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The incidence rate of surgical interventions in patients with Crohn's disease treated with anti-tumour necrosis factor biologics

Aleksandra Sobolewska-Włodarczyk[1,2,*], Anna Zielińska[2,*], Paweł Siwiński[2,3], Ewa Jędraszczyk[2], Krystyna Stec-Michalska[2], Marcin Włodarczyk[1,3], Maria Wiśniewska-Jarosińska[2]

[1]Department of Biochemistry, Medical University of Lodz, ul. Mazowiecka 6/8, 90-647 Łódź, Poland
[2]Department of Gastroenterology, Medical University of Lodz, pl. Hallera 1, 90-647 Łódź, Poland
[3]Department of General and Colorectal Surgery, Medical University of Lodz, pl. Hallera 1, 90-647 Łódź, Poland
*Contributed equally in this study

Corresponding author: Marcin Włodarczyk, MD
Department of Biochemistry, Medical University of Lodz
ul. Mazowiecka 6/8, pok. 127; 92-215 Łódź, Poland
Phone: +48 42 272 57 07, Fax: +48 42 272 56 94; E-mail: dr.mwlodarczyk@gmail.com

Abstract: Background: Anti-tumour necrosis factor alpha drugs (anti-TNF-α) effectively reduce the risk of surgery in Crohn's disease (CD). Unsatisfactory response to anti-TNF-α agents leads to the development of disease complications in a great percentage of patients. Simultaneously, possible predictive factors for flares during biological treatment remain uncertain.
Aims: To investigate the incidence rate of intestinal resection during biological treatment and search for predicting factors for flares demanding a surgical intervention.
Methods: A retrospective study of 68 patients qualified for anti-TNF-alpha therapy. The data consisting of demographic details, disease duration and laboratory results before the first drug administration and at the post induction period were collected. The association between these parameters and loss of response (LOR) demanding a surgical intervention was evaluated.
Results: LOR to the anti-TNF-alpha therapy was observed in 10/68 patients (14.7%). Mean disease duration at initiation of therapy was statistically longer in operated patients (8.8 ± 2.04 y vs. 4.93 ± 4.29 y; p <0.02). That group revealed higher CRP values in post induction period compared to group with sustained response (48.24 ± 61.99 mg/l vs. 7.29 ± 13.43 mg/l; p <0.05), contrary to hematocrit levels, which were lower in this group at each point of the study (30.58 ± 6.19% vs. 36.69 ± 16.0%; p = 0.04) (18.62 ± 18.19% vs. 40.27 ± 4.72%; p <0.05) (4.01 ± 0.9 x10^6/µl; p = 0.009) (40.27 ± 4.72 g/dl vs. 18.62 ± 18.19 g/dl; p <0.05).

CDAI was significantly higher at post induction evaluation in the group with LOR (260.75 ± 98.1 vs. 118.12 ± 4.59; p <0.05).
C o n c l u s i o n: CRP and CDAI, expressing inflammation severity, RBC, Hgb, Hct and the disease duration may serve as predictive factors for LOR to biological therapy.

Key words: Crohn's disease, biological therapy, loss of response, colectomy, bowel resection.

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) characterized by the intermittent, destructive, transmural inflammation of the gastrointestinal tract [1, 2]. It often progresses to severe, quality of life decreasing complications, such as fistulas, abscesses, strictures, haemorrhages, which require hospitalization and surgery for management [3, 4].

In the past, up to 70% of patients underwent at least one abdominal surgery for CD during their lifetime with approximately 1 in 4 requiring an ileostomy [5].

As a positive example of advancement in CD management should be considered the identification of the tumour necrosis factor alpha (TNF-α) — a key proinflammatory cytokine holding a pivotal role in pathogenesis of IBD [6]. TNF-α induces other pro-inflammatory cytokines, including IL-1 and IL-6, activates leukocytes and enhances their migration and inhibits apoptosis of inflammatory cells. In CD patients the number of TNF-α producing cells is highly increased in the lamina propriety in the bowel [7]. Inhibition of TNF-α enables optimization of therapeutic interventions and is possible through biological therapy with the use of monoclonal antibodies targeted at TNF-α, such as infliximab (IFX), adalimumab (ADA) and certolizumab (CZP) [1, 2]. Biologics help to induce and maintain clinical response and remission, improve quality of life and productivity [3, 6].

Unfortunately, 25–40% of the patients who respond to this therapy need multiple dose and interval adjustments to maintain clinical response and about 10% per year discontinue therapy because of the loss of response (LOR) and hypersensivity reactions [1, 6]. Despite individualized approach to each patient still a substantial group of those undergoing treatment fails to respond to medication, thus require surgical interference [8].

The aim of this study was to investigate the incidence rate of intestinal resection during the biological treatment in CD patients. Additionally, we searched for predicting factors for disease flares demanding a surgical intervention.

Materials and methods

Patients

The medical charts of 68 CD patients (35 men and 33 women; mean age 33.5 years; range 19–59 years) treated with the use of anti-TNF-α inhibitors at the Department of Gastroenterology, Medical University of Lodz between 2008 and 2015 were studied retrospectively.

Elegible patients were over 18 years old and had a diagnosis of CD established and confirmed according to clinical, radiological, endoscopic and histological criteria developed by the European Crohn's and Colitis Organisation (ECCO) [9].

Clinical and demographic data of all patients was retrieved from medical charts. Parameters such as age, sex, duration of the disease, patient's age at diagnosis and previous biological treatment were analysed. Laboratory evaluation included serum levels of white blood cells (WBC), red blood cells (RBC), hemoglobin (Hgb), hematocrit (Htc), blood platalets (PLT), mean platelet volume (MPV), C-reactive protein (CRP) measured at initiation of anti-TNF-α treatment, induction and post induction period. Measurements performed on the day of infusion of anti-TNF agent served as a reference point for values reported later during the course of therapy. At each time point, patients' clinical state was evaluated with the use of Crohn's Disease Activity Index (CDAI) [9].

The CD patients enrolled in the study were divided in two groups. The first comprised individuals responding to biological treatment, achieving and maintaining long-term remission defined with reduction in CDAI score by ≥25% and ≥70 points from baseline and a CDAI score lower than 150 respectively.

The second group included patients who in the course of treatment failed to induce and maintain remission. Loss of response was defined as a CDAI score of ≥175 and an increase in CDAI score of ≥35% and ≥70 points for at least two following clinic visits.Patients who deteriorated or failed to respond to treatment, ceased the biological therapy and underwent demanded surgical resection. Each decision for such alteration was made individually and thoroughly reviewed with surgeons' assistance.

Patients undergoing operation (the group presenting LOR) were then compared with those who responded to the treatment in search for parameters predisposing negative outcome requiring surgical intervention.

The primary endpoint in this study was the resection rate in patients with loss of response to anti-TNF-α agents. The secondary outcome included defining predictive factors of loss of response and subsequent operation, that could help in modifing the management and therapeutical strategies individually.

Statistics

Statistical analysis was carried out using *Statistica 12* statistical software for Windows.

Descriptive statistics was used to summarize the data showing the number of individuals in the study and the rate of surgical procedures among the group.

Statistical comparisons were performed using parametric t test, non-parametric Mann Whitney test, chi-squared, applied as appropriate as possible predictive factors of resection several covariates were considered including disease duration, age, sex, laboratory findings and CDAI score. Multivariate analysis was performed to explore the correlation of loss of response resulting in surgery with laboratory and demographic parameters. *P*-values <0.05 were considered statistically significant.

Results

The demographics and disease characteristics of the study population are summarized in Table 1.

Table 1. Population demographics and disease charcteristics.

Variable	All patients (n = 68)	Biological therapy responsive (n = 58)	Non-responders (n = 10)
Gender			
Male *n, %*	35 (51.5)	32 (55.2)	3 (30)
Female *n, %*	33 (48.5)	26 (44.8)	7 (70)
Mean age, *years* (range)	33.5 (19–59)	33 (19–59)	36.4 (28–45)
Mean age at diagnosis, *years*	26.90	26.9	26.8
Mean disease duration	5.23	4.9	8.8

A total of 68 patients were identified and their medical charts were reviewed. Among those, 10 (14.7%) patients lost positive response to the treatment and underwent bowel resection and 58 (85.3%) presented substantial clinical response to the treatment without the need of surgical intervention. Significant difference was observed in mean disease duration from the onset to therapy initiation between two statistical groups. Higher values were noted with surgical patients compared to responders (8.8 vs. 4.9 y respectively Fig. 1).

Laboratory tests revealed statistically significant differences between two groups regarding levels of CRP, Hgb and RBC in the post induction period. Biological therapy responders demonstrated lower median values of CRP compared to those

who required surgical intervention (7.29 ± 13.43 mg/l vs. 48.24 ± 61.99 mg/l; p <0.05 Fig. 2). The RBC and Hgb levels after induction, presented a trend favouring the responders with values of 4.51 ± 0.6 x10^6/µl vs. 4.01 ± 0.9 x10^6/µl (p = 0.009) and 40.27 ± 4.72 g/dl vs. 18.62 ± 18.19 g/dl (p <0.05) respectively.

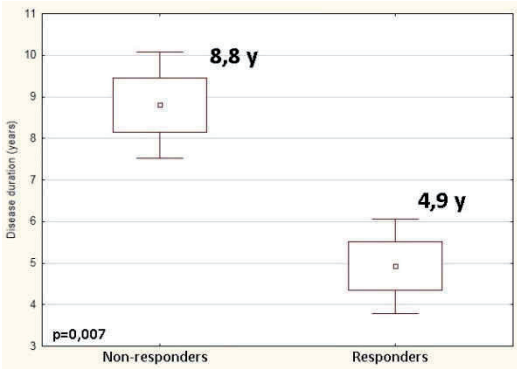

Fig. 1. Mean disease duration on biological therapy initiation.

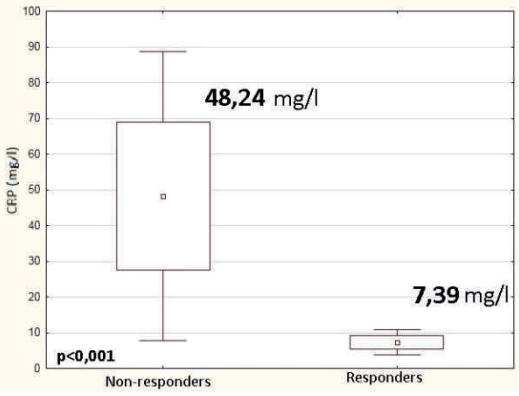

Fig. 2. CRP values in the post induction period.

Of the other clinical variables, differences in Hct both before therapy initiation and at the induction point were observed. Values differed between analyzed groups favoring biologics responders (36.69 ± 16.0% vs. 30.58 ± 6.19%; p = 0.04) before treatment as well as post induction (40.27 ± 4.72% vs. 18.62 ± 18.19%; p <0.05).

Among patients prone to biologics a trend towards higher CDAI levels was established. Statistically significant differernces were determined at the post induction evaluation. The score ranged around 118.12 ± 4.59 compared to substantially higher 260.75 ± 98.1(p <0.05) achieved by surgical patients.

Other, initially investigated variables, comprising white blood cells (WBC), blood platelets (PLT), mean platelet volume (MPV), neutrophile and lymphocyte rate, did not reveal statistical significance, therefore were not included.

Discussion

CD, being a relapsing and remitting, chronic inflammatory condition, requires difficult decissions. One of the most significant is choosing between pharmacotherapy and surgical treatment [10, 11]. Around 80% of patients suffering from CD undergo resection at some point of their lifetime, with a third of patients requiring surgery within 5 years from diagnosis and up to 50–60% in 10 years after the diagnosis [10, 11]. In our study nearly 15% of patients had to be operated due to unsatisfactory pharmacotherapy outcome, within averagely 9 years from the disease onset. Nevertheless, surgery in CD is not a curative procedure — 7 out of 10 operated patients will require a second operation due to high recurrence rate [12, 13]. The main goal of the pharmacological therapy is to prolong the remission time before the resection is required [14].

Anti-TNF-α agents have the potential to decrease the need for surgery and alter the natural history of the disease through induction and maintenance of clinical response, mucosal healing and quality of life improvement [15]. Biologics cause rapid supression of mucosal inflammation by reducing the number of lamina propria cells producing TNF-α [16].

First TNF-α inhibitor, approved by US Food and Drug Administration (FDA) in 1998, was infliximab. IFX is a chimeric monoclonal immunoglobulin G1 antibody against TNF-α [6]. It is composed of human constant and murine variable regions and is administered intravenously. It's effect is achieved by elimination of inflammatory cells expressing TNF-α on their membranes, mainly by induction of apoptosis of T-cells and monocytes [16–19].

The same effect is obtained by the second agent found to be effective for treatment of refractory luminal CD — subcutaneously administered recombinant, fully human monoclonal antibody to TNF-α — adalimumab (ADA), that induces apoptosis of monocytes [6].

Certolizumab pegol (CZP) represents the third anti-TNF-α antibody. It was FDA approved in 2007 and also is a human monoclonal antibody, but unlike IFX and ADA it is pegylated, which extends its halflife, what translates into prolongation of the dose interval [20]. Until 2013, only IFX and ADA were approved in Europe, while CZP is also approved in USA, Russia and Switzerland [21]. In our study the patients were treated with these three anti-TNF-α agents.

Following successful induction therapy, a subset of patients loses their initial therapeutic benefit leading to loss of response (LOR) [22], which is a serious limitation

of anti-TNF-α treatment, as the number of CD patients on maintanace treatment increases worldwide [23]. However despite ongoing and extensive search for aspects associated with LOR, little is still known about factors predicting a good response or failure of biological treatment [23, 24]. Current guidelines emphasize the need of complex assasement of CD activity by using endoscopy and cross-sectional imaging methods [12, 23]. Nonetheless, these methods of evaluation can be inconvenient for the patient, carry significant risks and costs [25]. Studies also focus on various biochemical markers of inflammation, alter alia faecal calprotectin and lactoferrin, serum albumin level, orosmucoid or fibrinogen [14, 26–28]. Also genetic risk alleles are identified to associate with non-response to anti-TNFs in CD [29]. Drug through levels and antidrug antibodies concentrations are strongly connected with the treatment outcome and [24] their measurement allows for the modification of the treatment algorithms [23]. All of these predictors though are not commonly available in clinical circumstaces.

We observed that total blood count elements may serve as a useful tool in CD therapy outcome observation. These automated measurements are cost-efficient and are routinely measured at each drug infusion. Lower RBC, Hgb in the post induction period and Hct both before therapy initiation and at the induction point were indicators of LOR. In the analyses from the PRECiSE 3 study Sandborn *et al.* suggested that Hct is a strong predictor of loss of remission and may be an indicative factor of poor overall health. According to the same study Hgb concentration is a significant predictive factor in the time to relapse after treatment withdrawal [4]. Other exploratory and long-term treatment studies suggested that low Hgb levels may negatively affect treatment outcomes in CD [30].

What is interesting, is that the responders to the therapy in our group did not present increased levels of PLT and MPV, commonly described in the works concerning LOR in CD [28, 31, 32].

Increased CRP levels were noticed in the group of patients who required surgery which is in accordance with a number of studies. Several of them revealed that high baseline CRP and its normalization after induction doses of biological therapy are predictive of clinical efficacy of the treatment [23]. CRP had been found to have low sensivity, but high specifity in diagnosing active disease [27]. A decrease in serum drug levels preceding LOR was easily detected by an increase in CRP in a study conducted by Hibi *et al.* in which CRP was recognized as an indicator of serum drug level in predicting LOR [33].

CDAI is a commonly calculated score, however should be approached cautiously and serve as an information only. In our study, surgical patients obtained significantly higher CDAI than responding controls therefore failing to maintain remission. CDAI is a commonly calculated score, however should be approached cautiously and serve as an information only. In the analysis of POCER study P. De Cruz *et al.* claim

that CDAI is insensitive to detect early disease recurrence, as endoscopic changes precede the development of symptoms [14]. In the very POCER study, conducted by M.A. Kamm CDAI presumed inferior to faecal calprotectin [34], while other study (Schoepfer *et al.*) proved that CDAI is inappropriate for assasement of inflammatory activity [26].

Early signs of LOR, which we tried to reveal in our study, should impel consideration of the surgical procedures or modifications of pharmacotherapy. Prolonging the time of anti-TNF-α treatment without clinical response may contribute to complications and vast, extensive surgery [35]. TNF-α promotes angiogenesis and collagen production. It's inhibition results in healing deterioration and lesser wound strength given the necessity of the operation [14]. Therefore physicians, both general medicine and colorectal surgery specialists, should cooperate to establish whether surgery conduction or pharmacotherapy modification is beneficial for the patient.

Conclusion

In conclusion, our study showed that simple and most accessible factors, such as RBC, Htc, Hgb, CRP and CDAI may serve as predicting markers of LOR in CD patients treated with biological agents. We suggest that these biomarkers will allow the phycisians to perform the decision of earlier surgery, as the one excellling prolonged pharmacotherapy. That will be advantageous for the patients, as it will allow to prevent disease's crippling complications and complicated, extensive operation. This study was retrospective and performed on a small group of patients. Further studies are desired to confirm our observations on the predictig role of RBC, Htc, Hgb, CRP and CDAI in CD patients.

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