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Original article

Monitoring Adalimumab concentration, Adalimumab antibodies, fecal calprotectin, and QuantiFERON test positivity in patients with inflammatory bowel disease

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Summary

Introduction. Inflammatory bowel diseases (IBD) are a serious global health problem affecting mostly younger and middle-aged persons. Despite the availability of variety of treatment approaches, the disease often progresses unpredictably. Biological drugs offer hope for IBD treatment. Our research share our preliminary findings regarding the monitoring of adalimumab (ADM) and adalimumab antibodies (ADA) concentrations, fecal calprotectin levels, and the frequency of QuantiFERON test positivity in IBD patients treated with biological drugs.

Methods. The study was designed as a retrospective, descriptive, single-center study and was conducted at the University Clinical Center of the Republic of Srpska, Banja Luka, from January 2018 to June 2022. Medical records of patients treated at the Internal Medicine Clinic were analyzed. Patients were categorized based on underlying disease and duration of biological therapy. ADM and ADA concentrations were monitored at intervals, and QuantiFERON test positivity and fecal calprotectin levels were recorded. Statistical methods, including analysis of Variance (ANOVA) and paired t-test were performed using the SPSS program version 29.

Results. Medical records of 117 patients were analyzed. Most of them, 44 were treated with adalimumab. Male patients were predominant (59.10%) in our study over females. Patients were also categorized based on the length of biological therapy. ADM and ADA concentrations increased with time (after 6, 12, 18 and 24 months), but without statistical significance. Fecal calprotectin levels decreased after 12 and 24 months of treatment. Out of the total number of patients, 53.83% of QuantiFERON positive patients were treated with adalimumab. Prophylactic isoniazid therapy was carried out in 63.6% of patients.

Conclusion. Our initial experience in monitoring biological drug concentrations and fecal calprotectin levels in IBD patients showed a decrease in fecal calprotectin levels and an increase in ADM and ADA concentrations over time but there were no statistically significant differences.

Keywords: Inflammatory bowel disease (IBD), biological therapy, adalimumab concentration (ADM), adalimumab antibodies (ADA), QuantiFERON test

Introduction

Inflammatory bowel diseases (IBD) are on the rise among the younger and middle-aged population, emerging as a growing pandemic of new millennium [1, 2]. Despite the array of available therapeutic options, the disease often progresses unpredictably [3, 4]. Biological drugs, encompassing monoclonal antibodies targeting tumor necrosis factor alpha (anti-TNF) like infliximab and adalimumab, humanized monoclonal antibodies to the homing receptor $\alpha 4\beta 7$ integrin complex (vedolizumab), and those targeting the interleukin (IL) p40 subunit common to IL12/23 (ustekinumab) are raising expectations for treating IBD patients [5–7].

In our paper we share our first experience in monitoring adalimumab (ADM) and adalimumab antibodies (ADA) concentrations, along with fecal calprotectin levels in IBD therapy. Additionally, we seek to assess the frequency of QuantiFERON test positivity and its significance in patients undergoing treatment with biological drugs for IBD.

Methods

This retrospective, descriptive, single-center study was conducted at the University Clinical Center of the Republic of Srpska, Banja Luka, from January 2018 to June 2022. Discharged letters and medical histories from the Clinical Information System of patients treated at the Internal Medicine Clinic, Department of Gastroenterology and Hepatology were analyzed. Serological test results for the concentration of the biological drug adalimumab, adalimumab antibodies, fecal calprotectin and the QuantiFERON test performed at the Institute for Clinical Microbiology were also used.

Initially, patients were divided into two groups based on sex and on their underlying disease (Crohn's disease and ulcerative colitis) and then according to the duration of the biological therapy. The average concentrations of ADM and ADA were monitored after 6, 12, 18, and 24 months. The positivity of the QuantiFERON test was categorized as follows: before the introduction of the biological drug; during the first 6 months of therapy; from 6–12 months of therapy; from 12–24 months of therapy; and over 2 years of therapy. The value of fecal calprotectin was also monitored before the introduction of ADM and then after 12 and 24 months.

In our statistical analysis, we used ANOVA and t-test using the SPSS program version 29 to assess the significance of differences and relationships among variables. ANOVA, or Analysis of Variance, was used to assess whether there were any statistically significant differences between the means of three or more independent groups (ADM and ADA) while we used t-test to determine if there were significant differences between the levels of fecal calprotectin before the introducing of biological therapy and after 12 months, as well as before introducing biological drugs and after 24 months.

Results

Data from the discharged letters of 117 patients and their medical history documentation from the Clinical Information System were analyzed. Among them, 44 patients were treated with the biological drug adalimumab, out of which 25 patients had Crohn's disease and 19 had ulcerative colitis, with a mean age of 35.77±11.53 years. Male patients were more predominant - 26 (59.10%).

The patients were divided into four different groups based on the length of biological therapy: < 1 year (6 patients), from 1-2 years (11 patients), over 2 years (19 patients), and de novo adalimumab therapy (8 patients) (Figure 1).

The average concentrations of the biological drug ADM and adalimumab antibodies

(ADA) were analyzed at different time points. After six months, the average ADM concentration was 3.585±0.77 μg/ml, and ADA concentration was 1.8±0.12ng/ml. After 12 months, the average ADM concentration was 3.68±2.61 μg/ml, and ADA concentration was 4.09±2.32 ng/ml. After 18 months, the average ADM concentration was 4.57±2.80 μg/ml, and ADA concentration was 16.31±56.05 ng/ml. After 24 months, the average ADM concentration was 10.29±32.72 μg/ml, and ADA concentration was 19.88±56.20 ng/ml (Figure 2).

While ADM and ADA concentrations showed an upward trend over time, ANOVA analysis revealed no statistically significant differences among the observed data sets ($p>0.001$) (Figure 2).

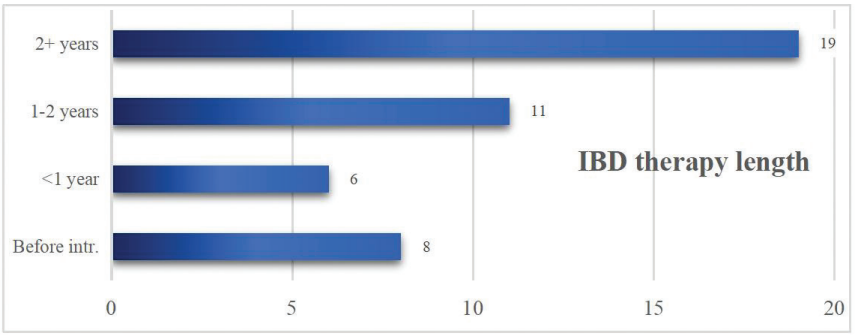

Figure 1. Number of patients per length of IBD therapy

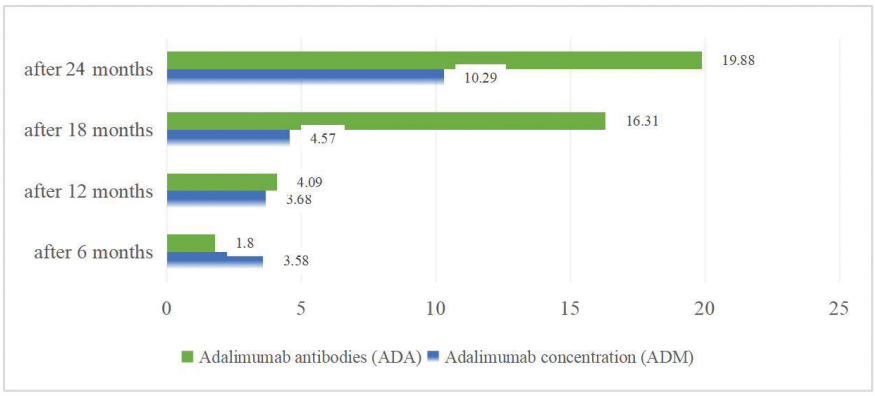

Figure 2. ADM and ADA concentrations at different time points

The average value of fecal calprotectin (FC) was also analyzed at the time of introduction of the biological drug and after 12 and 24 months. The average value at the time of introduction of the biological drug was 685.38±377.74 μg/g, after 12 months it was 494.45±363.27 μg/g, and after 24 months it was 390.39±378.87 μg/g (Figure 3).

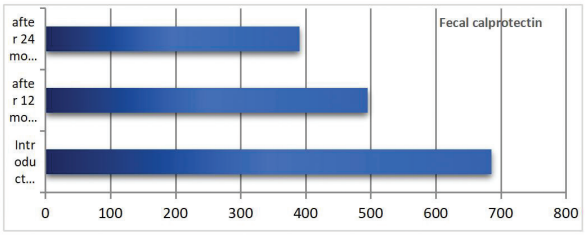

Figure 3. Fecal calprotectin values at different time points

Paired t-tests, conducted for the comparisons between the initial values and those at 12 months and 24 months after the introduction indicated no statistically significant differences ($p > 0.05$ in both instances).

Out of the total of 117 patients who were treated with the biological drug in our health institution, 33 patients (28.2%) had a positive QuantiFERON test, of which 15 patients (45.4%) had the positive test before the introduction of the biological agent; during the first 6 months 5 patients (15.1%); from 6-12 months 2 patients (6%); from 1 to 2 years, 5 patients (15.1%) and 6 patients (18.1%) had tne positive test 2 or more years after the introduction of the biological therapy (Figure 4).

It is important to note that one patient had the positive QuantiFERON test three times, four months after the introduction of the biological drug adalimumab, and after three and five years of vedolizumab therapy. Among patients undergoing biological therapy for IBD, 53.83% of those positive received adalimumab. Prophylactic therapy with isoniazid tablets (150 or 300 mg) for 2–6 months was carried out in 21 patients (63.6%), and after the QuantiFERON test was negative, the patients continued with the therapy. Almost all patients were asymptomatic.

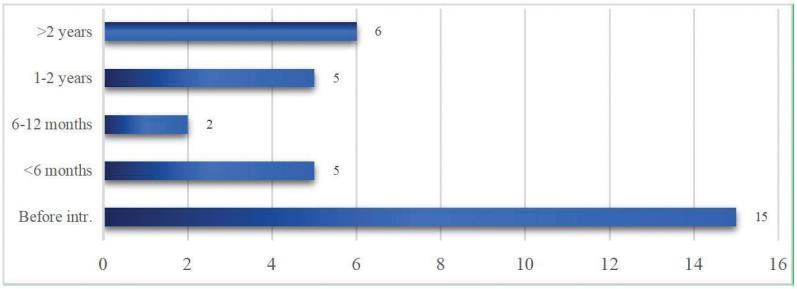

Figure 4. QunatiFERON test positivity per lenght of IBD therapy

Discussion

Biological drugs have become the cornerstone in the global treatment of inflammatory bowel disease (IBD), marking a significant shift in the management of these conditions at our healthcare institution since their introduction in September 2014 [1, 2]. While these drugs have revolutionized IBD treatment, their effectiveness can vary, and the development of antibodies to the drug can impact their efficacy over time [8].

Our findings align with prior research on ADM and ADA concentrations in IBD patients treated with adalimumab. Similar to Pellegatta et al's study, our results indicated a rise in ADM and ADA concentration over time [9]. Additionally, Nakase et al. demonstrated a significant correlation between ADA and clinical remission in Crohn's disease (CD) patients receiving ADM [10]. Masaichi et al's research suggested that high ADA levels were associated with greater treatment continuity, particularly in CD cases [10]. Consistent with Molander et al's findings, our study observed the decrease in fecal calprotectin values after one and two years of therapy compared to initial levels, reinforcing the potential of fecal calprotectin as a predictor of sustained clinical remission [11].

Given the risk of Tuberculosis (TB) reactivation in patients with Latent Tuberculosis Infection (LTBI) undergoing biologic therapies, particularly TNF-α inhibitors, our study emphasizes the importance of LTBI screening before initiating these medications [13]. Our findings align with a Spanish group's results,

showing a substantial decrease in TB infections following LTBI screening recommendations for patients on anti-TNF-α medications [14]. However, it is crucial to note that these interventions did not completely eliminate the risk of TB reactivation.

Our study supports existing guidelines for LTBI management in IBD patients undergoing immunosuppressive therapy, emphasizing the significance of screening before initiating biologics. Nonetheless, further research is warranted to assess the long-term efficacy and safety of isoniazid prophylaxis in this patient population.

Conclusion

Our initial observations, while monitoring concentrations of biological drugs and fecal calprotectin levels in IBD patients, demonstrated the decrease in fecal calprotectin levels and the increase in ADM and ADA concentrations over time. However, noteworthy is the absence of statistically significant differences. Additionally, it is important to highlight that, despite a high positivity rate in the QuantiFERON test, almost all patients remained asymptomatic.

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Ethical approval. The Ethics Committee of the University Clinical Centre of Republic of Srpska, Banja Luka, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Praćenje koncentracije Adalimumaba, antitijela na Adalimumab, fekalnog kalprotektina i pozitivnosti QuantiFERON testa kod pacijenata sa zapaljenskim bolestima crijeva

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Uvod. Upalne bolesti crijeva (IBD) su ozbiljan globalni zdravstveni problem koji se javlja uglavnom kod osoba mlađih i srednjih godina. Uprkos dostupnosti različitih načina liječenja, bolest često napreduje nepredvidivo. Biološki lijekovi daju nadu u liječenju IBD. U ovom radu iznosimo naše preliminarne rezultate praćenja koncentracija adalimumaba (ADM) i adalimumab antitijela (ADA), nivoa fekalnog kalprotektina i učestalosti pozitivnosti QuantiFERON testa kod pacijenata liječenih biološkim lijekovima.

Metod. Studija je dizajnirana kao retrospektivna, deskriptivna, jednocentrična i sprovedena je u Univerzitetskom kliničkom centru Republike Srpske, Banja Luka, od januara 2018. do juna 2022. godine. Analizirana je medicinska dokumentacija pacijenata liječenih na Klinici za unutrašnje bolesti, koji su kategorisani na osnovu osnovne bolesti i trajanja biološke terapije. Koncentracije ADM i ADA su praćene u intervalima, a zabilježena je i pozitivnost QuantiFERON testa i nivoi fekalnog kalprotektina. Statističke metode, uključujući analizu varijanse (ANOVA) i upareni t-test, analizirane su korišćenjem SPSS programa verzije 29.

Rezultati. Analizirana je medicinska dokumentacija 117 pacijenata, od kojih je većina, njih 44 liječena adalimumabom. Muški pacijenti su bili dominantniji (59,10%) u našoj studiji u odnosu na žene. Pacijenti su takođe podijeljeni na osnovu dužine biološke terapije. Koncentracije ADM i ADA su se povećavale s vremenom (nakon 6, 12, 18 i 24 mjeseca), ali bez statističke značajnosti. Nivoi fekalnog kalprotektina su se smanjili nakon 12 i 24 mjeseca liječenja. Od ukupnog broja pacijenata, 53,83% QuantiFERON pozitivnih pacijenata liječeno je adalimumabom. Profilaktička terapija izoniazidom sprovedena je kod 63,6% pacijenata.

Zaključak. Naše početno iskustvo u praćenju koncentracija bioloških lijekova i nivoa fekalnog kalprotektina kod pacijenata sa IBD pokazalo je smanjenje nivoa fekalnog kalprotektina i povećanje koncentracija ADM i ADA tokom vremena, ali nije bilo statistički značajnih razlika.

Ključne riječi: upalna bolest crijeva (IBD), biološka terapija, koncentracija adalimumaba (ADM), adalimumab antitijela (ADA), QuantiFERON test