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Efficacy of biological treatment in inflammatory bowel disease – a single-center experience

Abstract

Introduction. Efficacy of biological treatment (BT) is a key issue among inflammatory bowel disease (IBD) patients. Laboratory markers and endoscopic procedures are basic diagnostic tools in the assessment of response to biological agents in the course of Crohn's disease (CD) and ulcerative colitis (UC).

Aim. The aim of our investigation was to assess the correlation between laboratory parameters and endoscopic picture in the course of BT in patients with IBD – CD and UC –treated with biological agents.

Material and methods. The total number of 71 patients were enrolled in the study, 25 with CD and 46 with UC. When it comes to 15 patients with CD, they were treated with infliximab (IFX) and 10 patients with adalimumab (ADA) – one year of therapy. Patients with UC were administered IFX – induction therapy. Laboratory tests (C-reactive protein (CRP) and platelet (PLT) count) and colonoscopy were performed in all patients before and during BT.

Results. BT improved endoscopic picture (SES-CD, MAYO) in all patients. BT lowered CRP ($p<0.05$) and PLT count ($p<0.05$) in CD group. CRP level and PLT count decreased in UC group, too ($p<0.05$). A positive correlation between PLT count and SES-CD score prior to the first dose was noticed in ADA group. CRP level correlated positively with PLT count in CD patients treated with IFX before the introduction of BT. Moreover, CRP level correlated positively with both MAYO score and MAYO endoscopic subscore after the second dose of IFX and after finished induction regimen in UC group.

Discussion. BT revolutionized a natural history of IBD and its efficacy was approved worldwide. Nevertheless, biological agents do not lead to a full remission of the disease in all patients. Because of this reason, laboratory parameters and endoscopic picture must be carefully monitored during BT to achieve the best outcome in IBD patients.

Conclusion. Full clinical and endoscopic remission of IBD was not achieved, although BT lowered CRP level, PLT count and improved endoscopic picture of patients enrolled into our study.

Keywords: biologics, inflammatory bowel disease, inflammatory parameters.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are characterized by remitting-relapsing course. An introduction of monoclonal anti-tumor necrosis factor α (TNF-α) antibodies has revolutionized an approach for induction and maintenance for inflammatory bowel disease (IBD) since late 1990s. From that time biologic agents have become a mainstay for IBD treatment [1]. A majority of non biological drug therapies in IBD (aminosalicylates, steroids and immunomodulators) leads to a symptomatic improvement but fails to inhibit an underlying inflammatory process. On the other hand, according to worldwide data, anti-TNF-α agents (infliximab (IFX), adalimumab (ADA), golimumab, certolizumab pegol) changed IBD course together with life of patients by reduced number of surgeries, less hospitalizations, steroid sparing, improved quality of life, greater clinical remission and mucosal healing rate [2]. Nevertheless, TNF-α inhibitors are reported to be not useful for one third of all patients and further one third lose effect over time. The response to these limitations is another group of agents, e.g. anti-adhesive molecules, antibodies targeting interleukins or small particles acting as Janus kinases' inhibitors. High health care expenditures on BT constitute another limitation of this form of treatment. The solution to this issue might be the generation of biosimilars (also available among anti-TNF-α agents). A lot of centres report a good experience with these generics [3]. The other key issue in the field of BT is a monitoring of its efficacy. Certain biomarkers specific to anti-TNF-α therapy, that could have an essential role in predicting unresponsiveness, have not been established yet. Their role would be the most important in the group of nonresponders and could make it possible to switch them on another biological therapy in the most proper moment to improve the outcome [4]. Another underlying problem is the utility of serological biomarkers in the assessment of remission in IBD patients. According to existing knowledge, CRP, PLT count and PLT indices (mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW) are common

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tools, available in great majority of centres, and together with endoscopic evaluation, they are worldwide used tests among IBD patients. The role of calprotectin in evaluating the severity of inflammatory process in gastrointestinal tract (GIT) has also been highlighted recently. However, it is frequently possible to observe severe discrepancies between serological markers values and endoscopic picture in the course of IBD. Additionally, certain cut-off of used endoscopic scales has not been established yet [5]. Taking all above into consideration, it might be assumed that despite a large number of diagnostic tools we are not able to rely on them in each case and we are not able to predict which type of IBD therapy will be the best approach in each patient.

AIM

The aim of a current study was to evaluate the efficacy of BT in the course of IBD and to find out if there is any correlation between selected laboratory parameters and the endoscopic picture in the course of BT.

MATERIALS AND METHODS

Local ethics committee ruled that no formal ethics approval was required in this study. Written consent was obtained from each participant of the study. The patients signed informed consent forms and agreed to present their laboratory results. The total number of 71 patients from the Department of Gastroenterology with Endoscopy Unit of Medical University of Lublin in Poland, with diagnosed IBD was enrolled in the study; 46 women and 25 men. Participant were qualified between January 2014 and December 2016. IBD diagnosis was based on commonly used criteria. The examined group contained 25 persons with CD (15 females and 10 males) and 46 with UC (31 females and 15 males). When it comes to 15 patients with CD. they were treated with IFX i.v. (5 mg/kg; an induction regimen of 3 doses at 0, 2 and 6 weeks, followed by maintenance regimen every 8 weeks – together one year of treatment) and 10 patients with ADA s.c. (an induction regimen of 1 dose 160 mg, followed by 80 mg two weeks later (Day 15); 2 weeks later the beginning of maintenance dose of 40 mg each other week (Day 29) – together one year of therapy). Patients with UC were administered IFX i.v. (5 mg/kg; an induction regimen of 3 doses at 0, 2 and 6 weeks). Laboratory tests of serological markers (C-reactive protein (CRP) and platelets (PLT) count) and colonoscopy were performed in all patients before and during BT. In CD group they were conducted prior to the first dose of anti-TNF-α therapy, after induction regimen (only laboratory tests) and one year after finished BT. In UC group laboratory tests and colonoscopy were performed each time prior to the infusion of anti-TNF-α and 6 weeks after a finished induction regimen of BT. To assess the severity of inflammatory process in the course of BT, CRP (a normal range 0-5 mg/L) and PLT count (a normal range 150-400x109/L) were measured in all participants. In patients with UC MAYO score was also calculated, with a special attention to endoscopic subscore. In patients with CD Simple Endoscopic Score for Crohn's Disease (SES-CD) scale was used to evaluate an influence of BT on endoscopic remission of the disease. In all patients with CD, panendoscopy was performed to exclude lesions in upper part of GIT. All the participants were unresponsive to 5-aminosalicylates, immunomodulators and corticosteroids and finally switched to BT; they continued previous pharmacotherapy during BT. Patients were tested for tuberculosis, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, hepatitis C virus, and hepatitis B virus prior to the initiation of BT. Performed tests excluded infections in all participants. Calculations and statistical analysis of obtained data were performed with Statistica 12 Software. Spearman's rank correlation, analysis of variance (ANOVA) and Wilcoxon signed-rank test were used to assess the dependencies between laboratory tests results and an endoscopic picture. A p-value of less than 0.05 was considered significant.

RESULTS

Demographic characteristic, results of laboratory tests and endoscopic procedures in examined patients together with statistical analysis are presented in Tables 1-5. All the participants completed BT. No side effects of introduced therapy were noticed. The study revealed statistically significant improvement of endoscopic picture (SES-CD, MAYO) in UC patients and CD group treated with IFX. BT lowered CRP level ($p<0.05$) and PLT count ($p<0.05$) in CD group. We also found statistically significant decrease in CRP level and PLT count among UC patients. Performed survey showed a positive correlation between CRP and PLT count in CD patients treated with IFX during qualification to BT. A positive correlation between PLT count and SES-CD score prior to the first dose was noticed in ADA group (Fig. 1). Mean final SES-CD score in IFX and ADA patients were 4 and 8, respectively. Mean final CRP and PLT count in IFX group were 4.2 and 275. In ADA patients CRP after finished yearly treatment achieved 18.97 and PLT – 331. CRP correlated positively with both PLT count and MAYO score during qualification to anti-TNF-α therapy in UC

TABLE 1. Demographic characteristic and results of laboratory tests and MAYO scale in examined UC patients. Age and results of laboratory tests are presented as mean±SD (standard deviation).

	Parameter	UC patients n=46
	Age	**38.8±14.38**
	Gender F/M	**31/15**
CRP [0-5 mg/L]	prior to the I dose	32.35±48.14
	prior to the II dose	5.02±8.96
	prior to the III dose	6.12±11.15
	6 weeks after induction regimen	7.05±11.6
PLT [150-400 x10^9/L]	prior to the I dose	398±148.41
	prior to the II dose	324±112.05
	prior to the III dose	304±99.03
	6 weeks after induction regimen	315±87.5
MAYO score [0-12 points]	score prior to the I dose	10±1.72
	score prior to the II dose	6±2.43
	score prior to the III dose	4±2.11
	6 weeks after induction regimen	3±1.67
MAYO endoscopic subscore [0-3 points]	prior to the I dose	3±0.38
	prior to the II dose	2±0.72
	prior to the III dose	2±0.77
	6 weeks after induction regimen	2±0.88

n – number of patients, UC – ulcerative colitis, F – females, M – males, CRP – C-reactive protein, PLT – platelets

TABLE 2. Analysis of variance (ANOVA) in UC patients. Mean values±SD (standard deviation).

Analysis of variance (ANOVA)	CRP	PLT	MAYO score	MAYO endoscopic subscore
prior to the I dose	32.35±48.14	398±148.41	10±1.72	3±0.38
prior to the II dose	5.02±8.96	323±112.05	6±2.43	2±0.72
prior to the III dose	6.12±11.15	304±99.03	4±2.11	2±0.77
6 weeks after finished induction regimen	7.05±11.6	315±87.5	3±1.67	2±0.88
p value	0.000001	0.00004	0.00001	0.00001

UC – ulcerative colitis, CRP – C-reactive protein, PLT – platelets

TABLE 3. A comparison of demographic characteristic and results of laboratory tests and SES-CD scale in examined CD patients with refer to administered anti-TNF-α agent. Age and results of laboratory tests are presented as mean±SD (standard deviation).

	Parameter	UC patients n=25	
		Infliximab group n=15	Adalimumab group n=10
	Age	**35.47±14.12**	**34.7±12.08**
	Gender F/M	**10/5**	**5/5**
CRP [0-5 mg/L]	prior to the I dose	41.55±39.41	36.47±40.0
	after induction phase	14.53±25.91	5.3±7.83
	1 year after finished BT	4.2±3.39	19.0±31.17
PLT [150-400 x10^9/L]	prior to the I dose	439±205.24	421±137.75
	after induction phase	320±92.44	293±53.34
	1 year after finished BT	275±47.93	331±134.30
SES-CD [0-56 points]	prior to the I dose	17±9.5	10±5.9
	1 year after finished BT	4±4.75	8±6.55

n – number of patients, CD – Crohn's disease, F – females, M – males, CRP – C-reactive protein, PLT – platelets

TABLE 4. A statistical analysis of Infliximab (IFX) group. Mean values±SD (standard deviation).

Analysis of variance (ANOVA) in IFX group	CRP	PLT	Wilcoxon signed-rank test in IFX group	SES-CD
prior to the I dose	41.55±39.41	439±205.24	prior to the I dose	17±9.5
after induction phase	14.53±25.91	320±92.44		
1 year after finished BT	4.2±3.39	275±47.93	1 year after finished BT	4±4.75
p value	0.00674	0.00155		0.001621

CRP – C-reactive protein, PLT – platelets

TABLE 5. A statistical analysis of Adalimumab (ADA) group. Mean values±SD (standard deviation).

Analysis of variance (ANOVA) in ADA group	CRP	PLT	Wilcoxon signed-rank test in ADA group	SES-CD
prior to the I dose	36.47±40.0	421±137.75	prior to the I dose	10±5.9
after induction phase	5.3±7.83	293±53.34		
1 year after finished BT	19.0±31.17	331±134.30	1 year after finished BT	8±6.55
p value	0.00552	0.02472		0.085832

CRP – C-reactive protein, PLT – platelets

patients (Fig. 2). Moreover, CRP level correlated positively with both MAYO score and MAYO endoscopic subscore after the second dose of IFX and after finished induction regimen in UC group (Fig. 3 and 4). Mean final MAYO endoscopic score and mean final MAYO endoscopic subscore were 3 and 2, respectively.

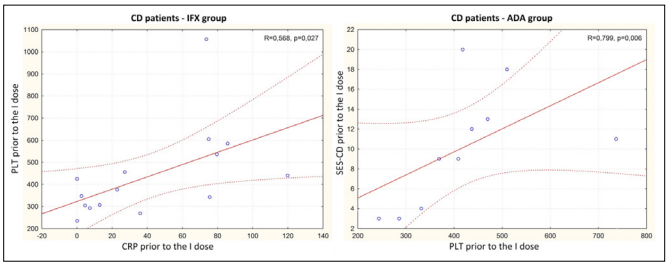

FIGURE 1. A correlation between CRP level and PLT count prior to the first dose of IFX in CD patients and a correlation between PLT count and SES-CD prior to the first dose of ADA in CD patients.

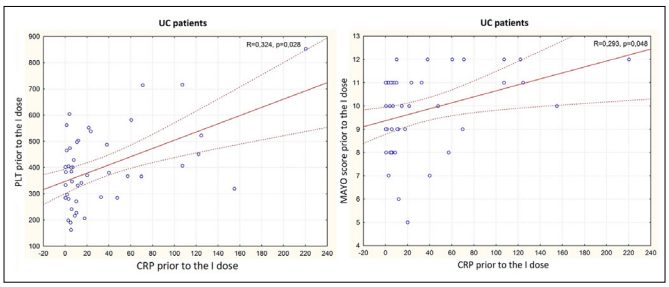

FIGURE 2. A correlation between CRP level and PLT count and a correlation between CRP level and MAYO score prior to the first dose of IFX in UC patients.

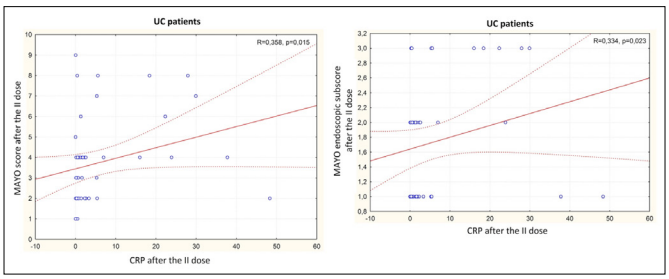

FIGURE 3. A correlation between CRP level and MAYO score after the second dose of IFX and after finished induction regimen in UC patients.

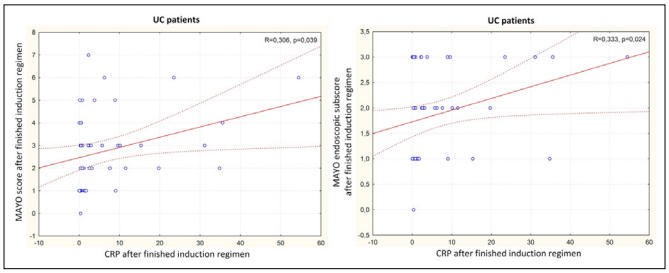

FIGURE 4. A correlation between CRP level and MAYO endoscopic subscore after the second dose of IFX and after finished induction regimen in UC patients.

DISCUSSION

Clinical trials usually indicate an endoscopic mucosal healing in UC as endoscopic MAYO subscore ≤ 1 [6]. In 46 UC patients in our investigation mean MAYO endoscopic subscore after 6 weeks from finished induction therapy was 2 and an endoscopic remission was not achieved, although the decrease in MAYO score, CRP level and PLT count was statistically significant.

Mean final CRP levels were still a little bit elevated. In all persons from CD group yearly BT led to a statistically significant decrease in PLT count, however an endoscopic remission was not observed and mean final SES-CD score in IFX and ADA group was 4 and 8, respectively. Similarly to UC group, mean final PLT count in CD patients remained in a normal range, but CRP level normalized only in ADA group ($p>0.05$). According to previous studies, SES-CD equal 0 stands for the mucosal healing in the course of CD [7]. Despite a relatively small group of patients enrolled in current survey, achieved results are noteworthy; they highlight present doubts connected with BT of IBD. In Poland a precise duration of anti-TNF-α treatment has not been established yet and existing recommendations refer to individual profiles of patients. Moreover, anti-TNF-α agents are used in top down pattern, strictly described by National Healthcare System. There is a great body of evidence, that IBD constitutes an even greater risk of thromboembolic events than other inflammatory conditions. Performed studies proved that IBD patients present defective intestinal barrier functions. As the result, pathogen-associated molecular patterns coming from bacteria located in GIT might get to a systemic circulation and activate innate immunity receptors on endothelial cells and platelets, leading to a procoagulative state [8]. What is more, a dysregulation of innate immunity was proved to correlate with unresponsiveness to anti-TNF-α agents. An altered protein C pathway, inflammatory cytokines, including TNF-α, increased thrombin generation and reduced fibrinolytic capacity also participate in increased prevalence of system thrombosis in IBD patients, which risk in IBD patients group is threefold higher in comparison to general population. All enumerated issues indicate a direct link between a coagulation and an inflammation in the pathogenesis of IBD. Interestingly, researchers proved that IFX induced significantly rescued pro-platelet formation by megakaryocytes in IBD group patients, what was not observed in healthy controls [9]. Several scientific sources suggest that PLT count has the best accuracy in refer to endoscopic activity in IBD. Other investigations revealed statistically significant correlation between Crohn's disease activity index (CDAI) and PLT indices including PLT count, MPV, PDW, PCT platelet large cell ratio (P-LCR). Researchers have also observed a notably higher PLT count and PCT level together with lowered P-LCR and PDW levels in an active CD in comparison to the controls. In our study PLT count correlated with SES-CD prior to the BT in ADA group, in the most active phase of disease, what confirms data collected so far in the literature [10]. Although CRP is commonly defined as a less specific and sensitive biomarker for determining active CD, it was positively correlated with PLT count in CD patients treated with IFX during qualification to BT. Subsequently, according to the literature, high CRP levels were observed to correlate notably with clinical relapse in both short-term and long-term follow-up of IBD patients. It was also proved that CRP has a better correlation with endoscopic and clinical findings rather in CD than UC. Another survey conducted on CD patients treated with IFX revealed that response to anti-TNF-α agent is positively correlated with high baseline level of CRP. More patients with high baseline levels of CRP responded to IFX than patients with normal levels. A major limitation of CRP is its lack of specificity for intestinal inflammation [11]. To overcome this problem fecal calprotectin (FC) is used in many centres because of higher specificity and better correlation with endoscopic findings. Serum procalcitonin (SP) is not recommended as a single parameter in the assessment of IBD activity, because it might be affected by accompanying infection, so it might be helpful in differentiating intestinal flare-up with systemic infection [12]. Despite a great advance in the management of CD, a single trustworthy endoscopic index to assess the remission of the disease has not been established yet. SES-CD was developed as a tool to simplify Crohn's Disease Endoscopic Index of Severity (CDEIS). Even though CDEIS is described as a standard tool in assessing CD severity, its utilization is connected with several limitations. Firstly, CDEIS measurement is quite complex and due to this fact – connected with lack of practicality. Furthermore, CDEIS was reported to underestimate disease severity, especially when disease involves only the one segment of bowel. Finally, validated score cut-offs are not elucidated, therefore CDEIS cannot be used as a reliable tool with prognostic values in CD patients. SES-CD was developed in 2004 as the response to deficiencies of CDEIS. However, it is still not an ideal tool and further clinical trials must be performed to clarify its certain cut-off, because data in literature regarding its prognostic values differ [13]. An endoscopy incessantly constitutes the 'gold standard' for IBD evaluation. It is worth mentioning that according to clinical trials, a higher rate of exacerbations was observed in UC patients with endoscopic macroscopic remission and histologic activity. Nowadays, no guidelines recommend routine evaluation of bioptic samples in UC patients. Future studies should clarify a role of histologic activity and its possible implications on the management of IBD patients. Next key aspect concerning the treatment with IFX is its possible deterioration by serological antibodies (ATIs). Researchers also proved that a level of ATIs to IFX associates with a response to treatment. Furthermore, according to other studies, the lack of perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) is correlated with early response to anti-TNF-α agents. Therefore, these serological tests could be performed in all patients qualified to treatment with IFX [14]. Another underlying issue in the management of IBD patients is an utilization of other anti-TNF-α drugs (golimumab, certolizumab pegol) and other agents, e.g. anti-adhesive molecules (natalizumab, vedolizumab), antibodies targeting certain interleukins (ustekinumab, etrolizumab) or small particles acting as Janus kinases' inhibitors. All enumerated possible therapies require further clinical trials, however already achieved results are promising [15].

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