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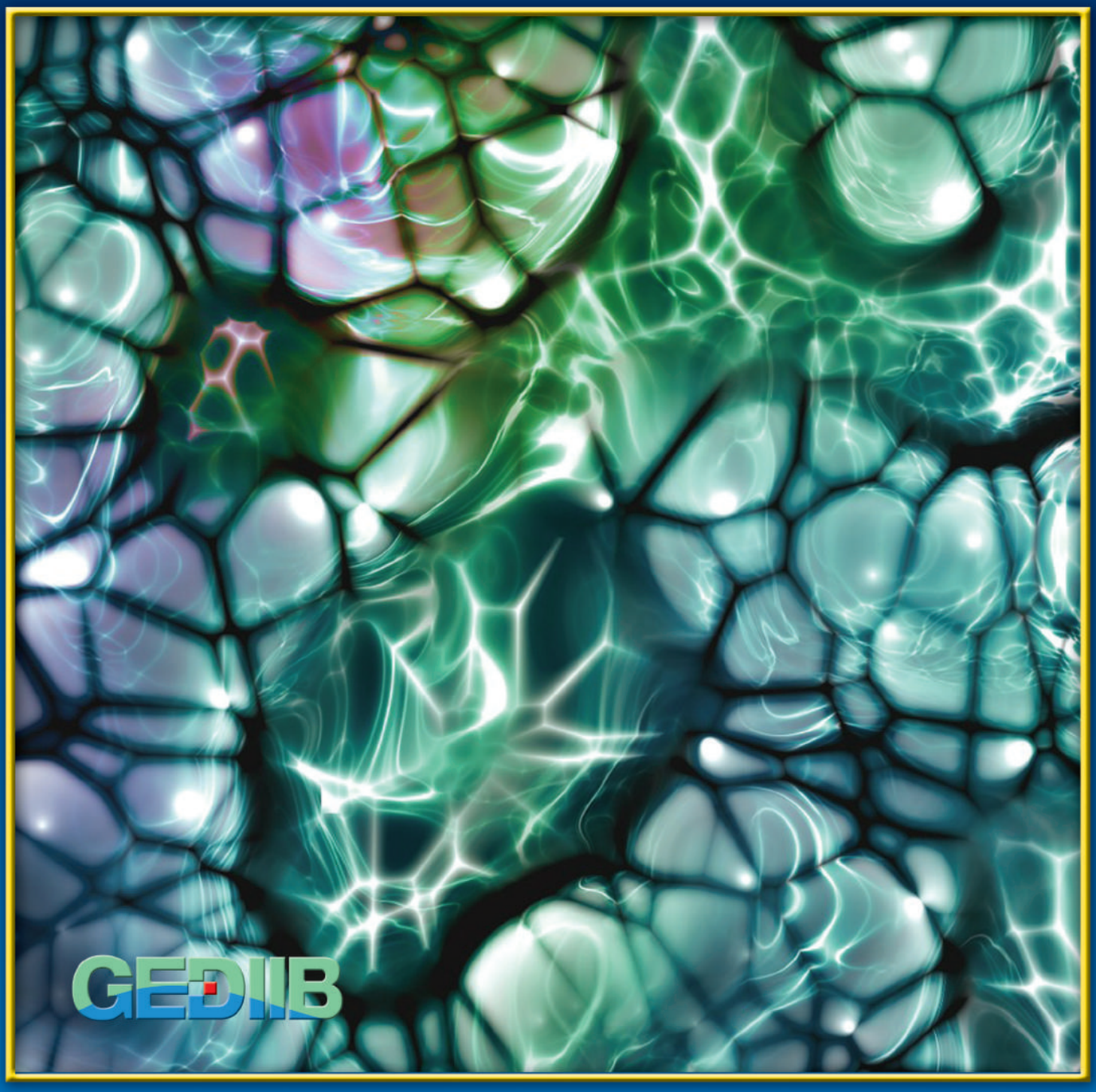

Quando a terapia convencional falha...

1997
Início dos ensaios clínicos de Artrite Reumatoide (AR)[4]

2002
Início dos ensaios clínicos de Doença de Crohn[4]

2003
Aprovado para AR moderada a grave com resposta inadequada a uma ou mais DMARDs[4]

2006
Aprovado para Artrite Psoriásica[4]

2007
Aprovado para Doença de Crohn e Espondilite Anquilosante ativa moderada a grave, que apresentam resposta inadequada à terapia convencional[4]

2008
Aprovado para Psoríase em Placas moderada a grave[4]

2011
Aprovado para Artrite Idiopática Juvenil ativa[4]

2014
Aprovado para Retocolite Ulcerativa moderada a grave no Brasil[4]

2015
Aprovado para Espondiloartrite Axial Não Radiográfica[4]

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, 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 confirmadasInsuficiência 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), glicocorticóides, 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

HUMIRA® (adalimumabe) proporciona remissão sustentada[1,2,3]

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.. **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 2 a < 4 anos e 40 mg para pacientes entre 4 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 k, 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. BU38.

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 abatacept tem sido associada a aumento do risco de infecções, incluindo infecções sérias, quando comparada a antagonistas de TNF isolado.

Referências Bibliográficas: 1. Rutgeerts P et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology 2012;142:1102–11. **2.** Colombel JF et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007 Jan;132(1):52-65. **3.** Colombel JF et al. Four-year maintenance treatment with adalimumab in patients with moderately to severely active ulcerative colitis: Data from ULTRA 1, 2, and 3. Am J Gastroenterol. 2014 Nov;109(11):1771-80 **4.** Bula do produto Humira® (adalimumabe)

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GRUPO DE ESTUDOS DA
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Exemples:

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Books and other monographs (list all authors/editors and do not use "et al."):

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Chapter in a book (list all authors and do not use "et al."):

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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,

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Editorial

Medical treatment of Crohn's disease (CD) and ulcerative colitis (UC) has greatly improved over the past several years. Two decades ago, the first reports of the use of monoclonal antibodies targeting tumour-necrosis factor alpha heralded a revolution in treatment options for more severely affected individuals. Golimumab and vedolizumab are the latest additions to the therapeutic landscape in inflammatory bowel disease. Vedolizumab, a monoclonal antibody that blocks integrin $\alpha 4\beta 7$, has recently received European and US regulatory approval for treatment of UC and CD on the basis of encouraging results from a large phase III trial programme. Preventing the infiltration of the gastrointestinal mucosa by circulating cells of the immune system using antibodies targeting the adhesion molecules involved represents an attractive new treatment option and a whole new line of research in IBD. Recognizing potential new therapeutic targets is often a time demanding and very expensive process. In May 2014 the wide-ranging approval for the marketing of vedolizumab brought to a close an approvals process lasting 14 years and a scientific development process of nearly three decades.

The increasing cost of new therapies, and the increased role of government as a payer for innovative new drugs highlight the necessity for an efficient use of resources. Many hope that biosimilars will provide less-expensive versions of branded biologic drugs in the same way generic drugs do for small-molecule chemical drugs. The EMA (European Medicines Agency) and ANVISA (National Health Surveillance Agency in Brazil) recently approved their first biosimilar monoclonal antibody, CT-P13, a version of infliximab designed to treat rheumatoid arthritis (RA). The approval was based on in vitro equivalence assays and comparability studies performed in patients with rheumathoid arthritis and ankylosing spondylitis (AS). Although also approved for IBD, questions remain as to whether efficacy and safety data for CT-P13 in AS and RA can be extrapolated to CD and UC as well as pediatric patients with IBD.

In this relatively unexplored area of biosimilars, a more conservative approach is advised by ECCO (European Crohn's and Colitis Organization)[3] and GEDIIB (Brazilian Study Group for IBD)[4-6]. Not surprisingly, most of gastroenterologists want to se the results of using biosimilars in patients with IBD rather than relying on comparability trials and extrapolated indications[5]. In this current issue of the GEDIIB Journal, Dr. Vieira highlights the most relevant data available on biosimilars for patients with IBD.

Questions about interchangeability aside, it is predicted that biosimilars will improve the costs of health care and increase access to all available treatment options. Post-approval surveillance of biosimilars will be crucial to evaluate the safety profile of the biosimilar vis-à-vis the safety profile of the reference product.

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S-ECCO committee member

Original Article
Ophthalmological Findings In Patients With Inflammatory Bowel Disease

Cristiane Vieira da Cruz[1]; Júlia Weise Antonelli[1]; Kelly Cristina Vieira[1]; Ana Moreira[1]; Ricardo Petterle[1]; Júlio César Pisani[1]; Heda Maria Barska dos Santos Amarante[1]

ABSTRACT:

Background: Inflammatory Bowel Disease (IBD) is a chronic disease of unknown etiology, which includes Crohn's disease (CD) and ulcerative colitis (UC). Commonly affects the intestine and may be, in up to one third of cases, associated with extraintestinal manifestations. The ophthalmologic manifestations classically described are scleritis, episcleritis and uveitis. However, more recent epidemiological surveys have shown a prevalence of nonspecific lesions such as dry eye. **Objectives**: To describe the main ophthalmological findings in patients with Crohn's disease and ulcerative colitis in Southern Brazil and to evaluate the correlation between dry eye and the use of azathioprine, mesalazine and sulfasalazine. **Methods**: Ninety-one patients participated in the study. Data were collected to calculate the CDAI (Crohn´s Disease Activity Index) and TrueLove Witts. Medications used for treatment of IBD were recorded. Patients underwent visual acuity tests, slit lamp, tonometry, fundoscopy and Break Up Time (BUT) test. In order to analyze whether there is an association between the use of azathioprine and/or derivatives of 5-ASA (5-aminosalicylic acid) with dry eye, the chi-square test was applied. **Results**: Dry eye was found in fifty-two patients (57%). Other findings were ametropia, cataract, keratopathy punctata, dry keratoconjuntivitis, glaucoma, uveitis scars. Statistical analysis did not find any association between dry eye and the use of mesalazine, sulfasalazine (p = 0.1567) or azathioprine (p = 0.4312). **Conclusions:** Dry eye was the most frequent ophthalmological finding and was not related to medications. Ocular manifestations classically described in inflammatory bowel disease were observed at extremely low frequency.

Keywords: Inflammatory Disease Bowel, Crohn disease, Ulcerative Retocolitis, dry eye, extra intestinal manifestations.

RESUMO:

Doença Inflamatória Intestinal (DII) é uma enfermidade crônica, de etiologia desconhecida, que inclui a Doença de Crohn (DC) e a Retocolite Ulcerativa (RCU). Acomete mais comumente o intestino podendo, em até um terço dos casos, cursar com manifestações extra intestinais. As manifestações oftalmológicas classicamente descritas são esclerite, episclerite e uveíte. Porém, levantamentos epidemiológicos mais recentes demonstram um predomínio de lesões inespecíficas, como olho seco. **Objetivos**: descrever os principais achados oftalmológicos encontrados em portadores de Doença de Crohn e Retocolite Ulcerativa e avaliar se há correlação entre olho seco e o uso de azatioprina, mesalazina e sulfassalazina. **Métodos**: noventa e um pacientes participaram do estudo. Coletaram-se dados para o cálculo do CDAI (Índice de atividade da Doença de Crohn) e Truelove & Witts, e registraram-se os medicamentos em uso para DII. Realizaram-se os testes de acuidade visual, lâmpada de fenda, tonometria, fundoscopia and Break Up Time test (BUT test). O teste do Qui-Quadrado foi aplicado aos usuários de azatioprina e/ou derivados do 5-ASA (ácido 5-aminossalicílico) para avaliar se há associação dessas medicações com olho seco. **Resultados**: olho seco foi encontrado em cinquenta e dois pacientes (57%) . Outros achados foram ametropias, catarata, ceratopatia *punctata*, ceratoconjuntivite seca, glaucoma, cicatrizes de uveíte. Conforme análise estatística, não há associação entre olho seco e o uso de mesalazina, sulfassalazina (p=0,1567) ou azatioprina (p=0,4312). **Conclusões**: olho seco foi o achado oftalmológico mais encontrado e não teve relação com as medicações utilizadas. As manifestações oculares classicamente descritas na doença inflamatória intestinal foram observadas em frequência extremamente baixa.

Palavras chave: Doença Inflamatória Intestinal, Doença de Crohn, Retocolite Ulcerativa, olho seco, manifestações extra intestinais.

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INTRODUCTION

Inflammatory Bowel Diseases (IBD) are chronic diseases of unknown etiology, that include Crohn's disease (CD) and Ulcerative Colitis (UC)[1-6]. They affect most commonly the intestine [1,2,6] and in up to one third of cases may be associated with extraintestinal manifestations - eyes, skin, liver, joints and others[2,3,6]. Ocular involvement is described in 4-10% of the cases[4-7]. Although ophthalmologic complications are infrequent, they can be associated with significant morbidity, including blindness[6]. However, the complaints of these patients are often nonspecific, leading to underdiagnosis[6]. The study by Huang et al. evaluated IBD patients concerning their level of awareness and knowledge about the extraintestinal manifestations and complications. Of the total group of 229 patients analyzed, only 47% of them were aware of the possibility of ocular involvement due to IBD[3]. The most commonly reported ophthalmologic manifestations are the ones of inflammatory etiology[2,5] and they rarely precede the diagnosis of intestinal disease[4,7].

The classically described ophthalmologic manifestations are scleritis, episcleritis and uveitis[3,7,8]. However, more recent epidemiological studies showed a predominance of nonspecific lesions, such as dry eye[2,4,8]. As a contribution to the knowledge of the clinical features of IBD in Brazil, this study describes ophthalmologic findings in 91 patients with CD or UC, treated at a specialized tertiary referral center in a state in Southern Brazil.

METHODS

This is a prospective, descriptive study conducted in patients with confirmed diagnosis of CD or UC, followed up at the IBD Outpatient Unit at the Clinics Hospital - HC / UFPR between April and December 2013. The project was approved by the Ethics and Research Committee of the institution. Patients were invited to participate and spontaneously agreed to the terms of the informed consent. Initially they had their data collected for calculation of inflammatory activity indexes - CDAI and Truelove & Witts - recording of the medications used to treat IBD, duration of disease and blood measurement of C-reactive protein as a serological marker of inflammation.

Ninety-one patients were included, 59 patients with CD and 32 with UC. They underwent visual acuity test, slit lamp examination, tonometry and fundoscopy, performed by the same ophthalmologist. Visual acuity was measured using a Zeiss projector and slit-lamp biomicroscopy was used for the diagnosis of dry eye. For this purpose, the method of BUT (break up time) was used. Fluorescein was dripped into the eyes, followed by closing and subsequent opening of the eyelid and visual assessment was made by using a blue filter on the slit lamp. Time counting was initiated at that moment and continued until breaking of the tear film. It was considered dry eye when this interval was less than 10 seconds.

Topical anesthetic and fluorescein were used for tonometry and tropicamide for pupil dilation for the fundoscopy. To assess keratopathies, fluorescein and examination with blue filter were used. Appropriate treatment and follow-up were set for patients with abnormal eye examination. Chi-square test was used to those who were taking azathioprine and/or 5-ASA derivatives in order to analyze a possible association between these medications and dry eye.

RESULTS

Of the 91 patients, 57% were female, with a predominance of whites - 83.5%, followed by mulattos - 10%, blacks - 5.5% and Asians - 1%. The mean duration of disease for CD patients was 10 years and 9 years for those with UC. The data are shown in Table 1.

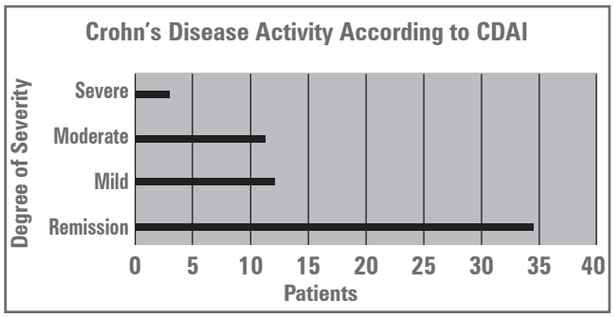
Table 1: Patient characteristics

	Crohn	UC	Total (nº of patients)
Mean age (years)	45.59 (22-86)	43.9 (17-76)	-
Mean duration of disease (years)	10.67 (3 months-33 years)	9.078 (6 months – 22 years)	-
Race:			
Whites	50	26	76
Blacks	4	1	5
Mulattos	5	4	9
Asians	0	1	1
Gender:			
Male	30	9	39
Female	29	23	52

Concerning the medications, of the 59 patients with CD, 37% of them (22 patients) were using azathioprine as monotherapy. The second most used drug was infliximab as monotherapy, in seven cases (12.5%). One patient was taking methotrexate (1.6%) and two patients (3.3%) were using mesalazine, as monotherapies. Concerning combination therapies, 15 patients (25%) were taking azathioprine and infliximab, and in two of these cases there was association with mesalamine to the other two drugs. Three patients (5%) were using infliximab and methotrexate, and of these, one was also treated with mesalazine associated

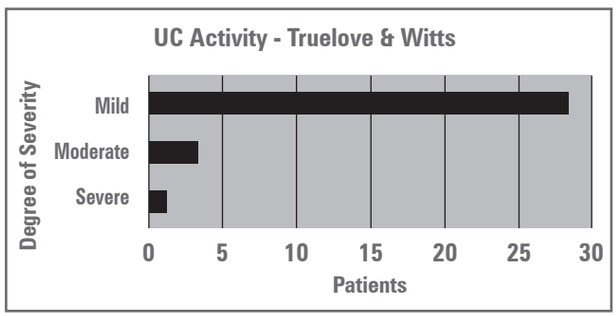
with the other two drugs. One patient (1.6%) was using azathioprine and adalimumab. There were three cases (5%) treated with prednisone and azathioprine during the study. Two patients (3.3%) were using infliximab and mesalazine and 3 patients (5%) were not receiving any medication. Graphic 1 shows the distribution of patients with CD by degree of disease activity.

Graphic 1 - CDAI: Crohn's Disease Activity Index



Among patients with UC, the most commonly used drugs were mesalamine or sulfasalazine in 24 patients (75%), three of them, in combination with another medication (two were using mesalazine and azathioprine and one was using mesalamine and methotrexate). Four patients (12%) were taking azathioprine, two of them mesalazine, as cited before. One patient was being treated with infliximab (3%). Five patients (15.6%) were not taking any drug. The Graph 2 illustrates the degree of activity of patients with UC.

Graphic 2: Activity of UC, according to the Truelove & Witts classification.



Concerning the ophthalmologic findings, the most commonly found was dry eye - in 52 patients (57%), being 38 among the 59 patients with CD and 14 in the 32 patients with UC. Table 2 shows the main ophthalmologic findings. Patients with keratoconjunctivitis sicca and keratitis sicca were included, since these abnormalities are due to dry eye.

Table 2: Ophthalmologic manifestations found in the study

Ophtalmologic			
Findings	Crohn	UC	Total
Normal	12	10	22
Dry eye	38	14	52
Uveitis Sequel	1	1	2
Cataract	3	1	4
Ametropia	17	8	25
Punctate Keratopathy	5	3	8
Glaucoma	1	0	1
Retinal scar	2	0	2
Keratoconjunctivitis sicca	2	1	3
Vascular Tortuosity	1	0	1

Of the 38 patients with CD who presented dry eye, 22 (57.8%) were in remission, 9 (23%) had mild disease, 6 (15.7%) had moderate disease and 1 (2%) had serious illness, as showed in table 3. All patients with UC and dry eye were classified as mild disease, according to Truelove & Witts' classification. There was no predominance regarding gender, duration of disease or age.

Table 3: Data from patients with IBD and the main ophthalmologic finding, dry eye.

Dry eye	Crohn	UC
Male/Female	15/23	3/11
Mean age (years)	48.26	46.57
Race	Whites (n=29)	Whites (n=11)
Duration of disease (years)	11,6	9,42
CDAI: (nº of patients)		
• Remission	22	-
• Mild	9	-
• Moderate	6	-
• Severe	1	-
True Love Witts	-	-
• Mild	-	14
• Moderate	-	-
• Severe	-	-

Table 4 shows the medications used by 52 patients (38 patients with CD and 14 patients with UC) who were diagnosed with dry eye. Among the cases of CD with dry eye diagnosis, we observed that 25 were using azathioprine (65.7%) being 13 as monotherapy (34%) and 9 (23%) in com-

bination therapy with infliximab. Three patients (7%) were treated with azathioprine and prednisone. Four patients (10%) were using infliximab alone, while one patient was using infliximab associated with mesalazine and methotrexate (2.6%). We had one patient using infliximab and methotrexate (2.6%), one patient being treated with infliximab associated with the derivative of 5-ASA (2.6%) and one patient with methotrexate alone (2.6%). There were two cases in which patients were using mesalazine as monotherapy (5%). One patient was with prednisone alone (2.6%). Two patients (5%) were not receiving any medication.

Of the 14 UC patients diagnosed with dry eye, 11 used mesalazine (78.5%) and of these, 9 were using derivatives of 5-ASA alone (64%) and in two cases (18%) there was association with azathioprine. One patient (7%) was being treated with infliximab as monotherapy and 2 patients (14%) were without medication. Compared to the whole sample, the proportion remained, as these are the most used drugs, as shown in Table 4. According to the statistical analysis, there was no association between dry eye and the use of 5-ASA (p = 0.1567) or azathioprine (P = 0.4312).

Table 4: Medications used by patients with diagnosis of dry eye (DE): monotherapy and combination therapy. SSZ= sulfasalazin; MSL= mesalazine; PDN= prednisone; AZA= azathioprine; ADA= adalimumab; IFX= infliximab; MTX= metotrexate

Medications	Crohn + DE	UC + DE
5-ASA	2	9
PDN	1	0
AZA	13	0
IFX	4	1
MTX	1	0
IFX+AZA	9	0
5-ASA+IFX	1	0
AZA+5-ASA	0	2
IFX+MTX	1	0
5-ASA+IFX+MTX	1	0
None	2	2
PDN+AZA	3	0
Total	38	14

DISCUSSION

Although CD and UC are diseases involving predominantly the gastrointestinal tract, extraintestinal manifestations are well described, with a prevalence of 25%, including eye, liver, skin and joint involvement[2].

Ophthalmologic complications can be classified in primary, secondary and coincident. Primary complications are those related to increased inflammatory activity of IBD. It can affect the anterior and posterior segments of the ocular globe and the orbital contents. They tend to go into remission with corticosteroids. The secondary ones are consequences of complications such as intestinal malabsorption or use of medications, such as cataract induced by steroids. The coincident ones have no causal relationship, such as conjunctivitis[1,4,8].

Rarely, eye complications precede the diagnosis of IBD[4,5]. The classically described findings are scleritis, episcleritis and uveitis[3,7]. It is estimated that ocular diseases are present in 10% of patients with IBD. Complications of therapy, such as cataract induced by use of corticosteroids, are also reported[2,4]. Felekis et al. and Yilmaz et al. reported that episcleritis may occur in up to 29% of these patients and can used as an indicator of disease activity[4,5]. There are reports in the literature that uveitis is present in up to 17% of patients with IBD[4].

According to Katsanos, et al. the ophthalmologic findings in IBD may have a significantly higher prevalence, when referred to tertiary centers and properly assessed by an ophthalmologist[9].

Cury & Moss[2] studied a population of Midwestern Brazil and assessed the ocular manifestations in 88 patients with IBD, comparing with a control group of 24 individuals. In 59% of cases there was activity of the intestinal disease. The most common ocular manifestation, as described in our work, was dry eye: of the patients analyzed, 43% were in the IBD group and 12% in the control group and it was related neither to the use of steroids or azathioprine, nor to age or gender. However, it was strongly associated with 5-ASA at a dose > 3g/day, which was not confirmed in our patients (p = 0.1567). According to those authors, ophthalmic disorders typically reported as associated with IBD - uveitis, episcleritis and even cataract - were uncommon (less than 2%). In our patients of Southern Brazil, the results were similar (2% of cases) to those described in that research and much lower rates than those reported by Faruque et al. in Europe: uveitis 17% and scleritis 18%[15].

In a study carried out in an eye hospital in Turkey, Yilmaz et al. cited rates of 5% for uveitis and cataract and 3.4% for scleritis[5]. By studying a population of 116 people with IBD, being 20 with CD and 96 with UC, ocular involvement was identified in 60% and 22% of patients with those diseases, respectively. The most common findings were conjunctivitis and blepharitis, followed by cataract and episcleritis. Ardizzone et al.

comment that uveitis has stronger correlation with UC while episcleritis is more common in patients with CD[10]. Our study did not register any cases of episcleritis. In line with the work of Cury et al.[2], this study showed a low prevalence of uveitis in the examined population: 2 cases among the 91 analyzed, one in CD and the other in UC.

The ophthalmologic alteration most commonly observed among the patients studied was dry eye, present in 52 cases (57%) of the total population. Several studies recently published also demonstrated a higher prevalence of this finding. Cury et al. and Felekis et al. reported a prevalence of dry eye of 42% and 22%, when compared to control groups, 12% and 11%, respectively [2,4]. A French study showed a prevalence of dry eye of 43% among patients with IBD[8]. Gonçalves de Lima et al. reported a prevalence of dry eye ranging from 8 to 20% in the general population[11].

The ophthalmologic manifestations are often associated with articular symptoms [1,10,12,14]. Besides, other factors are mentioned in the literature as potential contributors to eye disease, such as extent and disease activity[1,2,5]. However, several studies have questioned these associations because the relationship between disease activity and ophthalmologic anifestations is variable [2,12]. Lanna et al. analyzed the joint and ophthalmologic manifestations in 130 patients with CD and UC and found no association of ocular findings with the degree of activity of IBD or with arthropathies[13].

In our study, among the 59 cases of CD, three were enrolled with severe disease (CDAI > 450) and of these, one patient was diagnosed with dry eye. One patient had a normal eye examination and the other presented an anterior uveitis sequel.

According to Truelove & Witts' classification, among the 32 patients with UC, one had severe activity and three had moderate disease. All the other patients presented with mild disease activity. In none of the cases of moderate or severe disease there was associated eye disease. For that reason, it can be inferred that there was no significant association between the severity of intestinal disease and ophthalmologic manifestations in this population.

CONCLUSION

In our series, the most common ocular manifestation was dry eye, in a total of 52/91 patients (57% of cases). Dry eye was not related to any medication, age, gender or level of disease activity in patients with IBD treated at a tertiary service and evaluated by ophthalmologist. The ocular findings classically described as extraintestinal manifestations of IBD were observed in extremely low frequency.

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Original Article

Intestinal permeability measurements in healthy subjects: standartization of technique and analysis of results

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Abstract

Lactulose mannitol ratio tests are clinically useful for assessing disorders characterized by changes in gut permeability. Nevertheless, variations between currently used test protocols preclude meaningful comparisons between studies. The aim of our study is to describe the technique used and results obtained from the mannitol lactulose test of gut permeability performed in healthy subjects in order to minimize error and promote comparability of results. Twenty-seven healthy subjects were enrolled in the study. Lactulose and D-mannitol dissolved in water were administered to all the participating subjects; the urine excreted was collected and the total urine volume was measured. The concentration of the sugar probes present in the urine was measured using high performance liquid chromatography (HPLC). The data distribution was analyzed by applying the Kolmogorov-Smirnov test. The mean percentage excretion of lactulose in the urine was 0.07 ± 0.07. The median percentage excretion of lactulose in the urine was 0.04 [0.01 to 0.23]. The mean percentage excretion of mannitol in the urine was 12.88 ± 4.45. The median percentage excretion of mannitol in the urine was 12.79 [3.74 to 21.02]. The ratio of percentage excretion of the ingested dose of lactulose and mannitol in the urine varied from 0.0005 to 0.018 (mean = 0.006 ± 0.005). The reference value for lactulose excretion rate is less than 0.195, the reference value for the mannitol excretion rate is greater than 4.08 and the reference value for intestinal permeability test is less than 0.0157.

Resumo

O termo permeabilidade intestinal relaciona-se à função de barreira exercida pelo epitélio intestinal. As alterações na sua função resultam em uma maior permeação de antígenos por meio da mucosa intestinal e podem iniciar ou mesmo perpetuar processos inflamatórios. É objetivo deste estudo, descrever a metodologia empregada na realização do teste da permeabilidade intestinal, apresentar os dados referentes à estatística descritiva e os valores de referência deste exame. Para realização do exame, foram colhidas amostras de urina de 27 controles saudáveis após ingestão de 120mL de solução isosmolar contendo lactulose e manitol. As dosagens foram realizadas por meio de um aparelho de Cromatografia Líquida de Alta Eficiência (HPLC). O teste de Kolmogorov-Smirnov foi utilizado para avaliação da distribuição de cada uma das variáveis. A porcentagem de excreção da lactulose variou entre 0,01 e 0,23. A média foi 0,07, a mediana 0,04 e o desvio-padrão 0,07. A porcentagem de excreção do manitol variou entre 3,74 e 21,02. A média foi 12,88, a mediana 12,79 e o desvio-padrão 4,45. A relação entre as taxas de excreção da lactulose e do manitol, isto é, o teste da permeabilidade propriamente dito, foi de 0,0005 a 0,018. A média foi 0,006, a mediana 0,003 e o desvio-padrão 0,005. O valor de referência obtido para taxa de excreção da lactulose foi menor que 0,195, o valor de referência para taxa de excreção do manitol foi maior que 4,08 e o valor de referência para o teste da permeabilidade intestinal foi menor que 0,0157. Portanto, ao estabelecer seu próprio controle e explicitar adequadamente em seus métodos e resultados, o exame passa a apresentar maior confiabilidade e torna-se meio fundamental para futuras comparações.

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Introduction

The gastrointestinal tract has the complex task of absorbing nutrients while excluding the uptake of dietary antigens, luminal microbes and their products. The concept of intestinal epithelial barrier function is tightly related to the concept of permeability, which is the property of the membrane to allow non-mediated solute diffusion. When the barrier is intact, the permeability of substances is highly selective and controlled. Disturbances in gut barrier function can affect the control of permeating substances. Based on these principles the oral administration of specific probes has been commonly used to indirectly assess gut barrier dysfunction and measure IP. These probes are subsequently quantified in blood or more frequently in urine[1-11].

Injuries in the intestinal mucosa may impair its barrier function and trigger systemic inflammation and disease[4]. Intestinal permeability tests are not widely used in clinical practice. However, they can be a very useful in screening for small intestinal disease[2].

The aim of our study is to describe the technique and results obtained from the mannitol lactulose test of gut permeability performed in healthy subjects at the Alfa Institute of Gastroenterology in Minas Gerais, in order to minimize error and promote comparability of results.

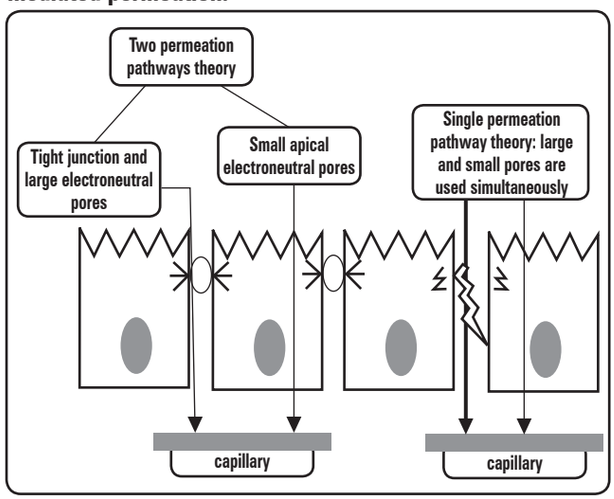
Molecular permeation routes

Transport of molecules across the intestinal epithelium takes place through two major routes: transcellular (through small pores) and paracellular. Transport of solutes across the transcellular route is not carrier-mediated and occurs with the no help of transporters and channels. Transport of molecules through paracellular route across the intestinal epithelium occurs by the process of diffusion and tight-junctions would have a key role. Intestinal permeability is the property of intestinal epithelium by which it allows the molecules to pass through by non-mediated diffusion[11].

Most of the probes used to measure intestinal permeability are water-soluble, which cannot penetrate the lipid cell membrane of enterocytes and thus use the paracellular route through the tight junctions. The most frequently high molecular weight molecules used are lactulose, cellobiose, 51Cr-labelled ethylenediaminetetraacetate (51Cr-EDTA) and polyethylene glycol. The smaller probes such as rhamnose and mannitol can easily pass through the numerous small aqueous pores present at the villous tips[11].

Unfortunately, we are still not certain of which route forms the principal pathway for mannitol. It is intriguing for instance that although the mannitol molecule has a low molecular weigh and is expected to use the transcellular route for permeation across the intestinal epithelium it has never been identified inside a living cell[1,2]. Using probe molecules of selected sizes and osmotic gradients applied to the mucosal or serosal surfaces, both large (6.5 nm) electroneutral and small (0.7 nm) cation-selective pores were also identified, probably located between cells. This observation supports the hypothesis of a single permeation route since large molecules would be restricted to large pores, but small molecules would likely pass through both large and small pores (Figure 1)[7]. Several physical factors relating to fluid dynamics need to be mentioned, however, which are well described in relation to permeation through capillary endothelium. Diffusion of a solute in aqueous solution is proportional to the square root of the molecular mass (Graham's law), but in a membrane with pores of dimensions comparable with those of the diffusing molecules, diffusion would also be restricted as a function of the ratio of the molecular radius to the radius of the pore (Faxtn-Ferry theory)[11].

Figure 1. Intestinal epithelial barrier: routes of non-mediated permeation.



Several mechanisms operate simultaneously to alter permeability in intestinal disease. Intestinal disease is likely to affect the permeability not only of the tight junctions, through the actions of chemical mediators or inflammatory cells, but of the cellular membranes and the total intestinal absorptive area as well. The total small-intestinal surface area is decreased in villous atrophy and this is no doubt the reason for reduced permeation of small molecules, such as mannitol in celiac disea se. In Crohn's disease, permeation is changed by disruption of membrane integrity (which is likely to increase permeation, especially of large molecules such as lactulose and PEG), and alterations in membrane lipid com- position as well[1,7].

Methodology

To measure intestinal permeability in the clinical setting a series of tests were developed based on probes that are not actively transported in the intestine and not metabolized but excreted in the urine to a constant degree. These probes have different molecular weight, which determines the route of permeation. They include 1) sugar probes; 2) isotope probes and 3) polyethylene glycols[1]. A number of substances have been selected for permeability tests. Most authors use different sugars and combine two sugar probes, one smaller molecule, like mannitol, and one bigger molecule, like lactulose. Subsequently, an index is calculated from the relationship of the two sugars. The lactulose-mannitol index and the lactulose-rhamose index are the most commonly used indices for determination of intestinal permeability[1].

Tests were performed under overnight fast (8 to 10 hours). After voiding their first urine, subjects were asked to ingest sugar probes (6.25 g of lactulose (Sigma–Aldrich, Missouri, USA), 3.0 g of mannitol (Sigma–Aldrich, Missouri, USA) in 120 mL water). No food or drink was allowed until after 2 hours from the ingestion of the test solution. All the urine passed in the subsequent 5 hours was collected. Subsequently, the urine was homogenized and the total volume was recorded. Aliquots of 50 mL were stored in labeled in sealed flasks after adding 0.01g of thimerosal to inhibit bacterial growth. Samples were filtered using a millipore filter (0.22 µm) (Millipore, Billerica, USA), and the ion-exchange resin and the material were stored in properly labeled cryotubes at −20 °C.

The mannitol and lactulose concentrations were measured in the urine using HPLC equipment (Schimadzu®, Japan) comprising an injection pump, an autoinjector, a controller with software that allows readings to be interpreted at a workstation, and a refractive index gauge. Fifty microliters of urine were introduced after thawing using the autoinjector. At the same time, a mobile phase of pure milli-Q sonicated water at a flow of 0.6 mL/min was carried out. A Phenomenex H^+ column (Phenomenex, USA) and a Supelcogel NH2 column (Sigma Aldrich, Bellefonte, USA) were used to separate the mannitol and the lactulose respectively. Standard curves were prepared by analyzing appropriate concentration of each compound in water and plotting the area of the peaks obtained[5,6,12].

Data were analyzed using SPSS version 21 software (SPSS Inc., Chicago, IL). Results are expressed as the mean and standard deviations (mean ± SD), median and [range]. The data distribution was analyzed by applying the Kolmogorov-Smirnov test. The level of statistical significance was 0.05.

The Research Ethics Committee of the Universidade Federal de Minas Gerais approved the study. All participants signed an informed consent term before the study was initiated.

Results

Twenty-seven healthy subjects, 15 female and 12 male, were enrolled in the study. The mean age was 38.3 ± 11.07 years [20 to 56]. The mean percentage excretion of lactulose in the urine was 0.07 ± 0.07. The median percentage excretion of lactulose in the urine was 0.04 [0.01 to 0.23]. The mean percentage excretion of mannitol in the urine was 12.88 ± 4.45. The median percentage excretion of mannitol in the urine was 12.79 [3.74 to 21.02]. The ratio of percentage excretion of the ingested dose of lactulose and mannitol in the urine varied from 0.0005 to 0.018 (mean = 0.006 ± 0.005) (Table 1).

Table 1. Summary of results

	% Lactulose	% Mannitol	Intestinal permeability test
Mean	0,07	12,88	0,006
Median	0,04	12,79	0,003
Standard deviation	0,07	4,45	0,005
Minimum value	0,01	3,74	0,0005
Maximum value	0,23	21,02	0,018

The data distribution was analyzed by applying the Kolmogorov-Smirnov test and was determined to be Gaussian. Because of the normal distribution, results were expressed as the mean and standard deviation (mean ± SD). The reference value for lactulose excretion rate was less than 0.195, the reference value for the mannitol excretion rate was gre-

Figure 2. Lactulose excretion rates expressed in histogram

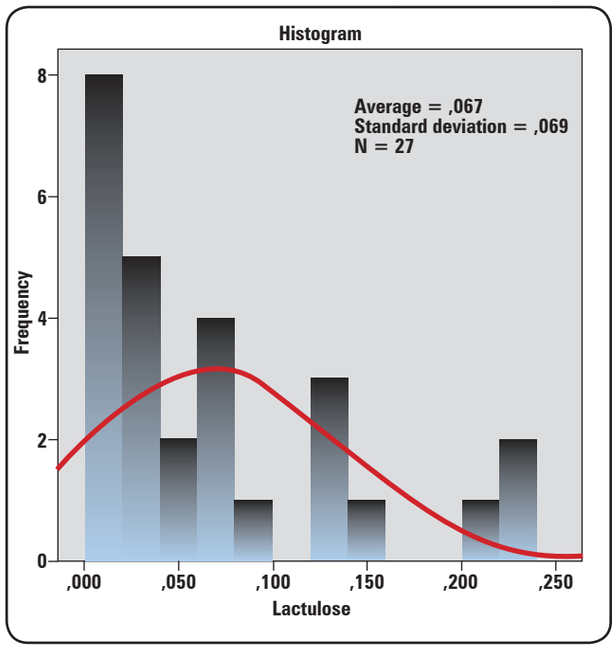


Figure 3. Mannitol excretion rates expressed in histogram

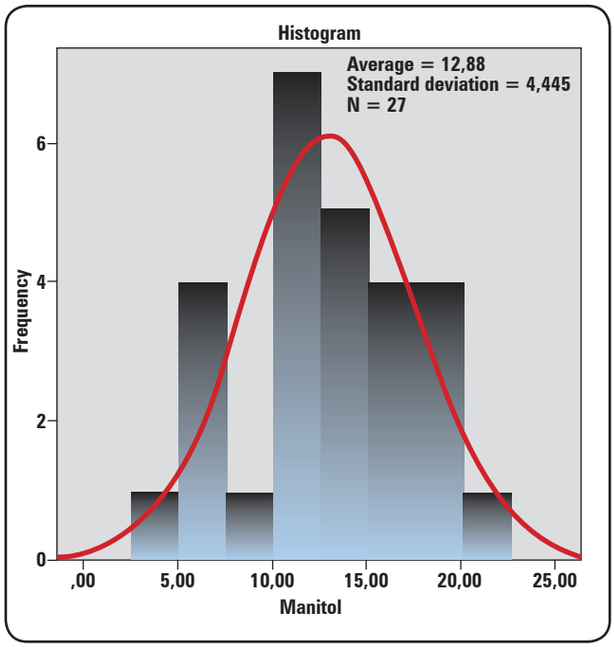
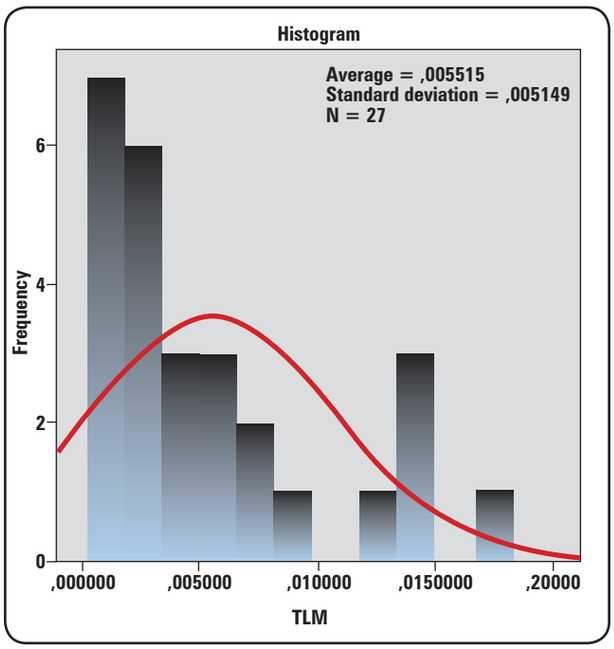


Figure 4. Lactulose excretion/ mannitol excretion ratio expressed in histogram



ater than 4.08 and the reference value for intestinal permeability test was less than 0.0157.Data distribution for mannitol, lactulose and relation between lactulose and mannitol are presented as histograms in Figures 2, 3 and 4.

Discussion

Published studies on intestinal permeability present little methodological uniformity, making comparisons between studies rather difficult[9]. It is not known if variation in results amongst studies correlate to environmental factors, specific population derived factors or exposition to different luminal antigens[7,10]. Nevertheless, until the standardization occurs, it is important that the research labs establish their own control and provide detailed information on methodology applied.

The current study achieved mean values of 0.07% and 12.88% for lactulose and mannitol excretion rates, respectively. In the study conducted by Maxton et al, urinary excretion rates of lactulose reached 0.39% at 5 hours[8]. In another study conducted in Italy, D'Inca et al found a mean value of lactulose excretion rate of 0.9% at the 6-hour urine collection[3]. Studies conducted at the United Kingdom and Italy demonstrated, respectively, mean values for mannitol excretion of 16.7% (5-hour urine) and 27.7% (6-hour urine)[3,8].

Many factors may influence the results of the intestinal permeability test. The use of non-steroidal inflammatory drugs, acute alcohol ingestion, psychological and physical stressful situations may cause transient loosening of tight junctions thus resulting in an increase in permeation of lactulose[1,2]. Vilela *et al* reported that urinary lactulose excretion in inactive Crohn's disease patients was significantly higher than healthy controls[12]. This mechanism is responsible for the reactivation of the disease in part of these patients[3]. Previous orientation of individuals to avoid – 3 days before the test – the use of non-steroidal inflammatory drug, alcohol ingestion and extenuating physical activity should be given as part of the protocol[1].

The combination of other sugar probe (mannitol) for assessment of intestinal permeability was suggested to overcome a number of factors (such as gastric emptying, intestinal transit, renal clearance and incomplete urine recovery) other than the mucosal integrity itself, which not only reduce the sensitivity and specificity of test procedure, but also pose a problem in the interpretation of the data. The individual variations due to the non-mucosal factors are circumvented when the urinary recovery is expressed as a ratio (lactulose: mannitol ratio) since both of them are equally affected by these factors, except for the route of permeation[9]. Even so, urinary mannitol excretion in Crohn's patients in remission or not is the same as healthy controls[12]. These results suggest that patients with Crohn's disease have changes in intestinal permeability associated to disruptions in the tight junctions and are not related to changes in the absorptive surface.

The method and quality of substances used when assessing intestinal permeability may also affect test results. In order to avoid overlapping peaks in liquid chromatogram,

Figure 5. A High performance liquid chromatography chromatogram of lactulose and mannitol ratio. The chromatogram shows retention time of mannitol (1) and lactulose (2)

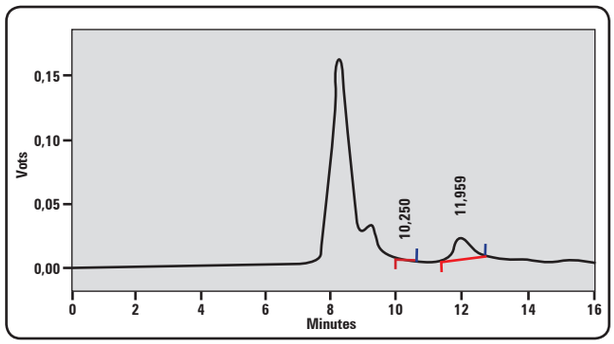
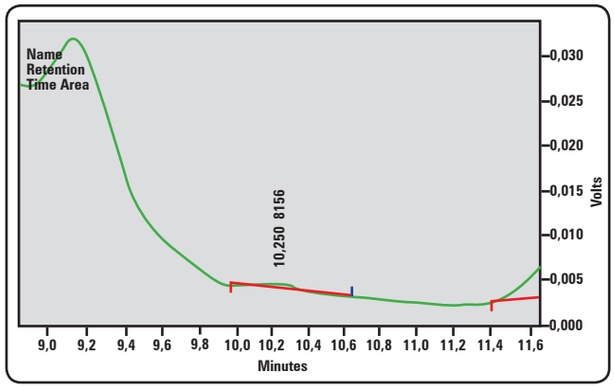


Figura 6. Magnified detail of the area under the curve (AUC) for lactulose excretion



retention times of coumponds of interest should differ by one minute (Figure 5). Overall excretion levels of the two reference sugars differed, that of lactulose being significantly lower than that of mannitol. Figure 6 shows a magnified detail of the area under the curve (AUC) for lactulose excretion.

In relation to minimum values detectable by this method, the sensitivity of the detector which operates refractive index does not detect numbers below 0.5 parts per million. Therefore, values inferior to 0.5mg/l are below the test detection limit. The linearity, however, exceeds the maximum values measured. Thus, the minimum value of lactulose excretion rate was 0.01%. In relation to the reference value considered as maximum, the result was 0,195%. For the mannitol, the device sensitivity is well below the measured values and the reference value is greater than 4.08%. Regarding the excretion rate between lactulose and mannitol, the minimum value is determined by the device sensitivity, because the numerator of the equation is the lactulose excretion rate. The reference value considered normal and less 0.0157.

In 2008, Vilela *et al* used the relation between excretion rates of lactulose and mannitol to measure the effect of *S. boulardii* on intestinal permeability in Crohn´s patients in remission[5]. After that, this technique was also used to assess the effect of biological therapy on intestinal permeability of patients with active Crohn's disease (in press).

The current study described the methodology and outcomes obtained from the test of gut permeability performed in healthy individuals. Results were analyzed by means of descriptive statistics and evaluated after verification of their distribution pattern, allowing comparisons between future studies.

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Review Article

Inflammatory Bowel Disease: General Aspects and Role of Inflammatory Markers

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ABSTRACT

A disrupted balance between gut microbiota and the host is related to several diseases, such as the inflammatory bowel disease (IBD) and its two major disorders Crohn's disease (CD) and ulcerative colitis (UC). Endoscopic examinations are the main form of diagnosis and monitoring these diseases, but they are invasive and expensive. Therefore, markers of inflammation can be useful in diagnosis and follow-up. The aim of this review was to point out the main aspects of IBD and the role of fecal calprotectin. We used several database and the studies were mainly from the last 5 years. The most used inflammatory markers to help in the diagnosis e evaluation of inflammation in CD and UC are the Reactive C Protein (RCP), calprotectin and lactoferrin. Calprotectin is mainly derived from neutrophils and reactive macrophages and like lactoferrin, is significantly correlated with endoscopic and histological findings in CD. However, calprotectin is considered more effective to define levels of inflammation than lactoferrin and RCP. We concluded that indications for colonoscopy might be 40% to 67% reduced by using markers, benefiting numerous patients.

Keywords: Inflammatory Bowel Disease, Crohn's Disease, Ulcerative Colitis, Calprotectin.

RESUMO

O desequilíbrio entre a microbiota intestinal e o hospedeiro está relacionado a diferentes doenças, como a doença inflamatória intestinal (DII) e suas duas formas principais que são a Doença de Crohn (DC) e a Retocolite Ulcerativa (RCU). Exames endoscópicos constituem a principal forma de diagnóstico e monitoramento destas patologias mas são invasivos e de alto custo. Em virtude disto, os biomarcadores de inflamação podem ser úteis no diagnóstico e segmento da doença. O objetivo desta revisão foi apontar os principais aspectos da doença inflamatória intestinal e o papel da calprotectina fecal. Foram utilizadas inúmeras bases de dados e os artigos consultados datam, principalmente dos últimos 5 anos. Os marcadores inflamatórios mais utilizados pelos pesquisadores para auxiliar no diagnóstico e monitoramento da inflamação na DC e RCU são o Proteína C Reativa (PCR), calprotectina e lactoferrina. A calprotectina é derivada principalmente de neutrófilos e macrófagos reativos e, como a lactoferrina, correlaciona-se de forma significativa com os achados endoscópicos e histológicos de atividade na DC, porém, considera-se que a calprotectina é mais efetiva do que a lactoferrina e PCR para definir os graus de inflamação. Conclui-se que o uso de marcadores pode reduzir de 40% a 67% a indicação de exames colonoscópicos, beneficiando assim, inúmeros pacientes.

Palavras-chave. Doença Inflamatória Intestinal, Doença de Crohn, Retocolite Ulcerativa, Calprotectina

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INTRODUCTION

General aspects of inflammatory bowel disease

The homeostasis of the gastrointestinal system is a dynamic and complex process with crucial role in the mucosal immunity. In normal physiological conditions there is a perfect balance between gut microbiota and the host. The disruption of this balance is involved in different diseases, including the inflammatory bowel disease (IBD) and its two major disorders the Crohn's disease (CD) and ulcerative colitis (UC). These conditions are the two main clinical phenotypical manifestations of the IBD. The IBDs are disorders of modern society and require management strategies that prolong life expectancy and improve quality of life[1-4].

Both Crohn's disease and ulcerative colitis are polygenic autoimmune disorders of multifactorial etiology and high complexity. They share similar characteristics that can be distinguished by genetic predisposition, risk factors, and clinical, endoscopic and histological features. The manifestations are systemic and can seriously affect the gastrointestinal tract, but also trigger frequent extraintestinal manifestations and other associated autoimmune conditions. These manifestations appear in susceptible individuals and usually relate to an environmental trigger that leads to an immunological response in the intestinal mucosa. The maintenance of mucosal homeostasis depends on the regulation between inflammatory manifestations and the ability of the immune system to provide a balance. This balance depends on the interaction of genes whose regulation is related to environmental responses, especially of the intestinal microbiota. Besides genetic and environmental factors, increase in inflammatory markers, oxidative stress and derangement of the colon are as well related to IBD[2,5,6].

Under normal physiological conditions the host has the ability to identify and respond appropriately to the luminal contents of the gastrointestinal tract. This ability of recognition and interaction evolved over millions of years and is made possible by the unique cell coating called colonic barrier. This barrier allows the separation between the intestinal lumen and the sterile cells that are protected by a mucus, which consists mainly of glycoproteins. This mucosal barrier is the main form of separation of the sterile portion from a huge load of microorganisms present in the gastrointestinal tract. Along with the epithelium, the intestinal immune system faces a critical challenge of distinguishing commensal and pathogenic microorganisms through mechanisms not yet fully understood[7,8].

The IBDs are a problem of public health that also affects the young population leading to prolonged and recurrent clinical courses, affecting education, capacity for work, productivity and quality of life[3,9].

The monitoring of patients with IBD is essential for maintenance of remission. Therefore, endoscopic examinations or use of biomarkers are recommended. Biomarkers are less invasive and have a lower cost. Among the markers, there is growing interest in research involving fecal calprotectin.

Thus, the aim of this article was to present a literature review on the main aspects of IBD and the role of fecal calprotectin as a tool in the diagnosis, a support in therapeutic management and monitoring of inflammation.

METHODS

This literature review was based on a retrospective search restricted to indexed scientific articles mainly published in the last five years. The following databases were used: **Medline, Scielo, Pubmed, Lilacs and Science Direct**. The key words used were: calprotectin, inflammatory bowel disease, Crohn Disease and Ulcerative Colitis.

GENERAL ASPECTS THAT DISTINGUISH CD FROM UC

Description of diseases

UC was cited primarily by Hippocrates in the fourth century BC and described in 1859 by Samuel Wilks. Crohn's disease was cited primarily by Sorano of Ephesus in 170 AD and described in 1859 by Samuel Wilks and in 1882 by N. Moore[11].

Epidemiology

UC is more prevalent than CD and North America and Europe have the highest rates of the disease, with 9 to 20 cases per 100 million people/year and the prevalence of 156 to 291 cases per 100.000 population. Rates are lower in the southern hemisphere and the increase in incidence accompanies industrialized countries. UC has a bimodal pattern of incidence, the main peak occurring between 15-30 years and a secondary peak between 50-70 years. Studies suggest that there is no gender preference. The incidence of UC is slightly higher in males, while CD is slightly higher incident in women[12].

Studies on IBD show an incidence of 6.5 to 16.0/100.000 inhabitants per year and a prevalence between 26 to 215 patients/100.000 inhabitants per year. These rates may vary according to the degree of the country industrialization. In a study conducted in São Paulo, individuals with age ranging from 15 to 74 years were evaluated and it was found that the incidence of IBD predominated in young people living in urban areas. The authors observed that UC was more prevalent (65.22%) than CD (25.22%) and other nonspecific colitis (9.65%) [1].

Genetic Factors

Some authors show that family history is the most important independent risk factor for IBD and the age range of highest incidence is between 20-40 years. The risk is greater in first-degree relatives and 5% of patients with UC have a first-degree relative with the disease. Monozygotic twins have agreement of 6-13%. There is also a relationship between UC manifestation and antigens of the major histocompatibility complex class II [12]. Moller et al [13] performed a Danish population study from the year 1977 until the year 2011 and estimated the incidence of IBD. This study found that the risk of developing IBD is significantly increased in young people with relatives of first, second and third degrees with the disease, more evident in those with first degree relatives. This evidence was more pronounced in patients with CD than with UC.

Despite the more frequent age range for IBD diagnosis be between 20-40 years, many young patients are diagnosed every year. There are new assumptions about what trigger these diseases. Connelly et al.[14] for example, found that there are nucleotide polymorphisms related to NOD2 (**NOD2 single nucleotide polymorphism rs2076756**) which is a molecule of the innate immune system related to age at diagnosis of CD. Nucleotide polymorphisms (POU5F1, TNFSF15, and HLA DRB1* 501 genes) may be associated with age at diagnosis of CD. UC could be associated with LAMB1 gene that is related to integrity of the mucosal basement membrane, which suggest a different mechanism in the pathogenesis of CD as compared to UC.

Environmental Factors

The incidence of IBD is higher in developed countries and urban areas compared with rural areas. The increase in incidence in developed countries is probably due to environmental factors and changes in lifestyle that accompany socioeconomic changes and industrialization[2,12].

Other environmental factors can be related to the manifestation of IBD. Cigarette smoking appears to exert a "protective" effect against UC, however worsens the course of CD. Quitting smoking increases the risk of developing UC. Previous episodes of gastrointestinal infections by **Salmonella spp, Shigella spp and Campylobacter spp** double the risk of subsequent development of UC, suggesting that a previous infection can modify the intestinal flora in genetically predisposed patients and trigger inflammation. There is also a correlation of UC with the use of nonsteroidal anti-inflammatory drugs. Regarding the relationship between diet and CD and UC there is no consensus in the literature. However, it is known that consumption of foods such as cow's milk by patients with sensitivity to milk's protein can be an aggravating factor for UC. Furthermore, the use of chemical additives beside the excess of sugar, fat and fiber restriction in diet may be factors contributing to trigger the diseases. The role of psychological stress as a trigger for onset or recurrence of colitis is still very controversial [15,16].

Mucosal Inflammation

In UC the inflammation is typically restricted to the mucosal surface, usually beginning in the rectum and extending uniformly throughout the colon. It rarely affects the terminal ileum. The distribution of the disease is stratified by the extension of colon involved (proctitis, left colitis or pancolitis). Histologically it is characterized by polymorphonuclear infiltration with cryptic abscesses, edema and congestion [17].

CD can be located in any segment of the alimentary canal (from mouth to anus). It occurs due to a transmural inflammatory condition which can affected all the wall layers (from mucosa to serosa). Furthermore, more than one affected area can be found and the inflammation leads to formation of ulcers which often produce fistulas in the perianal region and abdominal wall (intracavitary or superficial abscesses). Differently from UC, the inflammation is discontinuous [7,17,18].

Pathophysiology

The innate immune system is the first line of defense against the huge range of micro-organisms to which the body is daily exposed. It primarily produces a nonspecific response of macrophages, dendritic cells and granulocytes. The immune response is directly linked to pattern recognition of molecular structures expressed in microorganisms. This recognition is made by the PRP receptors (pattern recognition receptors) comprising the TLRs (toll-like receptors) that protect the extracellular space, the NOD-like receptors (nucleotide-binding oligomerization domain-like receptors, NLR) that protect the intracellular cytosolic compartment, and the RLR (retinoic acid inducible gene I- (RIG-I) like receptors). Antigen recognition is made by recruitment of adapter proteins and cellular kinases which trigger the activation of signaling cascades, leading to activation of MAPK (mitogen activated protein kinase) and NF-κB (nuclear factor-kappa B) pathways. These receptors are distributed in the intestine and have specific functions in the immune responses[3].

In UC, T-helper (auxiliary) cells are activated in the lamina propria and secrete inflammatory cytokines in the blood, leading to the activation of macrophages, β cells and the recruitment of inflammatory leukocytes and other cells of the immune system. The primary immune reaction in UC occurs by T helper 2 (Th2) while in CD the main immunological reaction occurs by T helper 1 (induced by IL-12 (interleukin-12) and mediated by the production of gamma-interferon: IFN-Y).

The abnormal Th2 response in UC is mediated by high concentrations of IL-5 and IL-13 and low IL-4. High amounts of β and plasma cells are found. In CD there is also the production of IL-17 produced by Th17 cells (which are induced by IL-23). The activation of immune cells is accompanied by the production of inflammatory mediators such as chemokines, growth factors, arachidonic acid metabolites (prostaglandins and leukotrienes) and reactive oxygen species (free radicals of oxygen). These mediators intensify inflammation and tissue damage leading to the clinical manifestations of the disease. The additional recruitment of leukocytes from the vasculature to the sites of disease is important to sustain the inflammation [6, 17,19,20].

In general, there is a disruption of the epithelial barrier (in the tight junctions) and increase of permeability, with consequently greater incorporation of antigens. Macrophages and dendritic cells of the innate immune system that recognize non-pathogenic bacteria (through the TLR receptors) change their activity, resulting in the activation of NF-kB which stimulates the production of inflammatory mediators: TNF-α (α tumor necrosis factor), IL-12, 23, 6, and 1β. After the processing of antigens, macrophages and dendritic cells, there is production of IL-4 and natural killer cells produce IL-13. The disruption of the epithelial barrier also causes release of integrins and adhesion-1 molecules, culminating in increased T cell input and production of chemokines (CXCL1, CXCL3, and CXCL8). This leads to the recruitment of circulating leukocytes to perpetuate inflammation. Many genetic polymorphisms have been found in TLRs, which can be associated with several diseases including IBD, with emphasis on patients with CD[3,12].

MARKERS OF INFLAMMATION: CLINICAL UTILITY OF CALPROTECTIN

In the treatment of IBD, apart from the combination of conventional medications with nutritional and psychological therapies, it is extremely important to induce and maintain remission. However, diagnosis, progression, severity and prognosis are still a challenge for gastroenterologists[21].

For clinical monitoring of CD the CD Activity Index (CDAI) can be used. However, this index might not have great importance to indicate persistence of inflammation in clinically asymptomatic patients. There may be intestinal inflammation without gastrointestinal symptoms, which leads to progressive tissue damage in the gut, reducing quality of life. In recent years the treatment goals have turned to a new concept called sustainable deep remission that takes into account clinical condition, biological, radiological and endoscopic remission. Endoscopic examinations are still considered the gold standard for investigation of the intestinal mucosa, but its use is limited because it is an invasive and expensive method. Thus, the need for a less invasive, fast, inexpensive and reproducible test is unquestionable. The use of P-ANCA (perinuclear anti-neutrophil cytoplasmic antibodies) and ASCA (anti-Saccharomyces cerevisiae antibodies) can help in the diagnosis of UC and CD respectively. Other markers with clinical utility are myeloperoxidases, metalloproteinases, polymorphonuclear elastase, CRP and lactoferrin. However, calprotectin has been noteworthy because of its sensitivity and specificity [21, 22-24].

CRP has hepatic origin and is useful as a marker of infection, inflammation and tissue injury. The production of CRP occurs by IL-6 stimulation, which is a result of inflammatory processes. Endoscopic findings of inflammation correlate positively to increased levels of CRP [23].

Lactoferrin, whose origin is primarily the mucosal epithelial cells and neutrophils, is an iron binding protein stable for 48 hours in the feces. Like calprotectin and CRP, lactoferrin is not specific. However, increased levels are present in IBD, in both UC and CD. Studies show that lactoferrin may exhibit a sensitivity of 56% to 100% and specificity of 61% to 100% in the differentiation between IBD and irritable bowel syndrome (IBS). It has also been used in the classification of IBD. Studies have shown that fecal lactoferrin may present sensitivity of 46% and specificity of 61% to predict UC relapse and sensitivity of 77% and specificity of 68% for CD. When the disease is active in patients with CD and UC, increased levels of this protein were observed in feces. Therefore, it can also be useful in assessing therapeutic response [23, 25-26].

Calprotectin is a small calcium binding protein derived mainly from monocytes, neutrophils, epithelial cell cytoplasm and reactive macrophages. It is represented by two light chains and a light polypeptide chain. It remains stable in the stool for up to 7 days at room temperature and is homogeneously distributed in the fecal material. Along with lactoferrin, calprotectin correlates significantly with the endoscopic and histological findings of the CD activity scores. However, calprotectin is considered more effective than lactoferrin, CRP or CDAI to define inflammation levels [8, 23, 26].

Fecal calprotectin (FC) has been used to monitor the course of the disease and the effectiveness of the therapy. Studies show sensitivity and specificity over 70% for CD and UC. It is important to remind that both lactoferrin and FC correlated with endoscopic and histological findings in CD, but are useless when the disease is restricted to ileum [27-29].

Studies show that FC may exhibit sensitivity of 93% to 95% and specificity of 91% to 96% for IBD identification in adults. Because of this sensitivity, the use of this

protein as a marker can reduce up to 67% of the indications for colonoscopy, which is an invasive procedure, it is costly and causes several discomforts to the patient in the preparation phase for the examination. FC may also be used for monitoring effectiveness of the treatment. There is evidence that levels of FC are significantly reduced after use of corticosteroids, infliximab and adalimumab. However, there are conflicting results in the literature since Nogueira et al. [31] studied 17 patients with CD and found that lactoferrin and FC are not useful for monitoring the inflammatory pattern in patients on treatment with infliximab [27-35].

Even after clinical improvement of symptoms of IBD, it is possible that inflammation is still present, in low intensity in the intestinal mucosa. This process, together with the lack of symptoms may lead to tissue damage and risk of relapse. An extensive literature exists regarding studies showing that FC can be elevated in such patients, indicating that it can be useful for monitoring subclinical inflammation of the mucosa and possible relapse. This allows the clinician to make adjustments in therapy to prevent worsening. The efficiency of FC in predicting clinical relapse is reported in several studies that show a high risk of relapse in a year when the levels of the protein are also high [26].

FC levels greater than 300µg/g is considered an independent risk factor for relapse, with sensitivity of 78% and specificity of 73%. The reported results indicate that FC is less useful in predicting relapse in patients with ileal CD as compared with ileocolonic CD or UC [23, 28, 30, 36-38].

Kotze et al[39] evaluated 279 patients with intestinal complaints and 112 of these presented IBD. Laboratory findings showed that FC was significantly higher when the disease was active and showed a mean of 50ug/g in patients with IBS, 405ug/g in patients with CD and 457ug/g in patients with UC. They found no significant differences between the values of the latter two groups nor between genders and concluded that FC can be useful to differentiate IBD from IBS as well as it can be useful for predicting activity in CD and UC.

FC can be useful as well in predicting recurrence of CD in patients undergoing ileocecal resection. After surgery, FC can suffer significant reduction in patients who have complications, but it has very high levels in post-surgery patients with severe clinical activity of CD or low levels when the disease is controlled. Studies show that surgery not always completely remove the pro-inflammatory state and FC can be found to have values above 200ug/g, which may be indicative of recurrence of the disease after 12 months. These studies show that this protein can be regarded as having high sensitivity to predict recurrence of CD, being superior to CRP and other markers such as fecal lactoferrina [40-45]. Some clinical trials have used FC as a marker of inflammation and proposes a cut-off of 250 ug/g as a predictor of severity of inflammation in CD, with sensitivity of 94% and specificity of 62% [29].

Louis et al.[30] suggested that the combined use of CRP and FC is more effective to monitor healing of intestinal mucosa, being possible to determine the risk of relapse, like for example after withdrawal of drugs such as infliximab. Meneses et al.[46] suggested that values less than or equal 0.5 for CRP and 40 ug/g to FC may be useful to exclude IBD patients with IBS symptoms. Alibrahim et al.[47] also remarked the importance of FC to differentiate IBD from IBS.

Mösli et al.[48] evaluated 19 studies in a meta-analysis (2499 patients) and showed that FC is more sensitive than CRP in both CD and UC. They also observed that the FC is more sensitive in UC than in DC.

Cerrillo et al [49] studied 100 patients with CD, measured CRP, FC and made association with entero magnetic resonance. The results showed that imaging is strongly related to FC levels, but not to CRP levels. The authors proposed that FC could be used as a disease marker to select patients to undergo imaging exams, helping to plan the clinical treatment.

Targownik et al [50] studied the role of stress in 478 patients with IBD and also used CF to measure inflammation. They considered that values greater than 250 ug/g were indicative of significant inflammation.

The above discussed studies show that the CF is an important tool in therapeutic management and monitoring of patients with CD or UC.

CONCLUSION

The use of markers of inflammation is important because they are not invasive and have relatively low cost when compared to radiological or endoscopic examination. FC can reduce the indication of colonoscopy exams benefiting many patients. Moreover, they are useful tools for therapeutic decision-making. CRP is widely used in clinical practice and can be useful for predicting relapses. However, CF is best correlated with the severity of endoscopic lesions and in general, is better to identify active IBD or relapses. The frequency at which the measurement of biomarkers should be done remains to be determined. Furthermore, there is the need for further studies to identify new tools to monitor the clinical progression of IBD.

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Review Article
Current management of severe ulcerative colitis

Adérson Omar Mourão Cintra Damião[1]

INTRODUCTION

The clinical course of ulcerative colitis is characterized by alternating periods of remission and relapse. The rectum is always affected with inflammation spreading from the distal to the proximal colonic segments. At diagnosis, most patients have mild to moderate symptoms, and less than 10% have severe disease[1-3]. Symptoms usually consist of abdominal pain, bloody and/or mucous diarrhea. Severe cases are defined as more than 6 bloody stools per day and signs of systemic involvement (fever, tachycardia, anemia)[4, 5]. These patients should be hospitalized for intensive treatment and surveillance as the development of a toxic megacolon and perforation is a potentially life-threatening condition. A plain abdominal radiograph should be obtained to estimate disease extent and exclude colonic dilatation (>5.5 cm) suggestive of megacolon. In patients with megacolon, daily abdominal radiographs are warranted until the colonic diameter decreases to an acceptable level or an operation is planned. The use of anticholinergic medications, antidiarrheal agents, and opioids can precipitate toxic megacolon and should be discontinued upon admission.

MEDICAL THERAPY

Patients with severe colitis should be admitted to hospital for treatment with intravenous corticosteroids. IV fluid and electrolyte replacement are prescribed to correct and prevent dehydration or electrolyte imbalance, blood transfusions are used to maintain a hemoglobin >9 g/dL, subcutaneous minidose heparin is ordered to reduce the risk of venous thromboembolism, enteral nutritional support is started if the patient is malnourished, and IV antibiotics are employed when a high likelihood of infection exists. Concomitant infection with *Clostridium difficile* and cytomegalovirus should be ruled out[4, 5].

IV corticosteroids (hydrocortisone 100 mg, IV, TID or prednisolone 60 mg, IV, OD) are the mainstay of conventional medical therapy, and their usage should not be delayed while awaiting microbiologic tests. The overall response rate to intravenous corticosteroids in severe acute colitis is almost 70%. No improvement after 3–7 days of intravenous steroids is an indication to start immediate rescue treatment. Infliximab, cyclosporin, tacrolimus, and surgery are all effective rescue treatments[4,5].

Cyclosporin is first given intravenously at doses of 2–4 mg/kg per day[4]. Doses are adjusted to maintain trough serum concentrations between 200 and 400 ng/mL[1,4,5]. Intravenous cyclosporin achieves marked short-term responses in 50%-80% of patients receiving it as rescue therapy. However, studies on long-term outcomes indicated that 58%-88% of these patients underwent colectomy within the following 7 years[6]. Patients starting cyclosporin after azathioprine failure are more likely to need colectomy than are those who have not received azathioprine. After successful induction of remission, an immunosuppressant such as azathioprine (2.5 mg/kg per day) should soon be added. Due to the elevated risk of opportunistic infection with *Pneumocystis jiroveci*, chemoprophylaxis is recommended in patients under triple immunosuppressive therapy[1,4,5].

Similar to cyclosporin, infliximab is likewise highly effective, achieving clinical response rates of 70% (95% CI 65–71) and remission rates of 40%. Infliximab is first given intravenously at a dose of 5 mg/kg at weeks 0, 2, and 6[7]. The clinical response usually occurs within 3 to 7 days of treatment. Infliximab also appears to induce a long-term remission comparable to that seen with cyclosporin. The number of infusions required is not clear, but 2 or 3 infusions seem to e more effective than a single administration for preventing early colectomy[9,10].

Whether the optimum rescue treatment in patients with severe steroid-refractory colitis is cyclosporin (or al-

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ternatively tacrolimus) or infliximab is unclear[1]. The data related to the use of infliximab in patients presenting with severe colitis is relatively limited, A randomized trial showed similar short-term response rates with both drugs (cyclosporin 85·4% vs infliximab 85·7%; p=0·97) and no difference in colectomy rates after 3 months (18% vs 21%; p=0·66)[7,8]. In view of these similar outcomes, infliximab might be preferred compared with cyclosporin because it can be continued as maintenance treatment in responding patients, particularly in those for whom azathioprine has been ineffective.

Treatment strategies should be individualized for each patient, accounting for age, comorbidities, and maintenance treatment at the time of relapse[4,12,13].

PREDICTION OF OUTCOME AND SURGICAL THERAPY

3rd Day Rule

The indications for operative intervention in patients with severe ulcerative colitis include massive hemorrhage, perforation, peritonitis, and unresponsiveness to medical therapy. Although the first three of these are absolute indications, the last is the most common indication and the most difficult to objectively define. Typically, patients are started on IV plus topical corticosteroids and closely observed as previously detailed. If no tangible improvement is witnessed after 3 days of therapy (3rd Day Rule), rescue therapy with cyclosporin or infliximab is initiated or surgery is recommended in those patients unlikely to respond to rescue drugs[4,5]. Table 1 shows the criteria used to predict the risk of colectomy in patients with severe disease activity receiving IV steroids (Table 1).

Table 1 – Predictive factors of colectomy in severe active ulcerative colitis receiving treatment with IV steroids (*3rd day rule)*

Parameters observed after 3 days of therapy with IV steroids	Risk of colectomy
>8 stools/day	85%
3-8 stools/day + CRP > 45mg/L	85%
Number of stools/day x 0,14 x CRP ≥ 8	75%

CRP: C-Reactive Protein

Edinburg h Score

The failure rate of medical therapy in severe ulcerative colitis is high. In 2004, Ho et al. employed multiple logistic regression to analyze parameters within the first 3 days of medical therapy in 167 patients with severe ulcerative colitis. Multiple logistic regression analysis identified mean stool frequency and colonic dilatation within the first 3 days and hypoalbuminaemia as independent predictors of outcome. A numerical risk score was formulated based on these variables, namely Edinburgh colitis risk score or Ho score (Table 2). It allows identification of patients with severe ulcerative colitis not responding at an early stage to intravenous corticosteroid therapy. Thus, facilitating referral for rescue therapy or surgery[12].

Table 2 – Edinburgh Risk Score.

Variables		Score
Mean stool frequency during the first 3 days of treatment		
≤ 4 / 24h		0
> 4 - ≤ 6 / 24h		1
> 6 - < 9 / 24h		2
> 9 / 24h		4
Colonic dilatation (≥ 5,5 cm)		
Absent		0
Present		4
Hypoalbuminemia < 30 g/l on first treatment day		
Absent		0
Present		1
Score		Risk of treatment failure
≥ 6 ≥ 4	High risk	100% 85%
2 - 3	Intermediate risk	45%
0- 1	Low risk	11%

CONCLUSION

Patients with acute severe ulcerative colitis that respond to intravenous corticosteroids after 3-7 days of treatment (70-80% of cases) should soon be started on an immunosuppressant such as azathioprine. No improvement after 3–7 days of intravenous steroids is an indication to start immediate rescue treatment. Patients presenting with toxic megacolon should be referred for surgery If less invasive treatments don't reduce the size of the toxic megacolon within 2 to 3 days[4,5,13].

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Point of View
Positioning of the Gediib on the use of Infliximab Biosimilar (Ct-P13) for the Treatment of Inflammatory Bowel Diseases

Fábio Vieira Teixeira[1]

Introduction

Over the past decade, the introduction of biological agents in the treatment of inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC) was of fundamental importance and represents a milestone in their therapeutic management. There is robust evidence that the use of biological agents in IBD induces and maintains clinical remission, reduces the number of hospitalizations and surgeries, as well as improves quality of life[1-4].

However, the treatment with biological agents is associated with high costs for public and private health systems. In 2008 in Europe, spending on biopharmaceuticals reached the mark of 60 billion euros and in the United States, 70 million dollars in 2009[4,5,6,7]. The long process of development and complexity of manufacturing these drugs are the causes of the high costs of these treatments. The use of biological therapy in IBD is an unquestionable benefit[1-4]. However, we cannot disregard the economic impact on the health systems responsible for the reimbursement costs of such medicines[4,5,6,7].

As patents of biological products expire, many pharmaceutical companies began developing copies of these drugs, the so-called biosimilars[4,8]. Undoubtedly, the main reasons for conception of these drugs with a similar pharmacological effect to the reference drug (innovator drug) are a less costly prescription and greater access to treatment.

At the end of 2013 in Europe (EMA - European Medicine Agency), more recently at the beginning of 2014 the Canadian Agency of drugs (Health Canada) and the Japanese Ministry of Health (Ministry of Health, Labour and Welfare - MHLW) approved the use of CT-P13 in those countries. CT-P13, the infliximab biosimilar, was the first biosimilar monoclonal antibody to be approved in Europe, Japan and Canada. The EMA approved the use of REMSIMA® (Celltrion, Incheon, South Korea) and the INFLECTRA® (Hospira, USA) for all indications shown on the label of infliximab reference medicine REMICADE® (Infliximab, Janssen Biotech, Pennsylvania, USA)[10,11,12]. However, the Health Canada has not approved the use of CT-P13 for plaque psoriasis, Crohn's disease (CD) and ulcerative colitis (UC) in adults and children. In other words, the Canadian agency did not allow the extrapolation of indications for other diseases that are approved for the reference drug[13]. The MHLW on the other hand, approved CT-P13 in Japan for rheumatoid arthritis (RA), CD and UC. The Japanese agency has not approved the use of CT-P13 for psoriasis and ankylosing spondylitis. In this case, the rejection of the latter indications was a patent not yet expired[12]. However, in the case of Canada, the causes for the non-approval of CT-P13 in some indications were efficacy and safety issues of the product in the IBD population[13].

At the end of April 2015, ANVISA approved the first biosimilar monoclonal antibody in Brazil. After analyzing the CT-P13 dossier by comparability regulatory pathway, the Brazilian agency decided to approve the use of infliximab biosimilar (REMSIMA®) for all indications of the reference product (REMICADE®)[14].

The aim of this article is to discuss whether there is scientific evidence at the present time to support the extrapolation of CT-P13 indications for inflammatory bowel diseases, emphasizing efficacy and safety of the treatment.

Discussion

In order for a biosimilar to have its use approved for the same indications as the original reference drug, some of its features need to be compared to the branded product. It is expected that the biosimilar presents same efficacy and safety, has similar effect on immunogenicity, showing to be effective for all diseases which aims to treat and must be able to replace the reference drug in the same indication, without significant differences in therapeutic results[15,16,17,18,19,20].

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It should be taken into account that the smallest details of the biosimilar production process and aspects of its structural heterogeneity may be sufficient to modify function and immunogenicity of the product, with high probability of not being identical to the original product and therefore generating unpredictable clinical consequences related to its efficacy and safety profiles[19-24]. Thus, the main concern about biosimilars is not only identifying differences that may exist when compared to the licensed product, but if they are clinically relevant[4,8,19,20,23,24].

The approval of CT-P13 by health agencies was based on two phase I and phase III studies sponsored by Celltrion laboratory. However, the phase I and phase III studies were conducted in a population of patients with rheumatic disorders: ankylosing spondylitis and RA, respectively[25,26]. For other indications of the reference drug, such as psoriasis and IBD in adults and children, both the European Union and Japan have approved the use of infliximab biosimilar by extrapolation of indications[10,11,12]. Canada was stricter in analyzing CT-P13 dossier[13]. The Canadian agency approved the use of the infliximab biosimilar for nearly all indications of the reference drug, except for plaque psoriasis and IBD in adults and children[13]. Three main arguments were presented to justify why the biosimilar was not approved for IBD: 1. The study design and studied population in phase I and III studies; 2. Possible differences found in the biological characterization of biosimilar (antibody- dependent cellular citotoxicity - ADCC and binding capacity of FcγRIIIa fraction), compared to the reference product. The third argument was the uncertainty about safety and efficacy of the biosimilar due to pathophysiological differences between rheumatic and intestinal diseases and especially the lack of clinical studies in people with IBD [13,27]. Once some differences between CT-P13 and infliximab reference drug were evident during the biological characterization of the product, the Canadian agency argued that it would be difficult to predict whether such differences would be clinically significant, with respect to efficacy and safety of the product in patients with IBD. Like the positioning of the European Organization for Crohn's disease and colitis (ECCO) and the Italian and Brazilian societies of Gastroenterology, Rheumatology and Dermatology, Health Canada suggested as well that studies with CT-P13 should be conducted in a population with IBD[24,29].

At the end of 2014, the Brazilian Study Group of Inflammatory Bowel Disease – GEDIIB - was invited by ANVISA to evaluate and comment on a possible approval of infliximab biosimilar produced by the pharmaceutical company Celltrion: the CT-P13 (Remsima®, Celltrion, Incheon, South Korea). After examination of the complete dossier presented to ANVISA by Celltrion, the GEDIIB, at least a priori, stood contrary to extrapolation of indications for CD and UC[28]. At the time, our main argument was the lack of clinical studies with CT-P13 in patients with IBD, which agreed with the position of European societies and the Canadian agency[13,23,24]. More recently, the Brazilian Society of Rheumatology, Dermatology, Gastroenterology and the GEDIIB, published a similar position on the extrapolation of indications of a biossimilar[29].

In April 2015, ANVISA approved the first biosimilar monoclonal antibody in our country[30]. After analysis of the CT-P13 dossier, the Brazilian agency decided to approve the use of infliximab biosimilar for all indications of the reference product, by a direct comparability pathway to the innovator drug (REMICADE®). As already discussed here, the clinical studies comparing CT-P13 to the reference product involved patients with rheumatic diseases[25,26]. ANVISA extrapolated the approval of CT-P13 for other indications including intestinal diseases. At the present time, is there evidence for this?

Clinical studies with CT-P13 in IBD

Until the end of April 2015, date of the last version of this manuscript, there were only two published clinical studies using CT-P13 in patients with IBD. Kang et al. described a series of 17 adult patients with CD (n = 8) and UC (n = 9) treated with CT-P13 in South Korea (Remsima®, Celltrion, South Korea)[31]. The mean age was 35 years and they were mainly male patients (64%). Forty-five percent of patients with CD and 55% with UC were naïve for biological drugs. Patients who interchanged infliximab reference product to CT-P13, were mainly refractory and/or used corticosteroids[31]. Forty-one percent of patients (7/17 - 2 patients with UC, 5 with CD) showed clinical response and remission at week 8 of treatment with CT-P13[31]. The authors reported intestinal mucosa healing after treatment with CT-P13, but did not describe the percentage of patients who achieved this goal. Like any case series, this study has limitations because it is merely a descriptive study. In addition, due to the short observation time, it was not possible to assess the drug safety profile in individuals treated with the biosimilar in the long term. As adverse drug reaction the authors described only a case of arthralgia reported by a patient who had exchanged the reference to the biosimilar. This was the first study to publish the interchangeability between infliximab reference product and infliximab biosimilar in patients with IBD. Eleven percent of the patients (1/9, 11%) that were being treated with infliximab reference product and received the biosimilar, lost response after the switch. The remaining 89% (8/9) presented a clinical response similar to that with infliximab reference product[31]. More recently, at the end of April 2015, Jung and colleagues published the largest series of patients with IBD treated with CT -P13. This retrospective study included 110 patients (59 with CD and 51 with UC)[32]. Fifty-four percent of patients with CD and 82% of those with UC were naïve for biological drugs. Seventy-five percent of patients

diagnosed with CD were in remission at week 54 of treatment. Half of patients with UC treated with CT-P13 were in remission after a year using the medication[32]. Furthermore, in this study some patients interchanged infliximab innovator (Remicade®) to infliximab biosimilar (Remsima®): 12 with CD and 9 with UC. The replacement of the innovator for the biosimilar drug was generally due to the higher cost of infliximab reference product. The clinical response after substitution was 95% in patients with CD and 67% in those with UC[32]. Regarding safety, no adverse events were observed in those patients with CD who received CT-P13. On the other hand, 12% of patients with UC presented adverse events during treatment: rash, infusion reaction, leukopenia, viral hepatitis B. Among these patients, four of them who were naïve to anti-tumor necrosis factor (anti-TNF) antibody and received CT-P13, discontinued treatment due to side effects. One patient presented dry palm skin with no need to interrupt the treatment with CT-P13[32].

Recently, some case series of adult and pediatric patients treated with CT-P13 have been presented in the most important conferences in the world. During the European Congress of IBD - ECCO, held in Barcelona, seven posters were presented[33,34,36,37,38,39,40]. Two weeks before the completion of this manuscript, Gecse et al. presented a case series of patients with IBD treated with CT-P13 during the Digestive Disease Week in Washington. In this observational study from Hungary, 141 patients (90 with CD and 51 with UC) received treatment with infliximab biosimilar. The mean age at diagnosis was 26 years for those with CD and 29 for those with UC. Most patients (62%) received combined therapy with azathioprine. Clinical remission defined as CDAI <150 points or no fistula drainage, was 60% in patients with CD at week 14 (n = 31). Sixty-two percent (n = 21) of patients with UC achieved clinical remission (defined as Mayo score <3 or 3 points decrease from baseline Mayo score). This series (cohort) is the largest published in the medical literature to date. The authors concluded that in this real-life study, clinical response and clinical remission achieved with the use of CT-P13 appear to be similar to results previously presented with infliximab reference product[35]. Some adverse effects were reported: 1 case of upper respiratory tract infection, 1 case of salmonellosis, 1 case of urinary tract infection, 2 cases of unknown fever and 1 death. Six patients (4.3%) had complications after infusions of CT-P13: infusion reaction (4/141), a case of urticaria and severe arthralgia after infusion and a case of anaphylactic reaction in the third infusion of the drug [35]. In a short-term period (54 weeks), CT-P13 showed to have a safety profile similar to the reference product.

Biosimilars have already been used in patients with IBD in Eastern Europe and Korea since more than one year. After approval of the product in those countries, the studies conducted with CT-P13 reported similar efficacy results (remission/clinical response and mucosal healing) and safety profile to infliximab reference product[33-39]. However, a retrospective study with controversial methodology conducted in Ireland showed a significant increase in hospitalizations, use of corticosteroids and surgery in patients treated with CT-P13 compared to those receiving infliximab reference product[40]. Since it is so far the only study to show discrepancy of efficacy and safety, these results should be carefully evaluated. On the other hand, we need to be attentive and cautious. Pharmacovigilance and a risk management plan for an approved product are essential. Even though similar to the reference product, it is not the same drug. So we should not draw analogies to adverse events published with infliximab reference product and extrapolate for the infliximab biosimilar.

Immunogenicity

The immunogenicity produced by monoclonal antibodies is the most important safety aspect related to the use of biological drugs. This characteristic contributes to various adverse events of these drugs, from loss of treatment response by developing antibodies against the product to the presence of undesirable clinical manifestations, imposing a withdrawal[4,8,19,20]. Thus, the regulatory agencies recommend that a new molecule with biological activity should always have its immunogenic potential evaluated. Another recommendation concerns the population to be treated: it must be the one most likely to develop immune responses to the drug, as well as to present immune-mediated adverse reactions[4,8,11,13,19,20]. In the case of infliximab, the ideal population would be that of patients with skin disease, psoríase [4,8]. This is also the position of the Italian and Brazilian Societies of Rheumatology, Dermatology, Gastroenterology and the Group of Inflammatory Bowel Diseases[24,29].

We can also argue that extrapolating results from a population with rheumatic disease to CD and UC patients is not convenient because of the distinct pathophysiology [4,8,27]. Rheumatoid arthritis is not considered the best model to assess immunogenicity on the development of new biological drugs. If the rates of development of antibody against the medicine reach high values in CD treated with infliximab - in some publications 60% and for psoriasis between 20% and 50% - this rate in RA is much lower[4, 8]. The greater the numerical difference in immunogenicity and efficacy rates between treatment and placebo, the more sensitive will be the population. It is evident that would be easier to identify differences between the reference medicine and its biosimilar in a more sensitive population[8,19,20].

In addition to possible adverse effects, immunogenicity can also lead to loss of efficacy of the product as the

formation of antibodies against the drug may block the biological effect of the drug or even destroy it. This phenomenon of loss of efficacy is a well-documented event in patients treated with anti-TNF agents[41,42,43]. Loss of efficacy is estimated in 8% to 10% annually. In Brazil, Kotze et al. recently observed similar loss of efficacy in patients with CD treated with adalimumab or infliximab[43]. Thus, although a similar efficacy between the biosimilar and infliximab reference product has been shown in two published studies and seven other abstracts, so far we cannot evaluate the safety of the product, at least in the long term.

Extrapolation of indications

Studies with CT-P13 were performed in patients with RA and ankylosing spondylitis[25-26]. In a randomized study with patients with RA the authors concluded that both products had equivalent efficacy. There were also similarities concerning adverse reactions and formation of antibodies against both drugs[26]. Similar results were reported in patients with ankylosing spondylitis[25]. It should be noted that the dose of infliximab in both studies was lower (3mg/kg) than that used in the treatment of IBD. These few equivalence studies supported the principle of extrapolation of indications of this new molecule in the treatment of other immune diseases such as CD, UC, psoriatic arthritis and plaque psoriasis.

Would RA be a suitable clinical model sensitive enough for the detection of differences between the biosimilar and the reference product[4,8,19,20]? Is the mechanism of action of infliximab to antagonize TNF the same in all the diseases for which it has been approved[27]? Have both safety and immunogenicity profile of the new molecule been properly characterized in those experiments?

RA showed to be a clinical model with limited sensitivity (the lowest response adjusted to placebo). In addition, could the dose of infliximab, below the one recommended for IBD, change the efficacy results confirmed by the equivalence studies[4,8,19,20]? In addition to its role of blocking TNF, different mechanisms of action for the same monoclonal antibody can be expected, depending on the disease[27]. For example, infliximab induces apoptosis of inflammatory cells in CD, but not in RA. Infliximab binding to the membrane TNF and inhibition of its action is stronger than other drugs from the same class (etanercept)[27]. This binding affinity may result in some intracellular mechanisms of action that make the extrapolation of biosimilar data on efficacy and safety more challenging[4,8]. These observations allow us to speculate whether the mechanisms of action of the biosimilar and the reference product differ for the same indication[4,8].

Moreover, it is necessary to consider that some aspects involved in IBD are not present in other immune diseases, the target group of biologic drugs. Beside differences in several genetic mutations predisposing the onset of inflammatory processes, the role of intestinal microbiota is remarkable on the pathogenesis of immunoinflammatory responses, which is probably less significant in arthropathies and skin diseases. The same occurs with environmental stimuli, smoking, non-steroidal anti-inflammatory drugs, stress and probably diet. These factors interact with changes in the microbiota composition and permeability of the enteric epithelium, damaging the defense mechanisms of cell surface (innate immunity), stimulating cel ls involved in adaptive immunity (T lymphocytes), proliferation and differentiation and production of large quantities of cytokines including tumor necrosis factor, a key player in the onset and maintenance of inflammation[4,8,19 20]. This immune response is not comparable to responses in other immune diseases[44]. It is accepted that some infectious agents can be connected to RA, stimulating the formation of immune complexes that act as triggers for the induction of the rheumatoid factor. The influence of intestinal microbiota in the pathogenic mechanism of RA has been investigated[44].

Pharmacovigilance

The arrival of biosimilar drugs on the Brazilian market and the approval of CT-P13 is only the beginning of a new scenario. However, little is discussed about pharmacovigilance of these new molecules. Pharmacovigilance is defined as the procedure of monitoring the safety of medicines in order to detect, access, understand and prevent adverse events or other related complications[45,46]. All pharmacovigilance systems should be simple and self-explanatory enough to promote the adherence of doctors and health care professionals responsible for identifying and reporting adverse events. Complex systems tend to generate inconsistent and unintelligible data, making difficult the data interpretation by the regulatory agencies and complicating the monitoring of adverse events. In Brazil, the regulatory agency has difficulties to regulate and perform pharmacovigilance of biological products, which is mostly performed by the pharmaceutical industry.

In most countries infliximab was approved for IBD in the beginning of the last decade. In the mid-2000s, 350 American gastroenterologists, most of them from community and university centers, created the database TREAT (The Crohn's Therapy, Resource, Evaluation Registry) which is an ongoing observational registry designed to evaluate the safety of drugs used in the treatment of CD, including infliximab. Lichtenstein et al. published post-marketing safety data on more than 5000 CD patients treated with infliximab in the US after 1999[47]. Infliximab was ruled out as an independent risk factor of serious infection in pa-

tients with CD, after multivariate and logistic regression analysis (OR, .99; 95% CI, .64- 1.54). On the other hand, the authors pointed prednisone and opioid narcotics as independent factors associated with severe infections in patients with CD[47]. Five years after publication of the TREAT data, the same authors published an update in 2012 [48]. More than 6000 patients were analyzed. The authors identified as independent risk factors for infection in patients with CD: prednisone, narcotics and infliximab (HR = 1.43, 95% CI = 1.11 1.84; P = 0.006)[48]. The TREAT registry is an active example of the importance of surveillance with biological drugs. Only a long post-marketing follow-up of a biological drug is able to identify adverse effects that might risk patients safety[47,48].

In conclusion, to date, only two post-marketing studies have been published showing efficacy and safety of the infliximab biosimilar compared to the reference drug. Beside them, seven other studies presented as posters in medical congresses reported similar efficacy and safety of CT-P13 compared to infliximab reference product. However, an Irish study showed an increase in the number of hospitalizations and surgeries in patients with IBD treated with CT-P13 compared to the reference product, despite controversial methodology and selection of patients. Nevertheless, there is evidence for the efficacy of CT-P13 in IBD patients, even though it is merely based on a cohort of 350 patients. The follow-up time of less than two years is insufficient to draw conclusions concerning the safety profile.

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Commented Article
Mongersen, an Oral SMAD7 Antisense Oligonucleotide, and Crohn's Disease

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Crohn's disease (CD) is a chronic relapsing inflammatory condition that is immunologically mediated. Although the precise cause of CD remains unknown, most of studies indicate that CD is characterized by various genetic abnormalities that lead to overly aggressive T-cell responses to commensal enteric bacteria. The onset and reactivation of disease is triggered by environmental factors that transiently break the mucosal barrier and stimulate immune responses.

The current generally accepted goal of Crohn's disease management is ulcer healing, made possible through the introduction of biologic therapies against tumor necrosis factor (TNF) α. But despite almost two decades of anti-TNF use, no convincing reduction in disease progression or surgical rates has been reported. One explanation for this lack of progress in the clinical management of Crohn's disease is that treatment with anti-TNF agents, such as infliximab and adalimumab, is usually initiated after the disease is long established. This explanation, however, seems unsatisfactory; mechanisms other than those mediated by TNF must play a role in the perpetuation of the inflammatory cascade.

It seems that counterregulatory processes are deficient in the pathogenesis of Crohn's disease and thereby contribute to inflammation. One such mechanism involves transforming growth factor (TGF) β1. In patients with Crohn's disease, TGF-β intracellular signaling is blocked by high levels of the SMAD7 protein. An oral antisense oligonucleotide called mongersen binds to and causes the degradation of SMAD7 messenger RNA; it therefore has the potential to restore TGF-β signaling and reduce proinflammatory cytokine production.

METHODS

A randomized phase 2 trial evaluated the efficacy of mongersen, for the treatment of patients with active Crohn disease. In this multicenter, randomized, placebo-controlled, double-blind, phase 2 clinical trial, 166 patients were randomly assigned to receive 10, 40, or 160 mg of mongersen or placebo per day for two weeks.

Because the active compound of mongersen is released in the terminal ileum and right (proximal) colon, patients with known lesions in the stomach, proximal small intestine, transverse colon, or left colon were excluded. Patients with strictures, fistulae, perianal disease, extraintestinal symptoms, active or recent infections, pregnancy or a history of cancer were also excluded.

Patients could continue to receive stable doses of steroids, or mesalamine during the 2-week treatment period. Oral Antibiotic agents, glucocorticoids, immunosuppressive drugs, and biologics could not be initiated before study entry or during the 2-week treatment period. Patients received no treatment with anti–TNF-*α* antibodies or other biologic agents within 90 days of their enrollment in the trial.

The primary outcomes were clinical remission at day 15, defined as a Crohn Disease Activity Index (CDAI) score <150, with maintenance of remission for at least two weeks, and the safety of mongersen treatment. Secondary end points included the rates of clinical response, defined as a decrease in the CDAI score of 100 points or more or a decrease of 70 points or more, at days 15 and 28, as well as the percentages of patients with a CDAI score of less than 150 at days 15, 28, and 84. Percentages of patients who had normalization of C-reactive protein after treatment, had elevated C-reactive protein levels at baseline and reached clinical remission, and were in glucocorticoid-free remission at day 84 were also evaluated. Additional end points included changes in plasma levels of proinflammatory cytokines (e.g., interleukin-8 and TNF-*α*).

RESULTS

A total of 160 patients (96.4%) completed the 2 weeks of treatment and the day 28 follow-up, and 138 patients (83.1%)

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completed the day 84 follow-up. Clinical remission rates were significantly higher in patients treated with 40 and 160 mg of mongersen, as compared with placebo (55 and 65 vs. 10%). The rate of clinical response was significantly greater among patients receiving 10 mg, 40 mg, or 160 mg of mongersen as compared with placebo (37, 58, and 72 vs. 17%).

The proportions of patients who had a 100-point clinical response at day 15 were significantly greater in the 160-mg and 40-mg groups than in the 10-mg and the placebo group (P<0.001). At day 28, the proportions of patients with a 100-point clinical response (i.e., a CDAI score reduction of ≥100 points) were significantly higher in the 160-mg group (72%), 40-mg group (58%), and 10-mg group (37%) than in the placebo group (17%).

Overall, 102 of 166 patients (61.4%) had an elevated C-reactive protein level (i.e., >3 mg per liter) at screening; among the patients who had elevated C-reactive protein levels at baseline, the proportions with normalization of these levels at day 15 were 4% in the placebo group, 22% in the 10-mg group, 18% in the 40-mg group, and 18% in the 160-mg group. The response rates were similar among patients with an elevated C-reactive protein level and patients with a normal C-reactive protein level at baseline.

No significant differences in the median dose of glucocorticoids were detected among the groups at baseline. At day 84, the percentage of patients who had a glucocorticoid-free remission was significantly greater in the 160-mg group than in the placebo group (6 of 9 [67%] vs. 1 of 9 [11%], P=0.04), and there was no significant difference between the 10-mg group (3 of 7, 43%) or the 40-mg group (6 of 13, 46%) and the placebo group (1 of 9, 11%).

Nine serious adverse events were reported, in six patients. Most serious adverse events were hospitalizations for complications or symptoms of Crohn's disease.

DISCUSSION

Targeting SMAD7 with mongersen was of clinical benefit for study participants with active Crohn's disease. The effect was rapid in onset and durable in many patients.The rates of remission were greater in the groups of patients treated with 40 mg or 160 mg of mongersen per day than in the groups receiving 10 mg per day or placebo. Nonetheless, all three groups receiving mongersen had a significantly greater rate of clinical response than did the placebo group, which suggests that even a dose of 10 mg per day may be therapeutic in a subset of patients.

Normalization of C-reactive protein levels was more common in each of the three groups of patients treated with mongersen than in the placebo group, although the differences in the numbers of participants in whom normalization was achieved were not significant. Although the absence of an association between improvement in the CDAI score and normalization of the C-reactive protein level in all the patients treated with mongersen remains to be clarified, it is conceivable that healing of tissue lesions, normalization of C-reactive protein levels, or both require treatment for longer than 2 weeks.

A diminished ability to mount an efficient counterregulatory TGF-β1 response to inflammatory stimuli is believed to be instrumental in the pathogenesis of Crohn's disease. The dosage effects that we observed are probably related to the amount of active compound delivered to the gut and thus the extent to which SMAD7 is down regulated and TGF-β1–dependent counter regulatory signals are up regulated.

Data from this phase 2 study, provide evidence of the efficacy and adverse-effect profile of mongersen in active Crohn's disease. The study results support earlier work showing that SMAD7 has a role in the inflammatory reaction of Crohn's disease.

COMMENTS

Monteleone and colleagues report on the results of a phase 2 study evaluating the efficacy of mongersen in patients with moderate-to-severe active Crohn's disease. The primary end point was clinical remission, defined as a CDAI score of less than 150 at day 15. The proportion of patients meeting this end point was 10% for the placebo group and 12%, 55%, and 65% in the 10-mg group, 40-mg group, and 160-mg group, respectively. The primary end point was met, and the secondary outcome of clinical response (defined as a reduction in CDAI score of at least 100 points by day 28) was highly significant for the two highest doses.

The remission rates of between 55 and 65% for the two highest doses are unprecedented when compared with those reported in the large pivotal induction studies of infliximab (32.5% glucocorticoid-free clinical remission at week 6 in the SONIC trial), adalimumab (36% clinical remission at week 4 in the CLASSIC-I trial), and more recently, vedolizumab (14.5% clinical remission at week 6 and 39% at week 54 in the GEMINI 2 trial), all of which also involved patients with moderate-to-severe active Crohn's disease. However, the inclusion criteria used by Monteleone and colleagues were based on the CDAI score and did not include more objective criteria for active disease. Endoscopic confirmation of active Crohn's disease was not an inclusion criterion, so it is unclear what proportion of patients underwent randomization without actually having mucosal lesions. The SONIC study provided important lessons in this respect[4]: it, too, recruited persons with Crohn's disease defined according to CDAI

score only, and analyses performed after the completion of the study showed that 18.3% of the participants had normal results on colonoscopic examination.

The impressive data on clinical remission reported by Monteleone et al. contrast with the relatively modest effect on the normalization of C-reactive protein levels: only 18% of the patients randomly assigned to the 40-mg or 160-mg group who had elevated C-reactive protein levels at baseline had normalization of C-reactive protein levels at the end of the treatment period, a proportion similar to that of the group who received 10 mg of mongersen, a dose that was not associated with clinical remission. In fact, among the patients with an elevated level of C-reactive protein at baseline, none of the doses of mongersen reduced the median levels. In short, there is a lack of congruence between clinical remission and biologic remission, an issue that will need to be addressed in future studies.

Another intriguing finding is that clinical remission was maintained for almost 3 months, even though the drug was administered for only 14 days. This contrasts with the rapid recurrence of symptoms on withdrawal of existing antiinflammatory drugs.

Among the adverse events the authors observed in their study, there was only one instance of intestinal obstruction, in the 40-mg dose group, although the duration of the trial was probably too short to draw firm conclusions about safety. Additional studies are needed to confirm these findings and define the role of mongersen in the treatment of Crohn disease.

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Brief Report
Metabolism of azathioprine in patients with inflammatory bowel disease.

Joselmo Willaymys[1]

BACKGROUND

Crohn's disease (CD) and ulcerative colitis (UC) are the most common types of inflammatory bowel disease (IBD). Although their exact etiology remains uncertain, it has been suggested that genetic, infectious and immunological factors play a pathogenic role in the inflammatory process and tissue damage. Pharmacological approaches include the aminosalicylates, corticosteroids, and immunosuppressant drugs such as azathioprine (AZA), a thiopurine prescribed to maintain clinical remission in IBD. Potential side effects of AZA treatment include gastrointestinal disturbances, pancreatitis, hepatotoxicity, and bone marrow suppression. Thiopurines are S-methylated by thiopurine methyltransferase (TPMT), a critical enzyme to thiopurine metabolism. Genetic polymorphisms in the TPMT gene are associated to decrease enzyme activity and marked AZA toxicity. In addition, the combination of AZA with aminosalicylates and biological anti-inflammatory drugs can modify the final levels of active metabolites by mechanisms not yet fully elucidated.

AIMS

The current study aimed to quantify thiopurine metabolites and to identify the frequency of allelic variations in the TPMT gene among IBD patients submitted to distinct AZA therapeutic regimens.

PATIENTS AND METHODS

The study was conducted at a university teaching hospital in the city of São Paulo, Brazil (Hospital São Paulo - Universidade Federal de São Paulo), and approved by the local Research Ethics Committee. After signing informed consent, 90 patients with IBD were included in the study. Two peripheral blood samples in a vacutainer tube with EDTA were collected from each subject, and immediately transported to the Molecular Pathology laboratory for processing and storage. Patients were allocated to one of five groups according to the specific therapeutic regimen: treatment discontinuation; monotherapy with AZA; AZA+ mesalazine; AZA + sulfasalazine; AZA + anti-TNF-α. Quantification of AZA active metabolites, 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine ribonucleotides (6MMPR), was performed in 75 patients by High Performance Liquid Chromatography-UV (HPLC-UV). Frequency of TPMT gene polymorphism was evaluated by polymerase chain reaction – restriction fragment length polymorphism (PCR-RFLP).

RESULTS

Fifty-three and thirty-seven patients were diagnosed, respectively, with CD and UC. Mean age of study subjects was 43 years old, the majority of them being male (58,8%, n= 53). Therapeutic, toxic, and sub-therapeutic levels of 6-TGN were identified, respectively, among 44%, 36% and 20% of study subjects. Toxic 6-TGN levels were higher in patients using AZA+anti-TNF-α (13.3%), while therapeutic levels were most often observed for the AZA + mesalazine group (16%). Elevated 6MMPR metabolite levels, associated with hepatoxicity, were identified in 25.3% of IBD patients. PCR-RFLP detected the following genotypes: TPMT*1 (87.8%), TPMT*2 (1.1%), TPMT*3A (1.1%) TPMT*3B (5.6%) and TPMT*3C (4.4%). Overall, 11.1% of patients presented heterozygous TPMT genotypes.

CONCLUSION

Drug interactions and other non-genetic factors may be involved in AZA metabolism among the selected IBD patients. Pretreatment assessment of each patient's genetic profile, periodic metabolite quantification, and measurement of TMPT activity could be valuable tools to guide optimization of AZA therapy.

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Brief Report
Association between serum vitamin D levels and inflammatory markers in patients with inflammatory bowel disease

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two main forms of inflammatory bowel disease (IBD), presenting as autoimmune disorders with periods of relapses and remissions. Recent studies have identified decreased levels of vitamin D in IBD patients. There is also clinical evidence to suggest a role for vitamin D deficiency on disease activity and severity. There is a small group of food containing vitamin D, such as egg yolks, fish oils, and mushrooms. However, because of this vitamin's decreased bioavailability, the primary source of vitamin D is ultraviolet B (UVB) radiation in sunlight[4,6].

The active form of vitamin D is calcitriol (1 alpha, 25-dihydroxyvitamin D). Calcitriol mechanism of action is similar to that of steroid hormones, working through receptors located primarily in the nuclei of target cells[3,9]. A number of studies have demonstrated the immunomodulatory effects of vitamin D, and the relevant autocrine role within immune cells such as CD4+, CD8+, T cells and antigen-presenting cells. In addition, vitamin D acts as an immune regulatory agent, modulating the balance between Th1, Th2 and Th17 responses. Low concentrations of vitamin D are associated with the potential risk of developing autoimmune disorders, by stimulating the development of autoreactive T cells and increasing pro-inflammatory citokines such as IL-12 and interferon-gamma. Given the importance of vitamin D for the immune system, recent studies have suggested its relevance in preventing IBD development and also its influence on disease severity[1-2,5].

The current report evaluated the association between serum vitamin D concentrations and inflammatory markers in patients diagnosed with IBD at the Gastroenterology Clinic from the Federal University of São Paulo.

Patients and Methods

The study was conducted at a university teaching hospital in the city of São Paulo, Brazil (Ambulatório de Intestino da Disciplina de Gatroenterologia - Hospital São Paulo - Universidade Federal de São Paulo), and approved by the local Research Ethics Committee. Subjects included in the study were adult ambulatory patients diagnosed with CD or UC, aged 18 to 70 years. All patients signed an informed consent form before enrollment.

The CD activity index (CDAI)[10] and Truelove and Witts' scale of UC[8] were used by ambulatory care physicians for clinical evaluation of the disease activity. Serum 25-hydroxyvitamin D [25(OH)D] concentrations and C-reactive protein (CRP) levels were determined for all patients. Analysis of fecal calprotectin was also requested, since elevated concentrations of this biomarker have been associated with increased migration of neutrophils into the gut lumen and fecal excretion of leukocytes[7].

Vitamin D status was recorded based on criteria proposed by Ulitsky et al [9], as follows: severe deficiency <10 ng/ml; deficiency <20 ng/mL; insufficiency 20-30 ng/ml; and sufficiency ≥30 ng/mL.

For descriptive analysis the quantitative variables were represented by their averages and standard deviations. The definition of normality was made through graphical analysis and Shapiro-Wilk test[11]. The categorical variables were represented by frequencies and percentages. Correlation analyzes were made through the Spearman correlation coefficient for non-normal distribution. The results were considered significant for p values < 0.05. Statistical analyses were conducted using the IBM software Statistical Package for the Social Sciences version 20.0 (SPSS ®, Chicago, IL, USA).

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Results

Overall, 111 individuals with IBD (62 CD and 49 UC) were included in the present study, mostly female (63.1%). Mean age at evaluation was 45.1 ± 14.2 years. Mean concentration of serum 25(OH)D was 21.8 ± 11 ng/ml. Mean concentration of serum 25(OH)D was 19.7 ± 11 ng/ml in patients with CD and 24.5 ± 10.5 ng/ml in patients with UC. Most IBD patients had insufficient serum levels of 25(OH)D.

The Spearman correlation coefficient, found a -0,350 coefficient of correlation ($p<0.001$) for CRP; -0,226 ($p=0.100$) for fecal calprotectina; -0.063 ($p=0.627$) for CDAI (classification); and -0,435 coefficient of correlation ($p=0.002$) for the index of inflammatory activity Truelove and Witts' criteria.

Based on the results, we can conclude that these patients present a framework of hypovitaminosis D, and that its low serum levels have a negative and significant correlation with serum levels of CRP and with the index Truelove and Witts' criteria, which was not observed with the CDAI index. We emphasize that the clinical indices for evaluation of inflammatory activity in UC and CD may present significant differences for the proposed objective. These data, suggest their relevance to the immune system, requiring more research in the area.

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Cases Report
Tuberculosis and Biological Therapy

Marjorie Costa Argollo, Orlando Ambrogini Jr., Sender Jankiel Miszputen

Introduction

After the appearance of biological therapy using anti -tumor necrosis factor alpha (anti -TNF α) for the treatment of inflammatory bowel disease (IBD) in their moderate to severe forms, it was necessary to regulate strategies to prepare the patient before initiation of treatment, at increased risk of developing opportunistic infections, especially tuberculosis and hepatitis B. Literature reports an increase of up to 18 times to develop tuberculosis in patients with IBD using biological therapy. Therefore considered for all patients receiving biologic therapy should undergo screening regimen for latent or active tuberculosis . Currently it is used as a screening for the diagnosis of latent tuberculosis (LT) conducting the tuberculin skin test (TST) also known as Mantoux test, and chest radiography . Then we present a case of peritoneal tuberculosis in a patient with Crohn›s disease (CD) after stroke with anti - TNF - α, despite negative screening .

Case Report

Male, 41 years old, storekeeper, born and raised in São Paulo, was admitted at our service due to daily high fever for about 10 days, with nocturnal predominance, accompanied by swets and weight loss of 2Kg in the period. Diagnosed with ileocecal Crohn's disease at 1999 and accompanied at another facility, began treatment with sulfasalazine (3g/day) and prednisone during bouts of abdominal pain. He denied smoking, disease complicatios and refered a family history of Crohn's disease (paternal cousin and maternal uncle). Remained asymptomatic until 2006 when he interrupted treatment on his own. In 2009 was sent to the Hospital São Paulo by complaining of abdominal pain and weight loss. Performed new tests for restaging of the disease with intestinal transit showing areas of stenosis in the terminal ileum without upstream dilatation, colonoscopy with the same findings reported at previous exam and evidence of elevated inflammatory activity. Treatment with azathioprine 2mg/kd was iniciated. In 2012 he started to complain of recurrent episodes of intestinal subocclusion, requiring further tests to study the small intestine. A CT enterography demonstrated a sharp parietal thickening and increased mucosal enhancement involving long segment of the distal ileum located at the right pelvis, engorgement of mesenteric vessels and densification of the adjacent fatty plans and mesenteric lymphadenopathy. No signs of fistula, obstruction or other complications of the disease were seen. Given the findings we chose to complement clinical treatment with the anti-TNF-α adalimumab, after screening for hepatitis B and tuberculosis with serological assays, TST and chest radiography, that resulted negative. After the fourth doseof adalimumab, patient reported fever, previously described. Physical examination drew attention for general preserved state, no findings of abdominal abnormalities or lynfadenopathy. Chosen to stop treatment for underlyng disease, initiated antibiotic therapy (ciprofloxacin and metronidazole) for possible abdominal infection while continuing the diagnostic workup. Tomography of the chest and abdomen pulled out complications and demonstrated improvement of enteritis compared to previous exam. Blood cultures for aerobic, anaerobic and the HACEK group, search for CMV, HIV, Cryptococcus and histoplasmosis came in negative. Echocardiography without evidence of vegetations suggestive of endocarditis. New TST negative. Study for possible lupus like syndrome were inconclusive. Patient remained febrile during diagnostic investigation when after 15 days of hospitalization he developed severe abdominal pain and we decided to perform a nuclear magnetic resonance of the abdomen. Demonstration of moderate ascites, not shown at previous exams, claimed attention and was punctured. Ascitic fluid was sent to laboratory study with the following findings: cellularity 680 (71% lymphocytes), protein 4.8/albumin 2.5, glucose 108, LDH 538, amylase 42, ADA 68.7 and direct search BAAR and cultures negatives. Despite the uncertain diagnosis, chose together with infectious diseases staff, we initiated treatment for peritoneal tuberculosis with quadruple therapy for nine months. Remained febrile until the second month of treatment whenthe fever began to sag with complete disappear-

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ance associated with the emergence of a left mobile, painless and fibroelastic ganglion which was then punctured and material collected with cytological findings compatible with chronic granulomatous lymphadenitis with necrosis vernix. Patient completed treatment for nine months for tuberculosis and at the end of it complained of slight abdominal pain without fever or change in bowel habit. New colonoscopy and CT enterography were performed and showed disease activity. We decided to restart treatment with biological therapy, made new induction and subsequent maintenance dosage. General improvement of abdominal discomfort was described with no other findings.

Discussion

The role of anti-TNF-alpha in the immune response to *Mycobacterium tuberculosis* remains uncertain. However, it is believed that TNF-α plays an important role in regulating the formation and maintenance of granuloma, preventing the progression of infection. Therefore deregulation may be in the process described above after introduction of agents that block the TNF-α. International guidelines suggest as the best way of screening for latent tuberculosis infection in asymptomatic individuals, conducting TST associated with chest radiography. In the presence of symptoms the patient should be referred to a specialist before starting treatment. Those who submit TST > 5mm or chest X-ray suggestive of scar should undergo chemoprophylaxis with isoniazid for 1 month before starting biologic therapy. It is known limitation of the TST for screening for latent tuberculosis, by its low sensitivity, especially in places where there is high prevalence of the disease. Concomitant factors may contribute to false-negative results and include protein-calorie malnutrition, steroids in doses of 20mg/day for at least 2 weeks and use of immunosuppressants. In these cases an alternative would be the use of IGRA (interferon gamma release assay), which is more sensitive in detecting cases of TL. But this test is not available in all centers and has higher cost, preventing its incorporation as a screening method for all patients. In the literature is described most commonly cases of reactivation of tuberculosis after the first 3 doses of induction, as described above in the case, as well as in extra-pulmonary tuberculosis in 50% of cases.

Conclusion

Latent tuberculosis should be traced in all patients candidates for receiving biologic therapy with TST and chest radiography. In selected cases include the IGRA during the investigation pretreatment. In suspected cases of reactivation of tuberculosis, even with presentation of nonspecific symptoms , you should insist on your diagnosis , as well as include a multidisciplinary team in conducting the case.

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Case Report
Adenocarcinoma arising from perianal fistula in Crohn's disease

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Abstract

Introduction: Crohn's disease (CD) is an inflammatory illness of unknown origin. The natural history of CD reveals a clear inflammatory behavior that reaches the wall of many parts of the gastrointestinal tract and can be manifested as stricturing and penetrating forms, leading to abscesses, perforations, stenosis, intestinal obstructions and perianal disease. Chronic inflammation has been clearly related to neoplastic risk. In Crohn's disease patients, perianal fistula is found in 10 to 26% of these patients. When these fistulas persist for a long time they can increase the risk of malignancy, but the neoplastic incidence is very low. Case report: we describe a rare case of a 59-year-old woman suffering from colonic and perianal Crohn's disease for 11 years who had an adenocarcinoma arising from a fistula. The patient had a tumor smaller than 5 cm in early stage and had a good recovery after surgical resection and adjuvant radiotherapy. Discussion: adenocarcinoma is an aggressive tumor that requires early diagnosis and rapid treatment to achieve a good prognosis. This case highlights the need for a complete physical exam and a proper biopsy of perianal fistula when there is any suspicion of neoplastic transformation, especially in patients with findings of severe active disease.

Keywords: *Crohn disease; Perianal fistula; Adenocarcinoma.*

Resumo

Introdução: A doença de Crohn (CD) é uma doença inflamatória de etiologia desconhecida. A história natural da CD revela um comportamento inflamatória claro que atinge a parede de várias partes do tracto gastrointestinal e pode ser manifestada como stricturing e penetrar em formas, levando a abcessos, perfurações, estenose, obstrução intestinal e doença perianal. A inflamação crônica tem sido claramente relacionado ao risco neoplásica. Em pacientes com doença de Crohn, fistula perianal encontra-se em 10 a 26% destes pacientes. Quando estas fístulas persistem durante um longo período de tempo que pode aumentar o risco de doença maligna, mas a incidência neoplásica é muito baixo. Relato de caso: Descrevemos um caso raro de uma mulher de 59 anos de idade sofrem de doença do cólon e perianal de Crohn há 11 anos que tiveram um adenocarcinoma decorrente de uma fístula. O paciente tinha um tumor menor do que 5 cm em fase inicial e teve uma boa recuperação após a ressecção cirúrgica e radioterapia adjuvante. Discussão: adenocarcinoma é um tumor agressivo que exige diagnóstico precoce e tratamento rápido para conseguir um bom prognóstico. Este caso destaca a necessidade de um exame físico completo e uma biópsia adequada da fístula perianal quando há qualquer suspeita de transformação neoplásica, especialmente em pacientes com achados de doença activa grave.

Palavras-chave: doença de Crohn; Fístula perianal; Adenocarcinoma.

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Introduction

Crohn disease is an inflammatory condition of unknown etiology that is characterized by transmural inflammation of the gastrointestinal tract. CD may involve the entire gastrointestinal tract from mouth to the perianal area[1]. Fatigue, prolonged diarrhea with abdominal pain, weight loss, and fever, with or without gross bleeding, are the hallmarks of CD. The transmural nature of the inflammatory process often results in fibrotic strictures[2]; development of sinus tracts and fistulas; abscess formation[2,4]; bowel perforation[5]; recurrent episodes of small bowel obstruction[6,7] and perianal disease. Manifestations of perianal Crohn disease include skin lesions such as Crohn tags, as well as anal canal lesions such as perianal abscesses, fistulas, and fissures. Perianal involvement usually denotes a more aggressive form of disease, and some classifications recognize perianal fistula as a distinct form of penetrating CD[8]. Perianal fistulas develop in approximately 10–26% of patients with CD[9,10,11]. Up to 15.5% of these patients have penetrating lesions at diagnosis[12]. Severe disease activity and longstanding fistula seem to increase the risk of squamous cell carcinoma and anal adenocarcinoma[13,14,16]. The relative incidence of anal cancer as a proportion of all colorectal cancer, in patients with Crohn's disease is significantly higher than the incidence of anal cancer in patients without inflammatory bowel disease (2%)[16-18]. Malignant transformation of perianal fistula in Crohn's disease has rarely been reported[20-22]. A systematic review of case series and reports published in English language between 1950 and 2008 revealed 61 cases of carcinomas arising in perineal fistulas in Crohn's disease[23]. We present a rare case of malignant transformation in colonic and perianal CD with good response to surgical excision and adjuvant radiotherapy.

Case Report

The patient was a 59-year-old woman suffering from CD for the past 5 years was referred to our hospital for intractable perianal fistula. She had a history of sigmoid colon removal due to obstruction 5 years earlier, when she was diagnosed with CD. She complained of recurrent nodule with purulent and bloody discharge in the perianal and buttock regions. The discharge had started about 1 year before the diagnosis of CD, resulting in multiple anorectal fistulas, treated with drainage, surgery, mesalazine and oral prednisone. On physical examination, we observed 3 perianal openings without spontaneous discharge and passage of stool through the vagina. A patch of erythematous, indurated skin overlying a 1.5 cm nodule near the anus was also observed.

Laboratory tests were unremarkable. Treatment with intravenous steroids, ciprofloxacin and metronidazole was started. Colonoscopy revealed partial stenosis in the descendent/rectum anastomosis. Azathioprin 50mg/ daily and mesalazine suppositories were added, with improvement. A few months later the patient relapsed from the rectovaginal fistula. Rescue therapy with infliximab 5mg/Kg was started with excellent response.

After 3 years in remission, patient came back referring new painless perianal nodule. At this time she also reported pain in peripheral joints. Physical exam disclosed a 3cm perianal tumor, with central ulceration (Figure 1). Biopsy confirmed adenocarcinoma. Colonoscopic and gynecologic examination showed no signs of tumor infiltration. Local tumor resection was performed. Pathologic assessment revealed mucinous adenocarcinoma around the fistula. Immunohistochemical findings did not support a colonic origin of the tumor. The resected specimen was positive for CK7 and negative for CDX2, which points out to the perianal glands or the fistula as the tumor origin (Figure 3). Postoperatively she received adjuvant radiotherapy. Patient's CD condition has remained stable without any signs of cancer recurrence so far 4 years since surgery for tumor removal. Magnetic resonance imaging and transvaginal ultrasonography are still unremarkable.

Discussion

Penner and Crohn described the first case of perianal fistula in a patient with regional enteritis in 1938[24]. Major perianal complications affect approximately 35 to 45 percent of patients during the course of the disease and can precede symptomatic intestinal disease by years[25,26]. Age, race, and disease location are factors associated with perianal complications in Crohn disease[8].

Anorectal fistulas develop in approximately 20 to 30 percent of patients with Crohn disease. Fistulas can present with persistent anal pain, painful defecation, and perianal openings with purulent discharge. The risk of intestinal carcinoma may be higher in patients with Crohn disease who have stricturing disease or longstanding perianal disease. Carcinoma should be suspected in patients who have fistulas containing exuberant granulation tissue and induration, implying severe inflammatory activity[27]. Carcinoma (squamous or adenocarcinoma) can rarely develop within the fistulous tract[13,14,16,28-31]. Early diagnosis is difficult because of the absence of a tumor within the lumen and in 80% of the cases, the tumor presents local invasion at diagnosis[32,33]. Endorectal ultrasonography, computed tomography scans and magnetic resonance imaging all play a role in evaluating disease extension[34]. However, there is no proof of their benefit as screening and/or surveillance method for detecting this type of cancer[35]. Therefore, when suspecting the presence of malignant tumor, biopsy of the fistula track is mandatory[36].

There is no consensus on the best treatment approach of perianal mucinous adenocarcinoma arising from an anorectal fistula. Surgical resection is generally accepted as the first choice of curative treatment. Abdominoperineal resection is advocated in the vast majority of patients to definitively remove the entire lesion and lessen the risk of local recurrence. In the present case, local resection was performed because the tumor margins could be confidently excised without damage to the anal sphincters[37-39]. We performed adjuvant radiotherapy to decrease the local recurrence rate.

In conclusion, a high level of suspicion for malignancy in chronic perineal fistulas associated with refractory/recurrent Crohn's disease should be maintained. The result of this case suggests that local resection followed by radiotherapy may be a valuable treatment option for patients with perianal mucinous adenocarcinoma arising from an anorectal fistula diagnosed at an early stage.

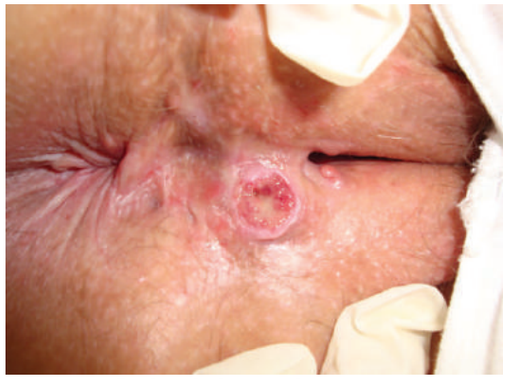

Figure 1 – Perianal ulcerated tumor arising from fistula in patient with CD.

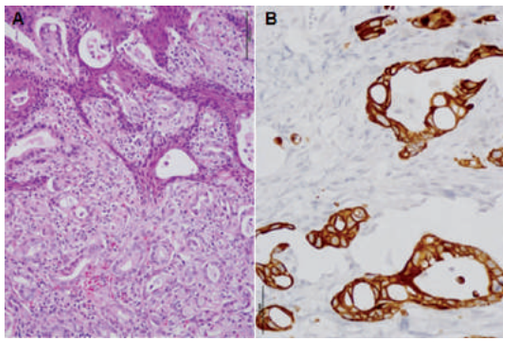

Figure 2 – A: Histopathological features of anal gland adenocarcinoma: tubular cells invading the squamous mucosa (H & E 200X). B: Immunohistochemical - CK7 staining (400X).

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