ARQGA/1686

DECISION TREE CONSTRUCTION AND COST-EFFECTIVENESS ANALYSIS OF TREATMENT OF ULCERATIVE COLITIS WITH PENTASA® MESALAZINE 2 G SACHET

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ABSTRACT - ***Context*** - Unspecified Ulcerative Rectocolitis is a chronic disease that affects between 0.5 and 24.5/10^5 inhabitants in the world. National and international clinical guidelines recommend the use of aminosalicylates (including mesalazine) as first-line therapy for induction of remission of unspecified ulcerative rectocolitis, and recommend the maintenance of these agents after remission is achieved. However, multiple daily doses required for the maintenance of disease remission compromise compliance with treatment, which is very low (between 45% and 65%). Use of mesalazina in granules (2 g sachet) once daily - Pentasa® sachets 2 g - can enhance treatment adherence, reflecting in an improvement in patients' outcomes. ***Objective*** - To evaluate the evidence on the use of mesalazine for the maintenance of remission in patients with unspecified ulcerative rectocolitis and its effectiveness when taken once versus more than once a day. From an economic standpoint, to analyze the impact of the adoption of this dosage in Brazil's public health system, considering patients' adherence to treatment. ***Methods*** - A decision tree was developed based on the Clinical Protocol and Therapeutic Guidelines for Ulcerative Colitis, published by the Ministry of Health in the lobby SAS/MS n° 861 of November 4 th, 2002 and on the algorithms published by the Associação Brasileira de Colite Ulcerativa e Doença de Crohn, aiming to get the cost-effectiveness of mesalazine once daily in granules compared with mesalazine twice daily in tablets. ***Results*** - The use of mesalazine increases the chances of remission induction and maintenance when compared to placebo, and higher doses are associated with greater chance of success without increasing the risk of adverse events. ***Conclusion*** - The use of a single daily dose in the maintenance of remission is effective and related to higher patient compliance when compared to the multiple daily dose regimens, with lower costs.

HEADINGS - Ulcerative colitis. Mesalazine. Mesalazine granules. Adhesion. Pentasa®.

INTRODUCTION

Unspecified Ulcerative Rectocolitis (UURC) is an idiopathic inflammatory bowel disease. It is a chronic disorder, characterized by inflammation of the diffuse mucosa limited to the colon[1, 5]. Its incidence varies widely around the world (between 0.5 and 24.5/10^5 inhabitants in the world), and it is more common in developed and industrialized countries. Its peak incidence is between 10 and 40 years old[5, 19, 21]. National data on the epidemiology of UURC are rare, but a study conducted in the Midwestern region of the state of São Paulo with 533,508 inhabitants showed incidence of 4.48/10^5 inhabitants and prevalence of 14.81/10^5 inhabitants[29].

The cardinal symptom of UURC is bloody diarrhea, and colicky abdominal pain and tenesmus may also be associated. Its clinical course is characterized by exacerbations and remissions[5, 20, 27]. Although excess mortality associated with URCC is not observed, a severe attack of the disease is potentially fatal[13, 20, 27]. The cumulative risk of colectomy after 10 years of diagnosis is around 10%, but reaches 20% in patients with extensive disease[27], who also have 15 times the risk of colorectal neoplasia[9].

The treatment is done with the use of aminosalicylates, including sulfasalazine and 5-aminosalicylates (5-ASA, e.g.: mesalazine). However, sulfasalazine is associated with the risk of discontinuation due to intolerance on the part of the patient of up to 30%[3]. The 5-ASA often have low adhesion (estimated at rates of approximately 50%[12], due to using of multiple daily doses. This fact potentially leads to poor quality of life of patients with increased risk of relapse and symptomatic colorectal neoplasia.

The new presentation of mesalazine micro granules coated in ethylcellulose (Pentasa® sachet) has a discrete microgranulation and slow release formulation, allow-

Declared conflict of interest of all authors: none

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ing continuous and controlled action from the duodenum to the rectum in pH conditions of the gastrointestinal tract[8] without changing the patient's treatment regimen, since the amount of daily milligrams remains the same. However, the sachet presentation has the advantage of reducing the number of applications per day, limiting it to only one, and contributing significantly to increasing the adhesion[7] and acceptance of the treatment[6, 18, 24], which is directly reflected in the improvement of patients' quality of life.

OBJECTIVE

The objective of this study is to assess the impact that the adoption of o.d. dosage of mesalazine (mesalazine granules in sachet - Pentasa® sachets – 2 g once daily) in the public health system of Brazil, compared to the current standard treatment with mesalazine b.i.d. (mesalazine granules in tablets - Pentasa® tablet - two tablets of 0.5 g twice daily), considering patients' adherence to treatment.

METHODS

Type of study and interventions

This study was built from the Therapeutic Clinical Guideline (TCG) for UURC published by the Ministry of Health at the ordinance SAS/MS n° 861, of November 4 th, 2002, and from the algorithms published by Associação Brasileira de Colite Ulcerativa e Doença de Chron. Based on these studies, it was developed a decision tree using the software Tree Age (Tree Age software Inc., Williamston, MA) in order to get the cost-effectiveness of mesalazine o.d. compared with mesalazine b.i.d.

Target Population

Patients with mild or moderate UURC in remission, ≥18 years.

Perspective

Brazilian public health system.

Time Horizon

A time horizon of 12 months was considered to be more appropriate in capturing cost data and clinical benefit of the patient in remission since data for longer periods are scarce and modeling to extrapolate data could cause a bias in results.

Model structure

It was developed a decision tree through the Tree Age software (Tree Age Software Inc., Williamston, MA, USA) of patients in remission with mild to moderate UURC in maintenance therapy. Figure 1 is a schematic representation of the model. A hypothetical cohort enters the model and can receive

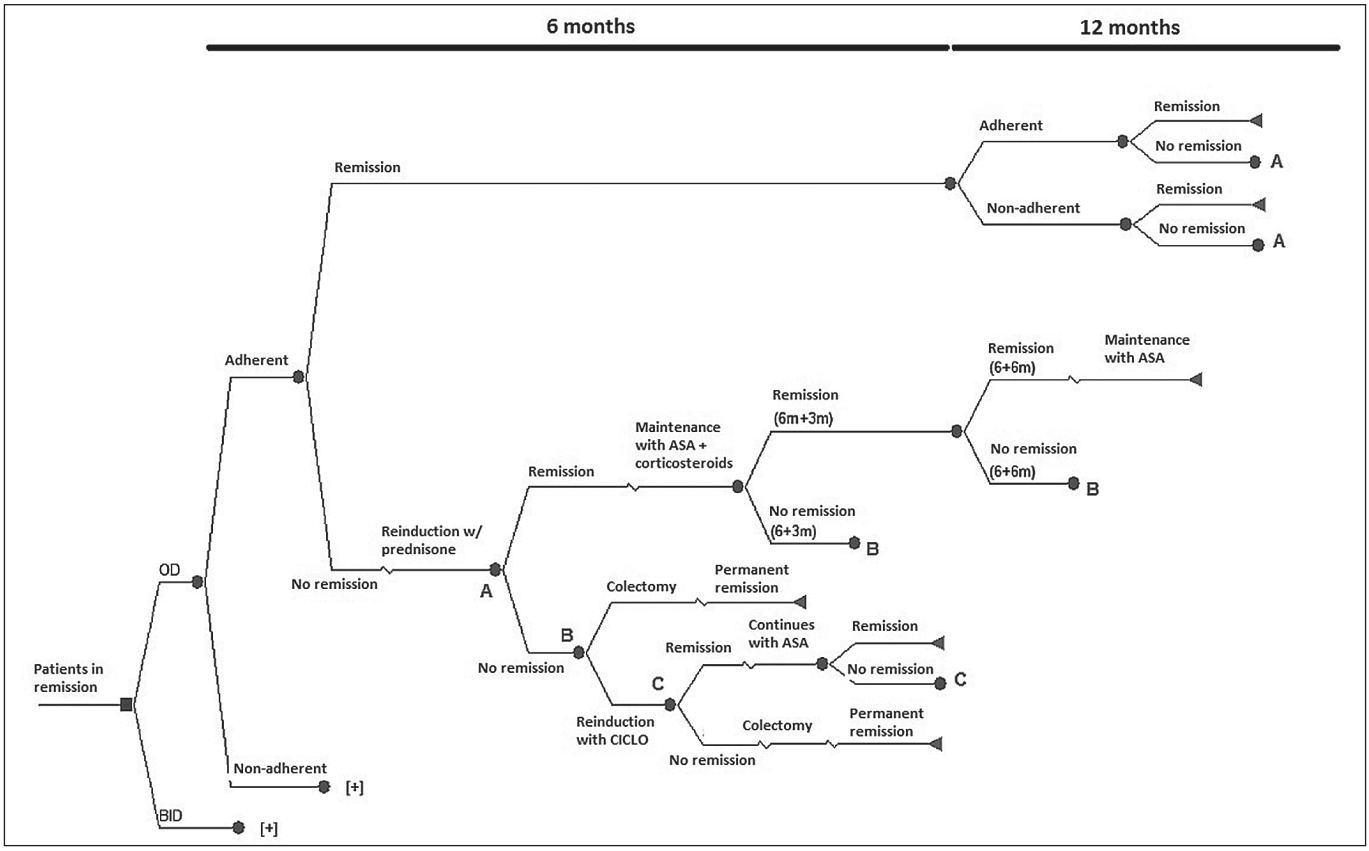

FIGURE 1. Scheme of the decision tree*
*The decision tree starts with the option of treatment with Pentasa ® under the o.d. or b.i.d. dosing schedule. In subsequent months, the tree continues to decision node with the letter indicated.

mesalazine o.d. or b.i.d., reaching treatment success (remission) or failure (no remission). Patients who fail to maintain the drug therapy continue to traverse the decision tree and can change to prednisone therapy, to immunosuppressive treatment with cyclosporine or receive surgical intervention. As described in the guidelines, it was assumed that in the state of remission, the patient keeps the treatment with the same drug used in the induction until the end of the modeling. Infliximab is not considered in the model because it is not part of the guidelines of the Ministry of Health in Brazil.

Clinical data

Data from clinical trials and publications were obtained for the construction of the decision tree for each branch.

Adhesion data

The difference in treatment compliance for maintenance of remission of UURC for once a day and twice a day doses was demonstrated in two studies by Kane et al., published in 2003 and 2008[15, 16]. The studies were designed to investigate the primary treatment adherence in both groups, as well as their outcomes. The adhesion was defined as the use of >80% of that prescribed by the physician.

The study published in 2003 consists of a randomized pilot trial that followed the patients for only 6 months and could not conclude the impact of the outcome between the two groups for adherence influence. Thus, the 2008 study was conducted, in which patients were followed for 12 months. It was concluded that adherence is an important factor in the outcome of the disease after 1 year of treatment. From these two studies, adherence to the treatment data were obtained for both dosages, which were used as input in the model (Table 1).

TABLE 1. Data of treatment compliance with dosing once daily or twice daily

Adherence			
Study	Time	o.d.	b.i.d.
Kane (2003)	6 months	75%	70%
Kane (2008)	12 months	42%	38%

Remission data

Once the adherence and non-adherence for each dose data were obtained, it was sought the remission rate for each condition. The superiority in the maintenance of remission of UURC in patients adherent to treatment was demonstrated in a prospective study published by Kane et al. in 2003[14]. A cohort of 99 UURC patients in remission who used mesalazine maintenance therapy for more than 6 months was accompanied. As previously described in other studies, adherence was defined as use of >80% of what was prescribed by the physician.

At 6 months, 12% of patients had clinical recurrence of disease symptoms, all of which were non-adherent to medication. At 12 months, 19 of the 86 patients had recurrences, of which 68% were nonadherent. Patients who were nonadherent to medication had an increasing in the risk of recurrence five times greater than adherent patients Hazard Ratio (HR) = 5.5; 95% Confidence Interval (CI): 2.3-13; $P = 0.001$) (Table 2).

TABLE 2. Likelihood of maintenance of Unspecified Ulcerative Rectolitis remission in both doses tested. The variation was set at 10% of the average

	Probability of maintaining in remission	
Time	Adherent	Nonadherent
6 months	100% (90%-100%)	60% (54%-60%)
12 months	84% (76%-92%)	59% (53%-65%)

Failure in remission

According to the Clinical Protocol and Therapeutic Guidelines for UURC[25], in failure to maintain remission of the disease, the patient with UURC receives treatment with prednisone reinduction (40 to 60 mg/day). The success rate in reinduction was taken from Marshall et al.[22] study (Table 3). After reinduction, the maintenance of the patient is performed with azathioprine along with prednisone, the latter being removed gradually as recommended in the guideline. The risk of a new recurrence with maintenance treatment with azathioprine was 16% every three months[11, 23].

In reinduction failure with prednisone or maintenance of remission with azathioprine, it was used the assumption that 50% of patients perform reinduction with intravenous cyclosporine and other patients undergo colectomy procedure.

The dose considered for intravenous cyclosporine therapy was 2 mg/kg/day, derived from clinical studies[28] and recommendations by the American College of Gastroenterology e British Society of Gastroenterology guidelines[5, 17]. The success rate of reinduction with intravenous cyclosporine was obtained from two studies utilized in a systematic review published in Cochrane, and the value is 73%[26]. In these patients, maintenance was performed with oral cyclosporine (8 mg/kg/day) during the first three months along with azathioprine, the latter being maintained in the case the patient remains in remission.

In these patients maintained in remission for at least 2 years, it was considered that they discontinue maintenance therapy after this period, returning to be treated in case of a relapse. According to a study by Ardizzone et al.[2], the rate of return for maintenance therapy was 26% per year.

In patients unresponsive to therapy with cyclosporine or recurrence of ulcerative colitis, colectomy was performed. It was not considered the small probability of death during the period covered in the model.

Economic data

Resource use and costs

All costs were denominated in reais (R$) in accordance with values of 2011. Aiming to demonstrate the perspective of the public health system, a baseline scenario was developed with the cost values for drugs obtained from Banco de Preços em Saúde (BPS) as described by methodological guidelines for preparation of technical-scientific reports of the Ministry of Health[4] (Table 4).

TABLE 3. Systematic review evaluating 5-ASA[10]

Comparison	Included studies	Results
Induction of remission 5-ASA vs placebo	11 RCT (n = 2086) Duration of treatment: 03-08 weeks	Failure to induce remission: 60.3% vs 80.2% (RR = 0.79; 95% CI: 0.73-0.85)
Induction of remission mesalazine vs placebo	07 RCT (n = 1722) Duration of treatment: 06-08 weeks	Failure to induce remission: 58.1% vs 76.6% (RR = 0.79; 95% CI: 0.71-0.88)
Induction of remission mesalazine (>2.5 g/d vs 2-2.5 g/d)	10 RCT (n = 2414) Treatment duration: 04-08 weeks	Failure to induce remission: 69.1% vs 70.2% (RR = 0.95; 95% CI: 0.89-1.02)
Induction of remission 5-ASA (≥2 g/d vs <2 g/d)	08 RCT (n = 1015) Treatment duration: 04-08 weeks	Failure to induce remission: 58.7% vs 69.8% (RR = 0.91; 95% CI: 0.85-0.98)
Induction of remission mesalazine (≥2g/d vs <2g/d)	07 RCT (n = 912) Treatment duration: 04-08 weeks	Failure to induce remission: 56.4% vs 67.3% (RR = 0.89; 95% CI: 0.82-0.97)
Induction of remission 5-ASA vs placebo	11 RCT (1502) Treatment duration: 06-12 months	Relapse risk: 40.3% vs 62.6% (RR = 0.65; 95% IC: 0.55-0.76)
Induction of remission mesalazine vs placebo	05 RCT (1096) Treatment duration: 06-12 months	Relapse risk: 42.2% vs 65% (RR = 0.65; 95% IC: 0.56-0.76)
Induction of remission 5-ASA (≥2 g/d vs <2 g/d)	07 RCT (n = 1534) Treatment duration: 06-12 months	Relapse risk: 34.7% vs 42.8% (RR = 0.79; 95% IC: 0.64-0.97)
Induction of remission mesalazine (≥2g/d *vs* <2g/d)	03 RCT (n = 973) Treatment duration: 12 months	Relapse risk: 42.4% vs 42.8% (RR = 0.90; 95% IC: 0.79-1.04)
Induction of remission 5-ASA (2 a 2.5 g/d vs <2 g/d)	05 RCT (n = 661) Treatment duration: 06-12 months	Relapse risk: 39.2% vs 49.2% (RR = 0.74; 95% IC: 0.52-1.03)

5-ASA: 5-aminosalicylates; RCT: randomized clinical trial; RR: risk ratio; CI: confidence interval

TABLE 4. Laboratory tests, procedures and drugs costs

Procedure	Value	Reference
CBC	R$ 4,11	SIGTAP
Dosing of glutamic-oxaloacetate transaminase (SGOT)	R$ 2,01	SIGTAP
Dosing of glutamic pyruvic transaminase (SGPT)	R$ 2,01	SIGTAP
Serum creatinine	R$ 1,85	SIGTAP
Urea	R$ 1,85	SIGTAP
Dosing of urine micro albumin	R$ 8,12	SIGTAP
Micro albumin dosage of cyclosporine in urine	R$ 58,61	SIGTAP
total colectomy	R$ 2.921,64	DATASUS
Colonoscopy	R$ 112,66	SIGTAP
Hospitalization for administration of cyclosporine	R$ 582,42	DATASUS - TABNET
Attendance at emergency room	R$ 11,00	SIGTAP
Pentasa® (mesalazine granules - 0.5 g tablets) – Cost for maintenance of remission** (total of four tablets a day, or 2 g)	R$ 258,00	BPS
Pentasa® Sachets (mesalazine granules in sachet) 2 g Cost for maintenance of remission** (once daily)	R$ 258,00	BPS
Prednisone - Cost of induction therapy	R$ 24,42	BPS
Azathioprine - Cost for maintenance of remission**	R$ 43,05	BPS
Cyclosporine - Cost of induction therapy	R$ 455,02	CompraNet***
Cyclosporine - Cost for maintenance of remission**	R$ 209,70	BPS

CBC: complete blood coun: SIGTAP: Sistema de Gerenciamento da Tabela de Procedimentos; DATASUS: Departamento de Informática do Sistema Único de Saúde do Brasil; TABNET: applications software for DATASUS.
*taken from Baco de Preços em Saúde (BPS)
** Monthly / *** http://www.comprasnet.gov.br (accessed on 15/09/2011)

For the cost of monthly treatment of mesalazine o.d., the value was obtained from the indication and dosing in package insert. At baseline scenario, the price of mesalazine o.d. was obtained from the value per milligram of the mesalazine b.i.d., since the value per milligram of both presentations is the same.

For induction therapy with prednisone, price has been established from the mean initial dose of 60 mg/day with a reduction of dose of 5 mg per week until the withdrawal of the therapy. The cost of treatment in induction with intravenous cyclosporine (5 mg/kg/day) was obtained based on a 10-days therapy. Besides this cost, it was added the cost of dosage and hospitalization for the drug administration (the cost of hospitalization considered was from TABNET data described as Medical Clinic - Average amount paid by SUS in 2008, considering the same hospitalization value for pneumonia treatment).

In patients who had a successful induction therapy with cyclosporine, it has been established a maintenance therapy with azathioprine (2.5 mg/kg/day) together with oral cyclosporine (8.0 mg/kg/day) for 90 days. For these patients, it was considered dosage of cyclosporine, urea and creatinine every 15 days.

For each episode of failure in maintaining remission of UURC, it was considered the cost of colectomy, medical visits and laboratory tests (Table 5).

TABLE 5. Probabilities used in the treatment of second line for ulcerative colitis

Clinical probability	Value	Deviation	Reference
Induction of remission with prednisone	0.79	0.99-0.59	22
Induction of remission with cyclosporine IV	0.73	0.91-0.55	26
Risk of relapse with azathioprine (value for each 3 months)	0.16	0.20-0.12	11, 23

Univariate sensitivity analysis

A univariate sensitivity analysis was performed on the main variables of the model's baseline scenario. Each parameter cost varied by ±25% and clinical parameters of ±10%. The parameter that was more sensitive to the model were the values of monthly treatment of Pentasa®, followed by the probability of success in the reinduction of the maintenance phase of UURC by prednisone and the colectomy surgery cost (Figure 2).

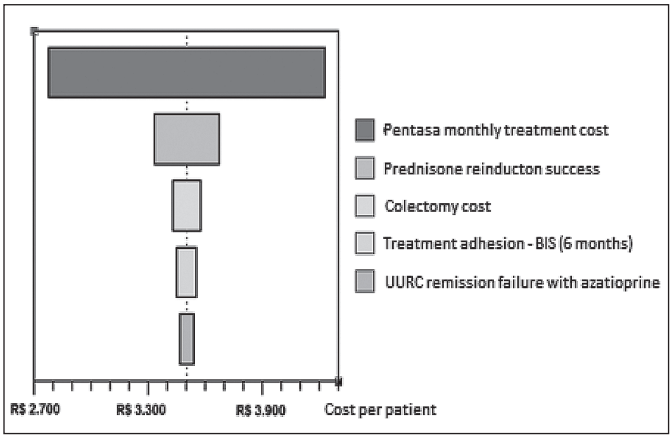

FIGURE 2. Univariate sensitivity analysis tornado diagram (o.d. vs b.i.d.)

RESULTS

Cost

By using mesalazine o.d., the total cost of treatment for 12 months estimated for each patient is R$ 3.535,25, while the cost of mesalazine twice daily is R$ 3.546,28. This amount includes the cost of the medication, consultations with the specialist, monitoring, hospitalization and surgery.

Effectiveness

In this analysis, it was assessed the likelihood of the patient with UURC remain in the remission maintenance phase. From the analysis, it was observed that patients treated with mesalazine o.d. had higher remission rate and a lower chance of performing colectomy surgery. Modeling a population of 1000 patients over 12 months, the use of mesalazine o.d. resulted in 16 cases of recurrence of the disease prevented and less four surgical colectomy performed when compared with the use of mesalazine b.i.d.

Incremental cost-effectiveness ratio (ICER)

For the standard scenario, where the cost was set at R$ 80.000,00, the value of the ICER (cost/LYG) over 5 years was approximately R$ 86.200,00.

Sensitivity analysis

Despite all the changes in the model, in 100% of cases presented, mesalazine o.d. proved to be dominant over mesalazine b.i.d., confirming the robustness of the result.

DISCUSSION

A major challenge for the treatment of UURC is treatment adherence by patients that is below that recommended by the specialists. This becomes a major health problem, since the treatment and maintenance of remission of the disease require long periods of drug administration and the utilization rate is directly related to the clinical outcomes of the patient. The non-adherence to treatment carries a potential deterioration in quality of life, with increased risk

of relapse and symptomatic colorectal neoplasia. So, it is essential to take into consideration, beyond effectiveness, the patient adherence. Several studies indicate that the reduction of daily doses of the drug contributes significantly to greater treatment adherence. Thus, once daily dosing of mesalazine demonstrated to be superior to the dosage of two shots, and it contributes to the effectiveness of treatment. Further, higher adherence is directly reflected in the quality of life of patients.

From an economic standpoint, the value of implementing mesalazine o.d. by the Brazilian public health system is equivalent to mesalazine b.i.d., already adopted by SUS (R$ 3.535,25 vs R$ 3.546,28). However, the adoption of mesalazine o.d. has advantages: it can, by increasing the adhesion, potentially increase the rate of remission and, consequently, reflect in lower costs for hospitalizations and colectomy surgeries.

CONCLUSION

The use of a single daily dose in the maintenance of remission in UURC patients is effective and related to higher patient adherence compared with the multiple daily dose regimens. From an economic standpoint, the daily dose is dominant over the twice daily dose. The effectiveness of treatment with the new drug submission is considerably higher in the maintenance of remission of UURC and shows a lower cost. It is estimated that the incorporation of o.d. mesalazine (Pentasa® Sachets 2 g) results in savings of approximately R$ 1.044.541 over the next 5 years for the Brazilian National Health System.

Nishikawa AM, Paladini L, Delfini R, Kotze PG, Clark O. Construção de árvore de decisão e análise de custo-efetividade do tratamento da retocolite ulcerativa com Pentasa® (mesalazina) 2 g sachê. Arq Gastroenterol. 2013,50(4):297-303.

RESUMO - ***Contexto*** - A retocolite ulcerativa inespecífica é uma doença crônica que atinge entre 0,5 e 24,5/10^5 habitantes no mundo. Diretrizes clínicas nacionais e internacionais recomendam o emprego de aminosalicilatos (entre eles, a mesalazina) como terapia de primeira linha na indução da remissão da retocolite ulcerativa inespecífica, com manutenção destes agentes após a remissão. Mas as múltiplas doses diárias necessárias comprometem a adesão ao tratamento, que é muito baixa (entre 45% e 65%). A utilização de mesalazina em grânulos (sachê 2 g) dose única diária - Pentasa® sachê 2 g - pode aumentar a aderência ao tratamento, refletindo numa melhora nos desfechos dos pacientes. ***Objetivo*** - Avaliar as evidências sobre o uso de mesalazina para a manutenção da remissão em pacientes com retocolite ulcerativa inespecífica e sua eficácia quando tomada uma vez versus mais de uma vez ao dia. Do ponto de vista econômico, avaliar o impacto que a adoção desta posologia teria para o sistema público de saúde do país, comparada ao tratamento padrão atual, considerando a adesão dos pacientes. ***Métodos*** - Foi elaborada uma árvore de decisão construída a partir do Protocolo Clínico e Diretrizes Terapêuticas de Colite Ulcerativa, publicado pelo Ministério da Saúde na portaria SAS/MS n° 861, de 04 de novembro de 2002, e de algoritmos publicados pela Associação Brasileira de Colite Ulcerativa e Doença de Crohn, objetivando-se obter o custo-efetividade da mesalazina dose única diária em grânulos comparado com mesalazina duas vezes ao dia em comprimidos. ***Resultados*** - O emprego de mesalazina aumenta as chances de indução da remissão e sua manutenção, quando comparado a placebo, sendo que doses maiores se associam a maior chance de sucesso sem aumento no risco de eventos adversos. ***Conclusão*** - O emprego de dose única diária na manutenção da remissão é efetivo e relacionado à maior adesão do paciente em comparação a posologias com múltiplas doses diárias, além de ter menor custo.

DESCRITORES - Colite ulcerativa. Mesalazina. Mesalazina em grânulos. Adesão. Pentasa®.

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Received 10/4/2013.
Accepted 20/5/2013