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Short Communication

Vedolizumab has no effect on the course of non-alcoholic fatty liver disease: A retrospective cohort analysis

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Abstract

Background and Aim: Non-Alcoholic Fatty Liver Disease (NAFLD) is the commonest cause of chronic liver disease and is a leading cause of liver transplantation in the United States, with no approved medication to halt or reverse its progression. Recent animal-model prospective trial-suggested that drug Vedolizumab leads to improvement and reversal in the NAFLD-related metabolic derangements. Vedolizumab is an α4β7 integrin-inhibitor that is approved for use in IBD patients. Our study aims to understand Vedolizumab's impact on the course of NAFLD in inflammatory bowel disease (IBD) patients.

Methods: We conducted a retrospective cohort analysis of 158 subjects with NAFLD who received Vedolizumab at Cleveland Clinic Foundation (CCF). One cohort of 79 patients with NAFLD who received Vedolizumab were matched with control group of 79 patients. We determined the primary outcome as the response to Vedolizumab measured as Fibrosis-4 (Fib-4) regression to <1.3 points after one year of treatment.

Results: We observed that there was no statistically significant difference response (p= 0.576), progression of the disease (p= 1.000) or change in the number of cirrhosis decompensation episodes (in those with NAFLD cirrhosis) among Vedolizumab recipients.

Conclusions: In this retrospective cohort analysis, and unlike in the previous animal model, Vedolizumab was not associated with statistically significant improvement or progression in the Fib-4 score after one year of treatment, and among those with NAFLD-cirrhosis, there was no statistical difference in the complication rates.

Keywords: Non-Alcoholic Fatty Liver Disease (NAFLD), Vedolizumab, α4β7 integrin-inhibitor, Fib-4 score

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is the commonest cause of chronic liver disease and is a leading cause of liver transplantation in the United States, with no approved medication to halt or reverse its progression [1,2]. Patients with inflammatory bowel disease (IBD) often have a higher risk of incidence and prevalence of NAFLD, essentially because inflammation plays a key role in the pathogenesis of NAFLD. A recent animal-model prospective trial suggested that inhibiting integrin-mediated CD4 T cell recruitment leads to improvement and reversal in the NAFLD-related metabolic derangements [3]. Vedolizumab is an α4β7 integrin-inhibitor that is a gut-selective antibody that selectively prevents the infiltration of leucocytes into the gastrointestinal submucosa [4]. Vedolizumab has been previously approved for the treatment of active ulcerative colitis and Crohn's disease patients [5-7]. Unfortunately, there are no FDA-approved medications available for treating NAFLD. This study aims to evaluate Vedolizumab's influence on NAFLD in IBD patients.

Methods

A retrospective cohort analysis of all subjects with NAFLD who received Vedolizumab at

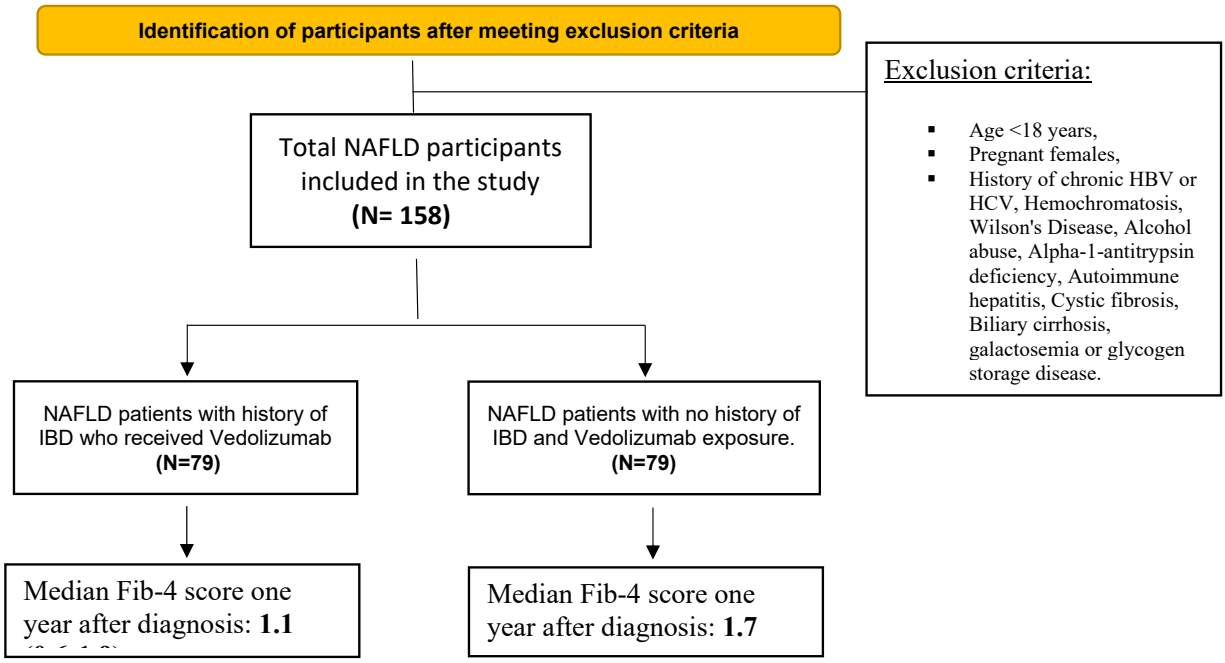

Figure 1. Patient Selection and Exclusion Criteria.

Cleveland Clinic Foundation (CCF) was conducted. Institutional Review Board approval at CCF was obtained for this study.

Cases of adults (above the age of 18 years) diagnosed with IBD who received Vedolizumab with a history of NAFLD at any lifetime point lifetime were included. A matching group of patients with NAFLD and no history of IBD/ Vedolizumab exposure was later created. We excluded patients with age <18 years, pregnant females, history of chronic HBV or HCV, Hemochromatosis, Wilson's Disease, Alcohol abuse, Alpha-1-antitrypsin deficiency, Autoimmune hepatitis, Cystic fibrosis, Biliary cirrhosis, galactosemia or glycogen storage disease. Patient Selection and Exclusion Criteria are shown in **Figure 1**.

We determined the primary outcome as the response to Vedolizumab measured as Fibrosis-4 (Fib-4) regression to <1.3 points after one year of treatment [8]. FIB-4 score and transient elastography may be used as alternatives to liver biopsy for fibrosis staging and patient follow-up. FIB-4 threshold of 1.3 was acceptable for excluding the presence of advanced fibrosis [9]. The secondary outcomes were the progression of the disease, which was defined as Fib-4 rise to >1.3 points, and a reduction in the number of decompensated cirrhosis episodes among those with NAFLD cirrhosis. FIB-4 has been shown to be a prognostic marker of liver-related outcomes in patients with NAFLD [10]. Studies have shown a high FIB-4 ≥ 2.67 as a strong predictor of both all-cause mortality and liver-related adverse outcomes independently of the baseline diagnostic group and common risk factors.

Appropriate weights were applied for all analyses using Stata version 17 (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC.). Chi-Square test and student t-tests were used for statistical analysis using SPSS (SPSS Inc, Chicago, Illinois, United States). P-value <0.05 was considered significant. Results were reported as mean ± standard deviation (SD) for quantitative variables and percentages for categorical variables. Statistical significance was based on two-sided design-based tests evaluated at α=0.05.

Results

A total of 158 patients with diagnoses of coexisting IBD and NAFLD in the Cleveland Clinic system were included in the final analysis. 79 patients with NAFLD have also received Vedolizumab, in contrast to the 79 matching control group. The baseline characteristics of the study population is shown in **Table 1**.

The primary outcome was the response to Vedolizumab measured as Fibrosis-4 (Fib-4) regression to <1.3 points after one year of treatment in both groups. Median Fib-4 score one year after diagnosis in Vedolizumab group was 1.1 (0.6-1.9) vs non-vedolizumab group 1.7 (1.2-2.1).

There was no statistically significant difference in response (p= 0.576), progression of the disease (p= 1.000), or change in the number of cirrhosis decompensation episodes (in those with NAFLD cirrhosis) among Vedolizumab recipients. The predictors for response are shown in **Figure 2**.

Table 1. Baseline Characteristics of the Study Population.				
	All patients N= 158	Vedolizumab N= 79 (%)	No Vedolizumab N=79 (%)	P-value
Age, years	62 (52-71)	54 (39-66)	66 (60-74)	0.000
Male gender	75 (47)	40 (51)	35 (44)	0.426
Past medical history				
Hypertension	98 (62)	40 (51)	58 (73)	0.003
Type 2 diabetes	66 (42)	27 (35)	39 (49)	0.061
History of cirrhosis	21 (13)	13 (16)	8 (10)	0.241
Dyslipidemia	80 (51)	35 (45)	45 (58)	0.109
Hypothyroid	28 (18)	11 (14)	17 (22)	0.211
Laboratory results				
Median AST at diagnosis	27 (20-40)	23 (17-34)	29 (22-48)	0.003
Median ALT at diagnosis	28 (19-44)	25 (18-38)	30 (21-52)	0.045
Median AST one year after diagnosis	27 (21-36)	27 (19-36)	28 (22-35)	0.370
Median ALT one year after diagnosis	28 (17-42)	27 (17-42)	29 (17-42)	0.450
Median Fib-4 score at diagnosis	1.4 (0.9-2.0)	1.1 (0.6-1.8)	1.6 (1.2-2.2)	0.000
Median Fib-4 score one year after diagnosis	1.4 (0.8-2.1)	1.1 (0.6-1.9)	1.7 (1.2-2.1)	0.0001
Response	14 (9)	6 (8)	8 (10)	0.576
Progression	20 (13)	10 (13)	10 (13)	1.000
Complications				
Hepatic encephalopathy	4 (3)	3 (4)	1 (1)	0.311
Variceal bleeding	3 (2)	1 (1)	2 (3)	0.560
Ascites	6 (4)	3 (4)	3 (4)	1.000
HRS	2 (1)	1 (1)	1 (1)	1.000

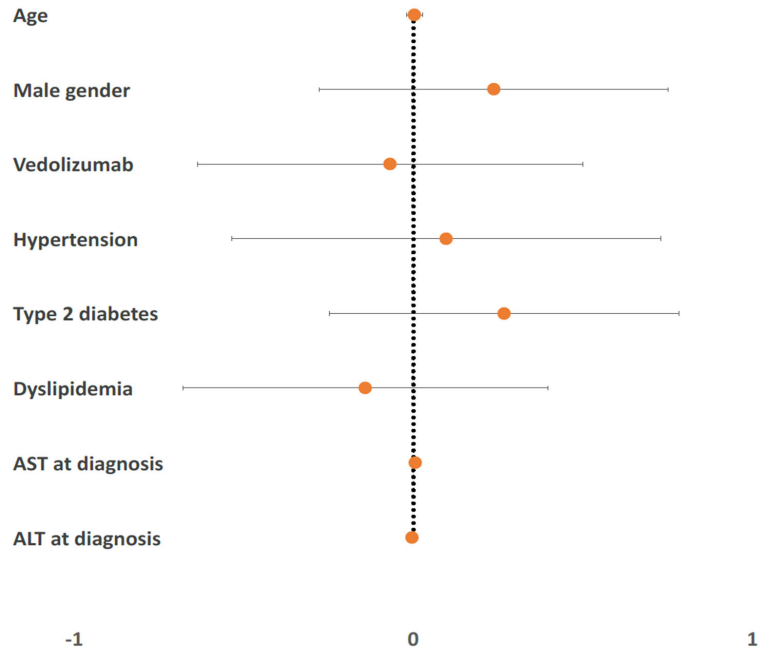

Figure 2. Predictors of Positive Response.

Discussion

In our retrospective cohort analysis, we found that Vedolizumab was not associated with statistically significant improvement or progression in the Fib-4 score after one year of treatment, and among those with NAFLD-cirrhosis, there was no statistical difference in the complication rates.

NAFLD is a spectrum of liver disease characterized by the presence of extra fat in liver cells without any linkage to alcohol consumption. Over the last couple of decades, globally, NAFLD has emerged as one of the most common causes of chronic liver disease. A large part of the cause is the global epidemic of obesity and diabetes. It is estimated that the overall prevalence of NAFLD in North America is 24% [11]. Currently, there are no specific FDA-approved treatments for this disease. Hence there is a dire need for appropriate therapeutic agents. For over a decade, certain lifestyle modifications have been the cornerstone for treating NAFLD. Some of these widely practiced lifestyle changes include physical activity, caloric restriction, and time-restricted feeding. There have been a number of randomized controlled trials on pharmacological agents that have shown histological improvements in the NASH/NAFLD spectrum.

Indirect pharmacological therapeutic agents have been used in cases with advanced fibrosis. These agents primarily aim to curb the inflammatory response mount by steatosis. Insulin sensitizers, including thiazolidinediones [12] and Peroxisome proliferator-activated receptors (PPARs) [13], have been studied extensively in the past, but their role and long-term benefits have remained controversial. Pentoxifylline , a non-selective phosphodiesterase inhibitor, is another pharmacological agent which showed some promising results in animal studies models but failed to replicate the same results in human subjects [14]. As per ongoing the FLINT trial [15] and REGENERATE Trial [16], which is a double-blinded randomized control trial that studies the role of obeticholic acid as an anti-inflammatory agent. The earlier phase of this trial has shown some promising results with improvement in liver histology and halting hepatic fibrosis. However, the resolution of NASH was not seen in any of the subjects. Up to this date, the most remarkable study done in the arena is the PIVENS trial [17], which compared Vitamin E role with pioglitazone and placebo for the Treatment of Nondiabetic Patients With NASH.

Several trials conducted in the past failed to show a therapeutic effect for reversing if not halting inflammatory process in NAFLD/NASH axis. A cutting-edge animal model-based trial established that a mucosal vascular addressin cell adhesion molecule 1 ($\alpha_4\beta_7$/MAdCAM-1) plays a vital role in NASH development through colonic and hepatic CD4 T cell recruitment. Vedolizumab is an α4β7 integrin-inhibitor that is a gut-selective antibody that selectively prevents the infiltration of leucocytes into the gastrointestinal submucosa [4]. We conducted a first retrospective cohort analysis on human subjects to speculate on the anti-inflammatory response of Vedolizumab drug on the NASH/NAFLD axis. We created a retrospective database and did a cohort analysis to compare 158 patients with commitment diagnoses of NAFLD & IBD. We fail to show a statistically significant difference in response (p=0.576), progression of the disease (p=1.000), or change in the number of cirrhosis decompensation episodes (in those with NAFLD cirrhosis) among Vedolizumab recipients.

Though our results are negative, and we are discouraged that Vedolizumab doesn't demonstrate, our study opens a great opportunity door to reassess similar pharmacological therapies for the management of NAFLD. Perhaps the hepatology community needs better studies with a better sample size to show statistical significance. While there is no FDA-approved medication for NAFLD/NASH, dietary and lifestyle intervention is the mainstay of treatment.

Conclusion

In conclusion, our retrospective cohort analysis showed that Vedolizumab did not have a significant impact on the Fib-4 score or complication rates in NAFLD-cirrhosis patients after one year of treatment. NAFLD is a prevalent cause of chronic liver disease, and while lifestyle modifications are the mainstay of treatment, various pharmacological agents have been studied with controversial long-term benefits. Our study highlights the need for further research into pharmacological therapies for NAFLD management, as several trials have failed to demonstrate a therapeutic effect. Ultimately, larger studies are necessary to provide statistical significance and supplement current dietary and lifestyle interventions for treating NAFLD/NASH.

Authors' Contribution

Prabhat Kumar: First Co-author and manuscripts writing.

Ashraf Almomani: First Co- Author and scientific review.

Almaza Albakri, Motasem Alkhayyat, Tariq Kewan: Biostatistical analysis.

Antoine Boustany, Somtochukwu Onwuzo: Data collection.

Prabhat Kumar, Eduard Krishtopaytis, Dana Alshaikh: Literature review.

Disclosure

There are no potential conflicts (financial, professional, or personal) to disclose by all the authors.

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