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Inflammatory Bowel Disease Treatment Options: A Vedolizumab Treatment Perspective

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ABSTRACT

Introduction: Treatment options for IBD include 5-aminosalicylates, corticosteroids, immune suppressants and Tumor Necrosis Factor **(TNF)** alpha inhibitors. A newer class of drugs, integrin receptor antagonists has recently made its way into the pharmaceutical world, used for the treatment of moderate to severe cases of refractory IBD. These drugs are immune directed, suppressing the immune response, inducing and helping in sustaining remission. These include Natalizumab and Vedolizumab which are monoclonal antibodies targeting the alpha integrin chains on T cells.

Material and Methods: The phase 1 clinical trials, which were a placebo controlled double blind study, took place in 2000. The study was conducted on 29 patients suffering from moderate to severe UC. An upgraded formulation of the drug, Vedolizumab was used in 2012 to carry out a phase 2 dose ranging investigation headed by Parikh et al. It was a randomized placebo controlled study involving 46 participants with UC. A phase 3 trial also known as GEMINI 1 trial was also conducted. The aim was to evaluate the effectiveness of the drug in the induction and maintenance of remission in patients of moderate to severe UC. To evaluate the efficacy and safety of Vedolizumab in patients of active CD, a phase 2 trial was carried out by Feagan et al in 2008.

Results: Successive phase one two and three trials were carried out, that led to FDA approval of Vedolizumab, discussing the drug's efficacy.

Conclusion: The usage of Vedolizumab is encouraging as an induction and maintenance therapy for moderate to severe Ulcerative Colitis refractory to other forms of treatment. Patients who respond well to the induction therapy should continue to receive Vedolizumab for at least one year to maintain remission on account of adequate safety and efficacy. Biological therapy has proven to be a stepping stone in the treatment of IBD for patients who are non- responsive to steroids or immune modulators.

Keywords: Vedolizumab; Gemini trials; Inflammatory bowel disease

Abbreviations: UC: Ulcerative Colitis; **CD**: Crohn's disease; **IBD**: Inflammatory Bowel Disease; **TNF**: Tumor Necrosis Factor

INTRODUCTION

The incidence of IBD is on escalation worldwide, particularly in developed nations; however, its the prevalence is geographically divergent. 30,000 new cases are being diagnosed every year in United States of America [1]. Usually these patients are in their early twenties or thirties but for a small percentage it may occur in the sixth or seventh decade of life. People with first degree relatives suffering from IBD are five times more likely to develop Ulcerative colitis or Crohn's disease on account of genetic predisposition as per epidemiological data [2]. Once diagnosed though it demands life-long management and care, either medical or surgical, resulting

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in considerable expenditure which can be appreciated by the fact that the direct costs of IBD treatment in the USA amounts to roughly $6.3 billion per annum [3].

Inflammatory bowel disease is a chronic condition involving the gastrointestinal tract; subdivided into two, namely, Ulcerative colitis and Crohn's disease. While Ulcerative Colitis is restricted to rectum and the colon; Crohn's disease may involve any part of the alimentary canal from oral cavity to the anus. However, it is seen that Crohn's disease has a predilection for the ileocolic junction. Either case may present with diarrhea, fever, fatigue, abdominal pain, anorexia, weight loss and blood in stools. Inflammatory bowel disease is an episodic disease, with clinical relapses and remissions. The relapse phase is characterized by leukocytic infiltration of the gastrointestinal mucosa resulting in epithelial damage. The goal of therapy is to keep the disease in remission once a relapse has been controlled.

Treatment options for IBD include 5-aminosalicylates, corticosteroids, immune suppressants and Tumor Necrosis Factor **(TNF)** alpha inhibitors [4]. 5-aminosalicylates and corticosteroids are pivotal at reducing mucosal inflammation and leukocyte extravasation. Aminosalicylates have moderate efficacy and are unsuccessful in treating severe forms of the disease. Corticosteroids on the other hand are useful in inducing remission but are ineffective at maintenance and are linked to significant adverse effects on long term therapy. Immune suppressants including Azathioprine, Mercaptopurine, Methotrexate and Cyclosporine show no real statistical advantage in inducing remission when compared with placebos in a meta-analysis [5].

TNF alpha antagonists have been a breakthrough in the treatment of moderate to severe cases of refractory IBD. These drugs are immune directed, suppressing the immune response, inducing and helping in sustaining remission. Drugs in this category include Infliximab, Adalimumab and Certolizumab. A newer class of drugs, integrin receptor antagonists has recently made its way into the pharmaceutical world. These include Natalizumab and Vedolizumab which are monoclonal antibodies targeting the alpha integrin chains on T cells. The infiltration of gut vasculature by leukocytes is followed by disruption of the endothelial barrier on account of cell signaling inflammatory cytokines. Integrin receptor antagonists work by inhibiting the interaction of leukocytic integrin with their ligands on endothelial cells. This hinders T lymphocyte trafficking; preventing extravasation of these cells into the stromal tissue. The specific leukocytes integrin of therapeutic interest is the alpha4-beta7 integrin, expressed on a subset of gut homing T lymphocytes. Once activated, they bind to their ligand Mucosal Addressin Cell Adhesion Molecule-1**(MAdCAM-1)** present on endothelial surfaces of the gastrointestinal tract and mucosal associated lymphoid tissue [6].

Natalizumab, a monoclonal antibody, was an early discovery with regard to integrin antagonists. The drug targets the alpha4 integrin chain. It blocks both the alpha4- beta1 integrin and alpha4-beta7 heterodimers. Inhibition of the alpha4-beta7\MadCAM-1 interaction is the mechanism of action that has proved the drug to be effective in treating Crohn's disease. However, inhibition

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of the alpha4-beta1\ VCAM-1 interaction is thought to diminish immune surveillance of Central Nervous System, predisposing patients to Progressive Multifocal Leukoencephalopathy **(PML)**. PML is a central demyelinating disease caused by the John Cunningham virus [7].

Circumventing progressive multi focal leukoencephalopathy, without compromising therapeutic efficacy in the treatment of Crohn's disease and ulcerative colitis was a challenge that was overcome by the discovery of Vedolizumab. The drug was previously known by several names including LDP-02, MLN02 and MLN0002; until now. This drug acknowledged for its 'gut selectivity' targets the alpha4-beta7 integrin specifically without affecting binding at VCAM-1[8]. Studies conducted by Millennium pharmaceuticals concluded; that Vedolizumab does not affect T cells count in the cerebrospinal fluid of healthy volunteers, following a single dose. Moreover, it does not influence the immune surveillance of the central nervous system in non-human primates [9]. There have been no cases of PML reported in patients being treated with the drug for inflammatory bowel disease [10,11]. Vedolizumab shows dose dependent pharmacokinetics. Mean elimination half-life for the drug is 15-22 days. The use of immunosuppressant concomitantly, improved the regimen and decreases the hypersensitive immune reaction against the drug. Furthermore, higher dosing was linked to decreased immunogenicity. Such pharmaceutical choices improved efficacy and provided greater saturation of the drug at its site of action.

MATERIALS AND METHODS

The idea of handling colitis by blocking the alpha4-beta7 integrin, first came in the limelight when a study was conducted on chronically affected tamarin monkeys. The results were promising enough to welcome a sequential trial for human use and FDA approval. The phase 1 clinical trials, which were a placebo controlled double blind study, took place in 2000 [12].The study was conducted on 29 patients suffering from moderate to severe UC. The selection criteria for patients involved having an endoscopic finding of ulcerative colitis for minimum of 25 cm from the anus, and daily 3 or more bowel movements. The tests were carried out by giving a single dose of the drug but in varying quantities. The dosage forms and amounts were as follows, 0.15 mg/kg subcutaneously, 0.15 mg/kg or 0.5 mg/kg or 3 mg/kg given intravenously and finally the last group was given placebo. The 0.5 mg/kg intravenous dose proved to be the most ideal option at producing clinical remission which was observed in 40 percent of the subjects. These results showed great promise and prompted the initiation of Phase 2 trials.

Following the success of phase 1 trials, the second phase was conducted in 2005 on 181 active Ulcerative Colitis patients. The study was initiated as a double blind and placebo controlled; participants were randomly administered intravenous forms of either 0.5 mg/kg or 2mg/kg of the alpha4-beta7 antibody also known as MLN002 or placebo first on day 1 and then on day 29. The results showed a higher probability of inducing remission using Vedolizumab as opposed to placebo during the sixth week.

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The two groups receiving Vedolizumab, exhibited effective outcomes in comparison to the placebo group. There was however a peculiar anomaly in the results as clinical and endoscopic remission were higher in the group receiving 0.5 mg/kg of the drug compared to the 2mg/kg dose group. This result may have been influenced by a greater withdrawal rate in the latter group (8% as opposed to 2% in the 0.5mg/kg group) and hence becomes an unimportant point of discussion. Those who stopped taking the drug at an early stage in the study were categorized under not attaining remission.

An upgraded formulation of the drug, Vedolizumab was used in 2012 to carry out a phase 2 dose ranging investigation headed by Parikh et al [13]. It was a randomized placebo controlled study involving 46 participants with UC (provided they had a partial Mayo score of greater than 1). Groups were divided into those receiving 2, 6 or 10 mg/kg of the drug or placebo, administered on days 1, 15, 29 and 85 with a follow up period of 253 days. The study parameters were different from the previous trial because greater doses of the drug were used with a shorter interval between subsequent doses. The results were that the collective cohort of patients on Vedolizumab had a clinical response rate of over 50% as opposed to only between 22-33% in case of the placebo group.

Such promising results now called for advancing a step further. Hence in 2013, a phase 3 trial also known as GEMINI 1 trial was headed by Feagan et al [14]. The aim was to evaluate the effectiveness of the drug in the induction and maintenance of remission in patients of moderate to severe UC. With a total strength of 895 patients, this experiment was randomized and double blinded. The recruitment criteria involved patients who were refractory to first line treatment modalities including anti TNF alpha drugs, in addition to those who were anti TNF alpha naïve. These patients suffered from active UC, had an endoscopic score of 2 or greater and a Mayo score of 6 or higher even after receiving conventional drugs which included glucocorticoids, azathioprine or anti TNF alpha. In the induction phase, the participants were divided into 2 cohorts. One receiving 300 mg IV of Vedolizumab whiles the other a placebo on random basis on days 1 and 15. The aim was to achieve remission at week 6. It was observed that the clinical response and remission was higher among patients receiving Vedolizumab (irrespective of whether they had a history of anti TNF alpha therapy) when compared to the placebo group.

The maintenance phase involved patients who attained clinical response after induction therapy. They were divided into 3 cohorts, one receiving 300 mg Vedolizumab IV at an interval of 4 weeks, the other 300mg IV at an interval of 8 weeks and the third group receiving placebo for a period of 46 weeks. It was reported that patients receiving Vedolizumab achieved higher rates of clinical remission and mucosal healing compared to patients on placebo at the end of week 52. This holds true for both patients who may or may not have been exposed anti- TNF therapy.

To evaluate the efficacy and safety of Vedolizumab (known as MLN0002 at that time) in patients of active CD, a phase 2 trial was carried out by Feagan et al in 2008 [11]. This was a randomized,

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placebo controlled double blinded study performed on 183 participants. The eligibility criteria were CD of colon and/or ileum in adult patients who were never exposed to biological therapy and had a CD Activity Index score (CDAI) in the range of 220-400 at the time of recruitment. 3 groups were formed; one receiving 2.0mg/kg MLN0002 IV, the other 0.5 mg/kg MLN0002 IV and the third receiving placebo at days 1 and 29. The follow up period was 57 days. A 70 point or more, reduction in the CDAI score formed the basis for clinical response at day 57. It was recorded that the groups on Vedolizumab and placebo showed no appreciable difference in response rate. However, when the clinical response was redefined as a 100 or more, decrease in the CDAI score at day 57, there was an enhanced difference in response rate among the 2.0 mg/kg MLN0002 group and placebo (P=0.05) which was suggestive of a dose dependent influence of Vedolizumab in patients with active CD.

As with UC, to determine the efficacy and safety of Vedolizumab in patients with severe to moderate CD phase 3 trials also known as the GEMINI 2 trials were conducted by Sandborn et al [15]. It was a placebo controlled, double blinded randomized study divided into an induction phase and a maintenance phase. For the first phase, 2 cohorts were formed; one in which patients received 300mg IV of the drug and the other was administered a placebo on completely random basis. Previous use of glucocorticoids biologics, such as immune suppressants and TNF alpha antagonists was kept under consideration. The principal end result was clinical remission (set at 150 points on the CDAI scoring) and clinical response (taken as a reduction of 100 points from the baseline on the CDAI scoring) after 6 weeks. Changes in the serum CRP levels were also recorded at week 6 in patients with raised C-reactive protein. It was observed that whilst there was an appreciable difference in clinical remission in the two groups (patients on Vedolizumab being higher compared to placebo), the difference in response rate was not very significant. Similarly, there was no conspicuous distinction in the serum CRP level changes in the 2 cohorts. Previous anti TNF therapy had no influence on the positive outcomes observed in patients receiving Vedolizumab in terms of remission and response.

Patients who attained a clinical response to the drug at week 6 proceeded to the maintenance phase of the study. 3 cohorts were formed; one receiving Vedolizumab at 4 weeks' interval, the second at 8weeks' interval and the third group receiving placebo for a total of 52 weeks. A fourth group was made comprising of patients who did not respond to the drug in the induction phase and were administered the drug at 4 weeks' interval for 52 weeks. All this was completely randomized. Results showed a greater rate of clinical remission among patients on Vedolizumab as opposed to placebo at week 52.

RESULTS

The results for Vedolizumab in Phase 1-3 clinical trials are summarized in the following table.

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Table 1: Brief outline of results for Vedolizumab in Phase 1 - 3 clinical trials.

Participants	Trial Phase	Regimens	Clinical Remission	Follow up time
29	1	Placebo		30 days
Moderate to severe Ulcerative colitis		0.15mg/kg Intra venous		
		0.15mg/kg Sub -cutaneous		
		0.5mg/kg Intra venous		
		3 mg/kg Intra venous		
181	2	Placebo [63]	14	6 weeks
Active Ulcerative colitis		0.5 mg/kg Intra venous [58]	33	
		2.0 mg/kg Intra venous [60]	32	
185	2	Placebo [58]	21	57 days
Active Crohn's disease		0.5 mg/kg Intra venous [62]	30	
		2 mg/kg Intra venous [65]	37	
47	2	Placebo [9]	25-50	253 days
Ulcerative colitis for more than 2 years		2 mg/kg Intra venous [12]	68-89	
		6 mg/kg Intra venous [14]		
		10 mg/kg Intra venous [11]		
374	3			52 weeks
Moderate to severe Ulcerative colitis	_Induction phase	Placebo [149]	5.4	
		300 mg Intra venous [225]	16.9	
	_Maintenance phase	Placebo [126]	15.9	
		300 mg Intravenous 4-week interval [125]	44.8	
		300 mg Intra venous 8-week interval [122]	41.8	
368 patients	3			52 weeks
Moderate to severe Crohn's Disease	_Induction phase	Placebo [148]	6.8	
		300 mg Intra venous [220]	14.5	
	_Maintenance phase	Placebo [153]	21.6	
		300 mg Intra venous 4-week interval [154]	36.4	
		300 mg Intra venous 8-week interval [154]	39	

DISCUSSION

The usage of Vedolizumab is encouraging as an induction and maintenance therapy for moderate to severe Ulcerative Colitis refractory to other forms of treatment. However, it is not being preferred over anti TNF therapy for inducing remission in CD because of inferior effectiveness and slower response(clinically important results seen after 10 weeks of treatment)

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but is equally effective as TNF antagonist for maintenance of remission and may be sought as an alternative to TNF antagonist where safety is preferred over efficacy. It has been postulated that Vedolizumab is more beneficial for use in UC patients compared to patients with CD, probably because of the transmural nature of the latter linked to systemic inflammatory burden [14-17].

According to recent data combining azathioprine with infliximab can enhance therapeutic benefits [18]. Statistically speaking TNF alpha inhibitors will not induce remission in around 20 % to 40% of patients suffering from CD whilst with the passage of time 40% of the patients will stop responding to the drug [19]. Almost similar results are seen in patients of UC being treated with infliximab. Switching over to a second TNF antagonist e.g. adalimumab from infliximab or dose optimization maybe beneficial at first but eventually the response rates will drop again. Hence, patients presented with therapeutic failure with one type of TNF antagonist showed little response when administered a second TNF antagonist. The development of endogenous antibodies to these drugs, generation of aberrant immune pathways and accelerated drug clearance are thought to be the reasons for the decreased effectiveness of the drug overtime [20]. Finally, the immunosuppressive effects of TNF inhibitors have raised significant safety concerns as they predispose the patient to serious infections including tuberculosis and additional risks to patients suffering from congestive heart disease. Vedolizumab, however, is efficacious in both inducing and maintaining remission in patients of moderate to severe CD or UC demonstrated in phase 3 clinical trials which led to the FDA approval of the drug.

In Conclusion, Vedolizumab has an established role in treating UC and CD patients who failed to respond to conventional therapy with a good safety profile. Patients who respond well to the induction therapy should continue to receive Vedolizumab for at least one year to maintain remission on account of adequate safety and efficacy. Biological therapy has proven to be a stepping stone in treatment of IBD for patients non- responsive to steroids or immune modulators. These biological agents including Vedolizumab and TNF antagonists thus become the first line treatment option for such patients. Because of the differences in end point definition and enrollment criteria during randomized control trials, no single biological agent can be given complete superiority over the other and the choice of drug class comes down to individual patients based on the manifestation, severity, history and prognosis of the disease. That being said Vedolizumab still shows great potential in treatment of patients who encountered therapeutic failure with TNF antagonists and should strongly be considered as an alternative treatment when weighed against the serious adverse effects of TNF alpha inhibitors. All of this is dependent upon the condition of the patient, the gravity of his symptoms and the type of therapy indicated, whether induction or maintenance. Surgical intervention is opted for in severe cases where medical management fails to be sufficient.

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