SECTION: INFLAMMATORY BOWEL DISEASE

075

LONG TERM RESULTS OF BALLOON DILATION OF ANASTOMOTIC STRICTURES IN PATIENTS WITH CROHN'S DISEASE

Adamec S., Lukáš M., Novotný A., Bortlík M., Chalupna M.

4th Medical Department, General Faculty Hospital, Prague, Czech Republic

Introduction

Balloon dilation of anastomotic strictures in Crohn's disease is safe and effective procedure, but the effect of dilation is usually short with very high rates of recurrence.

Aims and Methods

Twenty six patients, 15 female, mean age 40.9 years (21–71yrs), and 11 male, mean age 34.5 years (22–47yrs) with Crohn's disease and enterocolic anastomotic strictures were included in this retrospective study. We pursued this aim: a relation between the effect of concomitant therapy (topic steroids, systemic steroids, azathoprin and mesalazin), type of disease, and the long-term results of balloon dilation of anastomotic strictures (number of sessions, intervals between dilations).
We used TTS balloon (Microvasive Boston).

Results

Since 1998 we have performed 63 balloon dilations in 26 patients (mean number of dilations was 2.42 per patient). The mean disease duration was 14.1 years in females and 12.4 years in males. 14 patients had a fiberstenotic form of the disease, 10 patients had fistulas, and two patients presented perforating form. 11 patients took topic steroids, two patients systemic steroids, eight patients azathioprin, and 20 patients mesalazin. The mean interval between dilations was 4.9 months in females and 5.1 in males. We had two complications (covered perforation) without the need of surgery. One patient underwent anastomotic resection because of dilation failure. We found no correlation between taking of topic steroids and intervals of dilations ($p = 0.299$), taking of topic steroids and number of sessions ($p = 0.337$), taking of systemic steroids and interval of dilations ($p = 0.501$), taking of systemic steroids and number of sessions ($p = 0.773$), taking of azathioprin and interval of dilations ($p = 0.421$), taking of azathioprin and number of sessions ($p = 0.374$), taking of mesalazin and interval of dilations ($p = 0.447$), and taking of mesalazin and number of sessions. There was no significant difference between the type of disease and the interval of dilations ($p = 0.517$).

Conclusion

Concomitant therapy for Crohn's disease had no influence on long-term effect of balloon dilation of anastomotic strictures. We observed the same relation between the type of disease and long-term effect of dilation. In spite of this, the balloon dilation is a very good alternative to the surgical management of strictures in patients with Crohn's disease.

076

THE BIOPTIC SURVEYING OF PATIENTS WITH ULCERATIVE COLITIS

Beneš Z., Chlumská A., Antoš Z., Puškárová G., Kohout P., Rozmahel M.

2nd Internal Clinic of Thomayer Hospital, Prague
Bioptic Laboratory, Pilsen

Background

Regular surveying of patients suffering from ulcerative colitis (UC) unambiguously proved that the distribution of inflammatory changes in the mucosa of colon is rather variable, moreover it changes during the disease.
On the basis of these findings two basic types of UC-diffused and non-diffused forms of UC are recognised to date. In the diffused form of UC the inflammation targets rectum and also the subsequent parts of the colon, respectively the whole colon.
In the non-diffusion form of UC the findings in rectum can be normal and the inflammatory changes in the proximal parts of colon are mostly of the patched type or of the segmental type.
Endoscopic examination does not necessarily prove the agreement between macroscopic finding and its histologic correlation. UC diagnosis and the follow-up observation of its duration therefore require a segmental bioptic sampling of colon mucosa.

Method and Results

A group of 17 patients suffering from UC (9 male and 8 female patients) from 19 to 76 years of age (mean age 42 years) was closely monitored. The diffusion type of UC appeared in 15 patients (88%). Histological findings in 9 patients corresponded to active pancolitis, in one case without inflicting cecum. Three patients suffered from active pancolitis with regress of inflammatory changes in the rectum. The remaining 3 patients recorded active inflammation of rectum and sigmoideum. Non-diffusion UC type was found in two patients (12%).

Conclusion

The endoscopic findings and dispersion of histological changes in UC can be rather variable with possible appearance of patched areas. The inflammation of rectum does not necessarily need to be expected in each case, which is not always the result of applied treatment. The detection of inflammatory changes in colon and rectum is important for the proper diagnosis and correctly applied treatment. This procedure requires taking of subsequent bioptic samples both from macroscopic normal and inflammatory mucosa.

References

Ulcerative Colitis. Am. J. Surg. Path. 22: 983–989, 1998.
Bernstein CN: On Making The Diagnosis of Ulcerative Colitis.Am. J.Gastroenterol 1997, 8:1247–52.

077

6-THIOGUANINE THERAPY IN PATIENTS INTOLERANT OR REFRACTORY TO AZATHIOPRINE OR 6-MERCAPTOPURINE THERAPY

Chalupná P., Lukáš M., Kumsta M., Bortlík M., Novotný A., Adamec S.

4th Medical Department, Charles University, Prague, Czech Republic

Background

Azathioprine (AZA) and 6-mercaptopurine (6-MP) are effective therapeutic agents in treatment of IBD. However, about 20–35 % of patients are unresponsive and about 15 % of patients develop intolerance to AZA/6-MP. 6-thioguanine (6-TG) is an alternative therapy to AZA/6-MP in children with acute lymphoblastic leucaemia which gives rise to high 6-TG nucleotides levels – the most active metabolites of AZA/6-MP.

Aim

1. To evaluate the efficiency of 6-TG therapy in patients with IBD who are refractory or intolerant to AZA/6-MP therapy.
2. To evaluate the tolerance of 6-TG therapy in these patients.

Patients and Methods

13 patients (10 CD, 3 UC) refractory (n=11) or intolerant (n=2) to AZA/6-MP therapy, mean age of 35 years, 7 men, and 6 women.
The dose of 6-TG ranged from 40 to 60 mg/day. Follow-up time was between 3 to 6 months. Efficiency of the therapy was evaluated based on laboratory markers and clinical improvement. We used paired t-test for statistical analysis.

Results

Decrease of leucocytes, C-RP, and erythrocyte sedimentation rate (ESR) were significant (leu 8.3 to 6.9, $p < 0.05$; C-RP 54.3 to 10.6, $p < 0.05$; ESR 35.5 to 17.9, $p < 0.005$).
Decrease of thrombocytes count was observed seen but insignificant (tromb 360.2 to 318.0, $p = 0.118$).
We observed clinical improvement in 69 % of patients (7/10 with CD, 2/3 with UC) and steroid sparing effect in 60 % (3/5).
Good response to the 6-TG therapy correlated with high plasmatic 6-TG levels ($p < 0,05$).
The side effects of 6-TG therapy were observed in 2 patients (leucopenia, nausea).

Conclusion

1. In 70 % of patients the 6-TG therapy is a good alternative to AZA/6-MP refractoriness or intolerance.
2. The side effects were observed in 15 % of patients.

078

NUTRITION SUPPORT IN SEVERE CROHN'S DISEASE

Hrabovský V., Martínek A.

Internal Department, University Hospital, Ostrava

Crohn's disease (CD) is a chronic inflammatory process that may affect any part of the gastrointestinal tract. Etiology of this disease is still unknown and therefore causal therapy is impossible. Moreover, the symptomatic therapy may be associated with serious complications.
There is evidence that a patient will often display various symptoms (e.g. abdominal pain, fever, diarrhoea with or without bleeding). Malnutrition is also a typical symptom of Crohn's disease with prevalence of 50–70 %. Weight loss often amounts to more than 10 % of standard patient's weight during three months (severe malnutrition). Depletion in energy stores, catabolism, hypoproteinemia (alteration of signal and transport mechanisms), water, and electrolyte disturbances may play an important role in the course of disease. In addition, digestive functions of altered intestine are negatively influenced by severe malnutrition.
Involved in the etiology of malnutrition in CD are: 1) cytokine – mediated anorexia, 2) impairment of digestion and absorption, 3) (not only) protein losing enteropathy, and 4) high-energy expenditure.
Enteral nutrition is preferred in the treatment of malnutrition in Crohn's disease. Nutritional support with enteral feeding as a primary treatment can achieve weight gain and favourably modulate various organ functions. Evidence exist that corticosteroids are more effective than enteral nutrition in inducing and sustaining remissions in patients with acute CD. Moreover, evidence-based data showed that elemental diets using simple amino acids are not superior to polymeric diets using peptides or a single whole protein and that bowel rest is not necessary to achieve a clinical remission. The use of fish oil (ω–3 PUFA, antioxidants) remains experimental.
The mode of action of enteral nutrition is based on: 1) intestinal microbial flora reconstruction, 2) elimination of dietary antigen uptake, 3) diminution of intestinal inflammatory mediators synthesis, 4) nutritional repletion, 5) micronutrients provision.
Parenteral nutrition is necessary in severe malnutrition and complicated forms.
Suppression of catabolism by adequate energy supply, substitution of macronutrients and micronutrients depletion, normalisation of water/electrolyte disturbances, and potential imunonutrition utilisation are the important components of nutritional support in Crohn's disease.

References

Griffiths AM.: Inflammatory bowel disease, Nutrition 1998,14,788–791.
Ashley Ch., Howard L.: Evidence base for specialized nutrition support, Nutrition reviews 2000, 58, 282–289.
Jeejeebhoy KN: Management of nutritional problems of patients with Crohn's disease. Canadian Medical Association. Journal 2002, 166, 913.

079

INFLAMMATORY BOWEL DISEASE AND THROMBOPHILIA

Krč I.[1], Krčová V.[2], Slavík L.[2], Konečný M.[1], Divoká M.[2], Ježáková J.[2]

[1] *2nd Department of Internal Medicine*
[2] *Haemato-oncological Department, Palacký University, Olomouc, Czech Republic*

Background

The etiopathogenesis of inflammatory bowel disease (IBD) remains to be elucidated. Besides well-known psychosomatic, infectious, immunological, and genetic (MOD – 2 gene) factors, the possibility of a hypercoagulable state in the frame of a thrombophilic disorder has appeared to be a recent hot topic. So far, some acquired abnormalities like the presence of antiphospholipoid antibodies as well as other inborn hereditary changes (Leiden mutation or methylentetrahydrofolate-reductase [MTHFR] polymorphism) have been observed in these patients. Nevertheless, the results of the most published reports are unequivocal, in some cases even controversial at the moment.

Patients and Methods

The objectives of our own study was a cohort of 33 patients with IBD who were referred to our institute because of the worsening of underlying condition. Among them, there were 18 subjects with idiopathic proctocolitis and 15 with Crohn's disease, all in the active stage of the disease. Haemocoagulation parameters tested were as follows: PT, aPTT, fibrinogen, AT III, thrombocytes, PC, PS, F II, F VIII, F XII, F XIII, vWF, lupus anticoagulant, APC/R, PLG, PAI–1, and t-PA. In parallel, genetic markers were also examined: F V Leiden, prothrombin gene mutation, MTHFR gene mutation, and PAI–1 polymorphism.

Results

In the examined group of patients, thromboembolic complications were detected anamnestically in eight subjects (24.2 %). Apart from this, the study confirmed several abnormalities in the majority of the above-mentioned coagulatory parameters. In particular, a significant increase in the levels of t-PA, PAI–1, vWF and F VIII was detected. From the genetic point of view, a great part of the patients had also important predispositions for thrombosis (F V Leiden, MTHFR, PAI–1 hetero- and homozygoty), but the actual risk could not be precisely evaluated due to a lack of precise data concerning the incidence of these changes in a normal Czech population.

Conclusion

Our results confirmed increased coagulation pathway activation in the subjects suffering from active IBD and thus strongly support the possibility of increased thrombogenesis. However, a direct etiopathogenetic significance of the observed changes should be confirmed by larger studies in future.

References

Ardizzone S, Bianchi Porro G. (2002) Inflammatory bowel disease: new insights into pathogenesis and treatment. J Intern Med 252, 475–496.
Gurlich R, Hrachovinová I, Salaj P, Lukáš K, Lukáš M, Vorlová Z, Maruna P. (2000) Výskyt Leidenské a protrombinové mutace u pacientů s Crohnovou nemocí. Čes a slov Gastroent 54, 206–209.
Larsen TB, Nielsen JN, Fredholm L, Brandslund I, Munkholm P, Hey H. (2002) Hyperhomocysteinaemia, Coagulation Pathway Activation and Thrombophilia in Patients with Inflammatory Bowel Disease. Scand J Gastroenterol 37, 62–67.
Musil D. (2001) Hluboká žilní trombóza – současný pohled na etiopatogenézu a diagnostiku. Int Med pro Praxi 3 347–354.

080

SUPERIOR MESENTERIC ARTERY BLOOD FLOW AND IBD

Mareš K., Cendelínová J., Schützнerová D.

Gastroenterology, Internal Department, Hospital Na Homolce, Prague

We have measured the superior mesenteric artery (SMA) blood flow in 75 patients with inflammatory bowel disease and in 20 patients with other diseases as a control (C) over the last one and half years. We used ultrasound Corevision Pro by Toshiba comp. Several patients we measured several times. Patients with Crohn's disease (CD) and proctocolitis (PC) were measured separately. Each group was divided into two subgroups according to their activity. Subgroups consisted of remission and active groups, and a third subgroup which included patients from other previous groups that underwent bowel operation.
We have measured blood flow in fasting patients and 20 minutes after drinking of one packet of Nutrisone. All patients were measured three times and then the average measurement was calculated.

Results

Average blood flow in SMA was 0,38 l/min in fasting patients and 0.66 l/min after Nutridrink.
There was an increase in blood flow after Nutridrink from 65 % in control group to 66 % in CD group until 70 % in IP group. Patients with active (CD and PC) disease had both fasting and Nutridrink blood flow higher than the patients in remission. Patients after operation for CD had lower fasting blood flow than the average, but the highest increase of blood flow following Nutridrink. One male patient after colectomy in the PC group had the highest blood flow both in fasting and after Nutridrink. Both blood flows in control group were the lowest. The patients with CDAI index higher than 150 had also higher percentage increase in "after Nutridrink" blood flow. These relations differed from those implied from the IBD Questionnaire values.

081

THE ROLE OF INTESTINAL MICROORGANISMS IN THE PATHOGENESIS OF INFLAMMATORY BOWEL DISEASES THE TWO-COMPONENT HYPOTHESIS OF "ULCERATIVE COLITIS"

Mařatka Z.

Praha, Czech Republic

Background

Inflammation of the large intestine occurs in an environment infested by a wealth of potentilly pathogenic microorganisms. None of them is directly involved in the etiology of IBD, but their participation in the pathogenesis and clinical picture is probable. The significance of this factor for the development, symptomatology and therapy of IBD has not been fully appreciated.

Method

Previously published studies on 1262 cases of IBD – 959 idiopathic proctocolitis (IPC)[1] and 303 Crohn's disease (CD)[2] have been revised and analysed with particular reference to the clinical course, symptomatology and response to treatment in the case of different types of disease [3, 4]. Bacteriological, serological and immunological studies were performed including investigations of intestinal microorganisms and their pathogenic potential, serological and immunological studies of antibodies and autoantibodies.[5–8] The role of immunity and autoimmunity in pathogenesis of ulcerative colitis was assessed.[9, 10] Treatment by autogenous vaccine was performed in 35 patients with ulcerative colitis and evaluated in a follow-up of several years.[11–13] Antiintestinal sera and their pathogenity were investigated in rats.[14]

Results

Analysis of the clinical aspects of IPC revealed that the most frequent mild disease manifests itself as a hemorrhagico-catarrhal inflammation affecting the terminal part of the digestive tube with periodic course proceeding in attacks of activity separated by quiet intervals. A severe form presents as an ulcerative inflammation with subtotal or total involvement and with symptoms of toxicosis and sepsis. In this situation intestinal microorganisms (E. coli, enterococci, etc.) could be cultured from the intestinal mucosa and contents. Whereas mild cases were resistant to the antiinfectious treatment the symptoms in severe cases could be partly or fully controlled by antibiotics according to the sensitivity of pathogens. The potential pathogenity of intestinal commensals was established in serological and immunological studies.

Discussion

The results of bacteriological-serological studies are in keeping with data from the literature pointing to the importance of intestinal microorganisms which under normal circumstances are innocuous commensals whilst in abnormal conditions acquire pathogenity and participate in the development of morphological changes and clinical symptomatology. This has been shown in the past not only in ulcerative colitis[15–17] but also in diversion colitis[18] and after by-pass operations for obesity.[19] Recently, the pathogenic role of colonic flora has been shown in Crohn's disease by establishing mutations of the susceptibility gene NOD2 (CARD15) which governs defence of the intestine against colonic bacteria.[20, 21]

Conclusion

Intestinal bacterial flora is potentially pathogenic and in case of loss of mucosal integrity and resistance may play a role in suppurative and ulcerative inflammation. Such non-specific complications may be engrafted on a primary lesion of any origin. In order to avoid ambiguity of the term *ulcerative colitis* the term *idiopathic proctocolitis (IPC)* has been proposed as a more precise term for both forms of the disease characterized by hemorrhagico-catarrhal inflammation in the mild rectal form and by purulent and ulcerative process in the severe subtotal or total form.

On this base a *two-component hypothesis of pathogenesis of idiopathic proctocolitis (IPC)* has been proposed.[22–25] According to this the basic process consists in a hemorrhagico-catarrhal inflammation of unknown (idiopathic) etiology appearing and disappearing periodically. In severe cases an invasion of potentially pathogenic intestinal microorganisms is superimposed on the primary inflammatory process and this leads to a more pronounced inflammatory process characterized by suppuration and ulcer formation.

The validity of the two-component hypothesis is supported by the effect of antiinfectious treatment which is effective in the ulcerative stage but not in the hemorrhagico-catarrhal stage of IPC. It explains the paradox that severe forms are relatively better controlled by treatment than the mild cases, which are often resistant to therapy.

References

1. Mařatka Z, Nedbal J, Kociánová J, Havelka J, Kudrmann J, Hendl J: Incidence of colorectal cancer in proctocolitis: a restrospective study of 959 cases over 40 years. Gut 26, 1985, 43–49.
2. Havelka J, Kociánová J, Mařatka Z *et al.*: Klinický obraz a diagnóza regionální enteritidy. Statistický rozbor 303 případů. Čs. Gastroent. Výž. 47, 1993, 3–9.
3. Mařatka Z., Spellberg MA: Observations on the clinical course of nonspecific ulcerative colitis. Gastroenterology 12, 1949, 79–86.
4. Mařatka Z., Wagner V.: Recherches sur les autoanticorps anticolon au cours de la recto- colite hemorrhagique. Rev. franc. Etud. clin.biol. 1961, 6: 182–185.
5. Mařatka Z., Wagner V.: On the role of the autoimmune mechanism in the genesis of ulcerative colitis. Acta allerg. 1963, 18:100–109.
6. Maratka Z, Wagner V: The treatment of non-specific ulcerative colitis by autogenous vaccine. Correlated bacteriological and immunological studies. Gastroenterology 11, 1948, 34–49.
7. Bargen JA: Experimental studies on aetiology of chronic ulcerative colitis. J. Am. med. Ass. 83, 1924, 332–336.
8. Dickinson RJ, Varian SA, Axon ATR, Cooke EM. Increased incidence of faecal coliforms with in vitro adhesive and invasive properties in patients with ulcerative colitis. Gut 1980, 21:787–792.
9. Cooke EM, Ewins SP, Hywel-Jones J, Lennard-Jones JE. Properties of strains of E. coli carried in different phases of ulcerative colitis. Gut 1974, 15:143–146.
10. Glotzer DJ, Glick ME, Goldman H. Proctitis and colitis following diversion of the faecal stream. Gastroenterology 1981, 80:438–441.
11. Thayer WR, Kirsner JB. Enteric and extraenteric complications of intestinal bypass and inflammatory bowel disease. Gastroenterology 1980, 78: 1097–1100.
12. Hugot JP, Chamillard M, Zouali H *et al.*: Association of NOD2 leucin-rich repear variants with susceptibility to Crohn's disease. Nature 411m 2001, 599–603.
13. Glasser M, Boudeau J, Barnich N *et al.*: Adherent invasive E. coli strains from patients wuth Crohn's disease survive and replicate within macrophages without inducing host cell death. Infect. Immunology 69, 2001, 5229–5537.
14. Mařatka Z.: Pathogenesis and aetiology of inflammatory bowel disease. In: De Dombal FT, Myren J, Boucher IAD, Watkinson G. (eds): Inflammatory bowel disease. Oxford Univ. Press, 1rd ed. 1986, 2nd ed. 1993.

082

REPEATED APPLICATION OF ANTIBIOTICS IN THE THERAPY FOR INFLAMMATORY BOWEL DISEASE CONTROVERSIAL PROBLEMS: OWN EXPERIENCE

Prokopová L., Zbořil V., Hertlová M.

3rd Department of Internal Medicine and Gastroenterology, University Hospital Bohunice, Masaryk University, Brno

Introduction

Ciprofloxacin and metronidazole have been effective in the therapy for Crohn's disease either separately (Cooperative Crohn's Disease Study) or in combination (Prantera) with the responsiveness of 25–46 %. The recommended daily dose of metronidazole is 25 mg–1500 mg, that of ciprofloxacin 500–1000 mg. Therapy lasted for 12–16 weeks in the trials mentioned. Some experience has been obtained in a controlled therapy with ciprofloxacin in ulcerative colitis. Metronidazole and other antibiotics are also a part of therapeutical algorithm of pouchitis. Idiopathic bowel inflammations have been

recently treated with non-absorbable rifaximin that has appeared effective in a controlled study on ulcerative colitis (Gionchetti) in the daily dose of 400–600 mg for a short period. The authors have compared clinical responses to antibiotic therapy with metronidazole, ciprofloxacin and rifaximin in repeated treatment.

Set and Methods

In the period of 1995–2002, monotherapy of metronidazole (750 mg/day for 10 days) was applied to 63 patients (42 with Crohn's disease, 22 with ulcerative colitis), combined treatment of metronidazole + ciprofloxacin (500–1000 mg/day ciprofloxacin and 750 mg/day metronidazole for 10 days) to 85 patients with ulcerative colitis and, finally, monotherapy of rifaximin (400mg/day for 10 days) to 17 cases (15 with ulcerative colitis and 2 with Crohn's disease). Therapy efficiency was evaluated clinically by CDAI and CAI, endoscopically using the Blackstone's classification. Antibiotic therapy was connected with the examination of faeces for usual pathogenes, starting in 2002 by the investigation of bacteriological smear with the sensitivity to antibiotics as well.

Results

The highest responsiveness was observed in primary antibiotic therapy for combination of metronidazole + ciprofloxacin in the treatment for relapses of ulcerative colitis (60 % with an error of small sets ± 8.4 %), while monotherapy with metronidazole and rifaximin did not exceed 30 %. Rifaximin has been used since 2001; repeated treatment was indicated in three cases only. On the other hand, metronidazole and ciprofloxacin was used repeatedly in 82 out of 166 treated patients, with the highest frequency four times and the lowest two times. The highest clinical and endoscopical responsiveness was obtained during the years 1995–1998 (56 %), while dropping by nearly 20 % in the following period. This finding was in correlation with the increased hospital resistance to ciprofloxacin. Therefore, the authors have used broader spectrum of examinations and confirmed the increase of this resistance by bacteriological smear sensitivity.

Conclusion

Long-term and repeated therapy for IBD with ciprofloxacin is associated with a real risk of developing antibiotic resistance and decrease of therapeutic response. This fact should be taken into account in the course of therapeutic strategy. Although the incidence of resistance to rifaximin, which is relatively the safest, has not been reported, this risk should be anticipated due to its relationship with vulnerable antituberculotics.

References

Ursing B, Alm T, Barany F, *et al.*: A comparative study of metroidazole and sulfasalazine for the active Crohn's disease: the Cooperative Crohn's Disease Study in Sweden. II.Results. Gastroenterology, 1982, 83:550–562.

Prantera C, Zannoni F, Scribano MI, *et al.*: An antibiotic regimen fr the treatment of active Crohnś disease: a randomized, controlled trial of metronidazole plus ciprofloxacin. Am J Gastroenterol, 1996, 2:328–332.

Turunen UM, Farkilla MA, Hakala K, *et al.*: Long-term treatment of ulcerative colitis with ciprofloxacin: a prospective, double-blind, placebo-cotrolled trial. Gastroenterology, 1998, 115:1072–1078.

SANDBORN WJ: Pouchitis after restorative proctocolectomy: diagnosis and treatment. Evidence based gastroenterology and hepatology. 2000, 192–203.

Gionchetti P, Rizzello F, Ferrieri A, *et al.*: Rifaximin in patients with moderate or severe ulcerative colitis refractory to steroid-treatment: a double-blind, placebo-controlled trial. Dig Dis Scien, 1999, 44, 6:1220–1221.

083

INCIDENCE OF OSTEOPENIA IN IDIOPATHIC BOWEL DISEASE

Roubalik J., Kojecký V.

Internal Clinic IPVZ, Bata Hospital, Zlin, Czech Republic

Introduction

Published data on the incidence of osteopenia and osteoporosis in idiopathic bowel disease (IBD) show considerable variation. The authors examined the incidence of this complication in patients with ulcer colitis (UC) and Crohn's disease (CD) attending their gastroenterology unit.

Patients and Methods

41 patients with CD (22 female, 19 male) and 31 patients with UC (12 male, 19 female) were examined in the period of 2002–2003. Patients with rectal type of UC were excluded, as well as those with other possible causes of osteopenia. Disease duration, mean age, corticoid therapy and past surgical procedures were followed. Mineral bone density was assessed by means of DEXAosteodensitometry. Basic biochemical measurements including serum vitamin D were also followed. The mean duration of CD vs UC was 10 (1–31) vs 11 (1–24) years, respectively. The mean age of patients with CD vs UC was 31 (18–57) vs 43 (21–70) years, respectively.

Results

Osteopenia was found in 21 % (15) of patients with IBD, 22 % (9) of patients with CD, 16 % (6) of patients with UC. The mean age in patients with CD vs UC was 36 (26-52) vs 49 (34–70) years, respectively. The average duration of CD vs UC was 7.4 (6–11) vs 13 (11–15) years, respectively. Six patients with CD vs three patients with UC had taken corticoids, and six patients with CD vs one patient with UC had undergone intestinal surgery. Osteoporosis was found in only 5 % (4) of patients with IBD (3 patients with CD vs 1 patient with UC). The mean duration of IBD in patients with CD vs UC was 13 vs. 15, respectively. All patients had been treated with corticoids and had intestinal resection surgery. Decreased serum levels of 25-hydroxyvitamin D were found in 49 % (20) patients with CD vs 29 % (9) patients with UC. No statistically significant differences in serum levels of D vitamin were found between the CD vs UC groups.

Conclusion

26 % incidence of osteopenia and osteoporosis was found in our study group of patients with IBD. No differences in D vitamin levels were found between both groups. Although the percentage of this complication is lower compared to some other published data, it should be taken into account while taking appropriate preventive as well as therapeutic measures.

References

Ardizzone S.,Bollani S. Bettica P. Bevilacqua M. Molteni P. Bianchi Porro G. (2000) Altereted bone metabolism in inflammatory bowel disease: there is difference between Crohn's disease and ulcerative colitis. J Intern Med. 247, 63–67.

Dinca M., Fries W., Luisetto G., Peccolo F., Bottega F., Leone L., Naccarato R. (1999) Evolution of Osteopenia in Inflammatory Bowel Disease. Am J Gastroenterology 94, 1292–1297.

Lukáš M. *et al.* (1998,Galen) Metabolické a endokrinní poruchy ISZ.In: Idiopatické střevní záněty. Nejistoty současné znalosti a klinický přístup, 240–241.

Schulte C., Dignass AU. Mann K., Goebell H. (1998) Reduced bone mineral density and unbalanced bone metabolism in patients with inflammatory bowel disease. Inflamm. Bowel Dis. 4, 268–75.

Ulivieri F.M., Lisciandrano D., Ranzi T. *et al.* (2000) Bone Mineral Density and Body Composition in Patients With Ulcerative Colitis Am J Gastroenterology 95, 1491–1494.
Calentine J., Sninsky Ch. (1999) Prevention and Treatment of Osteoporosis in Patients With Inflammatory Bowel Disease. Am J Gastroenterology 94, 878–883.

084

CLINICAL COURSE AND LABORATORY FINDINGS IN PATIENTS WITH CELIAC DISEASE AND MICROSCOPIC COLITIS

Utěšený J., Klusáček D.

2nd Department of Pediatrics, University Hospital, Brno

Introduction

Microscopic, lymphocytic, collagenous colitis are well-defined entities with typical pathological findings in large bowel mucosa. Corresponding clinical symptoms are much less stringently defined and their relation to other autoimmune disorders is not yet fully understood.

Methods

In a cohort of 12 patients aged 15 ± 4.5 years we performed colonoscopy because of chronic diarrhoea (9/12) abdominal pain with upper dyspepsia (4/12), loss of appetite (6/12), weight loss (3/12), irritable bowel according to Rome II for pediatric patients and GSRS (10/12). Sampling of mucosa was taken at 20, 60, and 90 cm respectively. We performed screening for celiac disease with antibodies anti-gliadin IgG, reticulin, endomysium and transglutaminase IgG and IgA and genotyping PCR SSR Dr3,5,7 and also, autoimmune screening with IBD, ASCA pANCA and ultrasonic examination of terminal ileum was done. Next, we performed enterobiopsy using Crosby capsula from the first part of jejunum. In both negative and positive patients, we followed compliance with dietary measures over 6 months using GSRS and serology.

Results

In this group we diagnosed celiac disease in four patients (33.3 %). In no subject did we demonstrate the presence of classic total atrophy or Marsh 3 and more. In one patient we observed minimum microscopic infiltrative changes with IEL/100 cells 50 and/or more and in the remaining, the picture corresponding to Marsh 3 was present. In the whole cohort, increase of anti-gliadin and anti-transglutaminase IgG was present. Moreover, in one patient with Marsh 3, positive EMA IgA was also observed. In all patients the presence of either mutation in DrHLADq was shown. Regarding compliance, no difference was observed between the patients with minimum lesions and those with fully developed celiac disease within 3 months, Z score was $p < 0.05$ after 6 months using dietary treatment only. In both groups, diet led to clinical improvement.

Conclusion

Mild coeliac disease with DQ positive and EMA negative is probably more frequent in patients with minimal colitis than hitherto thought. The problem may lie in the mode of diagnosis of celiac disease. Minimum differences in the influence of dietary measures consisting of elimination of gliadin can be caused either by the presence of non-HLA positive celiac patients in the group of minimum colitis patients or by some unspecific influence of diet on the course of minimum colitis. The results need to be confirmed in a larger group of patients.

Cerese B, Lofberg R, Bergman L (1995) Microscopic colitis syndrome Gut 39, 880–6
Lewis FW, Waren GH, Goff JS (1991) Collagenous colitis with involvement of terminal ileum Dig.Dis.Sci 36, 1161–3
Einarson K, Eusufzai S, Johanson V, Lofbrg R, Theodoresson E, Veres B (1997) Villous atrophy of the distal ileu mand lymphocytic colitis in female with bile duct malabsorption Gut 41, 561–6
Hamilton I, Snaders S, Hopwood D, Baouchier IA (1992) Collagenous colitis associated with small intestine villous atrophy (1986) Gut 27, 1394–8
Moayyedi P, O'Mahony S, Jackson P, Lunch DAF, Dixon MF, Axon ATR (1997) Small intestine in lymfocytic and collagenous colitis: mucosal morphology, permeability and secretory immunity to Iliadin (1997) J Clin.Pathol. 50, 527–9
McCashland (tm), Donova JP, Strobach RS,Linder J, Quigley EMM (1992) Collagenous enterocolitis: a mnifestatin of gluten sensitive enteropathy

085

LONG-TERM IMMUNOSUPPRESSION WITH CYCLOSPORIN IN THE THERAPY FOR INFLAMMATORY BOWEL DISEASE: OWN EXPERIENCE

Zbořil V., Prokopová L., Hertlová M.

3rd Department of Internal Medicine and Gastroenterlogy, University Hospital Bohunice, Masaryk University, Brno

Introduction

Immunosuppressive therapy for IBD with cyclosporin A (CyA) started in 1984. It is a part of therapeutic strategy particularly in ulcerative colitis, while its application in Crohn's disease is controversial. The dosage ranges between 4mg/kg/day and 8mg/kg/day, with increasing toxicity. Most reports have shown failure of effective therapy if it lasts for more than 6 months when the number of recurrences reaches 30–60 %. Maximum time limit of the effective CyA treatment is unknown and is usually terminated after 12 weeks by transition to azathioprine, 6-mercaptopurine, or methotrexate. Authors have evaluated their own experience with a long-term CyA therapy in a set of patients with planned combined sequential immunosuppression.

Set and Methods

In the period of 1998–2002, 52 patients with IBD, 38 with ulcerative colitis and 14 with Crohn's disease, were treated with CyA. The patients were resistant to corticosteroids and aminosalicylates. Our intention was to combine sequential immunosuppression in the scheme of 12 weeks with CyA 5 mg/kg/day perorally + azathioprine 2,5 mg/kg/day and to terminate the CyA therapy starting in the week 13 with a transition to immunosuppression by azathioprine. The evaluation was carried out using indices of activity CDAI and CAI. After discontinuing CyA, relapse was registered in 16 patients of the set given by 2 weeks. The situation was considered as a failure of the azathioprine therapy, and these patients had to restart the CyA monotherapy in the dose of 5 mg/kg/day. This therapy continued until the next relapse, symptomatic recurrence or the development of severe side effects. Therapeutic efficacy was evaluated by means of Wilcoxon's test.

Results

All 16 patients (9 with ulcerative colitis, 7 with Crohn's disease) showed positive response to the repeated therapy. Renal functions were monitored in regular three-months intervals; possible side ef-

fects of prolonged treatment were evaluated. Serious side effects – transient nephrotoxicity – were seen in only one case. The therapy proceeded with the dosage reduced by 25 % without any other manifestation of toxicity. Therapy failure was recorded in one female patient with ulcerative colitis 6 months later. Remaining 15 patients continued the therapy with the longest interval of 16 months and the shortest 9 months, the average duration of the therapy being 8,9 months. Long-term CyA therapy seems to be effective on the 5 % level of significance.

Conclusion

Based on our own experience and in partial disagreement with literature data, we have concluded that the effective CyA therapy for IBD may be associated with certain dependence when the treatment cannot be terminated by transition to other immunosuppressive agent without the risk of early recurrence. Long-term CyA therapy was effective with daily dose of 5 mg/kg, and the therapy toxicity minimum and well controllable. No direct explanation for the dependence of the effective CyA treatment in some patients is available, however, alternative hypotheses based on the knowledge of activities of MDRI (multi-drug resistance) -gene and TMPT (thiopurin-metyltranspherase) have been submitted for discussion.

References

Gupta S.: Sandimmun in ulcerative colitis: a case report. Lancter, 1984, 2: 1277–1280.

Stange EF., Modigliani R., Pena AS., *et al.*: European Study Group of cyclosporin in chronic active Crohnś disease: a 12months study. Gastroenterology, 1995, 109: 774–782.

Lichtinger S., Present DH., Kornbluth A.: Cyclosporin in severe ulcerative colitis refractory to steroid therapy. New Engl J Med,1994,330:1841–1845.

Lichtinger S.: To use or not to use cyclosporine A. That is the question. Inflam Bow Dis, 1995, 1:331–334.

Rutgeerts P.: Medical therapy of inflammatory bowel disease. Digestion, 1998, 59:453–469.

Zbořil V., Prokopová L., Pokorný A., *et al.*: Cyklosporin A v léčbě chronicky aktivních nespecifických střevních zánětů. Čsl. gastroent. a hep, 2001, 1:5–10

086

PARENTERAL AZATHIOPRINE AND CYCLOSPORIN IN INTRODUCTION INTO IMMUNOSUPPRESSION IN THE THERAPY FOR AGGRESSIVE TYPE OF CROHN' S DISEASE: OWN EXPERIENCE

Zbořil V., Prokopová L., Hertlová M.

3rd Department of Internal Medicine and Gastroenterology, University Hospital Bohunice, Masaryk University, Brno

Introduction

Parenteral efficacy of cyclosporine has been confirmed in the toxic megalocolon and fulminant course of ulcerative colitis. Various authors applied the doses in a broader range – 4–8 mg/kg/day. Refractory course of Crohn's disease and perianal fistulation were also the subject of non-controlled trials with parenteral application of cyclosporin in the dose as high as 14 mg/kg/day. While in ulcerative colitis with effective parenteral application the continual oral administration of cyclosporin usually follows, in Crohn's disease the therapeutic effects are of short-term duration. The decrease of high initial doses followed by an attempt of transition to oral application is often accompanied by relapse within 2–12 weeks in 60–100 % patients. Moreover, high – dosage regimens of application are risky because of toxicity and side – effects of cyclosporin. According to the results of controlled trials, azathioprine has shown higher efficacy in the therapy for Crohn's disease in comparison with cyclosporin, but its onset appears later (after about 8–121 weeks). Sandborn's trial has shown that this period may be shortened to about 2 weeks by parenteral application of azathioprine in continuous 36 hrs infusion. In their pilot study, the authors tried to evaluate safety, tolerability and effectiveness of parenteral 1) cyclosporin and 2) azathioprine in refractory, chronically active Crohn's disease not responding to conventional therapy, including infliximab.

Set and Methods

1. In the period of 1999–2003 the regimen of parenteral therapy with cyclosporin A was applied in three patients with refractory, chronicly active course of aggressive – perforating type of Crohn's disease who had been treated for at least 3 months with oral azathioprine in the dosage of 2,5 mg/kg/day without any clear clinical effect. In two of them the infliximab therapy failed, in one female patient this therapy had to be terminated due to a severe allergic response. The patients were given cyclosporin in 24 hr continual infusion in the doses of 4–5 ng/ml. This therapy lasted for 7 days, then the peroral application of the same doses followed. The efficacy was evaluated 7 and 28 days later by CDAI, ultrasonography of intestinal and endoscopical Blackstone's classification.
2. In the period of 2001–2003 the regimen of parenteral azathioprine therapy was used in two patients who did not respond to oral administration of cyclosporin in the dosage of 4–8 mg/kg/day. Azathioprine was applied in continual 36 hr infusion of 40 mg/kg. Then the therapy continued with a conventional peroral dose of 2 mg/kg/day, clinical efficacy was evaluated after 14 and 28 days using the same method as in the first group.

Results

1. In the course of applying parenteral cyclosporin, 3 patients refractory to oral azathioprine showed slight improvement expressed with the index of CDAI (decrease of the average of 331 to 176) that, however, was related to striking neurological side effects (paresthesia, cephalea, insomnia). The levels of monocyclosporinemia reached, at the daily dosage chosen, the average C0 = 420 ng/ml. After transition to oral cyclosporine, the levels decreased and side effects disappeared even with the daily dose maintained. Simultaneously CDAI increased to the average of 280. Morphological evaluation by endoscopy and ultrasonography carried out 7 and 28 days later demonstrated no principal changes.
2. After 14 days, two female-patients treated with 36hr continual initial infusion of azathioprine with maintained oral application of cyclosporin showed evident clinical improvement of their condition (decrease of CDAI from the average of 254 to 112) accompanied by regression of hypervascularization, oedema and lymphadenopathy demonstrated by ultrasonography of intestines. One month later, one of them also showed endoscopical regression of changes from the stage of Blackstone d) to b). Side effects of treatment were observed 14 days later only as the decrease of leukocytes within physiological range with changes of differential picture. However, these changes required no therapeutic intervention.

Conclusion

The pilot, uncontrolled trial has verified the safety, tolerability and efficacy of two regimens of combined immunosuppression in refractory course of chronically active Crohn's disease. The 1st regimen

consisted of parenteral application of cyclosporin combined with oral azathioprine which was ineffective in monotherapy. The method chosen led to a short-term clinical effect without morphological regressive changes and was connected with reversible neurological side effects of cyclosporin. It is considered as ineffective. The 2nd regimen combined parenteral application of azathioprine with oral administration of cyclosporin that was ineffective in monotherapy. In this case, persistent clinical effects were recorded after 14 days and were connected with morphologically demonstrated regression of inflammatory changes. This method is evaluated positively and considered as a suitable therapeutical alternative in refractory forms of Crohn's disease. However, the risk is represented by possible decreased activity of TMPT (thiopurin methyl transferase) with severe leukopenia about 14 days after the parenteral bolus application of azathioprine. The examination of TMPT activity before starting the therapy or, at least, previous experience with non-complicated oral application of azathioprine should be helpful.

References

Brynskov J, Freund L, Rasmussen SN, *et al.*: A placebo-controlled, double-blind, randomised trial of cyclosporine therapy in active Crohn's disease. New Engl J Med, 1989, 321:845–850

Stange EF, Modigliani R, Pena, AS, *et al.*: European trial of cyclosporin in chronic active Crohn's disease: a 12-month study. Gastroenterology, 1995, 109:774–782

Hanauer SB, Smith MB: Rapid closure of Crohns' disease fistulas with continuous intravenous cyclosporin A. Am J Gastroenterol,1993,88:646–649.

Feutren G, Mihatsch MJ: Risk factors for cyclosporine-induced nephrotoxicity in patients with autoimmune disease. International Kidney Biopsy Registry of Cyclosporine in Autoimmune disease. New Engl J Med, 1992, 326:1654–1660

Sandborn WJ, Van O EC, Zins BJ, *et al.*: An intravenous loading dose of azathioprine decrease the time to response in patients with Crohn's disease. Gastroenterology, 1995, 109:1808–1817.