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Grupo de Estudos da Doença Inflamatória Intestinal do Brasil

HUMIRA® (adalimumabe): experiência clínica que gera confiança.[1-3]

71 ensaios clínicos publicados na maior base de dados sobre indicação-cruzada em segurança de um anti-TNF.[4]

Mais de **23.000 pacientes** em estudos clínicos globais.[4]

Mais de 17 anos de experiência em estudos clínicos, começando com AR.[5]

10 anos de dados de eficácia de AR em bula.[1]

10 indicações aprovadas no Brasil Mais do que qualquer outro biológico de autoaplicação.[1]

- Artrite reumatoide — 2003
- Artrite psoriásica — 2006
- Espondilite anquilosante — 2007
- Doença de Crohn — 2007
- Psoríase — 2008
- Artrite idiopática juvenil — 2011
- Retocolite ulcerativa — 2014
- Doença de Crohn acima de 6 anos — 2015
- Espondiloartrite Axial Não Radiográfica — 2015
- APROVAÇÃO DA AMPLIAÇÃO DA INDICAÇÃO: Artrite idiopática juvenil acima de 2 anos — 2015
- Hidradenite supurativa — 2015
- Uveíte não infecciosa intermediária, posterior ou pan-uveíte — 2016

Contraindicações/Precauções: Assim como observado com outros antagonistas de TNF, foram relatados casos de tuberculose associados ao Humira® (adalimumabe). A administração concomitante de antagonistas de TNF e abatacepte tem sido associada a aumento do risco de infecções, incluindo infecções sérias, quando comparada a antagonistas de TNF isolado.

HUMIRA® (adalimumabe) – MS: 1.9860.0003. **Apresentações:** 40 mg em frasco-ampola de 0,8 mL (USO PEDIÁTRICO ACIMA DE 02 ANOS), 40 mg em seringa de 0,8 mL e 40 mg em caneta de 0,8 mL (USO ADULTO E PEDIÁTRICO ACIMA DE 06 ANOS). **Indicações:** Artrite Reumatoide, Artrite Psoriásica, Espondilite Anquilosante, Espondiloartrite Axial Não Radiográfica (Espondiloartrite Axial sem Evidência Radiográfica de EA), Doença de Crohn, Colite Ulcerativa ou Retocolite Ulcerativa, Psoríase em Placas, Hidradenite Supurativa, Uveíte, Artrite Idiopática Juvenil Poliarticular. Contraindicações: pacientes com conhecida hipersensibilidade ao adalimumabe ou quaisquer componentes da fórmula do produto. **Advertências e Precauções:** Infecções: foram relatadas infecções graves devido a bactérias, micobactérias, fungos, vírus, parasitas ou outras infecções oportunistas. Pacientes que desenvolvem uma infecção fúngica grave são também advertidos a interromper o uso de bloqueadores de TNF até que a infecção seja controlada. O tratamento com HUMIRA® (adalimumabe) não deve ser iniciado ou continuado em pacientes com infecções ativas, até que as infecções estejam controladas. Recomenda-se cautela ao uso em pacientes com histórico de infecções de repetição ou com doença de base que possa predispor o paciente a infecções. Tuberculose: foram relatados casos de tuberculose incluindo reativação e nova manifestação de tuberculose pulmonar e extrapulmonar (disseminada). Antes de iniciar o tratamento todos os pacientes devem ser avaliados quanto à presença de tuberculose ativa ou inativa (latente). Se a tuberculose ativa for diagnosticada, o tratamento com HUMIRA® (adalimumabe) não deve ser iniciado. Se for diagnosticada tuberculose latente, o tratamento apropriado deve ser iniciado com profilaxia antituberculose. Reativação da Hepatite B: o uso de inibidores de TNF foi associado à reativação do vírus da hepatite B (HBV) em pacientes portadores crônicos deste vírus podendo ser fatal. Deve-se ter cautela ao administrar inibidores de TNF em pacientes portadores do vírus da hepatite B. Eventos neurológicos: com exacerbação de sintomas e/ou evidência radiológica de doença desmielinizante, deve-se ter cautela ao considerar o uso de HUMIRA® (adalimumabe) em pacientes com doenças desmielinizantes do sistema nervoso periférico ou central, de início recente ou pré-existentes. A descontinuação do tratamento com HUMIRA® (adalimumabe) deve ser considerada na ocorrência de alguma destas desordens. Malignidades: foi observado maior número de casos de linfoma entre os pacientes que receberam antagonistas de TNF. Malignidades, algumas fatais, foram relatadas entre crianças e adolescentes que foram tratados com agentes bloqueadores de TNF. A maioria dos pacientes estava tomando concomitantemente imunossupressores. Casos muito raros de linfoma hepatoesplênico de células T, foram identificados em pacientes recebendo adalimumabe. O risco potencial com a combinação de azatioprina ou 6-mercaptopurina e HUMIRA® (adalimumabe) deve ser cuidadosamente considerado. Alergia: durante estudos clínicos, reações alérgicas graves foram relatadas incluindo reação anafilática. Se uma reação anafilática ou outra reação alérgica grave ocorrer, a administração de HUMIRA® (adalimumabe) deve ser interrompida imediatamente e deve-se iniciar o tratamento apropriado. Eventos hematológicos: raros relatos de pancitopenia, incluindo anemia aplástica. A descontinuação da terapia deve ser considerada em pacientes com anormalidades hematológicas significativas confirmadas. Insuficiência cardíaca congestiva: casos de piora da ICC também foram relatados. Processos autoimunes: pode ocorrer a formação de anticorpos autoimunes. Se um paciente desenvolver sintomas que sugiram Síndrome lúpus-símile, o tratamento deve ser descontinuado. Uso em idosos: a frequência de infecções graves entre pacientes com mais de 65 anos de idade tratados com HUMIRA® (adalimumabe) foi maior do que para os sujeitos com menos de 65 anos de idade. Deve-se ter cautela quando do tratamento de pacientes idosos. Uso na gravidez: este medicamento só deve ser usado durante a gravidez quando, na opinião do médico, os benefícios potenciais claramente justificarem os possíveis riscos ao feto. Mulheres em idade reprodutiva devem ser advertidas a não engravidar durante o tratamento com HUMIRA® (adalimumabe). A administração de vacinas vivas em recém-nascidos expostos ao adalimumabe no útero não é recomendada por 05 meses após a última injeção de adalimumabe da mãe durante a gravidez. **Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista.** Uso na lactação: recomenda-se decidir entre descontinuar o tratamento com HUMIRA® (adalimumabe) ou interromper o aleitamento, levando em conta a importância do medicamento para a mãe. O aleitamento não é recomendado por pelo menos 05 meses após a última administração de HUMIRA® (adalimumabe). **Interações Medicamentosas:** metotrexato: não há necessidade de ajuste de doses de nenhum dos dois medicamentos. Outras: o uso concomitante de HUMIRA® (adalimumabe) e outros DMARDs (por exemplo, anacinra e abatacepte) não é recomendado. Vacinas vivas não devem ser administradas concomitantemente a HUMIRA® (adalimumabe). Não foram observadas interações com DMARDs (sulfassalazina, hidroxicloroquina, leflunomida e ouro parenteral), glicocorticoides, salicilatos, antiinflamatórios não esteroidais ou analgésicos. **Reações Adversas:** infecções no trato respiratório, leucopenia, anemia, aumento de lipídeos, dor de cabeça, dor abdominal, náusea, vômito, elevação de enzimas hepáticas, rash, dor músculo-esquelética, reação no local da injeção, infecções, neoplasia benigna, câncer de pele não-melanoma, trombocitopenia, leucocitose, hipersensibilidade e alergia, urticária, insuficiência renal, alterações da coagulação e distúrbios hemorrágicos, teste para autoanticorpos positivo, linfoma, neoplasia de órgãos sólidos, melanoma, púrpura trombocitopênica idiopática, arritmia, insuficiência cardíaca congestiva, oclusão arterial vascular, tromboflebite, aneurisma aórtico, doença pulmonar obstrutiva crônica, pneumopatia intersticial, pneumonite, pancreatite, aumento da bilirrubina, esteatose hepática, rabdomiólise, lúpus eritematoso sistêmico, pancitopenia, esclerose múltipla, parada cardíaca, cicatrização prejudicada. **Reações adversas de pós-comercialização:** diverticulite, linfoma hepatoesplênico de células T, leucemia, carcinoma de células de Merkel (carcinoma neuroendócrino cutâneo), anafilaxia, sarcoidose, doenças desmielinizantes, acidente vascular cerebral, embolismo pulmonar, derrame pleural, fibrose pulmonar, perfuração intestinal, reativação da hepatite B, insuficiência hepática, hepatite, vasculite cutânea, Síndrome de Stevens-Johnson, angioedema, novo aparecimento ou piora da psoríase, eritema multiforme, alopecia, Síndrome lúpus-símile, infarto do miocárdio, febre. **Posologia: ADULTOS:** Artrite Reumatoide, Artrite Psoriásica, Espondilite Anquilosante, Espondiloartrite Axial Não Radiográfica: a dose para pacientes adultos é de 40 mg, administrados em dose única por via subcutânea, a cada 14 dias. Doença de Crohn: início do tratamento - Semana 0: 160 mg por via subcutânea; Semana 2: 80 mg; Manutenção do tratamento: a partir da Semana 4, 40 mg a cada 14 dias. Colite Ulcerativa ou Retocolite Ulcerativa: início do tratamento - Semana 0: 160 mg por via subcutânea; Semana 2: 80 mg; Manutenção do tratamento: 40 mg a cada 14 dias. Psoríase: para pacientes adultos é de uma dose inicial de 80 mg por via subcutânea, seguida de doses de 40 mg administradas em semanas alternadas, começando na semana seguinte à dose inicial. Hidradenite Supurativa: 160 mg inicialmente, no Dia 1, seguida de 80 mg duas semanas depois, no Dia 15 (administrado em duas injeções de 40 mg em um dia). Duas semanas depois (Dia 29) continuar com uma dose de 40 mg por semana. Uveíte: 80 mg inicialmente, seguida de 40 mg em semanas alternadas, começando na semana seguinte à dose incial. **PEDIÁTRICOS:** Artrite Idiopática Juvenil Poliarticular: para pacientes entre 02 e 12 anos a dose é de 24 mg/m2 de ASC, até uma dose única máxima de 20 mg para pacientes com idade entre 02 a < 04 anos e 40 mg para pacientes entre 04 e 12 anos, por via subcutânea a cada 14 dias. Para pacientes com idade superior a 13 anos a dose é de 40 mg, administrados em dose única por via subcutânea, a cada 14 dias. Doença de Crohn: para pacientes pediátricos com 06 anos ou mais e com peso corporal menor que 40 kg, a dose inicial (Dia 01) é 80 mg por via subcutânea (duas injeções de 40 mg em um dia), seguidas por 40 mg após duas semanas (Dia 15). A dose de manutenção (Dia 29) para doença de Crohn ativa com intensidade grave é de 20 mg, a cada 14 dias e para doença de Crohn ativa com intensidade moderada é de 10 mg, a cada 14 dias. Para pacientes pediátricos com 06 anos ou mais e com peso corporal maior ou igual à 40 kg, a dose inicial (Dia 01) é 160 mg (quatro injeções de 40 mg em um dia ou duas injeções por dia por dois dias consecutivos), seguidas por 80 mg após duas semanas (Dia 15). A dose de manutenção (Dia 29) para doença de Crohn ativa com intensidade grave é de 40 mg, a cada 14 dias e para doença de Crohn ativa com intensidade moderada é de 20 mg, a cada 14 dias. O paciente pediátrico com doença de Crohn, cuja posologia for ≥ 40 mg de adalimumabe deve utilizar a apresentação em seringas preenchidas ou caneta. VENDA SOB PRESCRIÇÃO MÉDICA. Importado por: AbbVie Farmacêutica Ltda - Av. Guido Caloi, 1935, 1º andar, Bloco C - São Paulo - SP - CNPJ: 15.800.545/0001-50. AbbVie Line: 0800 022 2843. BU52.

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Adress: Av. Brigadeiro Faria Lima, 2391 10º andar – conj. 102 CEP 01452-000
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Exemples

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Ribeiro Jr U, Cecconello 1, Safatle-Ribeiro AV, Ziberstein B, Pinotti HW. Squamous cell carcinoma of the esophagus and multiple primary tumors of the upper aerodigestive tract. Arq Gastroenterol 1999; 36:195-200.
Books and other monographs (list all authors/editors and do not use "et al."):
Castell DO, Richter JE, editors. The esophagus. 3. ed. Philadelphia: Lippincott Williams & Wilkins; 1999.
Chapter in a book (list all authors and do not use "et al."):
Cohen RV, Roll S, Schaffa TD. Herniosplatia incisional videolaparoscópica. Rio de Janeiro: Reichmann & Affonso; 1999. p. 127-31.

Dissertations and thesis

Cecconello 1. Contribuição ao conhecimento e histopatologia do colédoco. [Dissertação de mestrado]. São Paulo: Instituto Brasileiro de Estudos e Pesquisas de Gastroenterologia - IBEPEGE; 1979,
Published proceedings paper (list all authors and do not use "et al."):
Nasi A, Cenatti A, Falcão A, Cecconello 1, Sallum RAA, Pinotti HW. Evaluation of lower esophageal sphincter pressure by two variant techniques in patients with endoscopic reflux esophagitis [abstract]. In: Meeting abstracts if the Esophagus ´98: 7th World Congress of the International Society for Diseases of the Esophagus; 1998; Montreal, Canada. Can J Gastroenterol 1998; 12 Suppl. B:93 B. [Abstract 278].

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Illustrations - Photographs, graphics and drawings should be sent sharp, glossy, black-and-white or color photographic prints, usually 127 mm x 178 mm. Each illustration should have a label pasted on its back indicating its number, the first author´s name and the article´s title. Illustrations in color only if the author pays for the extra cost.

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EDITORIAL

ROBERTO LUIZ KAISER JUNIOR[1]

Although the etiology of Crohn's disease is unknown, there is a consensus that the immune system becomes ineffective, exacerbating the body's response to luminal antigens with consequent damage to the intestinal mucosa[1]. Therapy has improved over the past several years and is based on anti-inflammatory drugs, immunosuppressants and biological agents. Many patients do not respond to any treatment, and in this scenario hematopoietic stem cell transplantation (HSCT) may be an alternative. The criteria for transplant are speculative, but this treatment can be indicated for patients who are refractory to available drug treatments, have active disease and repeated episodes, and face imminent risk of surgery that would lead to the placement of a ostomy, amputation, or mutilation.

Hematopoietic stem cell transplantation is an established procedure used to treat blood disorders, hereditary and autoimmune diseases, and in oncohematology[2]. As an autoimmune disorder, Crohn's disease is among the disorders for which this procedure in indicated. The aim of autologous transplant is to eradicate autoreactive T lymphocytes and thus promote new programming of the patient's immune system after bone marrow recovery. In allogeneic transplant, the patient's immune and genetic systems are replaced with those of the donor. Both modalities have been described in the literature to treat Crohn's disease since 1993.

The first report was of a patient who had Crohn's disease for 20 years and developed non-Hodgkin lymphoma. After treatment with autologous HSCT this patient achieved complete remission of both diseases. Similar results were observed in several patients with Crohn's disease and oncohematologic diseases using both types of HSCT. Several series of cases and isolated reports have been published on the treatment of Crohn's disease with autologous HSCT since 2003[3]. In Brazil, the first report dates from 2013[4].

The ASTIC trial published last year in JAMA by Hawkins et al. was interpreted as a failure of autologous hematopoietic stem cell transplant compared to the standard of care[5]. However, in reality, ASTIC did not compare transplant to standard of care; ASTIC compared two experimental treatments based on high-dose cyclophosphamide. At higher doses, patients develop cardiac dysfunction and hepatic sinusoid obstructive syndrome. Finally, ASTIC used a complex multifaceted primary endpoint that included all of the following: CDAI < 150, no active treatment, endoscopic remission, and radiologic remission. This endpoint has never been defined or attempted in any prior study[6,7].

Finally, we can also provide new hope for patients so that even if they relapse, they can be treated as naive patients and have good response to biological medications.

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1. Head of the Coloproctology Residency Program at the Kaiser Hospital and Beneficência Portuguesa Hospital in São José do Rio Preto, SP, Brazil

Correspondence to: Rua XV de Novembro, 3975 - São José do Rio Preto, SP, Brasil. CEP 15015-110.

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ORIGINAL ARTICLE

FOOD INTAKES OF ADULT PATIENTS WITH CROHN'S DISEASE

Raquel Rocha[1], Fernanda Gomes Coqueiro[1], Mirella Brasil Lopes[1], Vanessa Rosa Oliveira[1], Naiade Silveira Almeida[1], Genoile Oliveira Santana[2]

ABSTRACT

Aim: This study aims to evaluate food intake in a group of adult patients with Crohn's disease (CD). Patients and Methods: We evaluated 60 patients over 18 years of age with CD. Dietary intake was evaluated using two 24-hour recalls. The Estimated Average Requirements (EAR) were used as references to ensure adequate dietary intake of energy, protein, total fat, calcium, phosphorus, magnesium, potassium, vitamin D, vitamin K and vitamin C. Results: The CD patients were equally distributed between the sexes, with a mean age of approximately 37 years (SD = 8.2); most were in remission (75.0%). Their energy and lipid intake was low (1,694.6 ± 582.7 kcal/day and 7.6 ± 18.8 g/day, respectively). Intake of vitamins D and K and calcium, potassium, and magnesium was below the EAR values in most patients, but without statistically significant association with disease activity ($p > 0.05$). Few patients (6.6%) used calcium or vitamin D supplements or multivitamins. Conclusion: Poor dietary intake makes proper nutritional assessment and monitoring of these patients difficult.

Keywords: Crohn's disease; Dietary intake.

INTRODUCTION

Malnutrition is reported in 20% to 85% of patients with Crohn's disease (CD), and despite recent research showing an increase in the frequency of overweight patients in this population, nutritional deficiencies occur even in individuals with adequate or elevated BMI[1-4]. Many studies on food intake have evaluated the effect of developing inflammatory bowel disease (IBD)[5-6], but these vastly outnumber research assessing dietary intake by outpatients with CD[7-9]. The objective of this study was to evaluate food intake in a group of adult patients with CD.

PATIENTS AND METHODS

This cross-sectional study included 60 patients 18 years of age and above with a clinical, radiological, endoscopic, and histological diagnosis of DC. Patients were selected from the Professor Edgar Santos University Outpatient Hospital Complex Gastroenterology service and the Roberto Santos General Hospital in Salvador, Bahia, Brazil, from July 2012 to January 2013.

The following patients were excluded: those with a history of other diseases that cause changes in bone metabolism (chronic renal failure, chronic obstructive pulmonary disease, thyroid disease, liver disease, lupus erythematosus) or cancer; pregnant, menopausal or post-menopausal women or those using estrogen therapy; and patients with limitations impacting anthropometry.

The Harvey-Bradshaw index[10] was used to determine disease activity. Age at diagnosis, location, and disease behavior were described using the Montreal classification[11]. Data regarding the duration and extent of disease and drug treatment were collected from the medical records.

Patient height (in cm) and weight (in kilograms) were measured in duplicate using a scale (Filizola) with a capacity of 150 kg and an interval of 100 g with a stadiometer, coupled with a 0.5 cm enlarged scale[12]. Patient BMI was calculated using these data and rated according to the World Health Organization[13].

1. Department of Sciences of Nutrition, School of Nutrition, Federal University of Bahia, Brazil.
2. Gastroenterology Unit, University Hospital Professor Edgard Santos, Federal University of Bahia, Brazil.
Correspondence to: Avenida Araújo Pinho, 32 - Salvador, BA, Brasil. CEP: 40110-150. E-mail: raquelrocha2@yahoo.com.br

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ASSESSMENT OF FOOD INTAKE

The 24-hour diet recall (R-24h) was applied to assess the participants' food intake. Each participant completed two R-24h surveys on different days of the week. A photo album of food was used to assist in describing portions. DietWin Personal software, version 1.0 (DietWin, Porto Alegre, RS, Brazil) was used to calculate the participants' individual average intake of calories, protein, total fat, calcium, phosphorus, magnesium, potassium, vitamin D, vitamin K, and vitamin C. The limits proposed by the Dietary Reference Intakes (DRI): Estimated Average Requirements (EAR) suggested by the Institute of Medicine were used as references to ensure adequate dietary intake[14-16]. Of the 60 patients, 11 responded to only one of the R-24h surveys and were therefore excluded from this analysis.

STATISTICAL ANALYSIS

Verification of the normal distribution of the variables was performed using the Kolmogorov-Smirnov test. Descriptive analyses of the sample proportions were used for categorical variables and the mean (mean ± standard deviation) was used for continuous variables. Categorical variables were analyzed using the Fisher's exact test, and continuous variables were analyzed using the Mann-Whitney test.

The Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA, version 20.0) was used to tabulate and analyze the data. Differences were considered statistically significant when the probability of type 1 error was <0.05.

ETHICAL ASPECTS

This paper was submitted to the research ethics committee at the Professor Edgar Santos University Hospital Complex as opinion No. 117/2011. All participants gave informed consent after being informed about the procedures they would undergo and the objectives of the study. The test results were delivered to patients in the study in addition to nutritional counseling.

We evaluated 60 patients with CD, equal numbers of men and women, with a mean age of approximately 37 years (SD = 8.2). Most of the patients were in remission (75.0%) and showed simultaneous involvement of the ileum and colon segments (53.3%). Seventy percent of the patients did not have complications such as fistulas, fissures or abscesses at the time of the assessment, but 51.7% of the patients had more aggressive forms of the disease, penetrating or stenotic at 21.7% and 30.0%, respectively (Table 1).

Most (55.0%) of the patients were eutrophic. However, excess weight was observed in a high proportion of the study population (30.0%), and malnutrition was observed in 15.0% of the patients.

Table 1. Demographic and clinical characteristics in patients with Crohn's disease.

Characteristic	**n = 60**
Age (years), mean ± SD	37.4 ± 8.2
Gender, n (%)	
Male	30 (50.0)
Female	30 (50.0)
Age at diagnosis, n (%)	
< 17 years	04 (6.7)
17–40 years	47 (78.3)
> 40 years	09 (15.0)
Disease duration (years), mean ± SD	6.8 ± 5.3
Disease activity, n (%)	
Remission	45 (75.0)
Mild/moderate activity	12 (20.0)
Severe activity	03 (5.0)
Location of disease, n (%)	
Terminal ileum	9 (15.0)
Colon	19 (31.7)
Ileocolon	32 (53.3)
Behavior of Crohn's disease, n (%)	
Non-stricturing, non-penetrating	29 (48.3)
Stricturing	13 (21.7)
Penetrating	18 (30.0)
Perianal involvement, n (%)	
No	40 (66.7)
Yes	20 (33.3)
Complications, n (%)	
Fissure	06 (10.0)
Fistula	12 (20.0)

SD: standard deviation

FOOD INTAKE

The energy intake by the CD patients in the study ranged from 543.8 Kcal/day to 2,992.9 Kcal/day (median 1,631.1 Kcal/day) and lipid intake varied from 9.8 g/day to 92.5 g/day (median 45.3 g/day) (Table 2).

For vitamins D and K and the minerals calcium, potassium and magnesium, we observed consumption values below the EAR in more than 75.0% of the studied cases, reaching 100% for vitamin D. No association was found between nutrient intake and disease activity ($p > 0.05$). For protein, 10.2% of the patients presented intake below the EAR (Table 3).

Reported nutritional supplements in the dietary recall were quantified in the analysis of consumption. Only 4 patients (6.6%) used calcium supplements, vitamin D or multivitamins.

Table 2. Energy and nutrient intake by patients with Crohn's disease.

Energy and nutrient	Mean ± SD	Median	Minimum	Maximum
Energy, Kcal	1,694.6 ± 582.7	1,631.1	543.8	2,992.9
Protein, g	72.3 ± 28.7	70.7	20.7	152.5
Lipids, g	7.6 ± 18.8	45.3	9.8	92.5
Calcium, mg	493.1 ± 224.7	529.6	78.6	925.4
Phosphorus, mg	1,012.7 ± 369.1	1,033.1	292.2	1,744.4
Potassium, mg	2,363.0 ± 108.4	2,180.4	706.5	5,313.2
Magnesium, mg	246.0 ± 108.4	229.9	71.6	549.4
Vitamin D, mcg	4.24 ± 9.7	1.38	0.0	59.6
Vitamin K, mcg	27.5 ± 58.1	5.9	0.3	327.4
Vitamin C, mcg	293.5 ± 597.0	81.1	6.5	3,248.6

SD: standard deviation; Kcal: kilocalorie; Mann-Whitney test

Table 3. Energy and nutrient intake by patients with Crohn's disease, according to disease activity.

Energy and nutrient	Total N (%)	Remission N (%)	Activity N (%)	P*
Protein				
Above EAR	44 (89.8)	33 (89.2)	11 (91.7)	1.000
Below EAR	5 (10.2)	4 (10.8)	1 (8.3)	
Calcium				
Above EAR	3 (6.1)	2 (5.4)	1 (8.3)	1.000
Below EAR	46 (93.9)	35 (94.6)	11 (91.7)	
Phosphorus				
Above EAR	42 (85.7)	31 (83.8)	11 (91.7)	0.665
Below EAR	7 (14.3)	6 (16.2)	1 (8.3)	
Potassium				
Above EAR	2 (4.1)	2 (5.4)	0 (0.0)	1.000
Below EAR	47 (95.9)	35 (94.6)	12 (100)	
Magnesium				
Above EAR	11 (22.4)	8 (21.6)	3 (25.0)	1.000
Below EAR	38 (77.6)	29 (78.4)	9 (75.0)	
Vitamin D				
Above EAR	0 (0.0)	0 (0.0)	0 (0.0)	
Below EAR	49 (100)	37 (100)	12 (100)	
Vitamin K				
Above EAR	2 (4.2)	1 (2.8)	1 (8.3)	0.441
Below EAR	46 (95.8)	35 (97.2)	11 (91.7)	
Vitamin C				
Above EAR	29 (59.2)	21 (56.8)	8 (66.7)	0,738
Below EAR	20 (40.8)	16 (43.2)	4 (33.3)	

EAR: Estimated Average Requirements; *Fisher's exact test

The intake of energy, lipids, and micronutrients (vitamins and minerals), regardless of disease activity, is low in most patients with CD.

In the Canadian study conducted by Aghdassi et al.[7], the food intake of outpatients with CD was not associated with disease activity or BMI, findings similar to those of our study, but they had higher energy and lipid intake. And Lim et al.[17] observed lower nutrient intake in malnourished patients with IBD, an assessment which was not conducted in our study.

In a previous study of outpatients with IBD we observed that lipids tend to be more restricted[18], which may be attributed to dietary beliefs or associations with gastrointestinal symptoms[19-22]. However, restriction of this nutrient may affect caloric intake and absorption of fat-soluble vitamins.

Other studies have also noted low micronutrient intake in this population, especially calcium, which generally is the result of the frequent restriction of dairy products among patients with IBD[23-25]. Abitibol et al.[26] evaluated the effects of supplemental therapy with calcium and vitamin D (1 g and 800 IU, respectively) in individuals with IBD aged 18 to 68, and found an increase in bone mineral density. However, although intake of calcium and vitamin D was well below the recommended values in our study population, supplemental therapy with these nutrients was infrequent. This is because the study population consists of outpatients, most of whom were in remission and may exhibit low use of corticosteroid drugs.

One limitation of this study is the sample size. In addition, a control group was not used to compare data with the healthy population.

We believe that the long term effects of restrictive diets can be harmful, and that as a consequence health professionals need training to provide more specialized nutritional care and develop nutritional education in this population.

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SPECIFIC AUTHOR CONTRIBUTIONS

Fernanda G Coqueiro, Raquel Rocha and Genoile O Santana designed and conducted the research, Fernanda G Coqueiro, Mirella B Lopes, and Vanessa R Oliveira collected the data, and Fernanda G Coqueiro and Naiade S Almeida performed the statistical analyses and wrote the paper, with all the other authors providing critical input.

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ORIGINAL ARTICLE

NOVEL THERAPEUTIC APPROACHES FOR INFLAMMATORY BOWEL DISEASES BASED ON BASIC AND PRE-CLINICAL STUDIES: AN IMMUNOLOGY EXPERIENCE

Cristina Ribeiro de Barros Cardoso[1]

ABSTRACT

Although modern approaches currently exist for management of inflammatory bowel disease, treatment is still a challenge in some refractory cases. Here we review some basic and pre-clinical strategies used by our group in an attempt to establish future therapeutic alternatives for Crohn's disease or ulcerative colitis.

INTRODUCTION

The obscure field of inflammatory bowel diseases (IBD) is based on immunological mechanisms which, when associated with genetic factors and environmental challenges, initiate and perpetuate inflammation in susceptible individuals[1]. The deregulated inflammatory responses that postpone the breakdown of mucosal tolerance are responsible for destruction of gut tissues, augmented bacteria translocation from the lumen, and induction of innate or adaptive immune responses that together lead to uncontrolled reactions and disease chronification.

The regulation of these responses that culminate in IBD is not an easy task since, as we have stated in a previous review study[2], they depend on a very intricate net of genes and production of inflammatory mediators resulting from extensive immune deregulation and altered patient microbiota, also known as dysbiosis[3].

A wide range of treatments is currently available and most aim to control exacerbated inflammatory responses in order to maintain patients in prolonged disease remission or avoid undesirable relapses (also reviewed by our group in[4]). Nevertheless, many patients are resistant or do not respond adequately to these therapies, which may be expensive and inefficient, thus leading to disease complications and worsening of the patient's overall condition.

Against this complex backdrop, in recent years we have been working to understand the basic immunological mechanisms of IBD as well as to develop novel therapeutic approaches to controlling intestinal inflammation. This work focuses on clinical (data not yet published) and mainly pre-clinical studies which use experimental mice models of IBD as described below.

DEXTRAN SODIUM SULFATE (DSS) AND TRINITROBENZENESULFONIC ACID (TNBS) MODELS OF INTESTINAL INFLAMMATION

Studies of IBD pathogenesis as well as evaluation of novel therapies or drug formulations for Crohn's disease (CD) or ulcerative colitis (UC) require the use of animal models, especially rodents, which spontaneously develop these diseases or are susceptible to them by artificial induction[5].

In our laboratory, experimental and pre-clinical studies are performed using two specific chemical models to induce gut inflammation in which mice are exposed to dextran sodium sulfate (DSS) or trinitrobenzenesulfonic acid (TNBS). DSS is a chelating agent administered to the mice in drinking water which causes rupture of the intestinal epithelia and inflammatory responses in the colon characterized by intense infiltration of leukocytes, abscesses, ulcers, depletion of goblet cells, and mixed CD4 T helper (Th) cytokine responses. These reactions may mimic immunological responses of both CD or UC depending on the mice lineage, dose, or period of exposure to the drug[5,6]. The TNBS acute model, on the other hand, is related to a typical Th1 immune reaction

1. School of Pharmaceutical Sciences of Ribeirão Preto - University of São Paulo, Ribeirão Preto, SP. Department of Clinical Analysis, Toxicology and Food Sciences.

Correspondence to: Av. do Café, s/n, Ribeirão Preto, SP, Brasil, CEP: 14040-903. E-mail: cristina@fcfrp.usp.br

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(as in CD) with notable IFNγ production and transmural inflammatory infiltrate in the colon. Skip lesions are induced by an intrarectal enema of TNBS. This hapten is instilled after dilution in ethanol, causing disruption of the epithelial barrier and permitting immune reactivity to the conjugates of hapten self-proteins in the gut[5,7]. We used these different approaches to experimental intestinal inflammation, and below we summarize two of the studies our group has performed to test novel therapeutic alternatives for IBD.

IBD TREATMENT BASED ON CELLULAR THERAPY

One of the first studies conducted by our group involved evaluating cellular transplantation for IBD, since this therapy has been used as an alternative for treating immune mediated diseases[8]. Nevertheless, the mechanisms by which this treatment could work were still unknown, especially in IBD. Therefore, we induced experimental intestinal inflammation in BALB/c mice via a TNBS enema and these animals were subsequently subjected to high-dose immunosuppression with cyclophosphamide as a pre-transplant conditioning treatment to cause immune ablation and elimination of all putative pathogenic cell clones.

The mice then received syngeneic hematopoietic stem cell transplantation (HSCT) and were followed for 60 days (Figure 1). The results showed notable improvement of the disease, mainly mediated by cyclophosphamide immunosuppression. The infused bone marrow cells were found in the colon of recipient mice in the short and long term periods post-transplant, indicating that these cells were able to migrate to the inflamed tissue.

In addition, there was reduced accumulation of CD4 and CD8 leukocytes in the colons of the transplanted mice, along with a decrease in inflammatory cytokines that characterize human IBD. Most interestingly, one of the main findings of this study was the therapeutic effect of cyclophosphamide alone, regardless of cellular transplantation. However, as expected in patients, HSCT was essential for avoiding early mortality in high-dose immunosuppressed recipients, indicating that this therapy could in fact be an option for CD or UC, although accelerating immune reconstitution with bone marrow cells has been shown to be essential for a successful approach[9].

In line with these results, we also studied the effects of total body irradiation (TBI) followed by bone marrow transplant in the control of intestinal inflammation (Figure 1), since radiotherapy may be used for patient conditioning before HSCT for some hematological disorders. In this work colitis was induced using the hapten TNBS in BALB/c mice. TBI was effective in controlling gut inflammation, as demonstrated by the reduced percentage of leukocytes infiltrated in the intestine, decreased inflammatory cytokine production, and restored mucus production.

Nevertheless, mice which were treated with TBI alone and not with HSCT did not recover weight gain, and presented extremely higher mortality post-therapy, probably due to a delay in immune system reconstitution. We therefore indicate radiotherapy as an important option for control of experimental intestinal inflammation, although bone marrow cell transplant is essential to a better outcome for colitis and control of the prejudicial side effects of this therapy[10].

PROSPECTS FOR NEW IMMUNE MODULATORY DRUGS: THE EXPERIENCE WITH *AEDES AEGYPTI* SALIVA

Besides studies with cellular therapy, our efforts have also been directed at discovering novel drug formulations for IBD treatment. One example is a recently published study by our group[11] which investigated immune modulatory molecules in the saliva of arthropods. It is well known that these invertebrates possess an important pharmacological arsenal in their saliva which they use to facilitate blood sucking and transmission of diseases[12].

We isolated salivary gland extract from the *Aedes aegypti* mosquito and used these compounds to treat mice with established intestinal inflammation induced by DSS (Figure 2). Notable improvement was seen in the clinical signs of the disease in the mice that received the saliva extract along with a reduction in circulating lymphocytes, indicating control of immunity without detectable toxic effects. Interestingly, this clinical improvement was accompanied by a reduction in inflammatory mediators in the colon responsible for worsening of colitis, such as IFN-γ, TNF-α, IL-1β, and IL-5 cytokines. Accordingly, we also observed reduced inflammatory infiltrate in the gut biopsies.

Most importantly, the saliva treatment in the acute phase of the disease was able to control colitis relapse, mimicked by a late re-exposure to the trigger DSS. Together, these results pointed to the mosquito saliva as an important source of

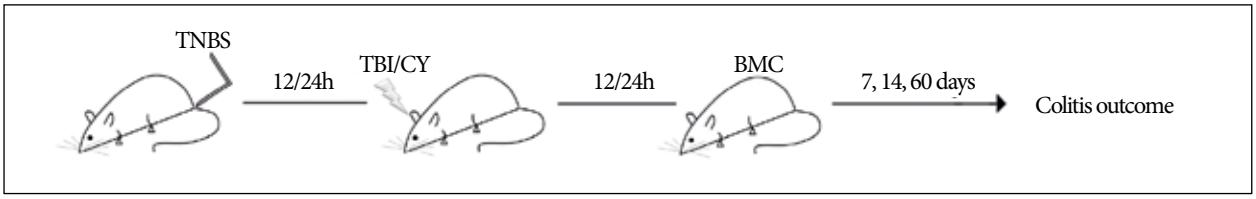

Figure 1. Protocols of pre-clinical studies based on hematopoietic stem cell transplantation to treat colitis. Mice were subjected to colitis induction by infusion of trinitrobenzenesulfonic acid (TNBS), followed by immunosuppression with total body irradiation (TBI, 12h after TNBS) or cyclophosphamide (CY, 24h after TNBS). Transplant of bone marrow cells (BMC) was performed 12h or 24h after TBI or CY administration, respectively, and mice were followed for 7, 14, or 60 days to evaluate colitis outcome.

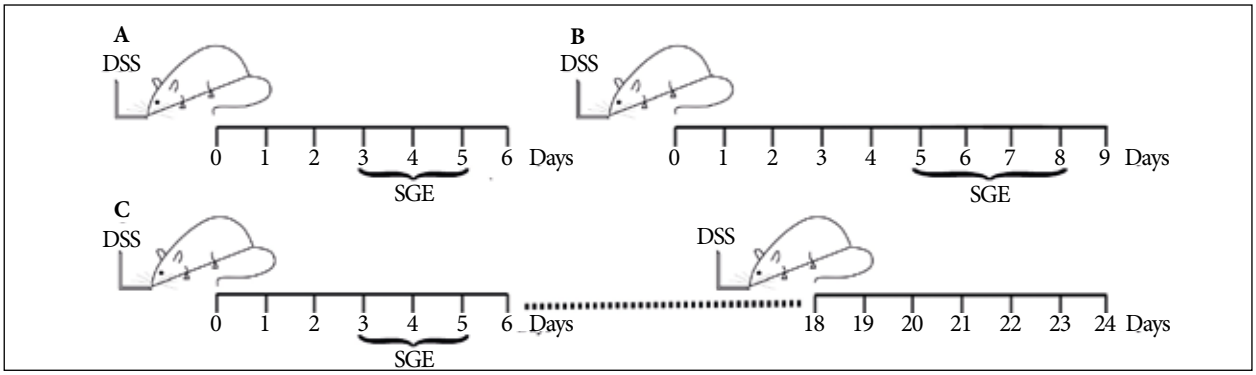

Figure 2. Protocols of the pre-clinical study for treatment of experimental colitis with *Aedes aegypti* salivary gland extract (SGE). Mice were subjected to colitis induction by drinking water containing dextran sodium sulfate (DSS) for 6 (A) or 9 (B) days, along with treatment with SGE on days 3–5 or 5–8, respectively. In the chronic relapse model, animals were exposed to DSS two times, with a 12–day interval between the two periods of colitis induction; treatment took place in the first phase, from days 3–5, as depicted in (C).

modulatory or anti-inflammatory molecules which were able to treat established intestinal inflammation. In fact, when the saliva was fractioned using high performance liquid chromatography (HPLC), we detected a specific fraction (F3) which had the capacity to control the experimental colitis.

We therefore concluded that mosquito saliva contains relevant compounds that could be used in promising therapies for IBD[11].

FUTURE DIRECTIONS

The institution of novel therapeutic approaches to IBD is a real challenge faced by clinicians and basic research. However, there are important alternatives that should be investigated in depth, such as the examples described above, and our group has been involved in a variety of strategies to address these tasks. Further and ongoing studies will focus on more specific pre-clinical and clinical studies of the effects of cellular therapy, on the neuroimmune modulation of gut mucosa, and on the effects of hormone supplementation for IBD.

Additionally, the molecules responsible for the therapeutic effects observed *in vivo* in the *A. aegypti* saliva study must be identified for further laboratorial synthesis (if possible) and large scale testing. In summary, although many pre-clinical and clinical studies are still necessary, there are encouraging data for the development of alternative treatments for these inflammatory disorders.

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REVIEW ARTICLE

THE PATHOGENESIS OF INFLAMMATORY BOWEL DISEASE

Marco Antônio Zerôncio[1]

INTRODUCTION

For many years after their initial characterization the two major phenotypes of inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD), were referred to as *diseases of unknown etiology*. In the last decade, however, much progress has been made in understanding the pathogenesis of IBD, particularly with respect to remarkable advances in the fields of genetics and microbiology.

It is at least reasonable to think that every physician who deals with IBD in regular practice should have a minimum understanding of what causes IBD whether they are involved with the basic science or not. Physicians are more than just technicians, so it is critical for these professionals to acknowledge the basic mechanisms underlying the diseases which affect the patients under their care. For instance, this familiarity allows doctors to better comprehend the relationship between IBD genetic mutations and some of their consequences, such as dysregulations of the intestinal immune system leading to chronic inflammation, and the existing links between genetics, disease phenotype and prognosis. The pathogenesis of IBD has important implications on IBD epidemiology, the relationship between IBD and other immune-mediated diseases and immune-mediated phenomena (including extra-intestinal manifestations), and response to therapies. Physicians also must be prepared to address fears and demands from patients and answer questions concerning the cause of their illnesses, individual prognoses, the possibility that their relatives may be affected by the same pathology, as well as many other relevant issues that are constantly brought up by patients.

This review highlights the most relevant aspects of IBD pathogenesis for gastroenterologists and surgeons in their daily practice with CD and UC patients. The major components of a multifactorial model of IBD pathogenesis are presented separately for didactic purposes, but we should bear in mind that they are intrinsically related, which will be evident by the end of this article.

GENETICS IN IBD

After "terminal ileitis" was described in 1932 by Crohn et al.[1], more than thirty years passed before Kirsner and Spencer observed familial aggregation in IBD[2]. Thirty-three years later in 1996, Hugot et al. showed an association between CD and chromosome 16[3]. Expanding technologies permitted the discovery of the first IBD gene (NOD2/CARD15) only five years after by Hugot[4], and a link was then established between this genetic alteration and CD located in the terminal ileum CD[5]. The first genome-wide association study (GWAS) in IBD using genome-wide single nucleotide polymorphism (SNP) chips was published in 2005 by Yamazaki et al.[6]. GWAS allowed rapid recognition of susceptible loci in complex polygenic diseases such as IBD in a highly accurate and reproducible manner. The first GWAS of IBD identified many new loci, which were consistently replicated among different studies[7]. The second IBD gene was found in 2006 by Duerr[8], identifying mutation in the IL-23 receptor (IL-23R). Only six years later, a meta-analysis identified 163 autosomal independent genetic risk loci associated with IBD (Figure 1). Of these loci, 110 conferred risk to both IBD subtypes, while 30 and 23 loci were unique to CD and UC, respectively[9]. It is likely that many other genes will be found in the near future; in fact, in the period following this publication, 38 new loci highlighting important overlap across populations have been characterized in IBD[10]. Twin and family studies of IBD have shown that there is a 26-fold risk of developing CD when a sibling already has CD, and this risk increases 9-fold for UC[11].

Since CD and UC share 110 out of 163 loci, it is not surprising that these molecular similarities may actually reflect comparable clinical scenarios, most notably in the cases of non-classified colitis. This may also indicate that these two entities could be viewed as the two major phenotypes of the same chronic inflammatory disease at the molecular level, with a common genetic core. It is interesting to note that most genetic variants that have been found in IBD as of this date

1. Inflammatory Bowel Disease Outpatient Unit, Potiguar University School of Medicine.
Correspondence to: Av. Joaquim Patrício, 2598 - Torre Azul 1901. CEP: 59161-900, Parnamirim - RN. Brasil. E-mail: zeroncio@gmail.com

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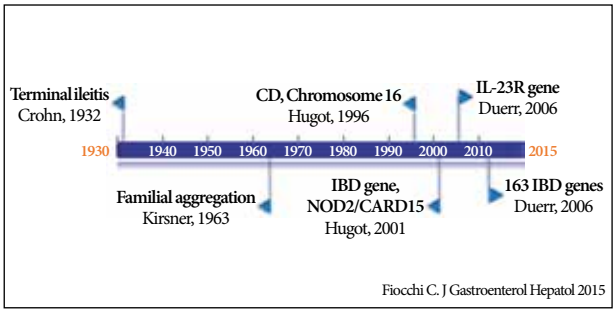

Figure 1. IBD pathogenesis timeline.

have been implicated in the regulation of the intestinal innate (e.g. NOD2, autophagy mutation ATG16L1) and adaptive (IL23R, human leukocyte antigen [HLA] locus) immune system. Aberrant genes may consequently cause unhealthy immune responses at the intestinal level. Furthermore, more than 50% of the known IBD loci overlap with those of other immune-mediated diseases such as ankylosing spondylitis, psoriasis, and primary sclerosing cholangitis[11]. This finding may explain overlapping clinical phenomena observed between IBD, ankylosing spondylitis, psoriasis, and other IBD-related chronic secondary inflammatory conditions in the context of extra-intestinal manifestations affecting joints (arthritis), skin (pyoderma gangrenosum), and eyes (uveitis). The existence of similar responses to analogous therapies (e.g. anti-TNF biologicals) in many of these diseases is also well-known. Similarly, IBD can be diagnosed as an extra-articular manifestation of chronic inflammatory articular diseases such as seronegative spondyloarthropathies[12].

Many individuals who carry risk alleles do not develop IBD, and most of these alleles only increase the total risk by a modest amount. These crucial observations lead us to believe not only that other factors may play an important role in turning a genetic predisposition into a clinically meaningful context, but also that the combination of alleles may have a relevant influence in triggering inflammation. On the other hand, very-early-onset IBD, such as IBD diagnosed before 8 years of age, can be clearly associated with certain high-risk mutations (e.g. homozygous mutations in genes for the IL-10 receptor [IL-10R] subunit proteins) with apparently less dependency on environmental factors or on the combination of alleles. These patients usually show a much more severe disease course with higher risk of complications. In contrast, it may be also true that late-onset IBD, which usually runs a less aggressive course, may be more dependent on environmental triggers[12,13].

The simple presence of a variant allele does not necessarily translate into a pathological role in disease development. Complex functional studies will probably need to address this issue in the future. What is the significance of transethnic variations of these mutations? How important are gene-gene and gene-microbiota-environment interactions? What is the exact role of adaptive immunity (HLA alleles)? How does each gene in a certain susceptibility locus play a role in this process? How can epigenetic phenomena influence the expression of these loci?[14,15] As we can see, despite the progress in recent knowledge regarding IBD genetics, many prominent questions have yet to be answered in this evolving field.

MICROBIOTA IN IBD

As mentioned previously, the majority of IBD-associated genes code for regulatory pathways which are important for intestinal immunological mucosal defense, including epithelial barrier function. On the other hand, it is well recognized that microbiota are the most abundant source of luminal antigens which have a regulatory effect on host gene expression[16]. Consequently, the role of intestinal flora has become one of the most relevant pillars in a multifactorial model for IBD pathogenesis in the last few years, the focus of intense research in this area. Many previous practical and scientific observations envisioned gut microbiota as playing a major role in IBD etiology. The diversion of the fecal stream can reduce inflammation in surgically-excluded intestinal segments in CD, and some probiotics have demonstrated some efficacy in controlling inflammation in pouchitis and in UC, while antibiotics can be effective in IBD and prevent relapse after surgery to some extent[13,16].

Dysbiosis is present in IBD and it is likely that this abnormal composition of luminal bacteria in IBD patients compromises immunological homeostasis in the gut mucosa. Many studies suggest that dysbiosis is caused by genetic and environmental factors rather than a consequence of inflammation. IBD-associated microbiota have less diversity and demonstrate great variability resulting from unstable composition over time[13]. A reduction can be seen in the Bacteroidetes and Firmicutes (*Clostridium leptum, Clostridium coccoides, Eubacterium rectale, Faecalibacterium prausnitziiand*) and increase in Proteobacteria (*Escherichia coli, Campylobacter* ssp, *Fusobacterium*). This shift causes decreased production of butyrate by Bacteroidetes and Firmicutes; this important microbial metabolite is used as an energy source by host enterocytes and colonocytes. Furthermore, butyrate possesses anti-inflammatory properties via stimulating differentiation of regulatory T cells (Treg), which may be essential for the mucosal inflammatory balance. In contrast, increases in Gram-negative Proteobacteria, a phylum that includes many species which are pathogenic to humans, may create a pro-inflammatory status in the human gut[16].

Toll-like receptors (TLR) are innate immune sensors represented by molecules located in the intestinal epithelial barrier which function as an interface between the gut microbiota and the immune system. Genetic variation within the TLR genes in IBD may impede adequate response to luminal bacterial antigens and result in altered susceptibility to infections and inflammation. Defects in TLR protein structure may influence ligand recognition and mucosal immune tolerance, leading to immune dysregulation in IBD. This is further evidence of how microbiota in conjunction with individual genetic mutations may contribute to inducing a pro-inflammatory status in patients with IBD[17].

MULTIFACTORIAL MODEL OF IBD PATHOGENESIS

Despite this progress in genetic studies, the most acceptable hypothesis for the pathogenesis of IBD is that it develops from a complex interaction resulting from an aberrant immune response from a genetically susceptible host to luminal microbial antigens with the participation of environmental factors[13] (Figure 2). Of the 163 IBD loci mentioned above, only 13.6% and 7.5% explained disease variances in CD and US, respectively[5]. It is therefore increasingly clear that a multifactorial model of IBD pathogenesis exists, since genetics and bacteria individually do not explain the full existence of IBD. Other components which are principally environmental in nature certainly need to be taken into account. In fact, some authors believe that susceptibility to IBD is *mainly* determined by environmental factors which remain largely unknown[11]. Some researchers have dubbed this concept "hidden unexplained heritability"[14] and others call it the "exposome[5]." Epidemiological data shows that the prevalence of IBD is increasing worldwide in recent decades, a fact that cannot be explained by genetics alone and reinforces this theory.

As expected, one of the elements cited most frequently as possible environmental triggers in IBD pathogenesis is diet. There are indications that food intake may significantly modulate disease onset and activity by influencing the composition of the microbiota. High vegetable intake has been associated with decreased risk of UC, while greater intake of fiber and fruit is associated with decreased risk of CD. Conversely, a "Westernized" diet rich in animal fat and protein and low in fiber has been strongly correlated with IBD. High intake of carbohydrates, starch, and refined sugar has been linked with development of CD. Despite these observations, there is great uncertainty in drawing conclusions on the role of diet in IBD due to considerable variabilities in study design. As a result, no formal dietary guidelines can be advocated today for patients with IBD[18].

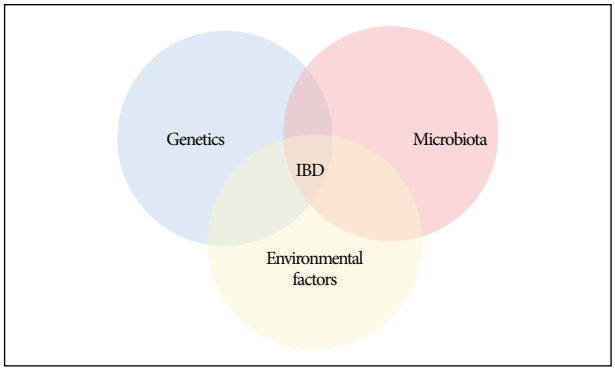

Figure 2. Multifactorial model of IBD pathogenesis.

Possible complementary environmental factors are pollution, urbanization, drugs, stress, hygiene, chemicals, smoking, and food additives[14,19], but all lack solid evidence of their exact mechanism in IBD etiology at present. We are sure to witness exciting efforts by scientists to unravel the role these components play in IBD pathogenesis in the future.

CONCLUSION

IBD is a chronic inflammatory condition primarily affecting the intestinal tract with possible involvement of other organs and tissues. Intense research in recent years has permitted a better understanding of the major pathogenic mechanisms of this disease in a multifactorial model involving altered immune genetic function and gut microbes, with very probable participation of environmental factors. Learning about the relevant biological pathways that ultimately lead to the development of IBD in susceptible individuals may help define efficient targeted therapies in years to come.

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INFLAMMATORY BOWEL DISEASE AND VITAMIN D

Ricardo de Alvares Goulart[1], Sandra Maria Barbalho[2,3]*, Marcelo Dib Bechara[2], Rodrigo Galhardi Gasparini[1], Antonely de Cássio Alves de Carvalho[4], Karina Quesada[2]

ABSTRACT

Background: Inflammatory bowel diseases (IBD) refer to an association with multiple pathogenic factors such as environmental modifications, genetic susceptibility, abnormal gut microbiota, and imbalance in the homeostasis of the immune response, as well as host genotype. These chronic inflammatory processes may be related to different components of the mucosal immune system such as the intestinal epithelial cells, innate lymphoid cells, macrophages, monocytes, neutrophils, dendritic cells, T and B cells, and chemical mediators released by these cells including cytokines and chemokines. Studies have shown that vitamin D may play an important role in the inflammatory process and in IBD. Objective: The objective of this review was to show some aspects of vitamin D and its role in inflammatory processes. Discussion: Vitamin D may be related to the immune system in different manners including gut barrier function, antigen presentation, antigen response, antimicrobial peptide synthesis, and regulation of adaptive and innate immunity. It may help improve macrophage responses and synthesis of antimicrobial proteins such as cathelicidins, and is related to downregulation of the synthesis of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukins (IL-1, IL-6, and IL-8). The interaction between this vitamin and its receptor interferes in the function of T-lymphocytes and cytokine patterns such as IL-2 and interferon γ (IFN-γ) and improves the Th-2 (T helper-2) cell response. These findings are corroborated by many recent studies which have shown that vitamin D deficiency may be a risk factor for the onset and evolution of gut inflammation. Nevertheless, many studies are still necessary to clarify how this vitamin may act in preventing, treating, or maintaining remission of IBD.

Keywords: Vitamin D, Inflammatory Bowel Disease, Inflammation.

INTRODUCTION

Inflammatory bowel disease (IBD) is a condition resulting from a chronic and persistent intestinal inflammation process, and mainly includes ulcerative colitis (UC) and Crohn's disease CD). Both diseases are related to the disruption of the mucosal immune balance[(1)].

Vitamin D has been associated with immune response and gastrointestinal function and is a fat soluble steroid hormone known mainly for the role it plays in regulating bone remodeling and metabolism based on control of intestinal calcium absorption. It appears in two different forms: ergocalciferol (vitamin D2) produced by plants and fungus, or cholecalciferol (vitamin D3: 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), which is synthesized in the skin when 7-dehydrocholesterol is irradiated with ultraviolet light. Besides endogenous production, this vitamin can be obtained from the diet (Figure 1)[(2-4)].

For most people, skin production is the main source of vitamin D and may be complemented to a lesser degree by diet and supplemental sources. The most important dietary sources of vitamin D include oily fish, egg yolk, and supplemented food. Authors have shown that 5 μg/day of this vitamin is needed from birth to 50 years of age, increasing to 10 μg/day in individuals 50–70 years, and 15 μg/day in individuals over 70 years old [(3-5)].

Besides its role in bone metabolism, many studies suggest that vitamin D is also associated with several cellular

1. Medical Doctor, University Hospital - ABHU – UNIMAR.
2. PHD, Medical School of Marília, UNIMAR.
3. Food Technology School, Marília - SP.
4. Medical Doctor, Diagnostic Center (CMD), Ibaiti - PR.

Correspondence to: Magaly Department of Biochemistry and Pharmacology, School of Medicine, University of Marília. Av. Higino Muzzi Filho, 1001, Marília, SP, Brasil. CEP 15525-902. E-mail: smbarbalho@gmail.com

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processes such as cell differentiation and proliferation, hormone secretion, and a number of diseases including immune responses such as asthma, rheumatoid arthritis, and IBD. As seen in Figure 1, the active form of this vitamin may interact with immune cells and in the macrophages, leading to the suppression of inflammation by reducing the production of interleukin-6 (IL-6), IL-12 and IL-23[2,6-12].

Literature findings show that vitamin D deficiency is increasing worldwide and affects between 30 to 50% of adults and children; this could profoundly influence the incidence and progression of IBD[1-2,13,14]. In light of this situation, our manuscript intends to bring a review of current evidence linking IBD and vitamin D.

METHODS

This review was based on a survey of articles linking vitamin D and IBD. Databases such as Pubmed, PMC, Medline, Scielo, Science Direct, and Lilacs were consulted and a retrospective search was carried out to identify relevant studies involving humans and animal models.

IBD: AN OVERVIEW

IBD comprises a complex chronic remittent or progressive inflammation process that affects the gastrointestinal tract. Its primary conditions, CD and UC, have been increasing over the past 50 years. The incidence of CD is 50 to 200 individuals per 100,000 people and UC affects 120-200 individuals per 100,000 people each year. Both conditions are polygenic multifactorial autoimmune conditions that share similar characteristics such as genetic predisposition, risk factors and, clinical, endoscopic and histological patterns, and may differ, for example in the area of the gastrointestinal tract that is affected[2, 15-20].

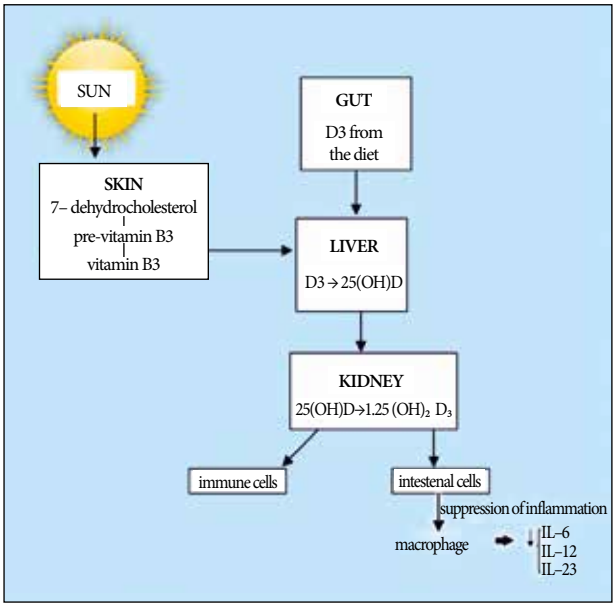

Figure 1. Metabolism of Vitamin D: This vitamin may be synthetized by conversion of 7-dehydrocholesterol present in the skin through exposure to sunlight's ultraviolet B (UVB) rays, or obtained through absorption from the diet. The active form may act in the immune cells and in suppression of the inflammation process in the macrophages (modified from Reich et al., 2014).[4]

These inflammatory diseases occur when homeostasis of the gastrointestinal system is disrupted. In healthy conditions the intestinal epithelium presents a barrier to commensal and pathogenic microorganisms, but if this balance is lost an increase in intestinal permeability and bacterial translocation across the intestinal mucosa are seen, resulting in a local and systemic immune activation. This mucosal immune system response to enteric antigens probably initiates the chronic inflammation[19-20].

UC is more prevalent than CD and exhibits a continuous pattern of inflammation in colonic mucosa restricted to the mucosal surface. The entire inflammation is uniform from the rectum, and rarely affects the colon or terminal ileum. Patients may experience periods of remission and flares. On the other hand, CD may involve any part of the gastrointestinal tract from mouth to anus, and mainly differs from UC because of its cobblestone pattern and skip lesions that can be seen endoscopically. Additionally, the terminal ileum is affected in nearly 50% of individuals. CD patients may also exhibit periods of remission and flares[21-24].

IBD: PATHOPHYSIOLOGICAL PROCESSES

Both CD and UC share common features despite representing different pathophysiological entities. In both diseases there is an association with multiple pathogenic factors as environmental modifications, genetic susceptibility, abnormal gut microbiota, and imbalance in the homeostasis of the immune response, as well as host genotype. These chronic inflammatory diseases may be associated with an overly aggressive T-cell response related to commensal bacteria and pathogens in the colon and distal ileum of genetically susceptible hosts[25-26].

The pathogenesis of IBD is related to different components of the mucosal immune system such as the intestinal epithelial cells, innate lymphoid cells, macrophages, monocytes, neutrophils, dendritic cells, T and B cells, and chemical mediators released by these cells such as cytokines and chemokines. Activation of the innate immune system due to mucosal vulnerability or a defect in the sampling of gut luminal antigen leads to recruitment of immune system cells, resulting in inflammation[2, 15, 25-26].

Under normal conditions, pattern recognition receptors (PRR) such as toll-like receptors (TLR) can recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). In IBD patients this ability is lost, resulting in the incapacity to differentiate pathogenic and commensal microorganisms. This allows the activation of a pro-inflammatory transcription factor named nuclear factor kappa beta (NFκB), triggering several signal transductional events and overproduction of inflammatory mediators such as TNF-α

(tumor necrosis factor α) and interleukin 1β (IL-1β), IL-6, IL-8, IL-12, and IL-13 (Figure 2). This chronic inflammatory pattern results in modifications in bowel habits, pain, and bleeding, and increases the risk of cancer[15, 27-29].

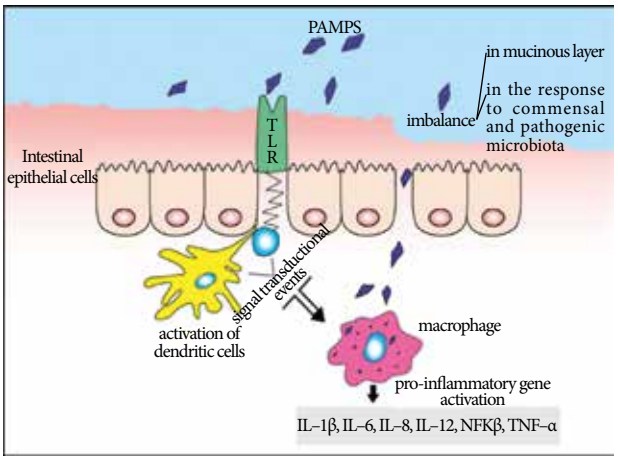

Figure 2. Pathophysiologic mechanism of IBD. A disruption in the mucinous layer increases the permeability and consequent uptake of PAMPs in the intestinal epithelium. Dendritic cells and macrophages are activated and there is an increase in the release of the pro-inflammatory cytokines such as TNF-α, IL-6, IL-12, IL-23, and IL-1β. PAMPs: pathogen-associated molecular patterns; TNF-α: tumor necrosis factor α; NF-kβ: nuclear factor kappa beta; IL: interleukin (modified from Ordas et al. 2012)[12].

VITAMIN D: ROLE IN THE IMMUNE SYSTEM

There are several genes which are influenced by vitamin D. Vitamin D may be related to the immune system in a number of ways including gut barrier function, antigen presentation, antigen response, antimicrobial peptide synthesis, and regulation of adaptive and innate immunity. The receptor for this vitamin (VDR) is present in almost all immune cells as activated or naïve CD4+ and CD8+ T cells, B cells, and neutrophils, and antigen-presenting cells (APCs) such as macrophages and dendritic cells, suggesting that this vitamin could have implications in the autophagy and modification of the antimicrobial barrier of the intestinal mucosa, controlling the microbiota. These findings lead to the conclusion that vitamin D may play a role in mediating protection from disease, and that polymorphisms in VDR could be related to a higher vulnerability to develop a number of inflammatory diseases, including IBD[2, 30-35].

Studies have shown that vitamin D3 improves macrophage responses (Figure 1) and synthesis of antimicrobial proteins such as cathelicidin. It also induces downregulation of the synthesis of pro-inflammatory cytokines such as TNF-α and interleukins (IL-1, IL-6, and IL-8). The interaction of vitamin D and VDR interferes in the function of T-lymphocytes and cytokine patterns such as IL-2 and interferon γ (IFN-γ) and improves the T_H2 (T helper-2) cell response[30, 35-37].

Expression of the NOD2 gene may establish a connection between vitamin D/immune system axis and CD. The NOD (nucleotide-binding oligomerization domain) product acts as a cytoplasmic sensor for bacteria peptidoglycans, and variations may be related to the development of IBD (Figure 3). The 1,25(OH)2D3/VDR stimulates transcription of the NOD2 gene, resulting in the expression of DEFB2/HBD2, which represents the antimicrobial peptide β-defensin 2, and cAMP, which is related to the codification of cathelicidin. Downregulation of the ATG16L1 gene, associated with decreased expression of the lysozyme by Paneth cells, increases susceptibility to colitis, suggesting that modifications of vitamin D status could affect autophagy and the antimicrobial barrier of the intestinal mucosa. Administration of 1,25(OH)2D3 and its analogs may inhibit dendritic cells (and consequently decrease transforming growth factor-β1 [TGF-β1] and collagen 1), fibroblasts, and peripheral blood mononuclear cells (PBMC) and lamina propria mononuclear cells (LPMC) and thus impact cytokine release. Modifications in VDR reduce the effects of this vitamin in Paneth cells, leading to the decrease of the host defense due to the reduction of cathelicidin, ATG16L1, and lysozyme (Figure 4)[30, 38-39].

It should be noted that cathelicidins are produced by neutrophils and cells in the gastrointestinal tract, and this production is stimulated by inflammatory cytokines and microbial products. When these molecules are stimulated, they may confer protection against infections caused by various microorganisms, promoting the activation of responses in leukocytes and other types of cells responsible for eradicating microorganisms. These defensins can be designated as alpha or beta and are mainly produced in Paneth cells; their function is to limit the number of microorganisms in the intestinal lumen. TGF-β is a peptide which is able to control the proliferation and differentiation of cell types by interacting with surface serine/

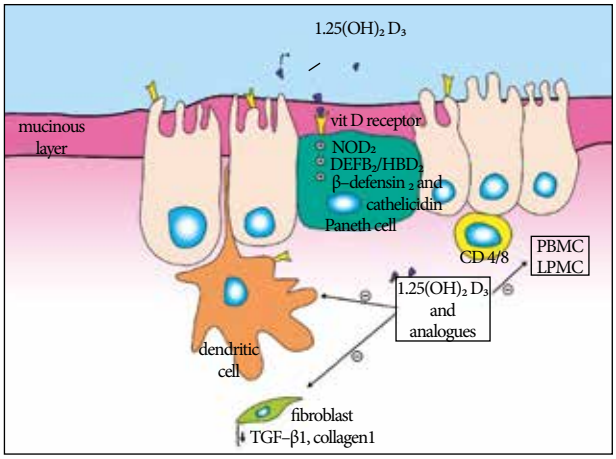

Figure 3. Relationship of vitamin D in the pathogenesis of IBD. Active form of vitamin D (1,25(OH)2D3) associates with vitamin D receptor in the Paneth cell. NOD2 and /HBD2 are stimulated and β-defensin 2 and cathelicidin are produced. 1,25(OH)2D3 and its analogs also show inhibitory effects on dendritic cells, fibroblasts, PBMC, and LPMC, and thus impact cytokine release. IBD: inflammatory bowel disease; NOD: nucleotide-binding oligomerization domain; PBMC: peripheral blood mononuclear cell; LPMC: lamina propria mononuclear cells; TGF-β: Transforming growth factor-beta (Modified from Ardesia, Ferlazzo, Fries, 2015)[29].

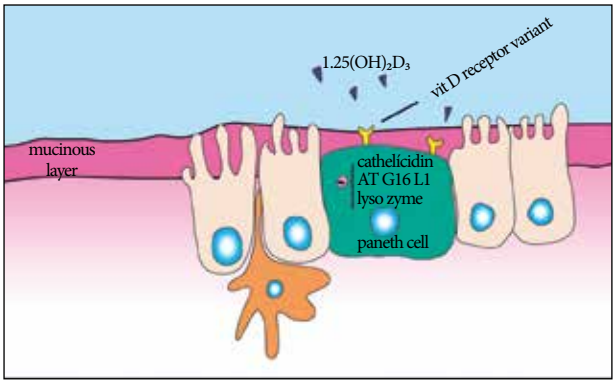

Figure 4. Modifications to the vitamin D receptor reduce the effects of this vitamin in Paneth cells, resulting in decreased host defense due to the reduction of cathelicidin, ATG16L1, and lysozyme (Modified from Ardesia, Ferlazzo, Fries, 2015)(29).

threonine-specific protein kinase receptors, resulting in the regulation of several biological processes such as regulation of the immune system[40-41].

CONNECTIONS BETWEEN VITAMIN D AND IBD

Several studies have shown that vitamin D is related to IBD. Concentrations of this vitamin are usually low in individuals with IBD, and are inversely related to the risk of developing this pathology. Nevertheless the reasons linking vitamin D deficiency and IBD development are still unclear[42].

Authors believe that vitamin D status can interfere in the efficiency of therapeutic approaches to IBD, since individuals with higher levels of vitamin D have demonstrated better outcomes before starting anti-TNF-α compared to those with low levels (Table 1). Vitamin D insufficiency is associated

Table 1. Studies showing the relationship between vitamin D and IBD.

Patients	Method	Results	Reference
18 CD patients	Administration of 1,000 IU/d to 5,000 IU/d during 24 weeks	Reduction of CD activity index scores suggesting that restoration of normal vitamin D serum levels may help in the management of patients with mild–moderate Crohn's disease.	Yang et al.[47]
141 CD and 79 UC patients	Evaluation of vitamin D levels and correlation with IBD were assessed	Quality of life in IBD patients is higher in patients with serum vitamin D concentrations of 50-59 ng/mL during the winter/spring period.	Hlavaty et al.[48]
Human and animal models	Review	The authors of this review concluded that vitamin D is important in therapeutic management of IBD but that the correct and precise level of 25(OH)D3 necessary for therapeutic effects is unknown; levels of 75 nmol/L or higher are normally adequate.	Reich et al.[4]
186 CD patients	Vitamin D status was evaluated and disease activity was measured	Low serum vitamin D levels were related to increased CD activity in South African patients.	Raffner Basson et al.[49]
51 patients	Administration of 3000 IU/d of vitamin D	A significant number of IBS patients in the study were vitamin D deficient; supplementation significantly improved vitamin D level over placebo; IBS symptoms were not significantly improved.	Tazziman et al.[50]
19 UC and 57 CD patients	Serum levels of vitamin D were evaluated	Patients with IBD normally are vitamin D deficient, mainly CD individuals, indicating the need for supplementation in patients with inflammatory bowel disease.	Castro et al.[1]
85 UC and 48 CD patients	Evaluation of Vitamin D levels and disease activity	There is an association between vitamin D deficiency/ insufficiency and disease activity in IBD patients.	Torki et al.[51]
Animal model (mice)	Diet with low levels of vitamin D	Animals with vitamin D3 insufficiency exhibit greater bacterial translocation to extra-intestinal tissues, and display increased inflammatory cell infiltrates and increased gene transcription for the inflammatory mediators TNF-α, IL-1β, IL-6, TGF-β, IL-17A, and IL-17F.	Ryz et al.[52]
Humans	Review	Vitamin D insufficiency leads to an increased risk for IBD.	Legaki, Gazouli[53]
56 CD and 12 UC patients	Vitamin D evaluation together with antinuclear antibodies	Vitamin D insufficiency was found in 93%; extreme vitamin D deficiency was a significant risk factor for adverse events associated with anti-TNF therapy; a significant connection was observed between extreme vitamin D deficiency and the presence of antinuclear antibodies.	Santos-Antunes et al.[54]
32 pediatric IBD patients	Administration of 10,000 IU or 5000 IU of oral vitamin D3/10 kg body weight per week	Both treatments were safe and effective at normalizing vitamin D in pediatric IBD.	Simek et al.[55]
Human and animal models	Review	Use of vitamin D in IBD individuals is simple and inexpensive, and it is important to determine which patient populations could benefit from this adjunctive therapy.	Meeker et al.[2]

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; TNF-α: tumor necrosis factor-alfa; IL-1β: interleukin-1β, IL-6: interleukin-6; TGF-β: transforming growth factor-beta.

with IBD, and vitamin D supplementation may be helpful in the treatment and prevention of IBD[42-43].

Studies using animal models associate vitamin D insufficiency with the intensity of IBD symptoms, and the variant of the vitamin D receptor is also related to susceptibility to colitis in mice. Administration of 1,25(OH)2D3 relieves colitis symptoms in mice, while vitamin D deficiency itself does not induce IBD but contributes to the development of experimental IB[44-46].

Many kinds of cells are related to homeostasis of the gastrointestinal cells and are consequently related to IBD. T cells are able to synthetize IL-17 and IFN-γ to deal with pathogens, but not the commensal microbiota. The role T cells play makes them crucial for maintaining homeostasis. Use of 1,25(OH)2D3 is indispensable for the production of regulatory cells such as Tregs (T regulatory cells), iNKT (invariant natural killer T cells) cells, and CD8αα T cells, and disconnecting T_H1 and T_H17 cells, leading to a balance that contributes to homeostasis of the gastrointestinal tract. Vitamin D deficiency leads to dysbiosis and an increase in the inflammation mediators, resulting in a shift of the microbiota as the host responds to injury. The association between vitamin D and its receptor may regulate the microorganism indirectly to maintain the homeostasis in the gastrointestinal tract[44-46].

CONCLUSION

Vitamin D is considered to play a significant role in inflammatory processes. Many recent studies have shown that insufficient levels of this vitamin may be a risk factor for the onset and evolution of gut inflammation. This leads to the conclusion that there may be a strong connection between vitamin D and IBD. Nevertheless, many studies executed by multidisciplinary teams are necessary to show precisely how this vitamin may act in prevention, treatment, or remission maintenance. Furthermore, a larger patient sample is needed to reach a conclusion about when doctors should indicate supplementation (in the acute phase, in remission, or both), what kind of patient should receive this supplementation, for how long patients should receive this vitamin, and the correct dose to obtain benefits instead of side effects. More research in this field is necessary to provide more insights on the link between vitamin D and IBD.

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POINT OF VIEW

STEM CELL TRANSPLANTATION FOR REFRACTORY CROHN'S DISEASE

Mikaell Alexandre Gouvêa Faria[1]

Crohn's disease is a condition with different presentations; it is an inflammatory disease that can affect the digestive tract from the mouth to the anus, and can manifest with symptoms that include abdominal pain, diarrhea and malnutrition[1]. The pathogenesis can involve environmental, immunological, emotional and dietary factors as well as genetic predisposition and intestinal flora infections[2].

Several drugs are used to treat Crohn's disease with good results and often control the disease, but unfortunately none of these treatments is curative. Moreover, some patients experience treatment failure described as non-response to initial treatment or loss of response to treatment with the persistence of symptoms, even after modifying the treatment, characterizing refractory disease[3-5]. Consequently, the possibility of transplant in more serious cases is being studied.

Hematopoietic stem cell transplantation is used to treat several autoimmune diseases, including Crohn's disease. This approach has proven effective in the treatment of Crohn's disease refractory to other therapies[6,7]. Even though the results with mesenchymal stem cells are still unsatisfactory[8], research is progressing; the best results have been seen in local applications, for example in fistulas[2,9].

Of the two options for hematopoietic stem cell transplantation, autologous and allogeneic, the latter presents greater risks due to elevated toxicity and risk of infection. On the other hand, while autologous transplants are better tolerated, they are associated with a higher risk of relapse[10,11].

INDICATIONS FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION

According to most studies, transplantation is indicated for patients who have active disease refractory to current drug[12], dietary or surgical therapies, when further surgery is required with the possibility of developing short bowel syndrome or needing a permanent ostomy, and when the Crohn's disease activity index (CDAI) is greater than 250[3,13].

Indications for the use of mesenchymal stem cells for intestinal diseases are basically the same, but they are most commonly used to close fistulas and for other more localized therapies[14,15].

DISCUSSION

Several studies are being performed around the world to identify the risks and benefits of transplantation in order to establish the best indications for this procedure and improve results with less toxicity[15,16]. These studies attempt to determine whether this type of treatment will replace or complement other modalities or will be restricted to patients who do not have other therapeutic options, as is the case currently[17,18].

Two approaches to mesenchymal cell transplantation are being studied in patients with Crohn's disease: the first aims to treat fistulizing disease and the second addresses luminal disease. There are few side effects and the risk of complications is low, but results are still inconsistent[19].

Hematopoietic stem cell transplantation has an important action as self-tolerant lymphocytes are generated, in effect 'resetting' the immune system. This causes the patient to again become sensitive to medications which may have lost their effectiveness due to anti-drug antibodies or caused allergies; consequently, the patient gains new treatment options in the case of relapse[2].

Reported complications are related to infections from the bone marrow ablation stage until after the infusion of stem cells and the initial formation of the immune new system[17,20,21].

Some series of allogeneic stem cell transplantations have been described with good results, but with a higher mortality rate and high toxicity because this modality requires high doses of medications. However, this approach is still promising because since the donated cells do not have the patient's genetic makeup, they tend to keep the immune system stable for longer, thereby reducing the probability of relapse[22,23].

1. Coloproctology Division at Beneficência Portuguesa Hospital, São José do Rio Preto, SP, and Kaiser Hospital, São José do Rio Preto, SP.
Correspondence to: Rua XV de Novembro, 3975 - São José do Rio Preto, SP, Brasil. CEP 15015-110.

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Series of patients treated with autologous hematopoietic stem cell transplantation have shown some good success rates. In one study, 24 patients with severe disease underwent autologous transplantation and one- and two-year remission rates were 91% and 57%, respectively[24]. Furthermore, a case report described a patient who remained stable for 2 years with the disease in remission[7]. Even so, the toxicity and safety of autologous hematopoietic stem cell transplantation is not yet considered acceptable[20].

In the recent ASTIC study, it was not possible to prove the benefits of the procedure because of the number of complications described, many of which were related to the toxicity of the drugs used during the transplantation procedure[25]. In the ASTIC study, the results seem to be related to the different endpoints considered, the methodologies used, and the use of high doses of cyclophosphamide which increase the number of complications, including cardiac dysfunction and hepatic sinusoidal obstruction syndrome (SOS)[20,25].

Because of these high doses of cyclophosphamide used during the conditioning regimen, the complication rate in the ASTIC study was high and comparable to rates in severe Crohn's disease unresponsive to treatment; the study concluded that there was no evidence to support the use of transplantation in Crohn's disease. However, other authors disagree and believe that because of the high doses of medications and the different endpoints chosen, the study was unable to contraindicate the procedure. In their letter of response to this article, Burt et al. stated that lower doses of cyclophosphamide are safer and more efficacious in other pathologies, and that the endpoints of the study differ from those normally used by researchers to define the success or failure of treatment[26]. Hommes et al. compared different studies and concluded that there was insufficient evidence to discontinue studies using stem cell transplantation in Crohn's disease. However, this procedure should only be performed in centers with experience to reduce the risk of complications[27].

Hematopoietic stem cell transplantation is a treatment option for patients with Crohn's disease refractory to conventional therapy. Given the risks, further studies are needed to evaluate the effectiveness of this procedure. Nevertheless, for now autologous stem cell transplantation induces remission of the disease and appears to be safe. Therefore, regardless of the possibility of relapse, the patient gains some time without symptoms with a better quality of life. More importantly, perhaps, the patient again becomes sensitive to other therapeutic options that previously failed.

In Brazil, this procedure has been carried out since 2013 with 18 cases treated, all of which had positive results and were tolerated well by the patients[7].

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COMMENTED ARTICLE

IMAGING IN THE EVALUATION OF INFLAMMATORY BOWEL DISEASE: HOW MUCH IS TOO MUCH?

Orlando Ambrogini Junior[1]

INTRODUCTION

Inflammatory bowel disease (IBD) has been increasing, and more frequently affects younger people and children. Diagnosis is usually made through a combination of taking the medical history, physical examination, laboratory and imaging tests. These tests should be more affordable, use low-dose ionizing radiation, and be used not only for diagnosis purposes but also to manage these patients. Current imaging tests like CT and MRI allow the physician to monitor the patient and investigate complications such as abscesses and obstructions, as well as assess the extent of the inflammatory process.

This paper will discuss the different imaging options which are currently available, their sensitivity in detecting inflammatory activity, and the risks of radiation, in order to permit physicians adequate time to request these tests.

The following is a list and brief description of imaging tests currently in use as well as their characteristics:

Barium fluoroscopy: After barium intake, the intestinal loops can be viewed by fluoroscopy in order to detect obstructions or thickening. This test can be considered the "gold standard" for pediatricians, even if they have the option to acquire images via tomography and resonance, since these types of imaging do not provide reliable information about the colon.

The advantages of this exam are low cost and great viability, and the ability to be performed without sedation. Drawbacks involve exposure to radiation, long duration, the fact that it is operator-dependent, and the inability of this method to assess extra-intestinal lesions. Radiation exposure from this examination estimated at 1.8 to 2.2 millisieverts (mSv) in children and 5 mSv in adults. The sensitivity of this method to detect ileal inflammation (based on histology) is 45 to 76%, with 67 to 96% specificity.

CT enterography (CTE): This assessment is similar to tomography, but the patient consumes a volume of neutral contrast to enhance visualization of the small intestine. Criteria for inflammatory activity include: parietal thickening, submucosal fat deposition, venous engorgement, and lymphadenopathy. This method also permits the visualization of complications such as obstructions, fistulae, perforations, and abscesses.

Its main advantages are: speed, ability to diagnose complications, lower cost compared with resonance imaging, and the fact that in most cases sedation is not required. The main drawback of this method is radiation exposure (10 to 20 mSv), as well as the use of oral and intravenous contrast agents. The most current examination techniques can reduce radiation to about 5 to 7 mSv with further reduction of procedure-associated noise without losing sensitivity and specificity. This can be considered the ideal test for early diagnosis of IBD, and if devices with lower level of radiation become available it can even be considered for management. CTE has a sensitivity of around 84% and specificity of 93%, and leads to the detection of complications requiring intervention in 18% of patients and alterations in treatment strategy in 61%.

Entero-magnetic resonance (EMR): Like CTE, EMR requires oral intake of neutral contrast agent as well as the use of venous gadolinium and anticholinergics. The exam lasts 1-2 hours and the patient is instructed to keep still or hold their breath, which is why this exam is usually performed under sedation in children. Signs of activity include: parietal thickening, increased contrast uptake in T2, vascular engorgement, and mesenteric fat change. The major advantage of EMR is the absence of ionizing radiation; drawbacks are lack of widespread availability, long duration, potential need for sedation, and high cost. It is currently the test of choice for patient monitoring, including assessment of perianal disease, with sensitivity and specificity of 93% for diagnosis. EMR surpasses CTE in differentiating inflammatory stenosis from fibrotic stenosis

1. Associate Professor, Gastroenterology - Federal University of São Paulo (UNIFESP).
Correspondence to: Praça Amadeu Amaral, 47, cj. 71 - São Paulo, SP, Brasil. CEP: 01327-010. E-mail: orlando.ambrogini@unifesp.br

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and clarifying colonic lesions; in fact, in this case it is more similar to endoscopy in diagnosing remission, including histologic remission.

Ultrasound: Although this technique has been available in Europe for quite some time, it gained even greater importance after association with the use of intraluminal contrast (SICUS), with the patient orally ingesting 200 to 500 ml of contrast agent 30 minutes before the exam. This exam requires a high-frequency device and Doppler to assess blood flow in the affected loop. Inflammatory activity is detected when the thickness of the intestinal wall exceeds 3 mm and hyperemia is present. This method can also detect complications such as abscesses, lymphadenopathy, stenosis, or fistulae and has the advantage of low cost and no need for ionizing radiation or sedation. Its potential drawback is the fact that a highly skilled operator is required. Under ideal conditions, its specificity and sensitivity are comparable to CTE and EMR, including in the diagnosis of complications.

Ionizing radiation: The amount of accumulated radiation capable of generating damage is still controversial. One recent study showed that doses exceeding 50 mSv in children increase the risk of leukemia and brain cancer threefold. On the other hand, another study investigating IBD reported that children with Crohn's disease receive an average of 20.5 mSv, and pediatric patients with ulcerative colitis receive 11.7 mSv. In adults, the average was 20.1 mSv for Crohn's Disease and 15.1 for ulcerative rectocolitis. Currently, tomography is widely used in emergency services, with use in Crohn's disease soaring from 47% to 78% over the last eight years, but increased risk has not been detected in these patients. Despite the lack of data, prioritizing the use of tests which do not utilize ionizing radiation is recommended, especially in the pediatric population.

"Guidelines" for imaging tests: Europe and US guidelines recommend that a small bowel imaging test be performed whenever the colonoscopy presents atypical findings at the initial diagnosis. This imaging test would be ultrasound or EMR in children with suspected diagnosis of IBD, EMR or CTE to monitor an existing diagnosis, and EMR to detect complications. In adults, EMR has gained ground in both diagnosing and managing IBD, particularly because recent studies have correlated this exam with the detection of mucosal healing.

CONCLUSION

Imaging examinations currently play an important role in the diagnosis and management of patients with IBD. Non-invasive techniques which do not require ionizing radiation are preferred, especially in children. All of these examinations have their advantages and disadvantages and it is the physician's responsibility to decide which examination is the best option for each patient. Caution is advised when indicating exams that use ionizing radiation; potential alternatives must be considered, whenever available.

COMMENTS

Imaging studies are essential for thorough evaluation of IBD, especially in Crohn's disease affecting the small intestine. Among the tests described above, CTE and EMR are gaining ground among physicians as the most frequently used techniques. CTE tends to be the most available technique in most healthcare services and meets our diagnostic needs quite well, except when perianal complications occur and magnetic resonance must be used. In reference centers where both tests are available, CTE is recommended for initial diagnosis and EMR for management.

Fluoroscopy and ultrasound are not commonly used by most centers in Brazil. Ionizing radiation can be considered disadvantageous, but its magnitude has not been evaluated adequately. Caution is required, especially in the young population.

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CASE REPORT

RECURRENT FULL-THICKNESS ILEOANAL J-POUCH PROLAPSE

Magaly Gemio Teixeira[1], Aline Pozzebon[2], Tauana Gonçalves[2], Juliana Zanco[2], Lorena Reuter Motta Gama[2]

ABSTRACT

J-pouch prolapse is a rare complication after ileoanal J-pouch (IPAA). We report a case of recurrent total ileoanal J-pouch prolapse treated by pouchpexy repair using a mesh.

Keywords: Ileoanal J-pouch, ulcerative colitis, pouch prolapse, pouch complication.

INTRODUCTION

Total restorative proctocolectomy with ileal pouch-anal anastomosis has become the gold standard of care for surgical treatment of ulcerative colitis and familial polyposis. Despite favorable long-term outcomes, this procedure has been associated with several complications. Full-thickness ileal J-pouch prolapse is a rare but debilitating complication. Here we describe a case treated with a mesh.

CASE REPORT

Patient is a 29-year-old male with a history of ulcerative colitis since 1995, treated with mesalazine, azathioprine, prednisone, and anti-TNF without success. He received an ileoanal J-pouch and diverting ileostomy in 2013. There were no immediate complications following ileostomy reversal. After one year he reported several bowel movements per day with effort due to a sensation of incomplete evacuation. The prolapse began and rapidly increased to a total prolapse, responsive to reduction (Figure 1). Anorectal examination revealed a patulous anus with diminished sphincter tone. Endoscopy of the pouch demonstrated edematous mucosa without evidence of pouchitis.

Pouchpexy was performed using a transabdominal approach with fixation of the pouch enclosed in a non-absorbable, macroporous polypropylene mesh to the sacrum using non-absorbable sutures. The mesentery of the pouch was positioned in the curvature of the sacrum with the pouch anterior. The pouch was of normal size, and there were no adhesions so it was very easy to move the pouch and apply the mesh. Care was taken to preserve the autonomic nerves of the pelvis as well as the vasculature of the pouch mesentery (Figure 2).

Patient is well, after 24 months without recurrence.

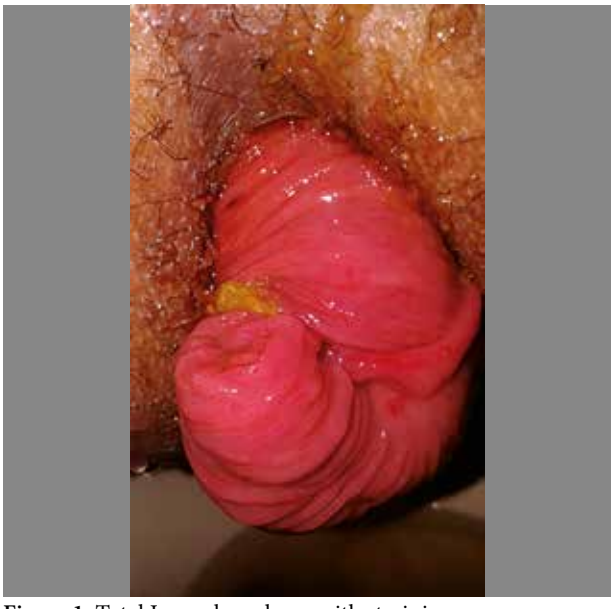

Figure 1. Total J-pouch prolapse with straining.

1. Director of Progastro - Beneficiência Portuguesa Hospital, São Paulo.
2. Resident at Progastro - Beneficiência Portuguesa Hospital, São Paulo.

Correspondence to: Magaly Gemio Teixeira. Progastro Clinic. Hospital Beneficência Portuguesa de São Paulo. Rua Martiniano de Carvalho, 927 - São Paulo, SP, Brasil. CEP: 01321-001. E-mail: magalygemio@gmail.com

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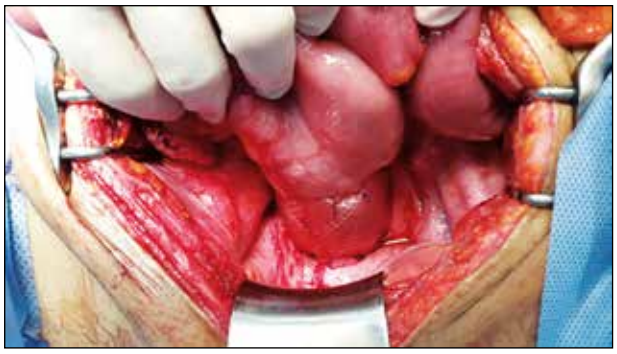

Figure 2. Pouch enclosed with a mesh with fixation to the **presacral fascia in the deep pelvis.**

DISCUSSION

Pouch prolapse is a rare complication (0.3%) of ileal pouch-anal anastomosis[1,2]. The rarity of this condition may be due to the fact that the mesentery of the small bowel places tension on the pouch, limiting the potential for distal intussuception. It is difficult to identify any significant risk factors associated with ileal pouch prolapse due to the small number of patients.

The condition, although rare, is very disagreeable for the patient. It compromises function and affects the patient's quality of life.

Differentiation of the types of prolapse is important to ensure appropriate treatment. Prolapse can be mucosal or full-thickness. Mucosal prolapse can be successfully managed using bulking agents or mucosal excision techniques[1], while full-thickness pouch prolapse requires pouch fixation using an abdominal or perineal approach. The majority of patients present within 1–2 years of pouch construction[2–4]. Most had a "J" pouch configuration with a stapled IPAA, and underwent this procedure in our service. Patients reported straining to evacuate, seepage, incontinence, and/or pain and external prolapse of tissue.

An abdominal approach using mesh seems to be the best indication to treat full-thickness prolapse[2,3,5]. Pouchpexy without a mesh resulted in recurrence in 50% of the patients operated on by Joyce et al.[2].

Some precautions must be taken during the operation. These include adequate dissection of the J-pouch to the level of the pelvic floor to decrease the risk of recurrence, as well as creating an adequately tight mesh wrap to avoid obstruction or, rarely, erosion of the mesh through the pouch[3].

There is no data on follow-up and no recurrence rates have been reported. Patients who recur may opt for an additional repair or, as a last resort, pouch excision with ileostomy.

A long-term follow-up of treated patients is required to determine outcomes.

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CASES REPORT

RELAPSED AND *DE NOVO* ULCERATIVE COLITIS AFTER LIVER TRANSPLANTATION

Eduardo Garcia Vilela[1], Roberto Gardone Guimarães[2]

ABSTRACT

Inflammatory bowel disease (IBD) following solid organ transplant (SOT) can be classified as either *de novo* disease or exacerbation of pre-existing disease. Diarrhea is a common symptom after organ transplantation, so some differential diagnoses should be considered; these include cytomegalovirus colitis (CMV, which mimics IBD), *C. difficile* colitis, protozoal infection, lymphoproliferative disorders, and drug toxicity. The natural history of IBD after liver transplantation varies. The incidence of posttransplantation *de novo* IBD was shown to be higher than in the general population. Here we report the case of a patient who developed a *de novo* case of ulcerative colitis after liver transplantation for cirrhosis resulting from congenital biliary atresia. After retransplantation because of chronic rejection, there was severe recurrence of intestinal disease concomitant with other causes of diarrhea, as CMV colitis, bacterial overgrowth of the small intestine, and lymphoproliferative disorder associated with the use of immunosuppressants.

Keywords: Ulcerative colitis, *de novo* ulcerative colitis, orthotopic liver transplantation, immunosuppressive agents

INTRODUCTION

Ulcerative colitis (UC) is a disease which results from a complex interaction between genetic and environmental factors, intestinal microbiota, and the immune system. In the absence of known etiology, treatment is based on control of inflammation through the use of immunosuppressive and biological agents.[1]

The first orthotopic liver transplant (OLT) was carried out in 1963, and without adequate immunosuppressive treatment graft survival was not long-lasting. In the 1970s, long-term results improved after azathioprine was introduced in immunosuppressive therapy. After the introduction of cyclosporine and tacrolimus (calcineurin inhibitors) in the 1980s and late 1990s, respectively, more effective control of immunological processes was achieved and survival rates reached 90% in 10 years in the major transplant centers. The number of these specialized centers increased while at the same time specific features of different diseases in the population were seen more frequently.[2]

Until recently it was believed that immunosuppression used to prevent and treat rejection would exert a protective effect against reactivation of IBD. However, the cumulative risk of pre-existing disease recurrence after OLT can reach 70% in 10 years.[3] The incidence of primo-diagnosis IBD after OLT (*de novo* IBD) is higher compared to the general population (206 vs. 20 new cases/100,000 persons, respectively).[4]

In this context, management of IBD becomes more complex since specific characteristics linked to risk factors, differential diagnosis, prognosis, and treatment have begun to be recognized.

In this paper we report the clinical case of a patient diagnosed with UC post-OLT secondary to biliary atresia and severe disease recurrence after retransplantation for chronic rejection. We also addressed the differential diagnosis of diarrhea in this scenario.

CASE REPORT

Female patient, 22, diagnosed with biliary atresia in the fourth week of life and subjected to Kasai portoenterostomy

1. Associate Professor of Medical Clinic Department of Medical School Federal University of Minas Gerais.
2. Resident Hospital Gastroenterology Clinics of the Federal University of Minas Gerais.

Correspondence to: Rua Sergipe, 472, Belo Horizonte, MG, Brasil. CEP: 30130-170. E-mail: robertogardone@yahoo.com.br

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two months later. Despite initial improvement of cholestasis, the patient developed progressive fibrosis and underwent live donor liver transplantation at 18 months of age (March 1996). At that time, immunosuppression was based on a combination of cyclosporine and corticosteroids to the fourth month post-OLT, and from the fifth month cyclosporine alone was used.

The patient recovered uneventfully until the fourth year post-OLT, when she presented a clinical diagnosis of mononucleosis-like syndrome with spontaneous resolution. On this occasion the IgG antibody to cytomegalovirus was positive, unlike the negative pre-OLT serology findings. At thirteen years of age, the patient began to experience diffuse abdominal pain accompanied by diarrhea and hematochezia. A colonoscopy showed pancolitis characterized by mucosa with diffuse erythema interspersed with small erosions and ulcerations.

Anatomopathological examination confirmed the presence of mucosal continuity solutions which were predominantly infiltrated by mononuclear cells and even led to the formation of crypt abscesses and cryptitis, consistent with the diagnosis of ulcerative colitis. Azathioprine and mesalazine were added to the cyclosporine at doses of 125 mg/day and 3.2 g/day, respectively. Within two years, the patient attained clinical and endoscopic remission of the disease.

At age 15, after persistent liver enzyme abnormalities due to prevailing elevated alkaline phosphatase and gamma GT, a liver biopsy suggested a diagnosis of chronic graft rejection. In April 2011 at 17 years of age, the patient was diagnosed with fibrosing liver disease secondary to chronic rejection and underwent liver retransplantation from a cadaveric donor. Cyclosporine was replaced with tacrolimus, azathioprine was suspended, and mesalazine was maintained at a dose of 3.2 g/day. The patient had an uneventful immediate postoperative period and was discharged in the third week. When she was reevaluated four weeks post-procedure, the laboratory results were within reference values and no clinical or surgical complications were observed.

However, three months later the patient showed elevated serum levels of alkaline phosphatase (6x > ULN) and aminotransaminases (ALT> 3x ULN). Abdominal Doppler ultrasound of the hepatic vessels showed no vascular changes, and cholangiography and MRI were normal. The liver biopsy showed endothelialitis, perivenulitis, and portal infiltration, confirming the diagnosis of acute graft rejection (Banff 6-7). Residual serum tacrolimus levels were around 5 ng/ml. After the dose was adjusted to maintain residual levels around 15ng/ml, liver enzymes normalized.

In August 2011 the patient again began to experience changes in bowel habits characterized by diarrhea (about six emissions per day with watery stools, mucus, and streaks of blood) and diffuse abdominal pain, along with urgency and defecation tenesmus. Colonoscopy showed signs of pancolitis with ulcerations in the rectum and sigmoid. Histopathological findings were very similar to the first pathology of the colon in 2007. Testing for *Clostridium difficile* through serological examination and cytomegalovirus antigenemia was negative. At that time prednisone and azathioprine were added to the immunosuppressive regimen.

After the initial response, bowel symptoms worsened (abdominal pain and diarrhea), and antigenemia for cytomegalovirus was positive (12 in 200,000 neutrophils). Azathioprine was suspended and ganciclovir was given for 28 days. Good clinical response was obtained and the patient showed negative results for antigenemia, which is now monitored monthly. In the following months, the patient experienced a slight but gradual increase in the number of bowel movements. Tacrolimus was given (residual level between 5 and 7 ng/mL) in combination with mesalazine. Sigmoidoscopy revealed rectal mucosa with moriform erythema associated with the presence of ulcerations throughout the entire examined segment. After ruling out a diagnosis of cytomegalovirus and infection with *C. difficile*, prednisone was initiated at a dose of 60 mg/day with no response after 6 weeks of use.

In July 2012, considering the corticoresistant nature of the disease infliximab was initiated according to the default schema. A partial response was obtained after the induction dose was maintained at 5 mg/kg every 8 weeks. However, about a year after the introduction of biological therapy the diarrhea worsened again, with reappearance of blood in the stool. The patient had no fever and testing for CMV and *C. difficile* were again negative; testing for isosporiasis and cryptosporidium were also negative. Control colonoscopy in September 2013 showed severe ulcerative pancolitis (Figures A and B). Testing for protozoa and CMV in the biopsy material were negative. Infliximab and mesalazine were suspended and the patient underwent proctocolectomy in three separate stages.

In the late postoperative period, before the patient experienced abdominal distention and increased frequency

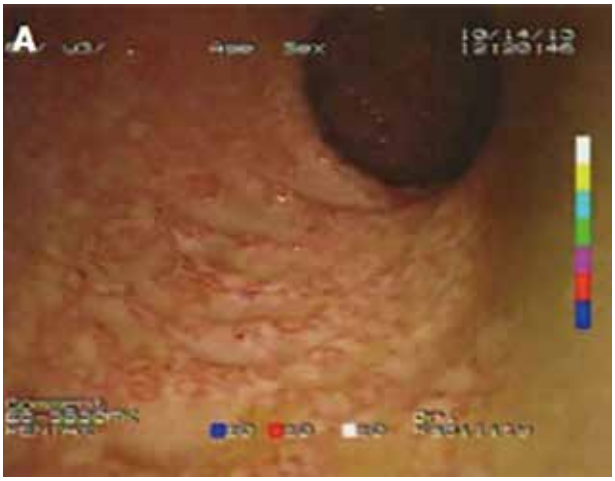

Figure A. Spontaneous bleeding and mucosa covered with fibrin (descending colon).

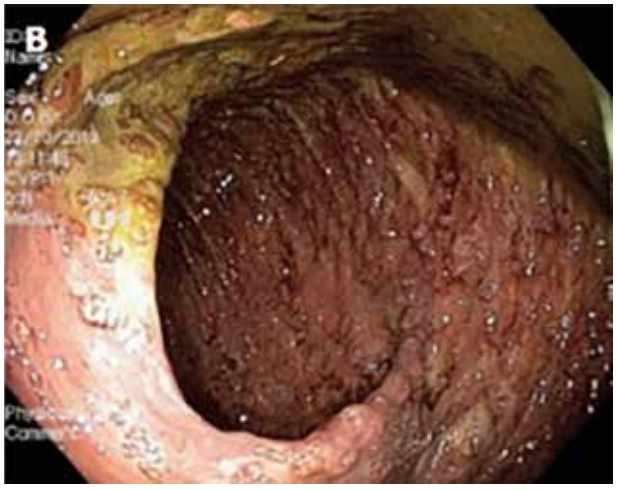

Figure B. Hyperemic mucosal erosions and fibrinous spots (cecum).

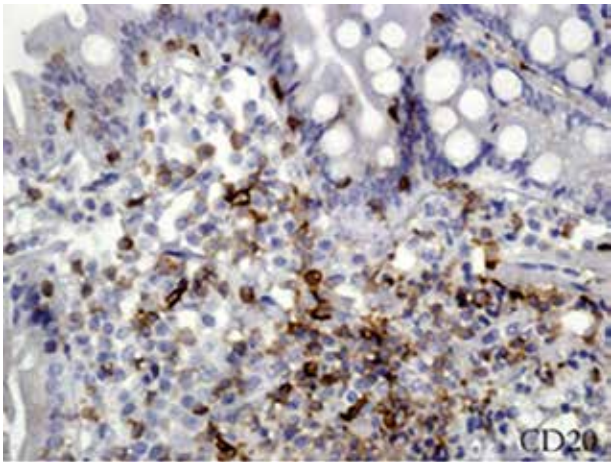

Figure D. Quantitative CD3 similar to CD20 (Mixed infiltrate B and T). Proliferation index by Ki67 / MIB1 20%.

of evacuations despite the use of loperamide, she was diagnosed with bacterial overgrowth of the small intestine through the expired hydrogen test using glucose as a substrate.

After repeated antimicrobial treatments (norfloxacin, ciprofloxacin, and tetracycline) and notably early recurrences, the second portion of the duodenum was biopsied and dense lymphocytic infiltration was seen in the lamina propria without invasion of the base of the crypts, showing a tendency to form lymphoid aggregates.

The immunohistochemical study showed foci of lymphoepithelial injury with concomitant B and T cells, reinforcing the hypothesis of post-OLT polymorphic lymphoproliferative disorder (Figures C and D).

More recently, the immunosuppressant regime was replaced with rapamycin and antibiotic therapy cycles with tetracycline. Currently the patient has 3 bowel movements per day, with more consistent feces and less need for loperamide.

DISCUSSION

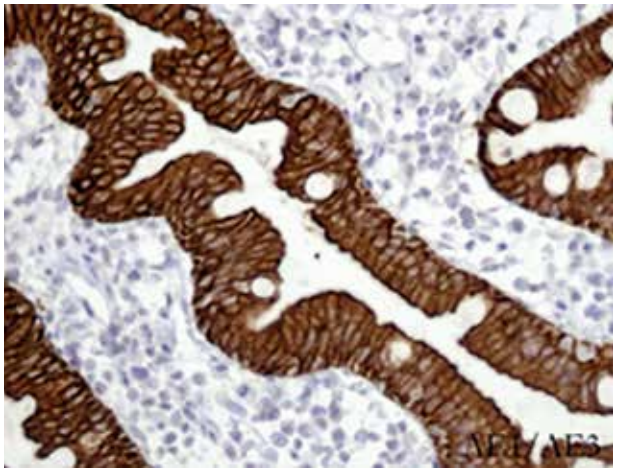

Figure C. Positivity in the epithelial component, with some outbreaks of lymphoepithelial injury

Diarrhea is a common symptom following solid organ transplant (SOT) or bone marrow transplantation (BMT) and its prevalence reaches 72% of the sample.[5] Its causes include IBD, which may recur or be diagnosed for the first time. In this context, other differential diagnoses should always be suggested. It is essential to rule out CMV colitis (which may closely mimic IBD in these patients) and other infectious causes such as *C. difficile* and protozoa, in addition to lymphoproliferative disorders and drug toxicity.

The belief that immunosuppression to prevent and treat graft rejection could prevent or control underlying IBD is not correct. In a systematic review, Singh *et al.* described post-OLT IBD in a series of 609 patients in 14 studies after a mean follow-up of 4.8 years (range: 1.8 to 7.2 years). About 31% experienced improvement in IBD activity, 39% had no significant changes, and 30% had clinical worsening which justified optimization of treatment or colectomy.[7]

In another review using the University of Pittsburgh database which included 6,900 patients who underwent SOT, 14 patients developed IBD, including 12 post-OLT cases. The annual incidence of IBD in this sample was significantly higher compared with the general population (206 vs. 20 new cases/100,000 persons).[8] A recent review documented 82 cases of *de novo* IBD in the literature to date: 63 were diagnosed with RCU, 10 patients with CD, and 9 with indeterminate colitis (Table 1).[7-26] The higher prevalence of RCU in relation to CD and the prevalence of new cases after liver transplant compared to transplantation of other solid organs is justified by the number of cases of primary sclerosing cholangitis (PSC) in this population.[6]

In this case report, the UC was diagnosed nine years after HRT for congenital biliary atresia. There are 2 IBD case reports after HRT for this etiology: Takeo *et al*. and Riley *et al*. reported Crohn's disease (CD) and indeterminate colitis (IC), respectively, 8 and 9 years after TH.[9,26] In the literature we did not find records of severe UC recurrence after a second OLT that did not respond to biological therapy and required proctocolectomy.

Table 1. Table reporting all cases of post-OLT IBD.

Autor, Revista, ano	*Doença de Base*	*DII de novo*	*RCU*	*DC*	*NE/CI*
Author, Magazine, Year	**Base disease**	***de novo* IBT**	**RCU**	**DC**	**NE/CI**
Shaked et al.,[7] Ann Surg, 1992	3-CEP	10	10		
Cuoco et al,, [8] Am J Gastroenterol, 1997	1-HBV	1	1		
Riley et al.,[9] Am J Gastroenterol, 1997	2-CEP,4-HAI,1-AVB,1-HCG,4-x	12	7	4	1
Befeler et al.,[10] Trans, 1998	1-CEP	1	1		
Chalasani et al.,[11] Am J Gastroenterol, 1998	2-CEP	2	2		
Khan et al.,[12] Pediatr Gastroenterol Nutr, 1999	2-HAI. 1-CEP	3	3		
Safadi et al.,[13] Transplant Proc, 1999	2-CEP	2	2		
Ramji et al.,[14] Dig Dis Sci, 2002	1-CBP, 1-HBV	2	2		
Wong et al.,[15] Eur J Gastroenterol Hepatol,2002	NE	2	2		
Haagsma et al.,[16] Aliment Pharmacol Ther, 2003	3-HAI. 3-CEP	6	3	1	2
Papatheodoris et al.,[17] Gut, 2003	3-CEP	3	1		
Van de Vrie et al.,[18] Eur J Gastoenterol Hepatol, 2003	1-CEP	3	1	2	
Papadakis et al.,[19] Gut, 2004	1- HCV	1	1		
Ho et al.,[20] Eur J Gastroenterol Hepatol, 2005	1-CEP	1	1		
Maclean et al.,[21] Dis Colon Rectum, 2005	6-CEP, 4-HAI	10	10		
Verdonk et al.,[4] Am J Transplant, 2006	4-CEP, 4-HAI	8	7	1	
Worns et al.,[5] Am J Gastroenterol, 2006	2-HAI,1-HBV/DW/Cryptogenic	5	5		
Vu et al.,[22] Gastroenterol Clin Biol, 2006	2-HAI,1-DHA,1-HCV	4	3	1	
Cholangitas et al.,[23] Liver Transplant, 2007	3-CEP	3	3		
Halsey et al.,[24] Dig Dis Sci, 2007	1- Def. alpha 1 antitrypsin	3	3		
Barritt et al.,[25] IBD, 2008	1-HAI/CEP/CBP	3			
Takeo et al.,[26] Liver Int, 2013	1-AVB	1	1		
TOTAL		**82**	**63**	**10**	**9**

CEP, primary sclerosing cholangitis; HBV, hepatitis B; AIH, autoimmune hepatitis; AVB. biliary atresia; HCG, giant cell hepatitis; X, hepatitis non-A/B/C; CBP, primary biliary cirrhosis; DW, Wilson's disease; DHA, alcoholic liver disease, NE, unspecified, CI, indeterminate colitis.

Certain risk factors have been associated with the recurrence of post-OLT IBD, notably disease activity at the time of transplant, which increases the risk of reactivation three times compared to transplanted patients in remission.[4] In another study, Joshi *et al*. evaluated 110 patients who underwent OLT for primary sclerosing cholangitis (PSC). In multivariate analysis, smoking at the time of transplant was the only risk factor for post-OLT recurrence. (RR = 17; 95% CI 2-180).[24]

Immunosuppressive therapy after transplantation has also been examined in recent studies. Tacrolimus, a calcineurin inhibitor, has been associated with an increased risk of recurrence for post-OLT IBD. (RR = 2.58, 95% CI 1.5 to 5.2).[4] Sonwalkar *et al.* separately evaluated IBD remission rates at 1, 3, and 5 years post-OLT in two groups of patients.[25] In this study, immunosuppression initially used cyclosporine, prednisone, or azathioprine. In the second group, tacrolimus and prednisone were used. In the tacrolimus group remission rates were 94%, 69%, and 58% at 1, 3, and 5 years post-OLT, while in the non-tacrolimus group remission rates were considerably higher in years 3 and 5 (96%, 96%, and 89%, respectively).[25]

A third study, which describes the largest *de novo* IBD sample, tacrolimus was used in 71% of the 14 reported cases.[26] This agent is a potent inhibitor of interleukin-2 (IL-2), which is required in the development of regulatory T cells (Tregs) that play an important role in immune homeostasis of the gut. It is believed that reduced IL-2 levels cause a decrease in the concentration of Tregs and could be involved in the development of UC or CD.[16,27] On the other hand, the efficacy of tacrolimus in treating IBD has been reported by several studies.[28,29,30] No explanation for this contradiction is found in the literature.

Cyclosporine also inhibits calcineurin activity but uses cyclophilin as an intracellular mediator; in contrast, tacrolimus uses its mediator protein, FK506, which is known to be less ubiquitous compared to cyclophilin and is more present on T lymphocytes, resulting in a greater suppression of IL-2 synthesis.[4,16,31] There is no evidence that cyclosporine is a risk factor for *de novo* or recurrent IBD.

Azathioprine reduces the risk of IBD recurrence post-TH.[6] Haagsma *et al.* evaluated the effect of azathioprine on the control of disease activity and found that remission occurred in 96%, 96%, and 88% of cases 1, 3, and 5 years after OLT in one group that used azathioprine and 87%, 63%, and 54% in a group that did not use azathioprine, respectively.[16]

Corticosteroids are effective in preventing acute and chronic rejection, and also induce remission in IBD.[16] Moncrief *et al.* and Navaneethan *et al.* observed that

prednisone favorably alters the course of post-OLT IBD, but generates undesirable side effects.[32,33]

Mycophenolate mofetil has demonstrated efficacy in preventing rejection, but its effect on IBD is still in question.[34,35] Moreover, it is associated with enterocolitis disorder, which can be a confusing factor in diagnosing IBD activity.[6]

In this patient, the first diagnosis of UC after the first OLT occurred when cyclosporine was being used. Azathioprine and mesalazine were added at doses of 125 mg/day and 3.2 g/day, respectively, with clinical and endoscopic remission for the following two years. After retransplantation, immunosuppression was modified to include tacrolimus, azathioprine was suspended, and mesalazine was maintained. A year later, there was recurrence of the disease, which evolved corticoresistance and activity which was difficult to control even after azathioprine. Anti-TNF therapy was also ineffective and the patient underwent proctocolectomy.

CMV infection plays a special role in post-OLT IBD, since its manifestations can mimic active IBD or even coexist. Verdonk *et al*., in a series of cases, noted that all patients who developed new post-HT IBD had previous CMV infections.

Increased intestinal permeability during CMV infection has been demonstrated in human and mouse models and this defective barrier function is known to expose the immune system to antigens from the intestinal mucosa of the luminal microflora. Concomitantly, there is increased expression of cell adhesion molecule in the endothelial cells, which promotes greater leukocyte adhesion and plays an important role in the pathogenesis of endothelialitis.

This damage to the intestinal microcirculation explains the development of erosions and/or ulcerations seen in IBD. This increased intestinal permeability is also observed in cases of asymptomatic infection. Serologic disagreement with CMV (positive IgG donor and negative IgG receptor) increases the risk of new post-HT IBD 4.5-fold.[6,16] Our patient underwent a serologic change after the first OLT; the time this change occurred could not be identified. With respect to donor serum status, unfortunately CMV serology is not performed in Brazil.

Differential diagnosis can be quite difficult. Apart from diarrhea, fever, abdominal pain, anorexia, weight loss, nausea and vomiting can also be found after OLT. When a nonspecific clinical presentation is seen, diagnostic accuracy depends on laboratory, endoscopic and histological findings. Although CMV infection may affect any part of the gastrointestinal tract, the colon is the most common. Antigenemia tests allow rapid and direct detection of proteins (CMV pp65) in peripheral blood leukocytes, but have limitations such as instability of the sample at room temperature and low sensitivity in neutropenic patients.

Endoscopic findings in CMV colitis include irregular erythema, exudate, microerosions, diffusely edematous mucosa, several erosions or deep ulcers, and inflammatory pseudopolyp. These findings may hamper differential diagnosis with severe IBD without concomitant CMV infection. Conventional hematoxylin staining reveals large and expanded cells two to four times larger than neighboring cells, usually with eosinophilic intranuclear inclusions, sometimes surrounded by halo and with lower and cytoplasmic inclusions. However, these inclusions are seen in fewer than half of infections. Immunihistochemistry via immunoperoxidase increases diagnostic accuracy.

With regard to the endoscopic findings for diarrhea associated with *Clostridium difficile*, the colon was seen to be edematous and pink, with firm yellow plaques and dispersed by colonic segments.[6]

Histologically, pseudomembrane, cryptitis, crypt abscesses, and ulcerations of the mucosa were present. The sensitivity of ELISA diagnostic testing does not exceed 70% and tests such as neutralization and toxigenic culture are only available in Brazil at research centers.[36]

Even though medication-related causes are also related to the use of tacrolimus and cyclosporine, mycophenolate seems to be more important. Although it is part of immunosuppressive regimens, especially in cases in which some degree of renal toxicity associated with calcineurin inhibitor usage occurs, this drug may cause changes resembling colitis, Crohn's disease, and the colopathy observed in patients with graft versus host disease (GVHD). Histologically, it is described as cryptitis, inflammation of the lamina propria, increased intraepithelial lymphocytes and neuroendocrine cells, and endothelial injury.[6]

In this case, we faced various diarrheal complications with different presentations and different diagnoses, each with its own prognosis and specific treatment. In more recent developments, the patient presented a distinct diarrheal condition characterized by fewer bowel movements and bulkier stools. The expired hydrogen test using glucose as a substrate confirmed the diagnosis of small bowel bacterial overgrowth.

The need for repeated antibiotic treatments raised the possibility of lymphoproliferative disorder, an increasingly diagnosed disease associated with the use of calcineurin inhibitors. The move to rapamycin was based on the potential for this disease to evolve to lymphoma, and the fact that rapamycin is known to exert an anti-proliferative effect. A previous case report showed total disappearance of small intestine infiltration after the use of rapamycin.[37]

The therapeutic strategy in post-OLT UC is similar to treatments in non-transplanted patients; 5-aminosalicylic acid at a dose of 2.4 g/day is indicated to induce remission and maintenance of mild to moderate UC. Topical therapy may be used in distal UC. In moderate to severe disease, oral or intravenous corticosteroids should be used (prednisone, 1 mg/kg/day, not to exceed 60 mg/day) in the induction phase and then gradually decreased by approximately 20% per week. Maintenance must continue with azathioprine at a dose of 2 to 2.5 mg/kg/day.

Anti-TNF agents may be useful in cases refractory to conventional treatment, but the small amount of research in the literature involving the use of biologicals in transplant patients (who are undergoing concomitant anti-rejection therapy) suggests caution related to the risk of infectious and autoimmune diseases and neoplasms.

Recently, Indriolo *et al*. conducted a systematic review of the literature on this subject, identifying only 22 patients using anti-TNF for post-OLT IBD. (Table 2).[26, 38-42] This number included patients with CD, UC, indeterminate colitis, and pouchitis treated with infliximab or adalimumab who were followed for an average period of 18 months. At week 54, endoscopic and clinical improvement was seen in 77% (17/22) and 63% (7/11) of patients, respectively. There were 5 infectious complications, cancer and 2 cases of the first report of autoimmune disease.[38]

Table 2. Anti-TNF Therapy for Inflammatory Bowel Disease after liver transplantation.

Author	Number of patients	Clinical Response	Endoscopic Response	Adverse effects
Sandhu et al.[26]	6	67%	-	Lupus Erythematosus Systemic
				Colorectal Cancer
Mohabbat et al.[39]	8	87.75%	42.9	Clostridium difficile colitis
Lymphoproliferative disorder				Bacterial pneumonia oral candidiasis Cryptosporidium
Lal et al.[40]	1	100%	100%	-
El-Nachef et al.[41]	2	100%	-	-
Indriolo et al.[42]	4	75%	33	molluscum Contagiosum

LUPUS ERYTHEMATOSUS COLORECTAL CANCER

In view of severe recurrence of UC after transplantation, corticoresistance, and CMV infection after starting azathioprine, we opted to use infliximab, but the disease proved refractory to biological therapy and the patient underwent total proctocolectomy.

The need for colostomy in patients with IBD post-OLT has also been evaluated in previous studies. Ho *et al*. observed colectomy rate of 35% after OLT.[23] Another study identified a need for colectomy in 7 of a total of 20 patients with post-OLT IBD which found UC in serious activity in three patients (43%), colorectal cancer in three patients (43%) and benign stenosis in one patient (14%).[20]

Post-OLT exacerbation of pre-existing IBD has a severe clinical course, requiring increasing drug therapy and colectomy.[26] On the other hand, primary diagnosed IBD usually responds to treatment. Takeo *et al*. reviewed 49 cases of active *de novo* IBD; 37 showed good therapeutic response with remission after clinical treatment. In our work, the unfavorable evolution of recurrence was observed.

In summary, this report presented a clinical case of a patient with *de novo* UC after an initial liver transplant to treat congenital biliary atresia and severe recurrence of IBD after retransplantation for chronic rejection, who presented intestinal CMV infection and lymphoproliferative disorder associated with the use immunosuppressants.

We did not find similar cases in the literature; in this patient we were able to assess risk factors, disease progression, and response to treatment in both primo-diagnosed disease and the recurrence.

CONCLUSION

The natural history of post-OLT IBD is variable. In a third of cases, the clinical course becomes more serious. The incidence of *de novo* IBD is about ten times greater than in the general population. The differential diagnosis in this scenario must be careful, mainly excluding infection, lymphoproliferative disorders, and drug reactions. Some risk factors have been identified, such as immunosuppression with tacrolimus and CMV infection. Recurrence of pre-existing IBD seems to have a more serious presentation when compared to *de novo* IBD. Anti-TNF agents may be useful in cases refractory to conventional treatment, but larger studies are needed to assess the safety of biological therapy combined with anti-rejection therapy.

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CASE REPORT

SMALL BOWEL SIGNET-RING NEOPLASM IN A PATIENT WITH CROHN'S DISEASE: CASE REPORT

Ludmila Resende Guedes[1], Henrique Carvalho Rocha[1], Isabel Pamplona Corte Real Forn[1], Guilherme Grossi Lopes Cançado[1], Julia Faria Campos[1], Francisco Guilherme Cancela e Penna[1], Eduardo Garcia Vilela[2], Aloísio Sales da Cunha[3], Maria de Lourdes Abreu Ferrari[4]

ABSTRACT

Crohn's disease is a chronic inflammatory process involving all three layers of the digestive system; in the long term it can lead to structural deformities and surgical procedures may be required in about 80% of cases. The most common complications include fistulas, stenosis, and abscess, besides an increased rate of neoplastic diseases in this population. Management of this disease has undergone many changes since the introduction of biological therapy. Here we report a case of severe Crohn's disease that did not respond well to clinical treatment and complicated with a rare condition: signet-ring cell carcinoma of the small bowel. At the time of diagnosis this case was already advanced and metastatic, with a poor prognosis and no possibility of cure. Due to intestinal resection, the patient presented with short bowel syndrome, intestinal malabsorption, and water and electrolyte disturbances, which are frequent causes of admissions to our service.

Keywords: Crohn's Disease, Signet-ring cell carcinoma, Short bowel syndrome.

INTRODUCTION

Since ancient Greece there have been reports of patients showing signs and symptoms similar to those understood today to be caused by Crohn's disease (CD). Although it is not a new disease, it was only formally described in 1932 in a paper published in JAMA entitled "Regional Ileitis"[1]. In 1960, the concept of the disease was finalized and distinguished from another inflammatory bowel condition: ulcerative colitis (UC). Both diseases were properly differentiated in terms of clinical characteristics, location, behavior and histology[2].

CD is a chronic inflammatory condition that can potentially involve any segment of the gastrointestinal tract from the mouth to the anus, but it is more likely to be found in the distal portion of the small bowel and the proximal section of the colon[3]. Management of inflammatory bowel disease (IBD) is being studied and has undergone changes particularly in the past 10 to 15 years since biological therapy was introduced in gastroenterology. Previously, the main objective was to obtain sustained clinical remission, while today physicians attempt to achieve mucosal healing[2,4,5]. Complications related to CD include not only structural damage to the digestive system like stenosis and fistulas, but also increased risk of colorectal cancer.

It is well known that Crohn's colitis elevates this risk according to its extension and duration. Although more rare, small bowel neoplasms can be associated with the persistent chronic inflammation present in CD, which explains the higher incidence in these patients compared to the general population. Intestinal carcinoma comprising signet-ring cells is very uncommon and diagnosis can be difficult, especially when the small intestine is involved[5].

Here we report a case of a patient with severe and refractory CD who was diagnosed with signet-ring cell small bowel carcinoma and developed short intestinal syndrome after enterectomy.

1. Gastroenterologist trained at the Clinical Hospital of the Federal University of Minas Gerais (UFMG).
2. Assistant Professor, Department of Internal Medicine, UFMG Medical School.
3. Professor, UFMG Medical School; Coordinator, Residency Program in Gastroenterology, UFMG Clinical Hospital.
4. Professor, Department of Internal Medicine, UFMG Medical School; Coordinator, Alfa Institute Bowel Clinic at UFMG Clinical Hospital.
Correspondence to: Avenida Alfredo Balena, 110, 2º andar - Belo Horizonte, MG, Brasil. CEP: 30130-100. E-mail: ludmilaresende@hotmail.com

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CASE REPORT

Male, 40 years old, retired, born in Belo Horizonte (Minas Gerais) was being followed in the intestinal diseases outpatient clinic at the University of Minas Gerais Clinical Hospital (HC-UFMG). He was diagnosed with penetrating CD in 2005 involving both the ileum and colon associated with perianal fistulas (Montreal A2 L3 B3p). There were no other past diseases and patient was not a smoker.

The patient was initially treated with mesalazine and azathioprine; in 2008 infliximab was introduced due to refractory symptoms.

The patient first underwent surgery in 2010. Right ileocolectomy was performed to treat fistulas affecting the intestine. Subsequent to this procedure, the patient took medications and attended appointments on an irregular basis.

In February of 2013 he was admitted to our emergency service with exacerbated perianal fistulas. MRI showed a complex intersphincteric fistula with an associated abscess, which was treated surgically using seton drainage. At that time the patient was taking mesalazine, azathioprine and infliximab.

Seven months later he was readmitted to the emergency room with abdominal pain, bloody diarrhea, and severely malnourished appearance. He also had sterile pyocytes in urine and hematuria. The initial hypothesis was exacerbated CD. Laboratory tests showed RCP < 5mg/L; HR 46mm/h; anemia and iron deficit; normal leucocytes, kidney function, electrolytes, and liver function; albumin: 3.1mg/dL; CEA: 2.2 ng/mL (up to 3.0 ng/mL) and negative screening for renal tuberculosis.

Exploratory x-rays and endoscopy were performed. The abdominal ultrasound showed a hard mass in the right lower abdomen near the bladder. Computerized tomography with enterography confirmed the hypothesis of a fistula between the small bowel and the bladder, as well as signs of active CD (Figure 1). Colonoscopy demonstrated erosive ileitis, which was confirmed by biopsy.

The patient underwent surgery on October 15, 2013; laparotomy showed a large mass of inflammatory tissue involving loops of small bowel and the bladder. The mass was resected, a long amount of small bowel was removed (leaving 100cm), and an ileostomy was performed. The bladder was also partially removed and a double J tube was implanted in the right ureter.

Post-surgical complications included suture dehiscence, the need for total parenteral nutrition, and sepsis at the catheter site, which was treated with vancomycin and meropenem and required a long hospital stay.

The biopsy revealed signet-ring cell carcinoma with CK 20+, EMA+ and Ki 67 60% in the immunohistochemistry (Figure 2).

The tumor stage based on the TNM staging system was IV because of a metastasis found in the ilium via bone scintigraphy. In November 2013 palliative chemotherapy with irinotecan, fluorouracil and leucovorin was initiated.

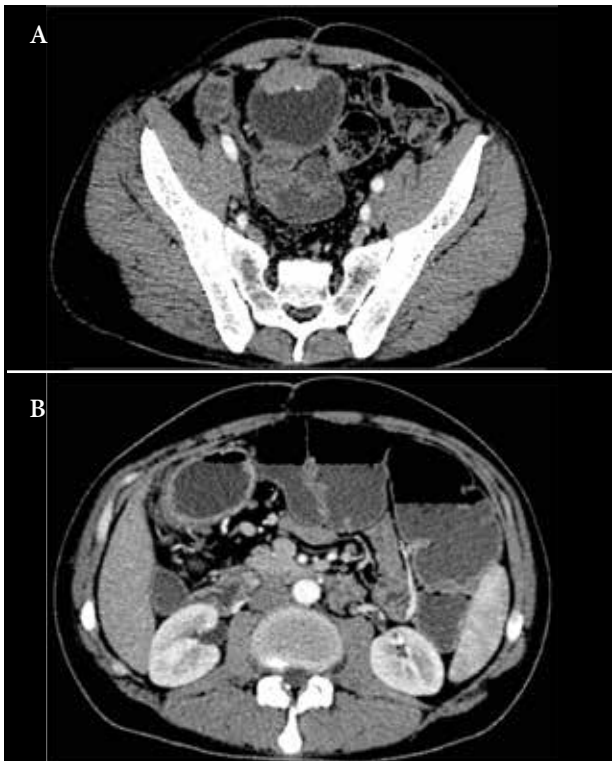

Figure 1. Abdominal CT. A: Mass and enterovesical fistula. B: CD activity (Courtesy of Radiology, HC-UFMG).

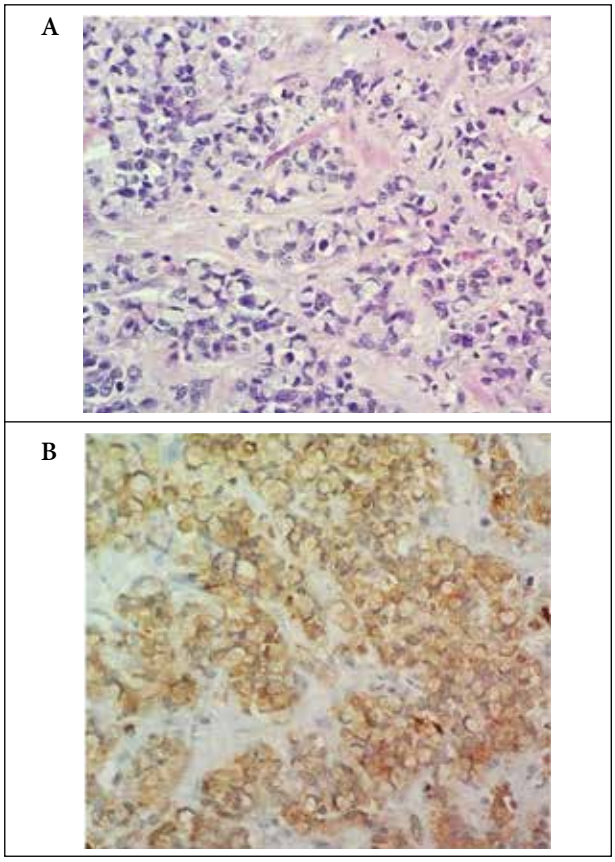

Figure 2. Biopsy. A: Signet-ring cells (hematoxylin-eosin 400x). B: CK 20+ (immunohistochemistry).

Due to the multiple loop resections, the patient developed short bowel syndrome which was difficult to manage. He is receiving reposition of magnesium, calcium, bicarbonate, sodium, potassium, and an antidiarrheal medication, but still requires parenteral support on a monthly basis. Specific treatment of CD was discontinued while the patient undergoes chemotherapy.

DISCUSSION

The physiopathology of CD is not completely understood. However, in recent decades the immune and inflammatory cascades have been the subject of study in an attempt to learn how the process can be interrupted.

Selection of the most appropriate management seems to rely on the presentation and the extension of the disease[2]. Location is best evaluated by endoscopy and radiography. The most common scale of phenotypes is the 2005 Montreal Classification, which modified the 1998 Vienna criteria (Table 1).

With regards to natural history, CD is a progressive illness with a high lifetime risk of developing stricturing or penetrating disease requiring surgery in 70-80% of cases[6]. The introduction of biological therapy with tumoral necrosis alpha inhibitors (anti-TNF α) has significantly changed management of CD. These medications are effective at maintaining clinical and endoscopic remission of inflammatory and penetrating behaviors. They also permit a reduction in the rates of surgery and hospital admission. Nevertheless, the long-term effects of changing the natural history of the disease are still unknown[10].

Most recent guidelines recommend early initiation of immunosuppressant therapy in extensive or complicated CD[6–8]. In cases with mild inflammatory behavior aggressive therapy should be withheld to avoid long-term side effects of the medication, which outweigh benefits in these cases. It is consequently necessary to determine the risk factors for poor prognosis and to identify which patients will benefit from early aggressive therapy. Markers for poor prognosis in 5–10 years which have already been identified include age under 40 at diagnosis, presence of perianal disease, need for corticosteroids in the first exacerbation, and upper gastrointestinal tract involvement[9].

Table 1. Montreal Classification of Crohn's disease.

Age of diagnosis	A1 – Under 16 years of age
	A2 – Between 17 and 39
	A3 – Above 40
Location	L1 – Ileal
	L2 – Colonic
	L3 – Ileocolonic
	L4 – Isolated upper disease
Behavior	B1 – Non-penetrating non-stricturing
	B2 – Stricturing
	B3 – Penetrating
	P – Perianal disease modifier

There are therefore basically two strategies for treating CD. The first one consists of a step-up system beginning with the use of aminosalicylates in mild ileal disease and budesonide in mild/moderate ileocolonic disease, followed by corticosteroids in moderate/severe or refractory cases and thiopurines in cases of dependency or resistance to corticosteroids, and finally biological therapy if no success is obtained from these medications. The other option, top-down management, begins with biological therapy associated with thiopurines without initial use of corticosteroids. Remission rates and mucosal healing in the top-down approach were superior after a two-year follow-up (73.1% top-down versus 30.4% step-up, p< 0.002) (Figure 3)[2,11].

In clinical practice, selecting the correct therapy for CD is a challenge we face every day. In our case report, some of the poor prognostic factors mentioned previously can be noted, such as the age of diagnosis under 40 years and penetrating disease with perianal involvement. Since this patient was diagnosed in 2005, management of CD has changed significantly. Even though he received optimized treatment after three years of the disease, he still experienced severe complications, needed surgery, and had a poor outcome with a neoplastic disease.

The rate of colorectal cancer in CD patients is higher than in the general population, and the age of diagnosis is lower while the mortality rate is higher. The risk is proportional to the magnitude and duration of the disease.

Although studies on UC are more consistent, Crohn's colitis may behave similarly in terms of carcinogenesis; consequently, the American Gastroenterological Association (AGA) and the British Society of Gastroenterology recommend the same UC colorectal cancer screening program for patients with Crohn's colitis[12].

Development of small bowel neoplasm is described as a rare complication of CD[3]. The most common location is the ileum and disease is usually in advanced stages at diagnosis (Table 2), as seen in this case report. There is no recommended screening in these cases; CEA is not an accurate marker and no IBD-specific risk factors have been identified[3,5,13].

Given the rarity of small bowel neoplasms (they account for only 5% of all gastrointestinal cancers), few

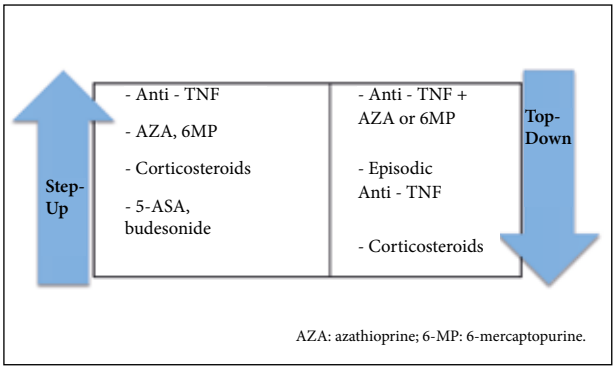

Figure 3. Step-up and top-down therapies.

Table 2. TNM staging system for small bowel adenocarcinoma[3].

Stage	Tumor (T)	Node (N)	Metastasis (M)	% Cases at diagnosis
0	Tis	N 0	M 0	2,7
1	T 1 or T 2	N 0	M 0	12,0
2	T 3 or T 4	N 0	M 0	27,0
3	Any N	N 1	M 0	26,0
4	Any T	Any N	M 1	32,3

studies have been conducted in this field[3]. Studies of colorectal cancer have shown that both risk of metastasis and prognosis depend on the histological type of the neoplasm. In 1675 autopsies, the rate of metastasis in mucinous and signet-ring types were significantly higher than in adenocarcinoma type neoplasms (33.9% and 61.2% versus 27.6%, respectively; $P < 0.0001$), and the risk of multiple metastasis increased (58.6% and 70.7% versus 49.9%, respectively; $P = 0.001$), respectively. While the liver was the most common metastasis site for cases involving adenocarcinoma, the peritoneum was most frequently involved in the other subtypes[14]. In another study, 2764 patients with colorectal cancer were subcategorized according to histological subtype. Of this total, 6% were mucinous carcinoma and 1.1% were signet-ring type. Both of these types were more common in patients under 50 years of age and in the right colon; they tended to be more undifferentiated, and the rate of recurrence and nodal metastasis, chance of locally invasive disease, and advanced stage at time of diagnosis were all greater compared to adenocarcinoma, with statistical significance. The 5-year survival rate was worse but not statistically significant in the signet-ring subgroup. Multivariate analysis showed that the presence of signet-ring cells was an independent factor for bad prognosis (HR 1.9, 95% IC 1.1–3.0)[15].

In this case, enterectomy was performed to treat both CD and the neoplasm, leaving 100 cm of small bowel. Patients with less than 180 cm of intestine are at risk for short bowel syndrome, a chronic malabsorptive state requiring water, electrolyte, or nutritional support. Furthermore, ileal resection promotes cyanocobalamin deficit and malabsorption of biliary acids, which reduces not only the absorption of fat-soluble elements but also increases oxalate absorption and the risk of kidney stones. The loss of the ileocecal valve increases the velocity of intestinal transit and allows bacterial overgrowth, which contributes to diarrhea[16].

CONCLUSION

Small bowel neoplasm associated with CD is an uncommon condition and diagnosis is challenging. The signet-ring cell histological subtype is even more rare and tends to have an ominous prognosis with an elevated incidence of metastasis. There are few studies in this field and as of this writing no risk factors related to IBD have been proven to increase the chance of developing this specific cancer. It is nevertheless possible that the duration and intensity of mucosal inflammation can contribute to the process of carcinogenesis, as in colorectal cancer. Consequently, new management of CD for mucosal healing can have an important impact in preventing this complication.

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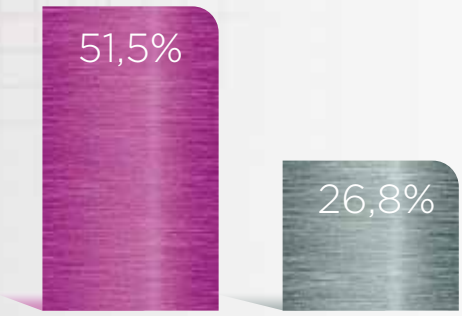

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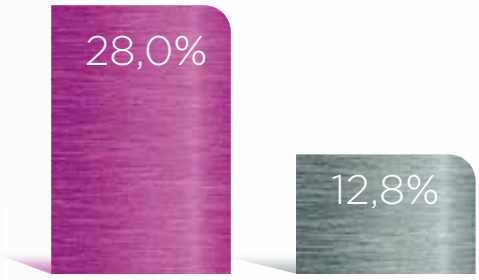
(n = 66)

Semana 52 - IC95% (8,9, 40,6)

Adaptado de: Hanauer S, *et al.* Am J Gastroenterol. 2012;107(Suppl1): A1542.

Subpopulação com falha prévia ao tratamento anti-TNFα[2]



Entyvio* 300mg
+ terapias concomitantes
(n = 82)

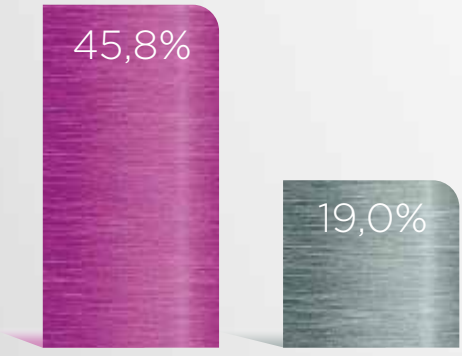
Placebo
+ terapias concomitantes
(n = 78)

Semana 52 - IC95% (3,0, 27,5)

Adaptado de: Hanauer S, *et al.* Am J Gastroenterol. 2012;107(Suppl1): A1542.

REMISSÃO DURADOURA DA RETOCOLITE ULCERATIVA (52 SEMANAS)[3]

Subpopulação virgem de tratamento anti-TNFα[3]



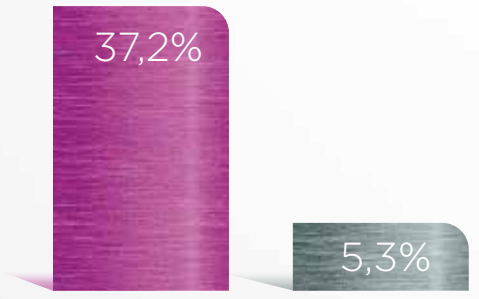
Entyvio* 300mg
+ terapias concomitantes
(n = 43)

Placebo
+ terapias concomitantes
(n = 79)

IC95% (12,4, 41,2)

Adaptado de: Feagan B, *et al.* Am J Gastroenterol.2012;107 (S1):S609-S610. Abstract 1522.

Subpopulação com falha prévia ao tratamento anti-TNFα[3]



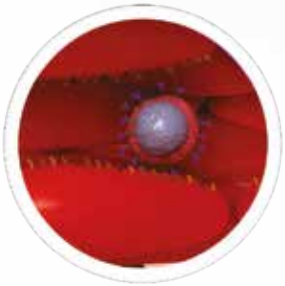
Entyvio* 300mg
+ terapias concomitantes
(n = 43)

Placebo
+ terapias concomitantes
(n = 79)

IC95% (15,8, 48,0)

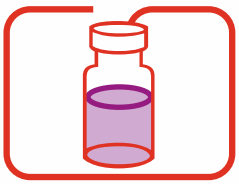
Adaptado de: Feagan B, *et al.* Am J Gastroenterol.2012;107 (S1):S609-S610. Abstract 1522.

O PRIMEIRO E ÚNICO BIOLÓGICO COM AÇÃO SELETIVA NO TRATO GASTROINTESTINAL APROVADO PARA TRATAMENTO DA ***DOENÇA DE CROHN (DC) E RETOCOLITE ULCERATIVA (RCU).***[1]



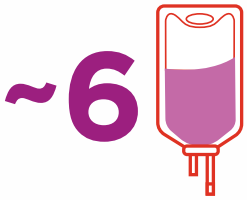
MECANISMO DE AÇÃO SELETIVO[1]

- Entyvio* liga-se especificamente à integrina α4β7 encontrada nas células T que migram preferencialmente para o trato gastrointestinal inibindo a adesão à MadCAM-1, restringindo o tráfego linfocitário e reduzindo a inflamação intestinal[1,4]



PERFIL DE SEGURANÇA[4]

- Taxas relatadas de infecções graves similares ao placebo[4]
- Baixa taxa de imunogenicidade[4]



POSOLOGIA[4]

- Dose padrão para todos os pacientes[4]
- Ajustes baseados no peso não são necessários[4]
- Infusão de frasco único nas semanas 0, 2 e 6 e depois a cada 8 semanas[4]

Referências bibliográficas: 1. Poole RM. Vedolizumab: first global approval. Drugs. 2014;74(11):1293-303. **2.** Hanauer S, *et al.* Vedolizumab Maintenance Therapy for Crohn's Disease: results of GEMINI II, a randomized, placebo-controlled, double-blind, multi-centre phase 3 trial. Am J Gastroenterol. 2012;107 (Suppl 1):A1542. **3.** Feagan B, *et al.* Vedolizumab Maintenance Therapy for Ulcerative Colitis: Results of GEMINI I, a Randomized, Placebo-Controlled, Double-Blind, Multicenter Phase 3 Trial. Am J Gastroenterol. 2012;107(S1):S609–S610. Abstract 1522. **4.** Entyvio* [Bula]. São Paulo: Takeda Pharma Ltda.

Entyvio* - vedolizumabe. USO INTRAVENOSO. USO ADULTO. Indicações: Entyvio* é indicado para o tratamento de pacientes adultos com: Colite ulcerativa moderada a grave na fase ativa que apresentaram uma resposta inadequada, perda de resposta ou são intolerantes ao tratamento convencional ou a um antagonista de fator de necrose tumoral alfa (TNF-α). Doença de Crohn moderada a grave na fase ativa que apresentaram uma resposta inadequada, perda de resposta ou são intolerantes ao tratamento convencional ou a um antagonista de fator de necrose tumoral alfa (TNF-α). **Contraindicações:** Entyvio* é contraindicado para pacientes com hipersensibilidade ao vedolizumabe ou a qualquer um dos excipientes do produto. Entyvio* é contraindicado na presença de infecções ativas graves, tais como tuberculose, septicemia, citomegalovírus, listerioses e infecções oportunistas, como leucoencefalopatia multifocal progressiva (LMP). **Cuidados e advertências:** Em estudos clínicos foram relatadas reações relacionadas à infusão e reações de hipersensibilidade, sendo a maioria delas de gravidade leve a moderada. Infecções: O tratamento com Entyvio* não deve ser iniciado em pacientes com infecções ativas graves até que as infecções sejam controladas, e os médicos devem considerar a suspensão do tratamento em pacientes que desenvolvem uma infecção grave durante o tratamento crônico com Entyvio*. Entyvio* é contraindicado em pacientes com tuberculose ativa. Alguns antagonistas de integrina e alguns agentes imunossupressores sistêmicos foram associados com leucoencefalopatia multifocal progressiva (LMP). Nenhum caso de LMP foi relatado em estudos clínicos com vedolizumabe. Uso anterior e concomitante de produtos biológicos:Não há dados disponíveis de estudos clínicos do vedolizumabe para pacientes previamente tratados com natalizumabe ou rituximabe. Uso durante a gravidez e a lactação - Categoria B de Risco na Gravidez - Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião dentista. As mulheres em idade fértil devem usar métodos contraceptivos adequados para evitar a gravidez e o seu uso deve ser mantido durante pelo menos 18 semanas após o último tratamento com Entyvio*. Lactação: Não se sabe se o vedolizumabe é excretado no leite humano ou absorvido sistemicamente após a ingestão. **Interações medicamentosas:** Não foram conduzidos estudos de interação. O vedolizumabe foi estudado em pacientes adultos com colite ulcerativa e doença de Crohn com administração concomitante de corticosteroides, imunomoduladores (azatioprina, 6-mercaptopurina e metotrexato) e aminosalicilatos. As análises da farmacocinética da população sugerem que a administração concomitante de tais agentes não teve efeito clinicamente significativo na farmacocinética do vedolizumabe. O efeito do vedolizumabe na farmacocinética dos medicamentos comumente coadministrados não foi estudado. Vacinações: As vacinas vivas, em particular vacinas vivas orais, devem ser usadas com cautela durante o tratamento com Entyvio*. **Reações adversas:** A proporção de pacientes que descontinuaram o tratamento devido a eventos adversos foi de 9% para os pacientes tratados com vedolizumabe e 10% para os pacientes tratados com placebo. Nos estudos combinados do GEMINI I e II, as reações adversas que ocorreram em ≥5% dos pacientes foram náusea, nasofaringite, infecção do trato respiratório superior, artralgia, febre, fadiga, cefaleia, tosse. Reações relacionadas à infusão foram relatadas em 4% dos pacientes que estavam recebendo vedolizumabe. **Atenção: este produto é um medicamento novo e, embora as pesquisas tenham indicado eficácia e segurança aceitáveis, mesmo que indicado e utilizado corretamente, podem ocorrer eventos adversos imprevisíveis ou desconhecidos. Nesse caso, notifique os eventos adversos pelo Sistema de Notificações em Vigilância Sanitária - NOTIVISA, disponível em www.anvisa.gov.br/hotsite/notivisa/index.htm ou para a Vigilância Sanitária Estadual ou Municipal. Posologia:** Colite ulcerativa A dose recomendada é 300 mg de Entyvio*, administrada por infusão intravenosa nas Semanas 0, 2 e 6 e depois a cada oito semanas. Em pacientes que responderem ao tratamento com Entyvio*, o uso de corticosteroides pode ser reduzido e/ou interrompido – à critério médico. Doença de Crohn A dose recomendada é 300 mg de Entyvio*, administrada por infusão intravenosa nas Semanas 0, 2 e 6 e depois a cada oito semanas. Os pacientes com doença de Crohn que não apresentarem resposta podem se beneficiar de uma dose de Entyvio* na Semana 10 (veja ADVERTÊNCIAS E PRECAUÇÕES). Nos pacientes que responderem, continuar o tratamento a cada oito semanas a partir da Semana 14. MS – 1.0639.0271 **SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO. MEDICAMENTO SOB PRESCRIÇÃO MÉDICA.** *Marca depositada por Millennium Pharmaceuticals. ENT_1014_0715_VPS.

Contraindicação: Hipersensibilidade a qualquer um dos componentes do medicamento.
Interação medicamentosa: não foram conduzidos estudos de interação.

Produzido em junho/2016.

SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.

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- **Pentasa®** oferece flexibilidade posológica e tratamento individualizado[1]
- **Pentasa®** sachê com tomada única diária* contribui para uma melhor adesão ao tratamento[4,5]

Pentasa® - mesalazina - Comprimidos: USO ADULTO E PEDIÁTRICO (em crianças acima de dois anos de idade). Enema, Sachê e Supositórios: USO ADULTO. INDICAÇÕES: Comprimidos, Enema e Supositórios: Doença Inflamatória Intestinal (Crohn e RCU). Sachê: RCUI. CONTRAINDICAÇÕES: hipersensibilidade aos salicilatos ou a qualquer componente das formulações; em casos de doenças renais ou hepáticas severas. CUIDADOS E ADVERTÊNCIAS: pacientes alérgicos à sulfassalazina devem ter cautela com uso de Pentasa; descontinuar em caso de reações de intolerância aguda, cólicas abdominais, dor abdominal aguda, febre, dor de cabeça severa e erupção cutânea, discrasia sanguínea, mio e pericardite. Usar com cautela quando coexistir asma, função hepática ou renal prejudicada. Uso durante a gravidez e lactação: Pentasa® deve ser utilizado com cautela durante a gravidez e lactação. Efeito na capacidade de dirigir e operar máquinas: O tratamento com Pentasa® não parece ter efeito na capacidade de dirigir e/ou operar máquinas. Uso em idosos, crianças ou outros grupos de risco: Comprimidos: Não é recomendado o uso de Pentasa® comprimidos em crianças com menos de dois anos de idade. Enema, Sachê e Supositórios: Não é recomendado o uso de Pentasa® em crianças. Interações medicamentosas e com exames laboratoriais: A terapia combinada de Pentasa® com azatioprina ou 6-mercaptopurina ou tioguanina mostra maior frequência de mielossupressão; raramente pode ocorrer alteração nas funções hepáticas e renais. Interação com alimento: Comprimidos e Sachê: O trânsito e a liberação de mesalazina após administração oral são independentes da coadministração de alimento, enquanto que a absorção sistêmica será reduzida. Enema e Supositórios: Não há dados disponíveis até o momento sobre a interação de Pentasa® com alimentos. Reações adversas: diarreia, náusea, dor abdominal, cefaleia, vômitos, eczema e erupção cutânea; reações de hipersensibilidade; como prurido, desconforto retal e urgência podem ocorrer. POSOLOGIA: Comprimidos: Retocolite Ulcerativa - Adultos: Tratamento agudo: Dose individual de até 4 gramas divididas ao longo do dia. Tratamento de manutenção: Dose inicial recomendada de 2 g uma vez ao dia; Retocolite ulcerativa - Crianças com mais de dois anos de idade: Tratamento agudo e de manutenção: Dose individual recomendada de 20 a 30 mg/kg de peso corpóreo ao dia, em doses divididas; Doença de Crohn - Adultos: Tratamento agudo e de manutenção: dosagem individual de até 4 g ao dia, em doses divididas; Doença de Crohn - Crianças com mais de dois anos de idade: Tratamento agudo e de manutenção: Dose individual recomendada de 20 a 30 mg/kg de peso corpóreo ao dia, em doses divididas. Enema: Para adultos: Um enema ao deitar. Sachê: Retocolite Ulcerativa - Adultos (em pacientes acima de 18 anos de idade): Tratamento agudo: Dose individual de até 4 gramas divididas ao longo do dia (4 sachês de 1g ou 2 sachês de 2g). Tratamento de manutenção: Dose inicial recomendada de 2 g uma vez ao dia (2 sachês de 1g ou 1 sachê de 2g). Supositórios: Proctite ulcerativa - Adultos: Um supositório, uma a duas vezes ao dia por 4 semanas. VENDA SOB PRESCRIÇÃO MÉDICA. Material de uso exclusivo à classe médica. SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO. Reg. MS: 1.2876.0002. Farm. Resp.: Helena Satie Komatsu - CRF/SP: 19.714 - Laboratórios Ferring Ltda. Praça São Marcos, 624 - 05455-050 - São Paulo - SP. CNPJ: 74.232.034/0001-48. (CCDS 2011/06_v1.0_2)

CONTRAINDICAÇÕES: hipersensibilidade aos salicilatos ou a qualquer componente das formulações. **INTERAÇÕES MEDICAMENTOSAS:** A terapia combinada de Pentasa com azatioprina ou 6-mercaptopurina ou tioguanina mostra maior frequência de mielossupressão.

REFERÊNCIAS: 1. Bula do produto. 2. Christensen LA, Fallingborg J, Abildgaard K et al. Topical and systemic availability of 5-aminosalicylate: comparisons of three controlled release preparations in man. Aliment Pharmacol Ther, 1990; 4(5): 523-33. PMID: 2129640. 3. Christensen LA, Slot O, Sanchez G et al. Release of 5-aminosalicylic acid from Pentasa during normal and accelerated intestinal transit time. Br J Clin Pharmacol, 1987; 23(3): 365-9. PMID: 3567055. 4. Kane S, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. Am J Med. 2003. 114(1):39-43. PMID: 12543288. 5. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther, 2001; 23(8): 1296-310. PMID: 12543288.

* Para tratamento de manutenção com Pentasa sachê 2g.

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