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Diagnostic and Treatment Algorithms of Ulcerative Colitis in Ukraine

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Diagnostic algorithms · Treatment algorithms · Ulcerative colitis, diagnostics · Ulcerative colitis, pathogenesis · Ulcerative colitis, Ukraine

Abstract
Questions concerning the diagnosis and treatment of ulcerative colitis (UC) in Ukraine are described. In recent years, there has been considerable progress in conservative therapy and new drugs have been developed that provide persistent remission of the inflammatory process after long-term application in many cases. The results of our own investigation on the efficiency of rebamipide in the complex treatment of UC patients are presented. Optimization of treatment with substitution of mesalazine in tablet or granule form, especially with an additional rebamipide prescription and a once-daily administration of budesonide, leads to an increased effectiveness of treatment and improvement of quality of life in UC patients. In the future, development of new approaches in the pharmacotherapy of UC will use medications as a basic therapy with the purpose of achieving high-quality and effective 'convalescence of mucous membrane', including cytoprotectors, bilious acids, endogenous substances, stabilization of membranes, antihypoxants and correction of microbiocenosis disorders.

Introduction

Ulcerative colitis (UC) is one of the most difficult and unsolved problems of modern medicine, and because of its severity, frequency of complications and lethality, it occupies one of the first places on the list of gastrointestinal tract diseases. There is an increasing tendency of UC frequency and an 'epidemic' is forecasted for Eastern Europe, including Ukraine. In Europe, UC morbidity has increased practically twofold in the last 10 years and comprises 8–12 cases per 100,000 inhabitants annually. The prevalence of UC has also had a tendency to grow and comprises 40–117 patients per 100,000 inhabitants [1].

The epidemiological indexes of this disease in Ukraine differ because of the predominance of its serious and complicated forms. The variety of clinical forms complicates diagnosis and estimation of activity of the process in the aggravation phase. Thus, the risk of complications rises due to inadequate treatment, the disability of patients being able to work, and the increase of lethality.

Pathogenesis

As the questions of etiology and pathogenesis of UC have not been studied too well, the development of early diagnosis principles of the disease is difficult. Recent de-

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cades are characterized by considerable expansion and deepening of concepts about the pathogenesis of intestine inflammatory diseases on the basis of the genetic and epidemiological research that has been conducted.

UC is a polyetiological disease in which the genetic predisposition plays a leading role, due to immunological mechanisms under the influence of stress factors, eating disorders and allergy. In the Donetsk region of Ukraine, a genetic predisposition of UC was found in 19.8% of cases, different types of allergy in 21.5%, and protracted chemical influences, related to the features of profession, in 6% cases. Immunological and eating disorders were observed in all patients [2].

60% of UC patients have a mild form of the disease, and the typical intermittent course of disease takes place in 30% of the patients. The existence of different types of UC is conditioned by genetic features (polymorphism of NOD2/CARD15 gene), the influence on the organism of external environmental factors, and patients having harmful habits [3]. It was recently determined that appendectomy as well as smoking reduce the risk of UC development associated with the severe course of the disease [4, 5]. Glycoprotein P plays a very important role in protecting against coli bacteria and toxins, and breaking the barrier's function for genotype 3435TT possessors can stipulate their predisposition to UC [6]. The important role of breaking the resistance of the intestine's mucous membrane-protective barrier in UC pathogenesis has been confirmed by the discovery of ASCA antibodies in the blood serum of these patients (antibodies to *Saccharomyces cerevisiae*). However, they are not a pathognomonic diagnostic UC index, because they are often found in UC patients' relatives who have no signs of this disease manifestation [3].

Diagnostics

The clinical picture consists of intestinal symptoms which are characteristic for all patients and intestinal indications are practically found in 50% of the patients. With the standardization of the clinical picture, the indexes of the clinical activity of Rachmilewitz and Mayo disease are presently used. However, these indexes are used for scientific research but not in doctors' surgeries in Ukraine. It is important to evaluate not only the prevalence of the inflammatory process in the colon and disease activity, but also the degree of gravity. Except for immune changes of patients with UC, a dysbalance of the cytokine regulation was revealed with a predominance of proinflammatory cytokines such as tumor necrotic factor-α (TNF-α), interleukins (IL)-1, -6, -8, -12 and a decrease of anti-inflammatory IL-4, -10, and -11 [7].

It is necessary to provide endoscopic research with a biopsy in dynamics. Capsule videoendoscopy is the most informative and objective method of investigation in this respect. Histological research is the standard in diagnosis of UC. For the patients with UC in the stage of remission, endoscopy of the colon must be provided not less than once during 6–8 months. Irrigography is an additional diagnostic method and allows to evaluate the prevalence of inflammation in colon in case it is not possible to perform colonoscopy.

High-quality determination of stool protein in feces as the most exact and sensible indicator of this disease activity is reasonable for the diagnosis of inflammatory diseases of the intestine and irritated intestine syndrome. Stool protein is produced by neutrocytes, and if patients suffer from intestinal inflammatory diseases, an increased amount secretes through the bowel wall as a result of leukocyte migration [8]. In UC feces stool protein, sensitivity is 94.1% and specificity is 80%. A marker is a more exact indicator of the inflammatory process than red corpuscles ($p < 0.01$) and C-reactive protein ($p < 0.001$). The level of feces stool protein correlates well with UC activity ($p < 0.001$) [9].

Treatment

The traditional and generally recognized tasks of treatment are to reduce disease activity, reduce expressed clinical symptoms, improve patients' quality of life, and prevent relapses. Before beginning treatment it is important to estimate therapy possibilities taking the following into account: localization and gravity of the process, presence of complications, response to the previously applied therapy is important to create an individual chart of the patient's treatment, and estimate the prospect of applied therapy.

Basic medicinal therapy of UC is conducted depending on the gravity of colitis and includes derivates of mesalazine, topical steroids (first-line), cytostatics and biological preparations (second-line). Basic UC therapy must be provided independent of the gravity of colitis according to ECCO recommendations. Mesalazine is prescribed in case of minimal activity at a dose of 3–4 g/day orally and is rectally independent of the process [10]. Mesalazine (Eudragit L) granules provide the prolonged

liberation of active matter and have maximal contact with the mucous membrane of distal parts of the intestine [11].

Rectal application of steroids, mainly topical steroids, is indicated with the purpose of minimizing side effects [12]. We prescribe mesalazine 4–8 g/day and budesonide 9 mg/day in cases of moderate activity. A daily dose of 9 mg budesonide possesses greater efficiency if taken once daily over an 8-week period than if taken 3 mg three times a day. The efficiency with single dose of budesonide is related to a considerably higher concentration of preparation in blood serum and also higher absolute bioavailability [13]. We prescribe high doses of mesalazine, >8 g/day, in patients with severe forms of UC. The dose of budesonide is increased up to 18 mg/day, and we then combine it with steroids. Because of the ineffectiveness of mesalazine and budesonide application, high second-line doses are prescribed, e.g. immunosuppressors or biological therapy preparations. Difficulties of therapy are that 25–30% of patients are resistant to basic therapy with standard doses, and that the side effects due to systemic glucocorticoids and immunosuppressants are forecasted.

Azathioprine is suitable for chronic slack steroid-resistant and steroid-dependent active forms of UC treatment, supporting disease remission and cannot be used in acute situations. To achieve a maximal effect, 4–6 months are required. Prescribing azathioprine in a complex with steroids allows to reduce the preparation dose. However, prolonged azathioprine use leads to the development of colon neoplasia in UC patients [14].

The observation in patients who had taken azathioprine for 7 years testifies the necessity of conducting colectomy in 88% of the cases. Patients who did not take azathioprine had better results [15]. Short-term cyclosporine treatment is effective in steroid-dependent UC and is an alternative treatment for glucocorticoid therapy in patients with a severe attack. In glucocorticoid and cytostatic refractory forms of UC, inhibitors of TNF-α are used such as adalimumab and certolizumab – the clinical effects of application of which are similar to that of in-fliximab. According to the results of two placebo-controlled reports [16, 17], infliximab application leads to a clinical improvement and remission in patients with severe intensity and middle gravity intensity of UC, which did not react to standard therapy. However, currently the US FDA has only approved natalizumab. The future perspective is application of recombinant human IL-10 [2].

The ultimate goal of treatment nowadays is removing or improving patients' complaints and symptoms, prophylaxis or reducing complications and in the future 'convalescence' of mucous membrane and development of etiotropic therapy. A promising trend in UC treatment is the use of cytoprotectors, which will lead to an increased resistance of the bowels' mucosal epithelial cells. Rebamipide is a novel agent that stimulates mucosal epithelial cell regeneration by increasing the expression of epithelial growth factor. We examined 25 patients with an average severe course of UC (the index of clinical activity 6–12; endoscopic index 4 according to Rachmilewitz, 1989) who were divided into three groups depending on curative complexes: group I (n = 9): mesalazine (tablets) 3 g/day and budesonide 9 mg/day taken 3 times; group II (n = 8): mesalazine (granules) 3 g/day and budesonide 9 mg/day taken once; group III (n = 8): mesalazine (granules) 3 g/day and budesonide 9 mg/day taken once + rebamipide 300 mg/day.

Clinical, endoscopic assessments were made at baseline and the end of the study and symptoms were recorded on a daily basis. The primary endpoint was introduction of clinical remission and clinical improvement was also measured using the UC disease activity index. The exchange of fuco- and sialoproteins was estimated according to their concentration in blood and the level of their excretion with urine, taking into account the state of the patients. Studying the state of the protective mucous barrier in intestinal inflammatory diseases is particularly important, as well as establishing any damage as a result of inflammation and ulceration.

The largest number of patients in the clinical remission phase after 8 weeks of therapy was recorded: in group III, 6 patients (75%), in group II, 5 patients (62.5%), and in group I, 5 patients (55.6%). The duration of clinical remission was: 24.7 ± 1.4 days in group I, 27.5 ± 1.7 days in group II, and 30.7 ± 1.8 days in group III ($p > 0.05$). Endoscopic remission was detected in 3 (33.3%) patients of group I, in 4 (50%) patients of group II, and in 5 (62.5%) patients of group III.

An increased concentration of *N*-acetylneuraminic acid was detected in the patients of all groups as well as a 1.8 times decrease of the blood fucose level in connection with albumin ($p \leq 0.05$). The prescription of curative complexes leads to a reduction of *N*-acetylneuraminic acid of 1.4 times and in fucose to an increase of 1.5 times in blood, which is significantly expressed in group III ($p < 0.05$). The same changes were detected in the examination of excretion of fucose in urine.

During a previously conducted multicenter research in patients with medially severe and severe UC, it was found that rebamipide's efficiency in enemas was similar to the effect of 5-aminosalicylic acid on the background of basic therapy in the disease activity index, endoscopic index score, endoscopic grading scale, and biopsy score [18]. Analogous results were obtained by the research of Ogata et al. [19] in which rebamipide's efficiency in enemas was observed in UC through strengthening the expressiveness of intercellular protein of claudin-1 in the intestine's epithelial cells. Rebamipide has a broad spectrum of pharmacological actions that include suppression of neutrophil functions and stimulation of mucosal epithelial cell regeneration. Thus, rebamipide renders a protective effect on the mucous membrane of intestine by strengthening the expressiveness of epithelial factor of growth, reducing peroxide oxidation in the mucous membrane of intestine, stimulating regeneration of the mucous membrane of intestine, and suppressing the function of neutrophils [20, 21].

When comprising treatment complexes for UC patients, it is necessary to take into account the presence of viral and bacterial superinfections that can imitate an intensification of the disease. Probiotic preparations of *Lactobacillus* GG are effective and safe for UC patients in a composition of antirecurrent complexes in combination with mesalazine. *Lactobacillus* GG treatment is more effective than standard therapy on the basis of mesalazine with regard to duration; it is free from intensification ($p < 0.05$) and can be used as a component of antirecurrent therapy [22].

Determining the important role of mucous barrier resistance of intestine in UC, pathogenesis serves as a basis for optimization of medical complexes with the use of antibacterial preparations, probiotics, phosphatidylcholine and preparations of bilious acids. In inflammatory diseases of the bowel, the protective ability of mucous membrane collapses with inflammation and ulceration that is related to the cooperation between the immune system, genetic predisposition and environment.

In experimental colitis using rat models, an increase of bacterial translocation is registered which diminishes when melatonin is administered. In the group of animals with experimental colitis that were given melatonin, there is a marked decrease of the TNF-α concentration, caspase-3 activity and endotoxin level in blood serum [23]. Essential phospholipids are prescribed with the purpose of strengthening the resistance of epithelial cell membranes in the intestine, improving their plasticity and also such effects as antioxidative, disaggregational effect, immunomodulation on a cellular level, restoring damaged membrane structures of the cell, and increasing prostaglandin synthesis [24–26]. Thus, simultaneously essential phospholipids render a hepatoprotective effect that is extremely important during the protracted therapy with aminosalicylates and glucocorticoids.

An important direction in the realization of the concept of 'convalescence of mucous membrane' is prescribing antihypoxants with the purpose of removing tissue hypoxia and improving blood circulation into the mucous membrane of the intestine. The preparation of choice is a deproteinized hemoderivate which provides an increase of the energetic potential of cells (an increase of 5 times the cell consumption of glucose), reduces inflammatory-cellular infiltration, anabolism action, improves blood supply and removes tissue hypoxia.

The influence of UC on quality of life, related to the health of patients, was estimated for 26 patients in an Italian university clinic study [27]. Three questionnaires given to the patients at the ambulatory visit were used, namely SF-36 (general well-confirmed method of measuring of quality of life, related to the health), SCL-90 (for the evaluation of the psychological state of patients) and the Holmes-Rahe scale (for evaluation of vital stress situations). The decrease of quality of life, related to health, and general severity of psychological symptoms is set in UC patients and irritable intestine syndrome. Thus, the gravity of the last vital stress situation is considered as being more difficult in irritable intestine syndrome patients in comparison with UC. The basic task of treatment is not only induction of remission and temporal removal of symptoms, but also maintenance of protracted remission, maintenance of the patient's quality of life and prophylaxis of new malignant formations of the colon [28].

Conclusion

Thus, optimization of the curative complexes with the substitution of mesalazine in tablet or granule form, especially with an additional rebamipide prescription, as a once-daily dose of budesonide will lead to an increase of treatment effectiveness and improvement of overall quality of life in UC patients. In the future, development of new approaches in the pharmacotherapy of UC will use medications on the background of basic therapy with the purpose of achieving high-quality and effective 'convalescence of mucous membrane', including cytoprotectors

(rebamipide), bilious acids (ursodeoxycholic acid), endogenous substances (melatonin), stabilization of membranes (phosphatidylcholine), antihypoxants (deproteinized hemoderivate) and correction of microbiocenosis disorders.

Disclosure Statement

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