smokers, and 70.5% did not smoke. It was observed that the majority of patients (58%) received immunosuppressive treatment, while 33% received biologic treatment, and only 8.9% received a combination of immunosuppressive and biologic treatment. In more detail, the patients receiving Azathioprine were 58%, patients receiving Infliximab were 13%, 20% received Adalimumab, and only 8.9% of patients received a combination of Azathioprine and Adalimumab. Response rates to treatment was high (92.9%), while non-responders were 7.1%. As for flare up rates, it was observed that (32.1%) of patients had flare ups during treatment, while the majority (61.6%) did not. As for the presence of other autoimmune diseases, it was seen that almost none (2.7%) had the presence of autoimmune diseases. The disease locations varied between the ileum, colon, and upper gastrointestinal system, or a combination of the above for Crohn's Disease, while for ulcerative colitis, the location was purely the colon. The majority of patients with Crohn's disease had the disease located in the colon (47.3%), while the second most common location for these patients was the ileum + colon (25.9%). Side effects were observed in 25 patients (22.3%), and 8 patients (7.1%) required surgery following treatment **TABLE 1**.

In regards to the descriptive statistics **TABLE 2** of the quantitative variables, it was seen that the mean age of the sample population was almost 36 years of age, the duration of disease was around 9 years, and the treatment duration was around 10 months on average. As for WBC count, prior to treatment the mean count was around 9,500 and 6,350 after treatment. Mean hemoglobin levels did not change before and after treatment. CRP levels however drastically decreased from around 34 to 4 prior and post treatment respectively. Mean platelet counts witnessed a slight drop from around 390,000 before treatment to 320,000 after treatment. Liver function tests; AST and ALT were seen to have a slight rise in their mean levels, however remaining in their normal limits. Mean SES before treatment was 9, and that decreased to 1.5 after treatment, and mean Mayo score was 7.7 prior to treatment and dropped to 1.4 after treatment completion.

It is seen that the non-responders which are a total of 8, were stratified equally between Crohn's and Ulcerative Colitis. The presence of responders and non-responders among disease type did not show any pattern or predilection for one disease type over the other. The p-value was insignificant and therefore there is no relationship between having either Crohn's or Ulcerative Colitis with having a response to treatment or not.

Smokers were outnumbered by non-smokers in this study (24 vs. 88). There were no statistical significant relationship between smoking and response to treatment. Furthermore, testing for the relationship between age and response, as well as age of onset of disease and response,

Table 1. Independent variables.				
Independent variables		**Response**	**No Response**	**p value**
Gender	Male	62	4	0.594
	Female	42	4	
Flare up	Yes	35	1	0.164
	No	69	0	
Side effects	Yes	24	1	0.093
	No	87	0	
Treatment class				
	Azathioprine	57	8	0.04*
	Biologic	37	0	
	Combo	10	0	
Disease				
	Crohn	55	4	0.8
	Ulcerative	49	4	
Disease Location	Ileum	7	1	0.934
	Colon	49	4	
	Up1per GI+Ileum	9	0	
	Upper GI + Colon	2	0	
	Ileum+Colon	26	3	
	Ileum + Perianal	1	0	
	Upper GI+Ileum+Colon	6	0	
	Colon+ Ileum +Perianal	3	0	

Table 2. Descriptive data.		
	N	**Mean**
Age	112	35.3737
Duration of Disease in Years	112	9.2339
Duration of Treatment in Months	112	10.7589
WBC Before Treatment	111	9477.3684
WBC After Treatment	104	6375.5385
Hemoglobin Before Treatment	111	12.583
Hemoglobin After Treatment	104	12.5532
CRP Before Treatment	109	34.8393
CRP After Treatment	105	4.7677
Platelets Before Treatment	111	394076.4444
Platelets After Treatment	104	318419.4839
AST Before Treatment	108	14.7632
AST After Treatment	108	18.1707
ALT Before Treatment	108	14.5641
ALT After Treatment	108	20.1163
Simple Endoscopic Score for Crohn's disease	48	8.5
Simple Endoscopic Score for Crohn's disease After Treatment	48	1.3
Mayo Score for Ulcerative Colitis	44	7.5
Mayo Score for Ulcerative Colitis After Treatment	44	1.2

showed that there was neither a relationship, nor a statistical significance of testing. In other words, it did not seem that patients' age correlated to their likelihood of responding to treatment. Moreover, as the age of onset of disease changes, the likelihood of response does not change either.

The Hypothesis testing in this research has rejected H0 (no benefit of one treatment regimen over another) and accepted H1 (There is benefit of one treatment regimen or class over others in terms of response rate) since there was proof of a statistically significant relationship between the use of biologic treatment as well as combination treatment over the immunosuppressive treatment. Response was assessed clinically and with endoscopic scores (SES, MAYO score) when available. Therefore, there is a highly

statistically significant relationship; meaning that it was seen that all 8 non-responders were under immunosuppressive treatment class. Meanwhile, those under biologic and combination (immunosuppressive and biologic) treatment did not witness any non-response to treatment. Chi-square value fit the expected distribution for 2 degrees of freedom with a p-value <0.05.

In an in-depth view of the response rates to different treatment regimens used, it was seen that the total 8 non-responders were all treated with azathioprine. There were no non-responders with Infliximab, Adalimumab, and Azathiorine + Adalimumab.

Disease location did not seem to have any effect on response to treatment, since there was no statistically significant relationship between the two. In regards to the relationship between gender and response rates, there was equal distribution of non-responders among males and females, and the relationship was found to be statistically insignificant. In other words, being male or female does not affect response.

It was observed that the relationship between presence of side effects and response was statistically significant to the p-value <0.1, with a Chi-square value that fits the distribution to 1 degree of freedom and the 90% confidence interval. There was 1 patient only that displayed side effects to treatment and that did not respond to treatment. Being statistically significant, this meant that the likelihood of having no response is associated with having side effects to treatment. It was seen that the largest number of patients exhibiting significant side effects had been receiving azathioprine (21 patients), while only 3 patients had side effects with Infliximab or Adalimumab, and only 1 patient with the combination of the latters. 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. This might be due to the fact that the proportion of patients receiving azathioprine we re the largest among all treatment groups, and therefore, it was bound to see the highest number of side effects with this treatment regimen. Investigation for the incidence of flare ups among treatment regimens showed that the highest rates of flare ups were with Azathioprine (38,4%), 35% with Adalimumab, 23% with Infliximab, and 10% for the combination treatment.

Discussion

An overview of the evidence based indication for azathioprine was done; the study of Caprilli R et al has shown that between the immunosuppressors only azathioprine and methotrexate are appropriate in the treatment of IBD [11].

The efficacy of anti TNF alpha in IBD patients is proven with different studies: A single center cohort study of N. Gies et al. reflecting real life experience with Adalimumab and Infliximab treatment in patients with UC has shown that both are effective in generating induction. In addition, Kestens C, van Oijen MG, Mulder CL, et al12 has shown that Adalimumab and infliximab are equally effective for Crohn's disease in patients not previously treated with anti-tumor necrosis factor-α agents. However, a systematic review in the study of Vicent and AL has shown that around 1/5 adults has lost response after initiation of Adalimumab therapy and has shown that dose escalation has been efficient in regaining the response in majority of patients. All those studies have shown the necessity of further evaluation of real life experience in IBD patients treated with those regimens. So in our study a description of outcomes observed in the IBD Lebanese population treated with Anti TNF alpha or Azathioprine or a combination of the 2 classes of treatment was done. Efficacy and response observed in each drug were similar to the results obtained in the literature.

Efficacy profile of Adalimumab and Infliximab have both been proved, but a comparison between their efficacy and safety profiles compared to Azathioprine treatment needs further investigation. This was done in our study in the Lebanese population and was based on real-life data of patients seen in a private clinic. In addition, the further benefits vs risks taken while adding azathioprine to biologic therapy also need to be evaluated. That is why we also studied outcomes in the combination therapy and it can be considered as an advantage in our study. However, combination therapy was done for 6 months and in only 10 patients: This might be the reason of the absence of significant side effects observed.

There are still no randomized controlled trials

that have directly compared outcomes of anti-TNF agents in patients with Crohn's disease but there are some indirect evidences in the literature suggesting that we have the same efficacy among infliximab and Adalimumab [12,13]. But further investigation and a comparison between Anti TNF alpha and Azathioprine treatment is necessary. For this reason, our study included a comparison of the response rate observed with the different therapeutic approaches. Concerning Infliximab, approval was the result of 2 studies in which patients have responded inadequately to conventional therapy but have reached a significant remission on infliximab. The systematic review and metanalysis of costa [14-21] has shown that Infliximab reduces hospitalizations and surgery interventions in patients with inflammatory bowel disease. Side effects described with infliximab are mainly infusion reactions (acute or delayed), neutropenia, infections, and demyelination.

In conclusion, the aim of this study was to assess the outcomes of different treatment options of Crohn's disease and Ulcerative Colitis in a real life experience. The treatment options investigated were Azathioprine, Infliximab, and Adalimumab, as well as the combination of Azathioprine and Adalimumab.

Parametric investigations regarding the main outcome, which is response, showed that the rate of response is already very high even with Azathioprine (>85%). The indicators of this were seen clinically and with the improvement in both SES and Mayo scores among patients following treatment. The data suggested that this improvement was substantial. Moreover, the improvement in mean CRP and WBC counts also suggest that overall treatment success was substantial. Mean CRP level decreased from 34 to 4 following treatment, and mean WBC count decreased from 9500 to 6350 following treatment. The decrease in CRP level generally correlates with the decrease in fecal calprotectin. Practically this decrease corresponds to mucosal healing for patients receiving immunomodulators and/or anti TNF alpha. Fecal calprotectin correlates better than CRP with disease activity and mucosal inflammation. A value above the cut-off level 250μg/g suggests that the patient might have an ongoing inflammation and might be prone to a flare up in the near future. Fecal calprotectin is used to monitor disease activity although laboratory values may be affected by other states and diseases. Fecal calprotectin is considered as a limitation in our study because it is a retrospective study and not all the variables were available. In addition, the majority of patients in our study were receiving Azathioprine. Furthermore, larger sample size is still needed in order to effectively prove the superiority of outcomes of anti-TNF alpha treatment over Azathioprine. The last limitation in this study is the disease severity;

The intensity of the disease was not taken into consideration in this study and no stratification regarding this issue was done.

The success of treatments involved in this study was not seen to be preferential for either Crohn's or Ulcerative Colitis. The rates of flare up among patients was high (30%), and although this did not seem to affect response in statistical testing, the flare ups do affect patient assessment at given times, their SES and Mayo scores, and in judgment of either treatment success or failure. Although the relationship was not seen to be statistically significant, the highest rates of flare up were seen to occur in patients receiving Azathioprine (38,4%), followed by Adalimumab (35%). The lowest rates of flare up were seen to occur in patients receiving the combination therapy(10%). Side effects were seen to be associated with diminished response, and that result is a valid one since patients that withdrew from treatment due to side effects were excluded from the study. Thus, either treatment success or failure was a valid entity as all patients were compliant with their assigned treatment protocols. Despite all the researches and medical therapy advances, surgery remains an outcome that need to be studied. Also, further studies are necessary in order to evaluate and assess the severity of side effects correlated with each treatment.

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