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DOCTORAL THESIS SUMMARY

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CLINICAL AND EPIDEMIOLOGICAL FEATURES, NUTRITIONAL STATUS AND QUALITY OF LIFE OF PATIENTS WITH INFLAMMATORY BOWEL DISEASES FROM DOBROGEA

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Key words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, prevalence, endoscopic activity, calprotectin, nutrition, quality of life, functional gastrointestinal symptoms, rifaximin

INTRODUCTION

Inflammatory bowel disease (IBD), chronic progressive diseases, occur by a disregulation in the immune system of the digestive tract resulting a chronic inflammation that determines the disease activity [1,2]. Management of these diseases is complex, there is no standard strategy, and the treatment must be personalized according to a number of associated factors. It affects often patients of young age and have a severe evolution, so decisions in such cases are difficult to take and apply.

The present study represents a complex approach of IBD and it is focused especially on disease activity which represents one of the most important point of view in these diseases and has the pivotal role in establishing the treatment strategy; also, disease activity is the one that determines all the negative effects felt by the patients and has a major impact on the quality of their life. This thesis is structured in three studies:

1. Epidemiological features of inflammatory bowel disease in Dobrogea

2. Nutritional status and quality of life of patients in correlation with the clinic, biologic and endoscopic activity

3. Efficacy of rifaximin in the treatment of functional gastrointestinal symptoms in patients with Crohn's disease in remission

Study number 1. Epidemiological features of inflammatory bowel disease in Dobrogea

In this chapter I collected necessary data to perform an epidemiological analysis of IBD in Dobrogea. I consider that such analysis is very useful because this kind of data is completely lacking in this region, and, moreover, few epidemiological data from Romania on this pathology were published. Mainly, I collected data to determine the IBD profile in this area, what type of disease is more prevalent and to establish disease features from this region.

Study number 2. Nutritional status and quality of life of the patients in correlation with the clinic, biologic and endoscopic activity

In this chapter I studied disease activity from several points of view that are in a close relationship (clinical activity, endoscopic activity, biomarkers that reflctes disease activity, nutritional status and quality of life) and I made various correlations between them in order to

define as precisely as possible the activity of the disease, which, although such a simple term, involves many aspects and it is of great interest for a proper management.

Measuring disease activity, which refers to the inflammatory burden and its impact on the patient at any time during the course of the disease, is an essential step in the evaluation of patients and definitive in choosing therapy strategies. Classifying disease activity in three areas - clinical symptoms, endoscopic inflammation and biomarkers of activity - and adding evaluation of quality of life and nutritional status - can help the clinician to establish and monitor disease activity using objective and standardized classification systems. In turn, this may also contribute to the evaluation of the response to treatment, which is of paramount importanance, as the IBD management paradigm is moving to a new "treatment - to - target" approach, the so - called "treat to target" concept. A clear understanding of the activity of the disease can facilitate better care of patients with IBD, addressing the impact of the disease as well as the risk of progression. The general aim of this thesis is to evaluate the tools for measuring IBD activity that can be used regularly in clinical practice in order to facilitate clinical care, to use a common vocabulary for IBD activity and to provide an objective basis for treatment and evaluation of treatment response. The description of the activity and severity of the disease in a way that is reproducible and useful represents a significant challenge. An additional challenge is also whether the activity and severity of the disease are best described using correlations between clinical symptoms, aspects seen on colonoscopy, impact of the disease on quality of life or on the nutritional status of patients with IBD. This study focuses in particular on IBD activity scores because these sccores influence daily medical practice, help at taking treatment decisions and help in assessing the response to treatment.

Areas of disease activity

In this study, I divided disease activity into the classical domains: clinical symptoms, endoscopic inflammation, activity biomarkers, and I added evaluation of quality of life and nutritional status of the patients. Each domain has its specific activity quantification tools for Crohn's disease and ulcerative colitis. It is useful to think separately about these areas, although, of course, they overlap and are in a close relationship. However, their consideration separately allows a standardized approach to quantify disease activity.

- *Clinical symptoms*

In daily practice, symptom assessment predominates in patient consultations and, therefore, it is essential to objectively assess symptoms, as they relate to disease activity and influence medical decisions. There are numerous scores that assess clinical symptoms in Crohn's disease and ulcerative colitis, but some are difficult to use in everyday practice. In this

paper, I used CDAI score for Crohn's disease and partial Mayo score for ulcerative colitis, which can be easily integrated into everyday practice.

Another important step in the assessment of clinical symptoms is to determine the extent of the disease in patients with ulcerative colitis and the phenotype of Crohn's disease patients, as this helps to understand the cause of the symptoms or guide to further investigations of possible complications that may be the cause of the symptoms. Montreal classification is a simple tool that classifies patients with ulcerative colitis according to extent of disease and patients with Crohn's disease according to phenotype and location.

❖ *Inflammation*

Inflammation is closely linked to disease progression and therefore has an impact on IBD severity; is one of the benchmarks of IBD activity and is gold-standard for endoscopy quantification. Complementary measures to quantify inflammation include histology (obtained by endoscopy), imaging (such as nuclear magnetic resonance imaging and computer tomography) and biomarkers (such as C Reactive Protein and fecal calprotectin). There are various endoscopic scores that quantify the lesions and are specific for Crohn's disease and ulcerative colitis; in this paper, I calculated CDEIS and SES-CD scores in patients with Crohn's disease, and Mayo endoscopic score and UCEIS score in patients with ulcerative colitis.

❖ *Quality of life*

Quality of life is a critical component of the activity of the disease, because it assesses the patient's social and emotional well-being, behavior, attitudes, as well as psychic symptoms caused by the disease and represents the ultimate goal of therapy [4]. As many quality of life questionnaires are long and difficult to use in daily practice, those that are quick to complete, validated, reliable and acceptable to patients are preferred. In this paper, I investigated quality of life of patients using SIBDQ.

Integration of disease activity assessment into clinical practice

Armed with precise, objective and reproducible assessment of disease activity in IBD, the clinician is able to understand the risks and benefits of continuing or changing therapy for their patients. Recently, a evidence-based expertise study was conducted to examine potential treatment targets in IBD with an emphasis on "treat-to-target" management strategy, and the results were published as recommendations under the name of specific therapeutic goals in IBD (STRIDE = Selecting Therapeutic Targets in IBD) [5]. The reason behind this "treat - to - target" approach is to focus attention on achieving remission or mild disease activity; Consequently, physicians and patients should discuss these goals and work together to achieve them within a

set time frame with the ultimate goal of improving outcomes (in all areas of disease activity, as described above).

Therefore, I believe that these areas of disease activity (clinical symptoms, inflammation, quality of life, to which nutritional status is added) present the opportunity to capture longitudinally the disease activity in order to improve the care of IBD patients. The use of a standardized approach to measure disease activity allows an objective evaluation of treatment response, standardizes current practices and facilitates comparisons between endoscopies, while also helping physicians achieving the ultimate goal of providing best care to IBD patients, not only capturing the impact of the disease, but also the risk of disease progression.

Study number 3. Efficacy of rifaximin in the treatment of functional gastrointestinal symptoms in patients with Crohn's disease in remission

In this chapter, I investigated the possible role that rifaximin might have in the treatment of functional gastrointestinal symptoms in Crohn's disease patients in remission. This idea rised after, in my daily medical practice, I met patients with apparently active IBD, gastrointestinal symptoms such as abdominal pain, semi-consistent stools, bloating, symptoms which were present despite adequate treatment of the underlying disease, symptoms which have a strong negative impact on patients quality of life. Approach of Crohn's disease activity focuses in this chapter, in fact, on demonstrating the absence of activity, namely, on confirming the remission which is analyzed from two points of view: endoscopic remission as guides recommend, also confirmed by the normality of inflammation biomarkers, in particular of fecal calprotectin. After excluding the possibility of a reactivation of Crohn's disease or other possible causes as a etiology of the symptomatology, I included in the study only patients who presented these symptoms as part of an associated irritable bowel syndrome (IBS). Since the role of rifaximin in IBS patients has already been well demonstrated, I set out to treat these IBD patients with the same treatment regimen prescribed in IBS patients and to establish its effectiveness in improving these functional type symptoms and in improving patients quality of life which is a very important aspect from the patients perspective.

This thesis consists of two parts: the general part - **Current state of knowledge** - made up of 5 chapters and the special part - **Personal contributions** - made up of 3 studies and 7 chapters in total. Content, numbering of figures or tables in this summary, as well as the references keep the order from the original thesis.

CURRENT STATE OF KNOWLEDGE

Chapter ***Epidemiology of inflammatory bowel diseases*** provides informations regarding the epidemiological situation of IBD worldwide, in the country or locally. Data presented in this chapter show that incidence and prevalence of inflammatory bowel diseases are constantly increasing, statistics showing worrying data, in addition to a large epidemiological variability, both temporal and spatial [10].

Chapter ***Activity of inflammatory bowel diseases***, IBD activity is further explored and is divided into biomarkers of activity, clinical and endoscopic activity. Data from literature regarding the various instruments for measuring disease activity are exposed. Existing activity scores have the role of assessing the severity of the disease activity and are mainly useful in making clinical decisions and choosing therapeutic strategy, especially when the patients do not respond adequately to the treatment and the desired target from the "treat to target" concept is not reached. There are several tools for objective measurement of the disease activity (based on symptoms, endoscopy, histology, radiology or biomarkers); based on "treat - to - target" concept [34], these are the targets that become objectives to be achieved after the introduction of various treatments. In addition to monitoring the clinical, endoscopic, histological activity, assessing the quality of life of patients is an important issue in the therapeutic strategy because its improvement is a major goal of the therapy; moreover, another important issue is an adequate nutritional status of the patients. Subchapter *Biomarkers of IBD activity* presents data from the literature regarding roles of C reactive protein and fecal calprotectin in IBD*, subchapter Clinical activity of IBD* provides data from literature regarding clinical activity measurement scores (CDAI, partial Mayo score), and subchapter *Endoscopic activity of IBD* present literature data regarding endoscopic activity assessment scores (CDEIS, SES-CD, endoscopic Mayo score, UCEIS). All these scores were calculated in patients with IBD in the special part of this thesis in study number 2.

Chapter ***Nutritional status of patients with inflammatory bowel disease*** provides informations regarding the associated IBD malnutrition and are described the modalities of assessing the nutritional status in IBD patients. Various tools for evaluating the nutritional status are detailed, especially those used in the special part of the thesis: MUST, NRS 2002, BMI, OPNI, CONUT and serum albumin.

Chapter ***Quality of life of patients with inflammatory bowel disease*** presents literature data that demonstrate the negative effect of IBD on the quality of life of patients. Following the spread of the concept "patient reported outcomes" (PRO), quality of life and tools that measure

the psychosocial effects of IBD have gained more attention. Therefore, quality of life of patients has become an important objective in the complex management of these diseases and is an important PRO [150]. In IBD patients, attention is particularly focused on response to different types of treatment, response whch is evaluated by measuring disease activity (by biomarkers or tools which evaluate endoscopic activity). These tools have the disadvantage of not reflecting the emotional state of the patients or their social dysfunctions [145,146]. Therefore, it is more useful to associate these activity measurement parameters with tools that can measure the impact of disease on quality of life; such an attitude helps in a more complex approach of the patients and an adequate management. Improving quality of life has become one of the most important goals of therapy and medical care in IBD.

Chapter ***Functional gastrointestinal disorders associated with inflammatory bowel disease*** presents data on prevalence of functional gastrointestinal disorders in IBD and on mechanisms by which they occur in patients with IBD, with particular emphasis on the symptoms of irritable bowel syndrome associated with IBD and on types of treatment applied in such cases, the role of rifaximin in modulating intestinal microbiota being detailed.

PERSONAL CONTRIBUTIONS

STUDY NUMBER 1. Epidemiological features of IBD in Dobrogea

Objectives

Establish the epidemiological profile of |IBD characteristic for Dobrogea region, as follows:

• Establish the total number of IBD in Dobrogea

• Establish the predominant type of disease: Crohn's disease or ulcerative colitis

• Determine the prevalence of Crohn's disease and ulcerative colitis

• Disease distribution by sex, age, ethnicity, place of origin, Montreal classification, complications and types of treatments followed

Material and method

The pesent study included 160 patients diagnosed with Crohn's disease and ulcerative colitis (cases which were already in evidence and newly diagnosed cases) who were admitted to Emergency County Clinical Hospital "Sf. Apostol Andrei" (gastroenterology department with continuous hospitalizations and day hospitalizations), outpatient clinic and to the Center dedicated to patients with inflammatory bowel disease between 01.01.2016 and 01.01.2019. Informations required for the epidemiological analysis were recorded according to the study sheet entitled The epidemiological study sheet of the patients with inflammatory bowel disease (Appendix 1).

Results

The study included 160 patients, of whom 109 (68%) were represented by Crohn's disease and 51 (32%) by patients with ulcerative colitis.

Crohn's disease

The prevalence of Crohn's disease in Dobrogea region in 2018 was 15.9 / 100.000 inhabitants. In terms of gender distribution, 58 (53%) of the patients were female and 51 (47%) of the patients were male. Mean age was 44 years +/- 10.2 years. A total number of 93 patients (85%) came from urban areas and 16 (15%) from rural areas. In terms of ethnic distribution, 76 patients (70%) were romanian, 24 (22%) tatar and 9 (8%) other ethnic groups, as follows: 5 turkish, 2 rroms and 2 lipovans. Montreal classification: regarding age of diagnosis of Crohn's disease, no patients were included in group A1 (<16 years), in group A2 (17-40 years) were

included 49 patients (45%), and in the A3 group (> 40 years) were included 60 (55%) patients; regarding disease location, the most frequent location of inflammatory lesions was ileo-colonic (L3) found in 55 (51%) of patients, followed by colonic (L2) found in 34 (31%) of patients and isolated ileum (L1) found in 20 (18%) of patients, and confirmed upper digestive tract damage (L4) was found in 2 patients; regarding phenotype, the most frequent phenotype was inflammatory (B1) in 65 (60%) of cases, followed by stenosis (B2) in 36 (33%) of cases and penetrating (B3) in 8 (7%) cases. No perianal manifestations were reported.

Intestinal complications were present in 44 (40%) of cases as follows: 36 (33%) of patients developed stenosis, 5 patients developed fistulas and 3 patients abscesses. Extraintestinal complications were present in 24 (22%) of cases as follows: ankylosing spondylitis was found in 7 patients, erythema nodosum in 3 patients, episcleritis in one patient, deep vein thrombosis in 2 patients, primary sclerosing cholangitis in 2 patients and the rest the complications being represented by peripheral atropathies, urinary infections and renal lithiasis. Complications that required surgery were analyzed: thus, 13 (12%) patients required surgery: 3 patients had right ileohemicolectomy with ileotransverse anastomosis, 7 patients had surgical perforation and 3 patients had surgical drainage. of the abscesses. Types of prescribed treatments were analyzed: 75 (69%) patients had 5-ASA, 71 (65%) patients had corticosteroids (intravenous or oral), of which 80 % received this treatment during the inaugural event, and 50% during the course of the disease; immunomodulatory agents (azathioprine) were prescribed in 43 (40%) cases and 46 (42%) patients received biologic therapy (32 patients received adalimumab, and 14 patients received infliximab).

Ulcerative colitis

The prevalence of ulcerative colitis in Dobrogea in 2018 was 7.4 / 100,000 inhabitants. In terms of gender distribution, 30 (59%) of the patients were female and 21 (41%) of the patients were male. Mean age was 42 years +/- 14 years. A total number of 45 patients (89%) came from urban areas and 6 (11%) from rural areas. In terms of ethnic distribution, 38 patients (75%) were romanian, 8 (15%) tatar and 5 (10%) other ethnicities, as follows: 2 turkish, 2 rroms and one lipovan. Regarding disease extension, most were left colitis (E2) found in 26 (51%) cases, followed by proctitis (E1) in 19 (37%) cases and pancolitis (E3) in 6 (12 %) cases. Regarding intestinal complications, 4 cases had entero-bladder fistulas and 2 cases had toxic megacolon. Extraintestinal complications have not been reported in patients with ulcerative colitis. One patient underwent total colectomy with ileostomy. Types of prescribed treatments were analyzed: 42 (83%) patients received 5-ASA, 26 (51%) patients had corticosteroids

(intravenous or oral), of which 15 at the time of the inaugural event; AZA was prescribed in 20 patients (39%), and biologic therapy was administered in 15 (29%) cases (11 patients received adalimumab and 4 patients received infliximab).

Important summary conclusions

1. Crohn's disease predominates compared to ulcerative colitis and both diseases have an increasing prevalence.

2. Crohn's disease has a more severe evolution than ulcerative colitis.

3. Common practice of prescribing 5 - ASA in Crohn's disease despite guidelines recommendations.

STUDY NUMBER 2. Nutritional status and quality of life of the patients in correlation with the clinic, biologic and endoscopic activity

Objectives

The main objective of this study is to evaluate tools which measure IBD activity that can be used regularly in clinical practice, to evaluate nutrition indices and scores, as well as quality of life of these patients, in order to facilitate the clinical care, to use a common vocabulary for IBD activity and to provide an objective basis for treatment and evaluation of treatment response. This objective can be achieved through the following strategies:

• Characterization of the study group from different points of view: clinical, endoscopic activity and biomarkers of activity, as well as establishing the degree of correlation between them and verifying the correlations obtained with data literature

• Assessment of nutritional status and quality of life of patients with IBD and their degree of correlation with clinical, endoscopic activity and biomarkers of activity

• Calculation of area under the curve of nutritional indices and quality of life in relation to endoscopic activity

Material and method

The present study included 120 patients (70 patients diagnosed with Crohn's disease and 50 patients diagnosed with ulcerative colitis) who were admitted to the gastroenterology department of the Emergency County Clinical Hospital "Sf. Apostol Andrei" in Constanta - continuous hospitalization and to the Center dedicated to patients with inflammatory bowel

disease between 01.01.2016 - 01.06.2019. In the first part of the study, patients were generally evaluated, activity was characterized from a clinical, endoscopic, biological point of view and various correlations were made between these, correlations which were subsequently verified with existing data literature; in the second part of the study, nutritional status and quality of life of these patients were evaluated and various correlations were made between them and tools that evaluated IBD activity; also, AUROC of nutritional indices and SIBDQ in relationship with endoscopic activity were calculated.

Results

General correlations

Correlations between clinical activity and biomarkers

In Crohn's disease, CDAI score correlated poorly with PCR (r = 0.28, p = 0.03) and moderately positive with calprotectin (r = 0.68, p = 0.02) (figure 20). A percentage of 93% of patients with CDAI scores > 150 were associated with elevated calprotectin values > 50 μg / g (p = 0.01). In ulcerative colitis, the partial Mayo score correlated moderately positively with C reactive protein (r = 0.61, p = 0.003) and strongly positive with fecal calprotectin (r = 0.75, p = 0.004). A percentage of 87.5% of patients with elevated partial Mayo scores > 2 had elevated calprotectin values > 50 μg / g. Further analysis of partial Mayo score indices showed the best correlation of calprotectin with the item "bleeding" (r = 0.77, p = 0.002) (table XV).

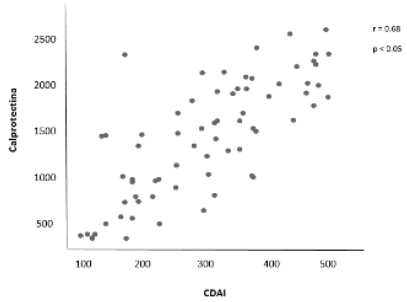

Figure 20. Correlation between CDAI and fecal calprotectin in Crohn′s disease

Table XV. Correlations between partial Mayo score subdomains and fecal calprotectin

Partial Mayo subdoimains	Calprotectin	
	r	p
Stool frequency	0.72	p = 0.03
Rectal bleeding	0.81	p = 0.002
Physician's global assessment	0.70	p = 0.04

Correlations between endoscopic activity and biomarkers

In Crohn's disease, CDEIS score correlated poorly with C reactive protein (r = 0.24, p = 0.01) (figure 23), and SES-CD score correlated poorly with C reactive protein (r = 0.21, p = 0.03). In contrast, CDEIS and SES-CD scores showed a strong direct correlation with calprotectin (r = 0.74, p = 0.001 - figure 25, respectively r = 0.70, p = 0.005). A percentage of 88.3% and 93% of patients with CDEIS and SES-CD scores > 3 had elevated calprotectin values > 50 μg / g (p = 0.03). Calprotectin correlated best with colonic localization of Crohn's disease (r = 0.76, p <0.001).

In ulcerative colitis, endoscopic Mayo score and UCEIS score were moderately positive correkated with C reactive protein (r = 0.47, p = 0.02, respectively r = 0.41, p = 0.03). Endoscopic Mayo score and UCEIS had a strong positive correlation with fecal calprotectin (r = 0.73, p = 0.003, respectively r = 0.70 p = 0.002) (figure 28). A percentage of 82.2% of patients with Mayo endoscopic score > 2 and 91% of patients with UCEIS score > 6 had elevated faecal calprotectin values > 50 μg / g (p = 0.01).

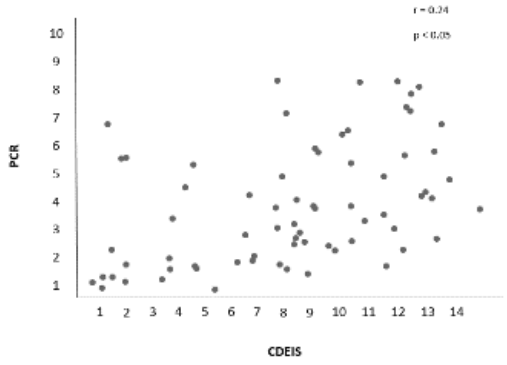

Figure 23. Correlation between CDEIS and C Reactive Protein in CD patients

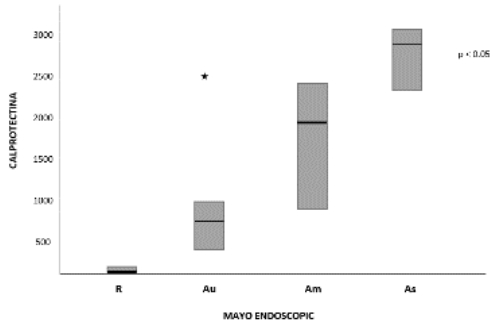

Figure 28. Distribution of patients with ulcerative colitis by categories of endoscopic activity according to fecal calprotectin values

Correlations between endoscopic and clinical activity

In Crohn's disease, CDEIS score correlated poorly with CDAI score values (r = 0.19, p = 0.04). Also, SES-CD score correlated poorly with CDAI score (r = 0.15, p = 0.05). In ulcerative colitis, endoscopic Mayo score showed a direct moderate correlation with partial Mayo score (r = 0.56, p = 0.003), and UCEIS score had a direct weak correlation with partial Mayo score (r = 0.26, p = 0.001).

Quality of life

Correlations between clinical activity and quality of life

In Crohn's disease, CDAI score correlated strongly with SIBDQ score (r = - 0.78, p = 0.002). Analysis of SIBDQ values for each activity category of CDAI score showed that lowest SIBDQ values were recorded in the patients with moderate and severe clinical activity (p = 0.007, respectively p = 0.001). Analysis of SIBDQ subscores showed that the lowest values were recorded in patients with moderate and severe activity, especially in gastrointestinal symptoms subdomain of SIBDQ (p = 0.002, respectively p = 002) (table XIX). Also, the strongest correlation of clinical activity was with subdomains represented by the gastrointestinal symptoms and systemic functions (p = 0.003, respectively p = 0.009).

Table XIX. Mean scores of SIBDQ subdoimans according to disease clinical activity assessed by CDAI

SIBDQ subdomains	**Remission** (n = 10)	**Mild activity** (n = 18)	**Moderate activity** (n = 32)	**Severe activity** (n = 10)
Gastrointestinal symptoms	14.1 +/- 9	10 +/- 2.8	4 +/- 2.7 *	2.9 +/- 1.1 *
Systemic functions	15 +/- 7.1	12 +/- 2.3	7 +/- 3.1 *	3.1 +/- 1 *
Emotional functions	16 +/- 3.5	15.5 +/- 4	11 +/- 2.6	12 +/- 2.7
Social functions	15 +/- 2.8	17.5 +/- 3.1	10 +/- 2.1	10 +/- 2.9

Values are expressed as mean +/- standard deviation.
* p <0.05: statistically significant compared to other categories of activity

In ulcerative colitis, partial Mayo score correlated strongly with SIBDQ (r = - 0.71, p = 0.005). Analyzing differences between mean values of SIBDQ for each activity category of partial Mayo score, it was observed that scores recorded significant differences, the lowest values of the SIBDQ being recorded in patients with moderate or severe clinical activity (p = 0.02, respectively p = 0.008), especially in the gastrointestinal symptoms subdomain, and the highest values of SIBDQ were registered in patients in remission (p = 0.002) (table XXII).

Analysis of SIBDQ subscores showed that the strongest correlation of clinical activity was with the subdomains represented by gastrointestinal symptoms and emotional functions (p = 0.003, respectively p = 0.001).

Table XXII. Mean scores of SIBDQ subdoimains according to the clinical activity assessed by partial Mayo score

SIBDQ subdomains	Remission (n = 10)	Mild activity (n = 13)	Moderate activity (n = 20)	Severe activity (n = 8)
Gastrointestinal symptoms	17 +/- 4.3	12 +/- 2.9	2.3 +/- 1.2 *	1.7 +/- 0.9 *
Systemic functions	15 +/- 4.1	12.1 +/- 3.1	10 +/- 3.1	9.1 +/- 5.2
Emotional functions	13.2 +/- 3.7	14 +/- 2.7	7 +/- 2.4 *	2.9 +/- 1.2 *
Social functions	14.3 +/- 2.7	10.4 +/- 3.6	11.7 +/- 3.2	11.3 +/- 3.5

Values are expressed as mean +/- standard deviation.
* p <0.05: statistically significant compared to other categories of activity

Correlations between endoscopic activity and quality of life

In Crohn's disease, a weak negative correlation between CDEIS and SES-CD with SIBDQ was observed (r = - 0.21, p = 0.01, respectively r = - 0.25, p = 0.03). Total mean SIBDQ score, as well as mean scores of SIBDQ subdomains, did not show significant differences between different degrees of endoscopic severity assessed by CDEIS and SES - CD, except for the severe forms of disease (p = 0.03) (table XXVI). Analysis of SIBDQ subscores showed the best correlation of endoscopic activity of Crohn's disease with the subdomain represented by gastrointestinal symptoms (r = 0.56, p = 0.003).

Table XXVI. Correlations between SIBDQ subdomains and CDEIS score

SIBDQ subdomains	CDEIS	
	r	P
Gastrointestinal symptoms	0.56	*p = 0.003*
Systemic functions	0.11	*p = 0.02*
Emotional functions	0.23	*p = 0.23*
Social functions	0.30	*p = 0.13*

In ulcerative colitis, a moderate negative correlation was observed between endoscopic Mayo score and SIBDQ (r = - 0.45, p = 0.004) and a strong negative correlation between UCEIS and SIBDQ (r = - 0.75, p = 0.008). Both mean SIBDQ mean score and mean SIBDQ subdomain scores were lower in patients with Mayo endoscopic 2 and 3 or UCEIS > 5 (moderate or severe

endoscopic activity), especially in gastrointestinal symptoms subdomain (p = 0.03, respectively p = 0.04) (tables XXIX). Analysis of SIBDQ subscores showed the best correlation of endoscopic activity of both Crohn's disease and ulcerative coliti with subdomain represented by gastrointestinal symptoms (p = 0.001, respectively p = 0.003).

Table XXIX. Mean total SIBDQ score based on endoscopic activity assessed by Mayo endoscopic score

	Mayo E0 (n = 5)	**Mayo E1** (n = 5)	**Mayo E2** (n = 28)	**Mayo E3** (n = 13)
SIBDQ	68 +/- 10.9	58.9 +/- 9.2	34 +/- 9.1 *	20 +/- 8.2 *

Values are expressed as mean +/- standard deviation.
* p <0.05: statistically significant compared to other categories of activity

Other SIBDQ correlations

In Crohn's disease, analysis of SIBDQ values by age groups showed that the lowest values were recorded in the age group < 40 years (p = 0.04), and gender analysis showed that the lowest SIBDQ values were recorded in female patients (p = 0.03). Regarding SIBDQ subdomains analysis, the lowest values for female patients were recorded in subdomains represented by gastrointestinal symptoms and emotional functions (p = 0.004, respectively p = 0.008). SIBDQ did not correlate with disease location (p = 0.35), but significantly lower values of SIBDQ were recorded in patients with stenosis and penetrating phenotype (p = 0.02, respectively p = 0.05). Types of treatments analysis showed that the highest values were recorded in patients who had biologic therapy and the lowest values in those who had corticosteroids (p = 0.005, respectively p = 0.006).

In ulcerative colitis, analysis of SIBDQ values by age groups showed that the lowest values were recorded in the age group < 40 years (p = 0.005). Regarding SIBDQ subdomains analysis, the lowest values for patients < 40 years old were identified in subdomains represented by gastrointestinal symptoms and social functions (p = 0.003, respectively p = 0.002). In contrast, no significant differences were observed between patients of different gender (p = 0.23). SIBDQ values analysis in relation with disease extent showed that the lowest values were recorded in patients with pancolitis (p = 0.02). Type of treatments analysis showed also that the highest values of SIBDQ were recorded in patients receiving biologic therapy (p = 0.007).

Nutritional status of patients with IBD

General nutritional assessment

General nutritional assessment is illustrated in table XXXVIII.

Table XXXVIII. Distribution of Crohn's disease and ulcerative colitis patients according to the evaluated nutritional indices

Nutritional indices	CD (n = 70)	UC (n = 50)
BMI, n		
Underweight/normal weight/overweight/obese	20 / 40 / 10 / 0	8 / 26 / 6 / 0
MUST, n		
Low risk/medium/high risk	25 / 38 / 7	14 / 18 / 8
NRS - 2002, n		
Without risk / with risk	28 / 42	22 / 28
O- PNI, n		
Without risk / with risk	18 / 52	20 / 30
CONUT, n		
Normal/mild malnutrition/moderate/severe	11 / 28 / 24 / 7	12 / 8 / 14 / 6
Albumină, n		
Normal/ low	14 / 56	8 / 42

Correlations between nutritional status and clinical activity, endoscopy and activity biomarkers

Table XL. Correlations between clinical, endoscopic activity and fecal calprotectin with nutritional indices in Crohn's disease

Crohn's disease, Rho	**Albumin**	**BMI**	**MUST**	**NRS 2002**	**OPNI**	**CONUT**
CDAI	- 0.74	- 0.68	0.27	0.61	- 0.62	0.61
SES-CD	- 0.67	- 0.28 †	0.52	0.50	- 0.61	0.26
Calprotectin	- 0.72	- 0.42	0.32	0.30	- 0.38	0.20 †

† $p > 0.05$

Table XLI. Correlations between clinical, endoscopic activity and fecal calprotectin with nutritional indices in ulcerative colitis

Ulcerative colitis, rho	**Albumin**	**BMI**	**MUST**	**NRS 2002**	**OPNI**	**CONUT**
Partial Mayo score	- 0.67	- 0.61	0.53	0.29	- 0.54	0.54
Endoscopic Mayo score	- 0.76	- 0.27	0.52	0.53	- 0.63	0.50
Calprotectin	- 0.69	- 0.38	0.36	0.31	- 0.45	0.11 †

† $p > 0.05$

Correlations between nutritional status and quality of life

Correlations between quality of life and nutritional indices in Crohn's disease and ulcerative colitis are illustrated in table XLII. In Crohn's disease, SIBDQ best correlated with BMI (r = 0.72, p = 0.008). It was observed a moderate correlation with NRS - 2002 (r = - 0.58, p = 0.003), MUST (r = - 0.51, p = 0.005), albumin (r = 0.45, p = 0.001) and O - PNI (r = 0.40 , p = 0.05). A weak and statistically insignificant correlation was observed between SIBDQ and CONUT (r = - 0.11, p = 0.007). In ulcerative colitis, SIBDQ correlated moderately with MUST (r = - 0.58, p = 0.003), albumin (r = 0.51, p = 0.01), BMI (r = 0.50, p = 0.03) and NRS - 2002 (r = - 0.49, p = 0.05). A weak correlation between SIBDQ and O - PNI (r = 0.26, p = 0.005) or CONUT (r = - 0.18, p = 0.004) was obsreved.

Table XLII. Correlations between quality of life and nutritional indices in Crohn's disease and ulcerative colitis

	SIBDQ, rho	
Nutritional indices	**Crohn's disease**	**Ulcerative colitis**
Albumin	0.45	0.51
BMI	0.72	0.50
MUST	- 0.51	- 0.58
NRS-2002	- 0.58	- 0.49
O-PNI	0.40	0.26
CONUT	- 0.11 †	- 0.18

Analysis of the usefulness of nutritional indices and SIBDQ as adjuvant tools for characterizing the disease activity

Crohn's disease

Serum albumin

Analysis of albumin accuracy to characterize endoscopic activity showed an area under the curve of 0.93 (95% CI, 0.85 - 0.97) (figure 38). An albumin threshold value of 3 mg / dl can differentiate between remission and activity with a sensitivity of 91.6% (95% CI, 75.8 - 97.2) and a specificity of 62% (95% CI, 46.3 - 89.2).

BMI

Analysis of BMI accuracy to characterize endoscopic activity showed an area under the curve of 0.51 (95% CI, 0.40 - 0.68) (figure 39). A BMI threshold of 18.5 can differentiate between remission and activity with a sensitivity of 77.5% (95% CI, 62.5 - 87.6%) and a specificity of 41.7% (95% CI, 33.3 - 54.9).

MUST

Analysis of MUST score accuracy to characterize endoscopic activity showed an area under the curve of 0.68 (95% CI 0.52 - 0.79) (figure 40). A threshold value of MUST score of 2 can differentiate betweem remission and activity with a sensitivity of 74.1% (95% CI, 65.7 - 87.2) and a specificity of 66.7% (95% CI, 51.5 - 75.4).

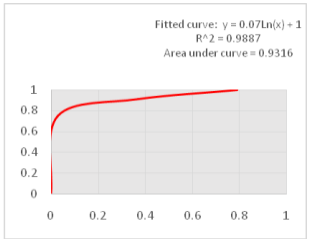

Figure 38. AUROC albumin

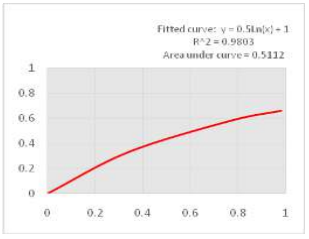

Figure 39. AUROC IMC

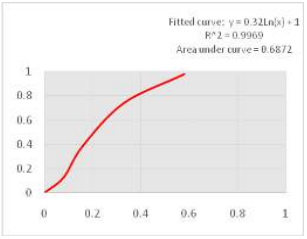

Figure 40. AUROC MUST

NRS 2002

Analysis of NRS 2002 score accuracy to characterize endoscopic activity showed an area under the curve of 0.71 (95% CI, 0.64 - 0.82) (figure 41). A threshold value of NRS 2002 of 2 can differentiate between remission and activity with a sensitivity of 86.2% (95% CI, 79.4 - 93.8) and a specificity of 58.4% (95% CI, 41.6 - 63.6).

OPNI

The analysis of the accuracy of the OPNI score to characterize the endoscopic activity showed an area below the curve of 0.86 (95% CI 0.76 - 0.96) (Figure 42). A threshold value of the OPNI score of 40 can differentiate remission and activity with a sensitivity of 83.3% (95% CI, 72.1 - 95.5) and a specificity of 62.1% (95% CI, 48.8 - 76.3).

CONUT

Analysis of CONUT score accuracy to characterize endoscopic activity showed an area under the curve of 0.71 (95% CI 0.60 - 0.89) (figure 43). A threshold value of the CONUT score of 5 can differentiate between remission and activity with a sensitivity of 84.4% (95% CI, 70.8 - 91.2) and a specificity of 58.4% (95% CI, 49.9 - 69.4).

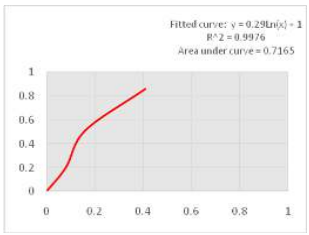

Figure 41. AUROC NRS 2002

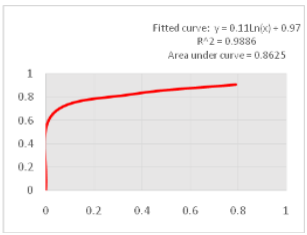

Figure 42. AUROC OPNI

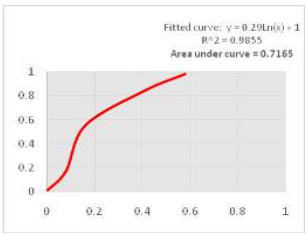

Figure 43. AUROC CONUT

SIBDQ

Analysis of SIBDQ score accuracy to characterize endoscopic activity showed an area under the curve of 0.79 (95% CI, 0.61 - 0.91) (figure 44). A threshold value of SIBDQ of 40 can differentiate between remission and activity with a sensitivity of 83.3% (95% CI, 73.2 - 93.3) and a specificity of 69% (95% CI, 52.6 - 79.1).

Ulcerative colitis

Serum albumin

Analysis of albumin accuracy to characterize endoscopic activity showed an area under the curve of 0.91 (95% CI, 0.80 - 0.99) (figure 45). An albumin threshold value of 3 mg / dl can differentiate between remission and activity with a sensitivity of 100% (95% CI, 92.3-100) and a specificity of 75% (95% CI, 63.3-191).

BMI

Analysis of BMI accuracy to characterize endoscopic activity showed an area under the curve of 0.65 (95% CI 0.53 - 0.79) (figure 46). A BMI threshold of 18.5 can differentiate between remission and activity with a sensitivity of 70.4% (95% CI, 60.4 - 85.8) and a s**pecificity of 66.7% (95% CI, 51.8 - 78.1).**

MUST

Aalysis of MUST score accuracy to characterize endoscopic activity showed an area under the curve of 0.56 (95% CI, 0.48 - 0.65) fFigure 47). A threshold value of MUST score of 3 can differentiate between remission and activity with a sensitivity of 86.3% (95% CI, 65.8 - 93.4) and a specificity of 33.4% (95% CI, 23.6 - 49.7).

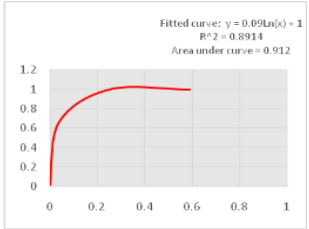

Figure 45. AUROC albumină

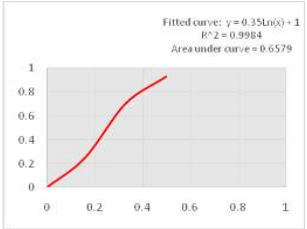

Figure 46. AUROC IMC

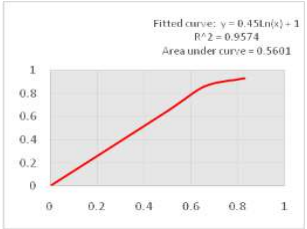

Figure 47. AUROC MUST

NRS 2002

Accuracy analysis of NRS 2002 score accuracy to characterize endoscopic activity showed an area under the curve of 0.61 (95% CI, 0.51 - 0.72) (figure 48). A threshold value of

the NRS 2002 score of 3 can differentiate between remission and activity with a sensitivity of 56.8% (95% CI, 40.4 - 63.8) and a specificity of 66.7% (95% CI, 52.2 - 73.1).

OPNI

Analysis of OPNI score accuracy to characterize endoscopic activity showed an area under the curve of 0.84 (95% CI, 0.70 - 0.92) (figure 49). A threshold value of the OPNI score of 40 can differentiate between remission and activity with a sensitivity of 83.3% (95% CI, 71.6 - 92.4) and a specificity of 61.4% (95% CI, 55.4 - 76.9).

CONUT

Analysis of CONUT score accuracy to characterize endoscopic activity showed an area under the curve of 0.47 (95% CI 0.38 - 0.57) (figure 50). A threshold value of the CONUT score of 5 can differentiate between remission and activity with a sensitivity of 86.3% (95% CI, 72.5 - 91.9) and a specificity of 16.7% (5% CI, 10.1 - 35.5).

SIBDQ

Analysis of SIBDQ score accuracy to characterize endoscopic activity showed an area under the curve of 0.87 (95% CI, 0.74 - 0.97) (Figure 51). A threshold value of SIBDQ score of 40 can differentiate between remission and activity with a sensitivity of 83.3% (95% CI, 71.6 - 95.5) and a specificity of 91% (95% CI, 85.3 - 99%).

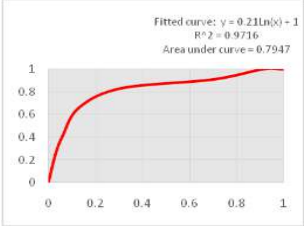

Figure 44. AUROC SIBDQ in CD

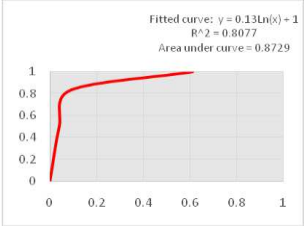

Figure 51. AUROC SIBDQ in UC

Important summary conclusions

1. Calprotectin is a more useful biomarker than C reactive protein in monitoring intestinal inflammation in IBD and correlates with both clinical and endoscopic activity.

2. Clinical activity correlates poorly with endoscopic activity in Crohn's disease and moderately in ulcerative colitis.

3. Clinical and endoscopic activity of IBD is reflected on the quality of life of the patients and on the studied nutritional indices.

4. Quality of life is more affected in patients < 40 years, in those treated with corticosteroids, in patients with stenosis or penetrating phenotype or in pancolitis.

5. SIBDQ correlates better with endoscopic activity in ulcerative colitis than in Crohn's disease.

6. SIBDQ threshold value of 40 can characterize the disease activity with an area under the curve of 0.79 in Crohn's disease and 0.87 in ulcerative colitis.

7. Evaluated nutritional indices correlate differently with the clinical and endoscopic activity of IBD.

8. Albumin and OPNI best correlate with endoscopic activity and have a weak correlation with BMI.

9. Albumin has the highest accuracy in characterizing IBD activity, and OPNI has a similar accuracy.

10. MUST has a poor accuracy in characterizing the activity of Crohn's disease and very poor accuracy in ulcerative colitis.

11. BMI has a very poor accuracy in characterizing Crohn's disease activity and poor accuracy in ulcerative colitis.

12. NRS 2002 has a satisfactory accuracy in characterizing Crohn's disease activity and poor accuracy in ulcerative colitis.

13. CONUT has a satisfactory accuracy in characterizing Crohn's disease activity and very poor accuracy in ulcerative colitis.

STUDY NUMBER 3. Efficacy of rifaximin in the treatment of functional gastrointestinal symptoms in patients with Crohn's disease in remission

Objectives

The main objective is to establish the efficacy of 1200 mg / day rifaximine, 10 days / month, for 3 consecutive months in the treatment of functional gastrointestinal symptoms - irritable bowel syndrome like symptoms (bloating, abdominal pain, diarrhea, and quality of life improvement) in patients with Crohn's disease in remission.

This objective is possible through:

• Demonstration of remission Crohn's disease patients (endoscopic remission and normal faecal calprotectin values)

• Evaluation of the presence and quantification of the severity of functional symptoms: bloating, abdominal pain, diarrhea and their effect on quality of life

• Improvement of functional symptomatology and quality of life after first month of rifaximin treatment in a dose of 1200 mg / day for 10 days

• Maintaining the effects obtained after first month of treatment by repeating medication for three months

Material and method

The present study included 86 patients with Crohn's disease with documented endoscopic remission (CDEIS score < 3 and SES - CD < 2), fecal calprotectin < 50 μg / g, with associated irritable bowel syndome like symptoms (bloating, abdominal pain, diarrhea) who were admitted to Emergency County Clinical Hospital "Sf. Apostol Andrei" in Constanţa - ambulatory and to the Center dedicated to patients with inflammatory bowel disease during the period 01.01.2018 - 31.12.2018. Infectious etiology was excluded by testing for Clostridium Difficile infection, cytomegalvirus infection, Epstein Barr virus infection, stool cultures and parazites. Patients were divided into two groups: rifaximin group consisting of 44 patients and control group consisting of 42 patients. In addition to baseline treatment of Crohn's disease, patients in the rifaximin group received 1200 mg / day rifaximin, 10 days / month, 3 months consecutively. Patients in the control group were only closely observed during the three months of the study.

Patients were evaluated from several points of view: disease activity was assessed by endoscopy (to confirm remission) and by biomarkers: fecal calprotectin and C Reactive protein; severity of bloating and abdominal pain was assessed by analogue visual scale (VAS); stool consistency was assessed by Bristol scale and quality of life by SIBDQ questionnaire (Appendix 3).

Table LVII . Study design

Item	Baseline	M1	M2	M3
Bloating	✓	✓	✓	✓
Abdominal pain	✓	✓	✓	✓
Quality of life	✓	✓	✓	✓
BSF	✓	✓	✓	✓
CDAI	✓	X	X	✓
CRP	✓	X	X	✓
Calprotectin	✓	X	X	✓

Improvement was defined as a decrease of at least 30% of mean bloating and abdominal pain scores and an increase of at least 30% of mean SIBDQ scores, and in the case of stool

consistency improvement was defined as a decrease of at least one point in the weekly BSF average. The required data were collected according to appendix 5 Crohn's disease patient in remission treated with rifaximin.

Results

Baseline characteristics of the two groups of patients are illustrated in table LVIII.

Table LVIII. Baseline characteristics

Characteristics	Rifaximin group (n = 44)	Control group (n = 42)
Age (years) *	39.5 +/- 11.5	35 +/- 9.8
Male / female, %	53 / 47	52 / 48
Location (L1/L2/L3), %	17 / 46 / 37	19 / 49 / 32
Phenotype (B1/B2/B3), %	87 / 2 / 11	90 / 1 / 9
Treatment, %		
AZA	55	54
Anti - TNF	15	14
Anti - TNF + AZA	30	32
Disease duration (years) *	6 +/- 3.5	8 +/- 5
CRP (<0.5 mg/dl) *	0.3 +/- 0.1	0.4 +/- 0.1
Calprotectin (<50 mg/kg) *	29 +/- 10	30 +/- 10
Abdominal pain (0 - 100 mm) *	72 +/- 12	69 +/- 10
Bloating (0 - 100 mm) *	69 +/- 10	65 +/- 10
BSF (1 - 7) *	6.2 +/- 1	5.5 +/- 1
SIBDQ (13 - 70) *	32 +/- 19	35 +/- 14

* mean value +/- standard deviation

Bloating

Evolution of mean bloating scores in the rifaximin group compared to control group is illustrated in figure 52. Post-Hoc Bonferroni comparative analysis in the rifaximin group showed that the mean bloating scores corresponding to the four groups differ significantly at least for two of the studied groups ($F = 163{,}352$; $p < 0.001 < \alpha = 0.05$). Post-Hoc Bonferroni analysis (Leven = 2.5, df1 = 3, df2 = 180, $p = 0.60 > \alpha = 0.05$) found significant differences between m0 - m1, m2, m3; m1 - m0, m3; m2 - m0, m3; m3 - m0, m2 ($p < 0.001$), but not between groups m1 - m2, m3 ($p = 0.245 > \alpha = 0.05$). Control group data analysis found that there was a difference between m0 - m1, but statistically insignificant ($p = 0.225 > \alpha = 0.05$). A percentage

of 60% of patients who received rifaximin had a significant improvement of bloating (p = 0.004).

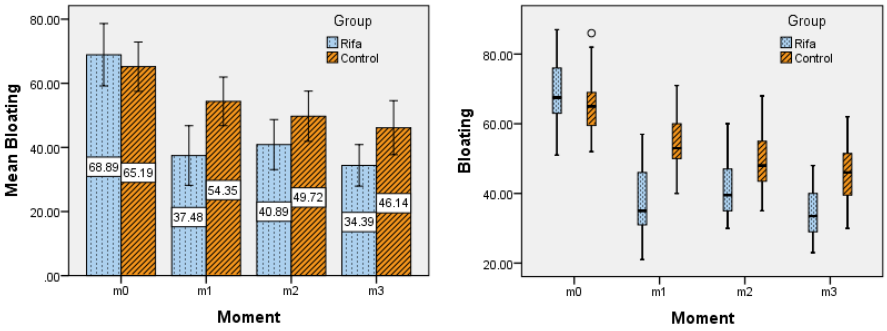

Figure 52. Bar + Error Bar (left) and Box Plot (right) graphic representation for mean bloating scores in rifaximin group compared to control group

Abdominal pain

Evolution of mean abdomnal pain scores in the rifaximin group compared to control group is illustrated in figure 53. Post-Hoc Bonferroni comparative analysis in the rifaximin group shows that mean abdominal pain scores corresponding to the four groups differ significantly at least for two of the studied groups (F = 199,626; p <0.001 <α = 0.05). Post-Hoc Bonferroni analysis (Leven = 0.445, df1 = 3, df2 = 180, p = 0.721> α = 0.05) found significant differences between m0 - m1, m2, m3; m1 - m0, m2, m3 (p <0.001), but not between m2 - m3 groups (p = 0.245> α = 0.05). Control group data analysis found that there was a statistically insignificant difference between m0 - m1 (p = 0.225> α = 0.05). A percentage of 55% of rifaximin treated patients had a significant improvement of abdominal pain (p = 0.002).

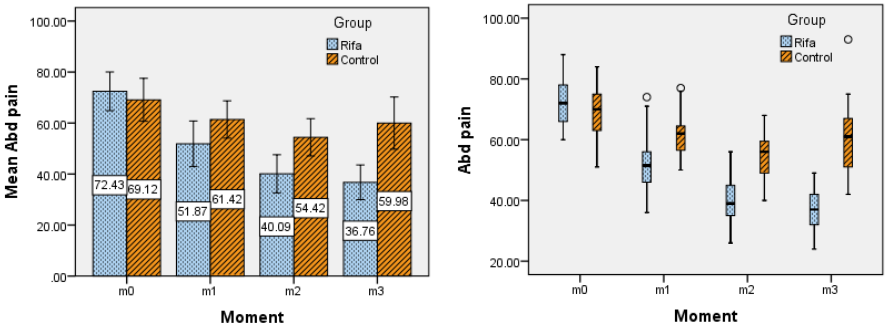

Figure 53. Bar + Error Bar (left) and Box Plot (right) graphic representation for mean abdominal pain scores in rifaximin group compared to control group

Stool consistency

Evolution of mean BSF scores in the rifaximin group and control group is illustrated in figure 55. Stool consistency was also improved in patients treated with rifaximin, with a decrease in the mean values of the BSF from 6.2 to 4.3 in the first month of treatment, effect that was maintained after repeated doses of treatment. In contrast, patients in the control group had an insignificant decrease from 5.5 to 5.1. A percentage of 64% of those treated with rifaximin had a significant improvement in stool consistency (p = 0.001).

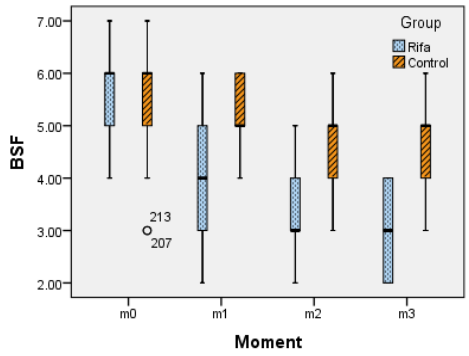

Figure 55. Box Plot graphic representation for mean BSF scores evolution in the studied groups

Quality of life

Evolution of mean SIBDQ scores in the rifaximin group compared to control group is illustrated in figure 54. Post-Hoc Bonferroni comparative analysis in the rifaximin group shows that the mean SIBDQ values corresponding to the four groups differ significantly for all studied groups (F = 151,222 p <0.001 <α = 0.05). Post-Hoc Bonferroni analysis (Leven = 1.382, df1 = 3, df2 = 180, p = 0.250> α = 0.05) found that significant differences are between all four groups m0, m1, m2, m3 (p <0.001). Control group data analysis found that there were no differences between the four different moments (p = 0.225> α = 0.05). Significant improvement in quality of life was achieved in 85% of patients receiving rifaximin (p = 0.004).

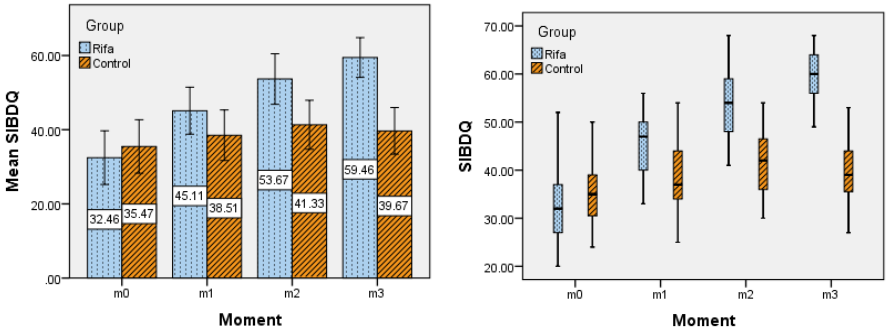

Figure 54. Bar + Error Bar (left) and Box Plot (right) graphic representation for mean SIBDQ scores in rifaximin group compared to control group

Important summary conclusions

1. Rifaximin in a dose of 1200 mg / day, 10 days / month, 3 months consecutively, is effective in improving functional symptomatology in patients with Crohn's disease in remission.

2. Repeatead treatment is effective for maintaining the effects obtained initially.

3. Quality of life was significantly improved in most of the patients treated.

Originality and innovative contributions of the thesis

Originality of the thesis is conferred by the unique results obtained in each of the three studies. In the first study, Epidemiological features of inflammatory bowel diseases in Dobrogea, originality results from the characteristic epidemiological IBD profile in Dobrogea region, being the only large study of this kind carried out in this region.

In the second study, Nutritional status and quality of life of the patients in correlation with the clinic, biologic and endoscopic activity, the originality is given by the complex approach of IBD activity from several points of view (clinic, biomarkers, endoscopy), and by the evaluation of nutritional status and quality of life of these patients, being the only study of this kind in Dobrogea. In this part, also, the originality is conferred by the evaluation of malnutrition and the risk of malnutrition through various scores and by the evaluation of quality of life through SIBDQ in correlation with IBD activity. The novelty is represented by the approach of activity in several domains, besides the classical ones (biomarkers, endoscopy, clinical), namely, identification of the nutritional indices that are associated with disease activity or remission, and, moreover, identification of SIBDQ threshold values that can

characterize IBD activity. To our knowledge, this is the only study in Romania that approached like this patients with IBD.

The originality of the last study,Effectiveness of rifaximine in the treatment of functional gastrointestinal symptoms in patients with Crohn's disease in remission, derives from the idea of treating gastrointestinal functional symptoms in Crohn's disease patients with rifaximin, which is currently effective for irritable bowel syndrome. Thus, efficacy was superior to control group in improving functional symptoms and quality of life among patients with Crohn's disease in remission, being among the few studies or even the only one in the country that treated like this this category of IBD patients.

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Publications

Articles from this thesis published in extenso:

1. Cristina Tocia, Luana Alexandrescu, Andrei Dumitru, Eugen Dumitru. Assessment of nutriţional status in correlation with quality of life and disease activity in hospitalized patients with inflammatory bowel diseases. *International Journal of Current Medical and Pharmaceutical Research.* 2019; 5(8): 4452-4456. ISSN: 2395-6429.
DOI:http://dx.doi.org/10.24327/23956429.ijcmpr201908719.
https://journalcmpr.com/sites/default/files/issue-files/1766-A-2019.pdf

2. Cristina Tocia, Luana Alexandrescu, Victoria Cristina Şuţa. Inflammatory bowel diseases (IBD) - associated spondyloarthropathy in the biologic era: a case series. *Journal of Clinical Gastroenterology and Treat*ment. 2019; 5:065 (early online). ISSN: 2469-584X.
DOI:10.2397/2469-584X/1510065.
https://clinmedjournals.org/articles/jcgt/journal-of-clinical-gastroenterology-and-treatment-jcgt-5-065.pdf

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