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GUIDELINE ON ULCERATIVE COLITIS

GEDIIB
Grupo de Estudos da Doença Inflamatória Intestinal do Brasil

Entyvio®
vedolizumabe

A Mudança* Começou com... ENTYVIO®[1-4]

INDICADO NA PRIMEIRA LINHA DE TRATAMENTO BIOLÓGICO NA RETOCOLITE ULCERATIVA (RCU)[5,6]**

- **INDUÇÃO: redução significativa** do subscore médio de **frequência de evacuações**, na semana 4, e do subscore de **sangramento retal**, na semana 6, em pacientes virgens de anti-TNF.[7++]
- **CICATRIZAÇÃO DE MUCOSA: 60%** dos pacientes virgens de anti-TNF alcançaram **cicatrização de mucosa**[#] em **12 meses** de tratamento.[8]
- **MANUTENÇÃO: 98%** de **resposta** e **90%** de **remissão clínicas**[+] ao longo de **5 anos** de tratamento.[9]

*Mudança nos escores de saúde relacionada à qualidade de vida.

**Os subescores clínicos de Mayo de frequência de evacuações (FE) e de sangramento retal (SR) foram avaliados.

**Colite ulcerativa moderada a grave na fase ativa que apresentaram uma resposta inadequada, perda de resposta ou são intolerantes ao tratamento convencional ou a um antagonista de fator de necrose tumoral alfa (TNF-α).

#Cicatrização de mucosa definida como subescore endoscópico de Mayo ≤ 1.

+Análise as *observed* considera o número de pacientes em resposta ou remissão clínicas sobre o número de casos observados na vista do estudo. Remissão clínica definida como escore parcial de Mayo ≤ 2, sem nenhum subescore individual > 1; Resposta clínica definida como diminuição no escore parcial de Mayo [PMS] de ≥ 2 pontos e ≥ 25% de mudança em comparação com o estado basal, com ou uma diminuição associada do subscore de sangramento retal de ≥ 1 ponto em relação ao estado basal ou subscore de sangramento retal absoluto de ≤ 1 ponto. O método de estatística descritiva foi utilizado para avaliação de efetividade clínica.

Referências bibliográficas: 1. Feagan BG, *et al.* Effects of vedolizumab on health-related quality of life in patients with ulcerative colitis: results from the randomised GEMINI 1 trial. Aliment Pharmacol Ther. 2016 Nov 17. doi: 10.1111/apt.13852. **2.** Vivio EE, *et al.* Vedolizumab effectiveness and safety over the first year of use in an IBD clinical practice. J Crohns Colitis. 2016;10(4):402-9. PMID: 26681763. **3.** Palmela C, *et al.* New Trends in Inflammatory Bowel Disease. GE Port J Gastroenterol.2015;22(3):103-11. **4.** Sandborn W, *et al.* Effect of vedolizumab on health-related quality of life (HRQoL) in patients with Crohn's disease. Journal of Crohn's and Colitis. 2015; 9 (suppl 1):S227. P300. **5.** Entyvio® [Bula]. São Paulo. Takeda Pharma Ltda. **6.** Poole RM. Vedolizumab: first global approval. Drugs. 2014;74(11):1293-303. **7.** Feagan BG, *et al.* Vedolizumab demonstrates early symptomatic improvement in ulcerative colitis: a GEMINI 1 post hoc analysis. World Congress of Gastroenterology at ACG 2017. Poster #1273. **8.** Feagan BG, *et al.* Efficacy of Vedolizumab Induction and Maintenance Therapy in Patients With Ulcerative Colitis, Regardless of Prior Exposure to TNF Antagonists. Clin Gastroenterol Hepatol. 2016. pii: S1542-3565(16)30655-3. **9.** Loftus EV, *et al.* Long-term effectiveness and safety of vedolizumab in patients with ulcerative colitis: 5-year cumulative exposure of GEMINI 1 completers rolling into the GEMINI open-label extension study. J Crohns Colitis. 2017;11(suppl_1):S182-3. Abs P209.

ENTYVIO® - vedolizumabe. Indicações: Entyvio® é indicado para o tratamento de pacientes adultos com: -Colite ulcerativa moderada a grave na fase ativa que apresentaram uma resposta inadequada, perda de resposta ou são intolerantes ao tratamento convencional ou a um antagonista de fator de necrose tumoral alfa (TNF-α). - Doença de Crohn moderada a grave na fase ativa que apresentaram uma resposta inadequada, perda de resposta ou são intolerantes ao tratamento convencional ou a um antagonista de fator de necrose tumoral alfa (TNF-α). **Contraindicações:** Entyvio® é contraindicado para pacientes com hipersensibilidade ao vedolizumabe ou a qualquer um dos excipientes do produto. Entyvio® é contraindicado na presença de infecções ativas graves, tais como tuberculose, septicemia, citomegalovírus, listerioses e infecções oportunistas, como leucoencefalopatia multifocal progressiva (LMP). **Cuidados e advertências:** Em estudos clínicos foram relatadas reações relacionadas à infusão e reações de hipersensibilidade, sendo a maioria delas de gravidade leve a moderada. Infecções: O tratamento com Entyvio® não deve ser iniciado em pacientes com infecções ativas graves, como tuberculose, sepse, citomegalovírus, listeriose e infecções oportunistas, até que as infecções sejam controladas, e os médicos devem considerar a suspensão do tratamento em pacientes que desenvolvem uma infecção grave durante o tratamento crônico com Entyvio®. Todos os pacientes devem ser observados continuamente durante cada infusão e medidas de suporte médico devem estar disponíveis para uso imediato enquanto vedolizumabe é administrado. Entyvio® é contraindicado em pacientes com tuberculose ativa. Alguns antagonistas de integrina e alguns agentes imunossupressores sistêmicos foram associados com leucoencefalopatia multifocal progressiva (LMP). Nenhum caso de LMP foi relatado em estudos clínicos com vedolizumabe. Os sinais e sintomas típicos associados com LMP são diversos, progridem ao longo de dias a semanas e incluem fraqueza progressiva em um lado do corpo, inépcia dos membros, problemas de visão e alterações no pensamento, memória e orientação levando à confusão e alterações de personalidade. A progressão dos déficits usualmente leva à morte ou incapacidade grave ao longo de semanas ou meses. Uso anterior e concomitante de produtos biológicos:Não há dados disponíveis de estudos clínicos do vedolizumabe para pacientes previamente tratados com natalizumabe ou rituximabe. Uso durante a gravidez e a lactação - Categoria B de Risco na Gravidez - Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião dentista. As mulheres em idade fértil devem usar métodos contraceptivos adequados para evitar a gravidez e o seu uso deve ser mantido durante pelo menos 18 semanas após o último tratamento com Entyvio®. Lactação: Vedolizumabe foi detectado no leite humano. O efeito do vedolizumabe em lactentes é desconhecido. O uso de vedolizumabe em mulheres em lactação deve levar em conta o benefício da terapia para a mãe e os riscos potenciais para a criança lactente. **Interações medicamentosas:** Não foram conduzidos estudos de interação. O vedolizumabe foi estudado em pacientes adultos com colite ulcerativa e doença de Crohn com administração concomitante de corticosteroides, imunomoduladores (azatioprina, 6-mercaptopurina e metotrexato) e aminosalicilatos. As análises da farmacocinética da população sugerem que a administração concomitante de tais agentes não teve efeito clinicamente significativo na farmacocinética do vedolizumabe. O efeito do vedolizumabe na farmacocinética dos medicamentos comumente coadministrados não foi estudado. Vacinações: As vacinas vivas, em particular vacinas vivas orais, devem ser usadas com cautela durante o tratamento com Entyvio®. **Reações adversas:** A proporção de pacientes que descontinuaram o tratamento devido a eventos adversos foi de 9% para os pacientes tratados com vedolizumabe e 10% para os pacientes tratados com placebo. Nos estudos combinados do GEMINI I e II, as reações adversas que ocorreram em ≥ 5% dos pacientes foram náusea, nasofaringite, infecção do trato respiratório superior, artralgia, febre, fadiga, cefaleia, tosse. Reações relacionadas à infusão foram relatadas em 4% dos pacientes que estavam recebendo vedolizumabe. **Atenção: este produto é um medicamento novo e, embora as pesquisas tenham indicado eficácia e segurança aceitáveis, mesmo que indicado e utilizado corretamente, podem ocorrer eventos adversos imprevisíveis ou desconhecidos. Nesse caso, notifique os eventos adversos pelo Sistema de Notificações em Vigilância Sanitária - NOTIVISA, disponível em www.anvisa.gov.br/hotsite/notivisa/index.htm ou para a Vigilância Sanitária Estadual ou Municipal. Posologia e modo de usar:** - Colite ulcerativa: A dose recomendada é 300 mg de Entyvio®, administrada por infusão intravenosa nas Semanas 0, 2 e 6 e depois a cada oito semanas. Em pacientes que responderem ao tratamento com Entyvio®, o uso de corticosteroides pode ser reduzido e/ou interrompido – à critério médico. - Doença de Crohn: A dose recomendada é 300 mg de Entyvio®, administrada por infusão intravenosa nas Semanas 0, 2 e 6 e depois a cada oito semanas. Os pacientes com doença de Crohn que não apresentarem resposta podem se beneficiar de uma dose de Entyvio® na Semana 10 (veja ADVERTÊNCIAS E PRECAUÇÕES). Nos pacientes que responderem, continuar o tratamento a cada oito semanas a partir da Semana 14. MS – 1.0639.0271. SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO. MEDICAMENTO SOB PRESCRIÇÃO MÉDICA. ENT_0418_0418_VPS.

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

Material destinado exclusivamente a profissionais de saúde habilitados a dispensar e/ou prescrever medicamentos e gestores de saúde.

Material produzido em agosto/2018.
BR/EYV/1806/0056(1)

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The titles, abstracts, and keywords are published in English and Portuguese. The publication follows the International Committee of Medical Journal Editors' (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals (Vancouver Style) [http://www.icmje.org/]. Submitted papers will undergo a double-blind peer review process. The peer reviewers will determine whether the article should be published, and if so, they will suggest improvements, ask the authors for clarification, and make recommendations to the Editor-in-Chief. [https://www.omicsonline.org/peer-review-process.php].
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ARTICLE TYPES

The Journal welcomes the following types of articles: Original Research, Review Articles (Narrative Reviews, Systematic Reviews and Meta-analyses), Update Articles, Perspective and Commentary Articles, Images in Focus, Letters to the Editor, and Editorials.

MANUSCRIPT SUBMISSION

Manuscripts must be submitted to the *International Journal of Inflammatory Bowel Disease by e-mail* to revistagediib@gmail.com and revistagediib@gmail.com

General Manuscript Preparation

Prior to submission, the author should choose three keywords from the list below that best characterize the manuscript. These keywords will be used to inform the reviewer selection process—ensuring reviewers with subject matter expertise.
1) Basic science, experimental models, and pathophysiology, 2) Biomarkers, 3) Clinical trials, 4) Endoscopy, 5) Epidemiology, 6) Genetics and molecular epidemiology, 7) Imaging, 8) Microbiology, 9) Immunology, 10) Pediatrics, 11) Pathology, 12) Quality of Life, including socio-economic and psychological endpoints, 13) Surgery, and 14) Nutrition.
The manuscript should be written in Portuguese and English. It should be double-spaced, with 3 cm margins on all sides. All text shoudl be in 12-point Times New Roman font. Manuscript files should be in a Microsoft Word® format (.doc or .docx). The manuscript should not exceed 20 typeset pages, including the cover page, abstracts, main text, acknowledgments, references, and tables.

Cover page

Title: Concise and informative. Written in Portuguese and English. Include the full name of each author (without abbreviations) and his or her respective institution. (The institution should be presented in diminishing order, e.g., university, college, and department.) The names of the institutions and programs should be referred to by their full title and in their original language. If there is more than one institutional affiliation, indicate only the most relevant (such as the location of the work or study's execution); name of the corresponding author with their complete address, telephone, and email.

ORIGINAL ARTICLE

Writing process

Authors: No more than six authors are allowed.
Maximum article length: 2,500 words excluding the abstract, references, tables, and figures. The article should have no

more than 20 references. A maximum of four figures and four tables is permitted.

Abstract and Keywords: These should be written in Portuguese and English. The maximum length is 250 words. For Original Articles, the abstracts should be structured as follows: Objective, Methods, Results, and Conclusions (which highlight the most significant results).

Introduction: The Introduction should contain the study objective and rationale. It should only contain immediately pertinent citations and should not include data or conclusions from the study.

Methods: This section should clearly and precisely describe how the study was conducted. It should include details regarding the study participants (e.g., patients or laboratory animals, controls), descriptive characteristics (e.g., age, gender) and inclusion/exclusion criteria. The definition and relevance of race or ethnicity are ambiguous, however, authors should be particularly careful when using these categories. This section should describe the methods, apparatus (include the name and address of manufacturer within parentheses), and procedures in sufficient detail to enable the reproduction of the results by other researchers. State if the study was approved by an institution's ethics committee and, if so, provide the approval identification number. At least one of the authors must be affiliated with the institution. The author(s) should also note if the Free and Informed Consent form was signed by all participants.

Results: The results should be presented in a logical manner, without repetition, using text, tables, and figures. The findings should be summarized, with an emphasis on the important observations.

Discussion: Without repeating the information in the Introduction or Results section, this section should emphasize the novel and important aspects of the study and its conclusions. New hypotheses should be presented only when they are clearly justified.

Conclusions: When presenting conclusions, ensure they are linked to the study's objectives. Avoid discussing unqualified conclusions, i.e., those not fully substantiated by the data. The conclusions should present a definitive argument that is supported by the data.

REVIEW ARTICLES

Review Articles do not have to be structured.

Review articles should address the current state of research within a particular topic. All relevant data for the subject matter should be discussed in a coherent manner, assessing how the material is considered to be state of the art. All review articles will be peer reviewed prior to being considered for publication.

Writing process

Authors: Individual authors may proactively submit to the Journal, or may be invited to do so by the editor(s). No more than two authors are allowed.

NARRATIVE REVIEWS: These should be organized in the following sequence: Title page, abstract, main text, acknowledgments, references, figure captions, tables, and figures (with a resolution of 300 dpi). The abstract should not exceed 200 words. The review should contain at least two, and no more than eight, graphics (figures and/or tables). The main article should be not more than 7,500 words, excluding references, figures, and tables. The article should have fewer than 125 references.

SYSTEMATIC REVIEWS AND META-ANALYSES

Authors: No more than two authors are allowed.

The systematic reviews and meta-analyses must cover topics related to inflammatory bowel disease (IBD).

All articles will be peer reviewed prior to being considered for publication. At a minimum, the literature search should be conducted in MEDLINE and EMBASE. The risk of bias in selecting studies for inclusion in the analysis should be systematically assessed, reported, and discussed. The article should include an abstract of no more than 300 words. The main article should be not more than 3,000 words, excluding references, figures, and tables. The review should contain at least two, and not more than eight, figures and/or tables. It should have fewer than 150 references.

UPDATE ARTICLES

Updates are short reviews that focus on evolving or controversial areas of research. Emphasis should be given to emerging concepts, findings, and theoretical frameworks. Illustrative examples from the literature are encouraged.

Writing process

The maximum length for the article is 4,000 words, excluding the abstract, references, tables, and figures. The article should have fewer than 40 references. The article should contain no more than three figures and two tables.

Updates do not have to be structured.

No more than two authors are allowed.

Abstract: Within 200 words, provide a summary of the main text, including the background and purpose, methods and subjects, essential results, and principal conclusions.

Introduction: Clearly and succinctly describe the study's background, rationale, and objective. Include a review of earlier publications only in so far as they are relevant to this article. Avoid presenting an exhaustive review of the literature.

PERSPECTIVE ARTICLES

These are opinion articles written by an individual or a group about a topic related to IBD or one selected by GEDIIB. Perspective articles are invited by the Editor-in-Chief or associate editors. The viewpoint must be clearly expressed and demonstrate a thorough and broad understanding of the literature and practices in the field.

No more than two authors are allowed.

Writing process

These are very short articles with a straightforward title that captures the essence of the topic. The piece immediately states the problems and provides a thorough analysis with the help of illustrations, graphs, and tables as necessary. It provides a brief, concluding summary and cites references at the end. An abstract and keywords are not required. The article should not exceed 3,000 words, excluding the abstract (if one is included).

COMMENTARIES

Commentaries are invited by the Editor-in-Chief or associate editors. The summary should not be structured. Commentaries are short narratives that interpret, evaluate, and provide an opinion, on an original research article. These commentaries are written by individuals (other than the authors of the original research) who are experts in their field. The article should not exceed 3,000 words, excluding the abstract. No more than two authors are allowed.

EDITORIALS

Editorials are concise commentaries on an article published in the current issue or an entire issue of the *International Journal of Inflammatory Bowel Disease*. Written by a subject-matter expert, the editorial provides context, analysis and a critique of the important articles published in that same issue The Editorial is invited by the Editor-in-Chief or associate editors. Should the Editorial Office approach an author to write such a piece, the author must submit the article within three weeks after receiving the invitation.

Writing process

The maximum length of the editorial is 1,999 words, including up to 10 references. No more than two authors are allowed.

IMAGES IN FOCUS

Submissions should contain no more than three color or black and white images with a minimal resolution of 300 dpi. Each image should be submitted as a separate .tiff file**.** Images containing patient identifiers will be immediately rejected. Each image must be associated with its respective text using letters, e.g., a, b, and c. Ensure that similar images have not been published previously in this Journal.

Writing process

Image files should be accompanied by a Microsoft Word document containing a brief description of no more than 200 words. Do not embed images into your Word document. Associate each image with its respective text/description using letters, e.g., a, b, c. Submissions must include a full title page showing 1) authors' names and affiliation(s), 2) contact information for the corresponding author, 3) information about conflict of interest/study support, 4) a statement confirming that informed consent was obtained from the patient for the publication of his/her information and image(s). Please do not include an abstract, references, image captions, or a study highlights section; these will not be published. Titles may be creative but should be sufficiently descriptive. No more than two authors are allowed.

LETTER TO THE EDITOR

Letters to the Editor will be considered for publication only if they do not contain material that has been submitted or published elsewhere. Two formats will be considered: 1) A comment related to an article recently published in this Journal or a reply from the authors of the Original Article that would be published along with the letter to the editor. The letter to the editor must clearly identify the article being discussed; 2) Brief reports with novel aspects (physical, histologic, radiologic, serologic, or other findings) related to IBD that have the potential to significantly influence clinical practice or stimulate further research in the field.

Writing Process

The letter to the editor is open to individual authors.

The maximum length of the letter should not exceed 450 words, excluding references. Up to five references and one figure or small table can be included. Informed patient consent must be confirmed on the title page, and the IRB approval must be provided (if it was required).

No more than three authors are allowed.

FIGURES

Figures include all illustrations such as photographs, drawings, maps, graphs, etc. Black and white figures will be reproduced free of charge. However, the editor reserves the right to set a reasonable quantity limit and charge the author for the expenses incurred due to producing more than the reasonable quantity.

Please note that it is the author's responsibility to obtain permission from the copyright holder to reproduce figures (or tables) that have been previously published elsewhere. Authors must have permission from the copyright owner if they wish to include images that have been published in other non-open access journals. Permission shall be indicated in the figure legend, and the original source must be included in the reference list.

Figures should be submitted on separate pages and numbered sequentially in Arabic numerals, in order of appearance. To avoid issues that could compromise the Journal's layout, all submissions will need to comply with the following parameters: all graphics, photographs, photomicrographs, electron micrographs or radiographs, and illustrations should have a minimum resolution (300 dpi) and include a title and caption. The following file formats will be accepted: .tiff, .jpg, .xls, .xlsx, .eps, and .psd (to curve graphics, drawings, and diagrams).

TABLES

Tables should be consecutively numbered in the text using Arabic numerals. Each table should have a title and, if necessary, an explanatory legend. Charts and tables should be sent in their original source data files (e.g., Excel); they should not be converted to images. Do not create a table or a chart that does not fit on one page. Do not use graphic elements, text boxes, or tabs.

ABBREVIATIONS AND ACRONYMS

Abbreviations and acronyms must be defined at first use in the text. Abbreviations used in figures and tables should be expanded on below the figure or table.

ACKNOWLEDGMENTS

When necessary, write a brief acknowledgement thanking those who provided expertise.

Individuals whose contributions were significant, but not sufficient to constitute co-authorship, should be acknowledged in this section. The author should ensure that these individuals consent to being recognized in this manner.

FUNDING

Financial support for the study as well as scholarships should be acknowledged (including the agency and grant number).

DECLARATION OF AUTHOR CONTRIBUTION

This should be expressed at the end of the article. Individuals claiming authorship should, at minimum, meet these two criteria: a) active participation in the discussion of results and b) review and approval of the final version of the work.

REFERENCES

References must be compiled in strict accordance with the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journal Editors* (October 2007). All authors and works cited in the text must appear in the references and vice versa. The entries should be numbered consecutively in the same order in which they are cited in the text. Use Arabic numerals for citations and references. When a single work has six or fewer authors, list all the authors. If there are more than six authors, list the first six followed by 'et al.' The titles of journals should be abbreviated according to the list of journals in *Index Medicus*.

Examples:

Journal Articles: Caetano MBF, Albertoni WM, Caetano EB. Estudo anatômico das inserções distais do tendão extensor longo do polegar. Acta Ortop Bras. 2004;12(2):118-24.

Hong-Wan N, Ee-Chon T, Qing-Hang Z. Biomechanical effects of C2-C7 intersegmental stability due to laminectomy with unilateral and bilateral facetectomy. Spine. 2004;29(16):1737-45.

Books: Defino, HLA. Lesões Traumáticas da coluna vertebral. São Paulo: Bevilacqua; 2006.

Book Chapters: Tencer AF. Biomechanics of spinal trauma. In: Cotler JM, Simpson JM, An HS, Silveri CP, editors. Surgery of spinal trauma. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 61-112.

Dissertations and Theses: Giglio CA. Caracterização funcional e histológica de modelos experimentais de estudo do trauma raquimedular [tese]. Ribeirão Preto: Universidade de São Paulo; 2000.

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Quality improvement studies use guideline SQUIRE
Economic evaluations use guideline CHEERS

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Actual or potential conflicts of interest should be made public and accessible to the editorial staff and the readership of the Journal. Editors, reviewers, and editorial staff must disclose any relationship to an institution or investigator on any submissions that they are called on to review.

AUTHOR CONFLICT OF INTEREST/STUDY SUPPORT: Authors submitting work for publication in the Journal, including those who write correspondence, are required to submit a Conflict of Interest Disclosure form. The Journal will not begin reviewing a submission for publication and will not permit a submission to be published unless and until said Disclosure is submitted. If there is no actual or potential conflict, the author must indicate such. On your title page, please include a section with the following headings: 1. Guarantor of the article: Identify the author who is accepting full responsibility for the conduct of the study. He or she must have had access to the data and have control over the decision to publish. 2. Specific author contributions: List the role played by each author, e.g., in planning and/ or conducting the study, collecting and/or interpreting data, and/ or drafting the manuscript. For each author, there should also be a statement that he or she has approved the final draft submitted. 3. Financial support: Disclose funding sources for the publication. If there was funding, this must be specifically stated. (Other types of assistance, such as non-financial assistance, may be acknowledged in the Acknowledgments section in the manuscript.) 4. Potential competing interests: List all potential conflicts.

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International Journal
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Bowel Disease

EDITORIAL

The drug treatment of inflammatory bowel disease (IBD) has evolved considerably over the years. In the 1930s and 1940s, sulfasalazine (SSZ), discovered by the renowned rheumatologist, Dr. Nana Svartz, was the basis of IBD treatment and, today, it is still used for ulcerative colitis (UC). In the 1950s, the elegant works of the Oxford group, led by Prof. Truelove, added corticosteroids to the IBD treatment scenario, significantly reducing mortality, especially in severe cases of UC. The immunosuppressants (e.g., azathioprine, 6-mercaptopurine), mesalamine (the main active ingredient of SSZ), and budesonide followed, until we arrived at the 21st century, the so-called era of biologics and small molecules for oral use.

Faced with such a diversity of therapeutic options, it is essential that we establish strategies and treatment recommendations taking evidence-based medicine into account. It is precisely within this context that guidelines, recommendations, directives, and consensuses are included as a relevant contribution to the therapeutic approach to a patient with IBD. It is worth remembering that drug guidelines, although relevant, are not the only component of the treatment of a patient with IBD and the physician must pay attention to the multidisciplinary and holistic nature of the therapeutic approach.

In this issue of the *International Journal of Inflammatory Bowel Disease,* a group of experienced professors, on behalf of the Inflammatory Bowel Disease Study Group of Brazil (GEDIIB), Brazilian Federation of Gastroenterology (FBG) and Brazilian Society of Coloproctology (SBPC), presents its Consensus on the Drug Treatment of Ulcerative Colitis. We hope it helps colleagues who deal with IBD in making the important and sometimes difficult decisions required for the management of patients with ulcerative colitis.

Good reading and enjoy.

Cordially,

Adérson Omar Mourão Cintra Damião
José Miguel Luz Parente
Editors

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CONTENTS

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GUIDELINE

GUIDELINE ON ULCERATIVE COLITIS

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1. INTRODUCTION AND GENERAL CONCEPTS

1.1 EVIDENCE COLLECTION METHOD

This guideline followed a pattern of a systematic recovery of evidence based on the movement of the Medicine in Evidence, where clinical experience is integrated with the ability to critically analyze and apply scientific information, rationally, improving so the quality of medical care. The MBE uses existing and currently available scientific evidence, with good internal and external validity, for the application of its results in clinical practice.[1,2] (D)

Systematic reviews are currently considered the level I of evidence for any clinical issue by systematically summarizing information on a particular topic, through primary studies (clinical trials, cohort studies, case-control or cross-sectional studies) using a methodology reproducible, in addition to integrating information on effectiveness, efficiency, effect and safety.[1,2](D)

We use an structure to formulate the question synthesized by the acronym P.I.C.O., where P corresponds to the patient or population, I of intervention or indicator, C of comparison or control, and O of "outcome". From the structured question we identify the keywords or descriptors that will be the basis of the search for evidence in the various available databases.[1,2](D) (Attachment I)

Degree of recommendation and force of evidence

A: Experimental or observational studies of better consistency.
B: Experimental or observational studies of lower consistency.
C: Case reports / uncontrolled studies.
D: Critical assessment based on consensus, physiological studies or animal models.

1.2 OBJECTIVE

The purpose of these guidelines is to provide recommendations which may assist in therapeutic decision making in patients with ulcerative colitis (UC).

1.3 INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are the main inflammatory bowel diseases (IBDs) with etiologies that are not yet completely clarified. CD and UC are caused

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by the interaction of genetic factors, intestinal microbiota, and immunoregulation of the mucosa.[3-4]

UC affects the mucosa – and eventually the submucosa – of the colon and rectum, whereas CD can occur in any part of the digestive tract, from the mouth to the anus, with predilection for the ileal and ileocolic regions, can affect the intestinal wall (transmural inflammation), and generate non-caseating granulomatous reaction in its characteristic presentation.[6,7]

Generally, extra-intestinal manifestations occur in 25% to 40% of the cases of IBD (e.g., arthralgia, arthritis, sacroiliitis, oral thrush, erythema nodosum, episcleritis, pyoderma gangrenosum),[8] but this rate can be higher in reference centers and depending on the definition of "extra-intestinal manifestations."

1.4 EXTENSION AND SEVERITY (ACTIVITY) OF ULCERATIVE COLITIS

The clinical picture of UC depends on the extent of the disease and its severity. Generally, the extension of UC is evaluated by colonoscopy (Table 1), and the severity or activity, by clinical and laboratory assessments, is classified in a manner similar to the Truelove & Witts classification (Table 2).[8]

Severe UC is clarified as at least six bloody bowel movements per day together with at least one of the following changes: a) fever (>37.5°C); b) tachycardia (>100 bpm); c) anemia (hemoglobin <10 g/dL); d) erythrocyte sedimentation rate (ESR) >30 mm, first hour; and e) albumin <3.5 g/dL.[9]

The fulminant form of UC is characterized by >10 bloody bowel movements per day, fever, tachycardia, need for blood transfusion, evidence of significantly altered inflammatory activity (e.g., ESR >30 mm, first hour; C-reactive protein >30 mg/L) with or without a toxic megacolon (colonic dilation, usually of the transverse colon ≥5.5 cm), or intestinal perforation.[10] However, some authors do not agree with the characterization of the "fulminant" form because this term was used in the 1950s to define a single acute UC presentation that results in death in the first year of progression. In fact, this outcome became the exception and not the rule with the improvement of treatment of acute outbreaks of UC. Thus, the tendency is to use the terminology acute severe UC alone.[8,11]

Several scoring systems have been used to quantify the inflammatory activity in UC.[8] One of the most common scoring systems is the Mayo score (Table 3). The complete Mayo score (maximum of 12 points) includes endoscopic data. The partial Mayo score (maximum of 9 points) does not consider endoscopic findings. Mayo's endoscopic score (0 to 3) is widely used in routine endoscopic evaluation of patients. Based on the complete Mayo score, scores of 0–2, 3–5, 6–10, and >10 indicates remission (as long as there is no subscore >1), mild disease, moderate disease, and severe disease, respectively.[6,8,11,12]

The intensity of the clinical picture of UC is correlated with the extent of the disease, namely:[6,8]

a. Proctitis: usually occurs in mild and moderate cases, commonly with rectal bleeding, feces with mucus and pus, and tenesmus. Diarrhea occurs in 80% of patients; however, constipation can also occur. Abdominal pain is usually colic, preceding evacuations, and not completely relieved with colorectal emptying. Patients may complain of urgency, incontinence, and anorectal pain. Extra-intestinal manifestations are less frequent.

b. Left-sided UC and pancolitis (total or universal colitis): in these cases, the patients usually have moderate or severe forms of the disease. Fever, asthenia, and weight loss with anorexia are common. Diarrhea can also occur with mucus, pus, blood, and tenesmus, in addition to more intense abdominal pain than in the case of proctitis. Very severe presentations, including toxic megacolon and colonic perforation, may occur.

Table 1. Classification of ulcerative colitis (UC) based on the distribution of inflammation (colonoscopic evaluation); E = extension.[8]

E1–Proctitis	Involvement limited to the rectum
E2–Left-sided colitis	Involvement up to the splenic flexure
E3 - Extensive colitis	Involvement beyond the splenic flexure, including pancolitis

Table 2. Classification of ulcerative colitis (UC) based on the severity of the acute outbreak (adapted from Truelove & Witts).[8]

	Mild	Moderate	Severe
1. Bloody stools/day	<4	≥4	≥6 and
2. Pulse (bpm)	<90 bpm	≤90	>90 or
3. Temperature (°C)	<37.5° C	≤37.8	>37.8 or
4. Hemoglobin (g/dL)	>11.5 g/dL	≥10.5	<10.5 or
5. ESR (mm/first hour)	<20 mm/h	≤30	>30 or
6. CRP (mg/L)	Normal	≤30 mg/L	>30

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Table 3. Mayo score of inflammatory activity.[12]

Stool frequency	**Appearance of the mucosa on endoscopy**
0. normal	0. Normal or inactive disease
1. 1-2 stools/day more than normal	1. Mild disease (erythema, reduction of the vascular pattern, mild friability)
2. 3-4 stools/day more than normal	2. Moderate disease (marked erythema, loss of vascular pattern, friability, erosions)
3. ≥5 stools/day more than normal	3. Severe disease (spontaneous bleeding, ulcers)
Rectal bleeding	**Physician's assessment of disease activity**
0. No blood seen	0. Normal
1. Visible blood in the stool less than half the time	1. Mild
2. Visible blood in the stool half the time or more	2. Moderate
3. Blood alone passed	3. Severe

1.5 PRE-TREATMENT EVALUATION

Before initiating treatment of UC, obtaining data related to the activity and the extent of the disease is advisable, whenever possible. The correct assessment of patients will serve as a guideline for the establishment of the best therapeutic approach in each case:[6,8,11]

a. The assessment of the degree of activity of the disease (mild, moderate, severe) must consider the clinical, laboratory (e.g., ESR, C-reactive protein, fecal calprotectin), and endoscopic data (Mayo 0, 1, 2, or 3);

b. The extension of the inflammatory process should preferably be assessed using colonoscopy. Completion of colonoscopy aimed at stage extension, in the clinical scenario of severe illness, should be carefully evaluated against the risk of perforation associated with the procedure. In these cases, rectosigmoidoscopy, without excessive air inflation, is recommended.[8,11]

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ATTACHMENT I

1. CLINICAL DOUBTS

a. What is the role (effectiveness and safety) of aminosalicylates in treatment of Ulcerative colitis?
b. Which is the roll (damages and benefit) of corticosteroids in treatment of Ulcerative colitis?
c. What is the role (damage and benefit) of thiopurines in treatment of Ulcerative colitis?
d. What is the role (damage and benefit) of methotrexate in treatment of Ulcerative colitis?
e. The calcineurin inhibitors (cyclosporine and tacrolimus) are effective and safe in the treatment of Ulcerative colitis?
f. The biological medicines are effective and safe in treatment of Ulcerative colitis?
g. The probiotics are effective and safe in the treatment of Ulcerative colitis?
h. When is surgical treatment effective and safe in Ulcerative colitis?

2. STRUCTURED QUESTION

Q: Ulcerative colitis
I: Intervention or indicator
W: _____
O: Benefit or damage

3. EVIDENCE-SEEKING STRATEGY

From the structured query we identify the keywords or descriptors that will form the basis of the search for evidence in the various available databases.

a. Aminosalicylates

#1 - Inflammatory Bowel Diseases OR Ulcerative colitis
#2 - Crohn Disease
#3 - Anti-Inflammatory Agents, Non-Steroidal OR Sulphasalazine OR Sulfasalazine AND Aminosalicylic Acid* OR Mesalazine OR Mesalamine OR 5-aminosalicylic acid OR 5-aminosalicylate OR Olsalazine OR Balsalazide
#4 - Therapy/narrow[filter] OR Prognosis/narrow [filter] OR Comparative study OR Comparative studies

1st RECOVERY = #1 AND #2 AND #3 = 517
((Inflammatory Bowel Diseases OR Colitis, Ulcerative) NOT (Crohn Disease)) AND (Anti-Inflammatory Agents, Non-Steroidal OR Sulphasalazine OR Sulfasalazine) AND (Aminosalicylic Acid* OR Mesalazine OR Mesalamine OR 5-aminosalicylic acid OR 5-aminosalicylate OR Olsalazine OR Balsalazide) AND (Therapy/narrow[filter] OR Prognosis/narrow [filter] OR Comparative study OR Comparative studies)

b. Corticosteroids

#1 – ((Inflammatory Bowel Diseases) OR (Colitis, Ulcerative)) NOT Crohn Disease
#2 – Adrenal Cortex Hormones OR Steroids OR Cortisone OR Hydrocortisone OR Prednisone OR Prednisolone OR Methylprednisolone OR Budesonide
#3 – Therapy/Narrow[filter] OR Prognosis/Narrow[filter] OR systematic[sb]

1st retrieval = # 1 AND # 2 AND # 3 = 534
((Inflammatory Bowel Diseases OR Colitis, Ulcerative) NOT (Crohn Disease)) AND (Adrenal Cortex Hormones OR Steroids OR Cortisone OR Hydrocortisone OR Prednisone OR Prednisolone OR Methylprednisolone OR Dexamethasone OR Budesonide AND (Therapy/Narrow[filter] OR Prognosis/Narrow[filter] OR systematic[sb]))

c. Thiopurines

#1 - Inflammatory Bowel Diseases OR Colitis, Ulcerative
#2 - Antimetabolite* OR Immunosuppressive Agents OR 6-Mercaptopurine OR 6-MP OR Azathioprine OR AZA
#3 - Therapy/Narrow[filter] OR Prognosis/Narrow[filter] OR systematic[sb]

1st RECOVERY = #1 AND #2 AND #3 = 930
(Inflammatory Bowel Diseases OR Colitis, Ulcerative) AND ((Antimetabolite* OR Immunosuppressive Agents OR 6-Mercaptopurine OR 6-MP OR Azathioprine OR AZA) AND (Therapy/Narrow[filter] OR Prognosis/Narrow[filter] OR systematic[sb]))

d. methotrexate

#1 - Inflammatory Bowel Diseases OR Ulcerative colitis
#2 - Immunosuppressive Agents OR Methotrexate
#3 -Therapy/narrow[filter] OR Prognosis/narrow [filter] OR Comparative study OR Comparative studies

1st RECOVERY = #1 AND #2 AND #3 = 856
(Inflammatory Bowel Diseases OR Ulcerative colitis) AND (Immunosuppressive Agents OR Methotrexate) AND (Therapy/narrow [filter] OR Prognosis/narrow [filter] OR Comparative study OR Comparative studies)

e. Calcineurin (cyclosporine and tacrolimus)

#1 – ((Inflammatory Bowel Diseases) OR (Ulcerative colitis))
#2 - (Immunosuppressive Agents OR Calcineurin OR Calcineurin Inhibitors OR Cyclosporine OR ciclosporin OR Tacrolimus OR FK506 OR FK-506)
#3 - (Therapy/narrow[filter] OR Prognosis/narrow [filter] OR Comparative study OR Comparative studies)

1st RECOVERY = #1 AND #2 AND #3 = 89
(Inflammatory Bowel Diseases OR Ulcerative colitis) AND (Immunosuppressive Agents OR Calcineurin OR Calcineurin Inhibitors OR Cyclosporine OR ciclosporin OR Tacrolimus OR FK506 OR FK-506) AND (Therapy/narrow[filter] OR Prognosis/narrow [filter] OR Comparative study OR Comparative studies).

f. Biological products

#1 – (((Inflammatory Bowel Diseases) OR (Colitis, Ulcerative)) NOT (Crohn Disease))
#2 – (Antibodies, Monoclonal OR Antibodies, Monoclonal, Humanized OR Tumor Necrosis Factor-alpha OR anti-TNF OR Infliximab OR Adalimumab OR Golimumab OR Vedolizumab OR Integrins)
#3 – Random*

1st RECOVERY = #1 AND #2 AND #3 = 310
((Inflammatory Bowel Diseases OR Colitis, Ulcerative) NOT (Crohn Disease)) AND (Antibodies, Monoclonal OR Antibodies, Monoclonal, Humanized OR Tumor Necrosis Factor-alpha OR anti-TNF OR Infliximab OR Adalimumab OR Golimumab OR Vedolizumab OR Integrins) AND Random*

g. Probiotics, prebiotics and synbiotics

#1 - (Inflammatory Bowel Diseases OR Colitis, Ulcerative)
#2 – (Probiotic* OR Microbiota OR Prebiotic* OR Synbiotic*)
#3 - Random*

1st RECOVERY = #1 AND #2 AND #3 = 239
(Inflammatory Bowel Diseases OR Colitis, Ulcerative) AND (Probiotic* OR Microbiota OR Prebiotic* OR Synbiotic*) AND Random*

h. Surgical treatment

#1 – (Inflammatory Bowel Diseases OR Colitis, Ulcerative)
#2 – (Surgery OR Colectomy OR Proctocolectomy OR Ileostomy OR Ileoproctostomy OR Ileal pouch-anal anastomosis)
#3 – (Therapy/Narrow[filter] OR Prognosis/Narrow[filter])

1st RECOVERY = #1 AND #2 AND #3 = 2028
((Inflammatory Bowel Diseases OR Colitis, Ulcerative) AND (Surgery OR Colectomy OR Proctocolectomy OR Ileostomy OR Ileoproctostomy OR Ileal pouch-anal anastomosis) AND (Therapy/Narrow[filter] OR Prognosis/Narrow[filter]))

ATTACHMENT I

4. RECOVERED WORKS

The scientific information databases consulted were Medline via Pubmed, Lilacs and Central via BVS, EMBASE and CINAHL via EBSCO. Manual search from revisions references (narrative or systematic), as well as the selected works, was held.

5. INCLUSION CRITERIA OF THE SELECTED WORKS

The selection of studies, assessment of the titles and abstracts obtained from the search strategy in data bases was conducted by two researchers with skills in preparing systematic reviews, with independency and blinded manner, strictly observing the established inclusion and exclusion criteria and described in the components of PICO, separating finally the work with potential and relevance.

5.1 According to the study designs

Narrative reviews, case reports, case series, works with presentation of preliminary results were, in principle, excluded from the selection. Systematic reviews and meta-analyzes were used with the principle of recovery of references that may had been lost in the first time from the initial search strategy. Systematic reviews were included in meta-analysis and randomized controlled trials (ECRs). The evidence was recovered from the selected critical evaluation using a tool "A MeaSurement Tool to Assess Reviews" (AMSTAR)[1] for RSs and instruments (scores) and discriminatory JADAD[2] GRADE[3] for ECRs

5.2 Language

They included studies available in Portuguese, English or Spanish.

Table 1. Script of critical evaluation of randomized controlled trials.

Study data	**Sample Calculation**
Reference, Study design, JADAD2, force of evidence	Estimated differences, power, significance level, all patients
Patient Selection	**Patients**
Inclusion and exclusion criteria	Recruited, randomized, prognostic differences
Randomization	**Patient follow-up**
Description and blindfolded allocation	Time, loss, migration
Treatment Protocol	**Analyze**
Intervention, control and blinding	Intention of treatment, intervention and control analyzed
Considered outcomes	**Result**
Primary, secondary, measuring instrument of the outcome of interest	Benefit or damage in absolute data, average for benefit or damage

5.3 According to the publication

Only works with full texts were available were considered for critical evaluation.

6. CRITICAL EVALUATION METHOD

The AMSTAR[1] was used to assess the quality of systematic reviews. This tool provides a global quality rating on a scale from 0 to 11, where 11 is a review of the highest quality. Quality categories were determined as follows: low (scale 0 to 3), average (score 4 to 7), and high (score from 8 to 11). RSs of low and moderate quality were excluded.

When, after the application of the inclusion and exclusion criteria, the selected evidence was defined as randomized controlled trial (ECR) and subjected to an appropriate check-list of critical evaluation (Table 1). The ECR critical assessment allows to classify it according to JADAD[2] score, considering the JADAD < three (3) as inconsistent (Grade B), and those with scores ≥ three (3) consistent (grade A), and according to the score GRADE[3] (moderate or strong evidence).

When the selected evidence was defined as comparative study (observational cohort or non-randomized clinical trial), this was subjected to an appropriate check-list of critical evaluation (Table 2), allowing the classification of the study, according o score NEW CASTLE Ottawa SCALE[4], considering the cohort studies consistent with score ≥ 6 and inconsistent < 6.

7. EXPOSE OF RESULTS

For the results with available evidence, it will be defined in a specific way, wherever possible, the population, intervention, outcomes, the presence or absence of benefit and/or damage and controversies.

The results will be exposed preferably in absolute data, absolute risk, number needed to treat (NNT) or number to produce damage (NNH), and eventually in mean and standard deviation (Table 3).

8. RECOMMENDATIONS

Recommendations will be made by the authors of the review, with the initial characteristic of the synthesis of evidence, being subjected to validation by all participating authors of the elaboration of the Directive.

The grade of recommendation being used comes directly from the available strength of the studies according the Oxford[5], and the use of GRADE[3] system.

Table 3. Sheet used for description and explanation of the results of each study.

Evidence included
Study Design
Selected population
Follow-up
Considered outcomes
Demonstrative of results: percentage, risk, odds, hazard ratio, average

Table 2. Script of critical evaluation of cohort studies.

Representativeness of exposed and unexposed selection of (Max. 2 points)	Display Resolution (Max. 1 point)	Demonstration that the outcome of interest wasn´t present at baseline (Max. 1 point)	Comparability on the basis of the design or analysis (Max. 2 points)	Outcome assessment (Max. 1 point)	Appropriate follow-up (Max. 2 points)	Score and level of evidence

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2. TREATMENT WITH AMINOSALICYLATES

INTRODUCTION

The aminosalicylate group includes sulfasalazine (SSZ) and 5-aminosalicylic acid (5-ASA) compounds (mesalamine or mesalazine).[1-3] When ingested, SSZ is cleaved in the distal ileum and colon by bacterial action into sulfapyridine (largely absorbed) and 5-ASA (poorly absorbed), and the latter is the active ingredient of the drug, acting topically.[1] 5-ASA differs from salicylic acid (aspirin) by the addition of an amino group at position 5 (meta). This molecular modification confers different properties to 5-ASA compared to other salicylates, such as aspirin. Thus, unlike other salicylates, which exclusively block prostaglandin synthesis through the inhibition of cyclooxygenase enzymes 1 and 2, 5-ASAs modulate the synthesis of prostaglandins and prostacyclin from arachidonic acid and can inhibit (high concentration) or increase (low concentration) their production.[4] In addition, 5-ASAs inhibit the 5-lipoxygenase pathway by blocking the production of leukotrienes (e.g., leukotriene B4), potent proinflammatory agents related to neutrophil chemotaxis.[4-6] 5-ASA also acts as an antioxidant and is a potent free-radical scavenger.[7] One of the most important findings related to the mechanism of action of 5-ASA in ulcerative colitis (UC) is its ability to activate the gamma-form of peroxisome proliferator-activated receptor (PPAR-γ).[7-12] The PPAR-γ receptor is an important member of the superfamily of nuclear receptors, which play a role in various biological processes.[8-12] It is present in large amounts in colonic epithelial cells and, to a lesser extent, in macrophages, dendritic cells, and lymphocytes.[8-12] PPAR-γ is a nuclear receptor that controls the expression of regulatory genes related to lipid metabolism, insulin sensitivity, inflammation, proliferation, differentiation, and cellular apoptosis.[8-12] Its activation promotes the reduction of proinflammatory cytokines, such as IL-1β, IL-2, IL-6, and TNF-α, and the inhibition of the NF-κB pathway, another important nuclear regulator of the expression of genes related to the immune response in the intestine.[12] Therefore, PPAR-γ activation exerts a direct anti-inflammatory effect in the colonic mucosa.

Since 5-ASA is the active ingredient of SSZ and there is a high frequency of side effects (13–60%, requiring interruption in 2–22% of cases) associated with the use of SSZ, especially at doses higher than 4 g/day and due to excessive absorption of sulfapyridine,[4,13,14] new salicylic derivatives were developed. Thus, from the 1980s, several formulations of mesalazine were developed, without sulfapyridine.[15-18] The central idea was to protect 5-ASA from total release, absorption, and metabolization in the proximal small intestine, thus allowing therapeutic doses of 5-ASA, the active ingredient of SSZ, to reach the most distal portions of the gastrointestinal tract (GIT).[1-3,8] Four strategies were then developed.[1-4,8,18]

a) Coating of 5-ASA with acrylic resins that dissolve and release 5-ASA at a given pH: Two resins have been used widely: Eudragit-S (e.g., Mesacol®), which promotes the release of mesalamine at pH > 7 (terminal ileum and colon), and Eudragit-L (Claversal®, Salofalk®), which has the same action but at pH > 5.6–6.0 (jejunum, ileum, and colon).

b) Mesalazine in the form of capsules of individually coated microgranules with an ethylcellulose semipermeable membrane (e.g., Pentasa®): The release of 5-ASA occurs throughout the entire GIT and is time- and pH-dependent (greater release in higher pH).

(c) Substitution of sulfapyridine, which is largely responsible for the side effects of SSZ, by, for example, 4-aminobenzoyl-β-alanine, an inert carrier (balsalazide), or 4-aminobenzoylglycine (ipsalazide) or another 5-ASA (olsalazine or disodium azodisalicylate), forming a dimer: The release, as in the case of SSZ, depends on the cleavage of the nitrogen bond by the intestinal bacteria.[1,15-18] An important detail is that olsalazine causes liquid diarrhea in up to 17–19% of cases.[16] This effect is dose-dependent and occurs more in patients with extensive UC (pancolitis). Olsalazine is known to reduce the absorption of water and sodium in the ileum and colon.[16] This observation is fundamental when comparing the results of various studies on 5-ASA for which the inclusion or removal of studies on olsalazine influences the final conclusions.[19]

d) Mesalazine coated with the acrylic resin Eudragit-S and in a matrix (Multi-Matrix System [MMX]) that gradually disintegrates in 24 h throughout the colon.[3]

Brazil only sells products with Eudragit-S (e.g., Mesacol®), microgranules (e.g., Pentasa®), and MMX technology (e.g., Mesacol® MMX). Formulations with a higher mesalazine content are available, which allows taking the medication in a single daily dose, leading to increased patient adherence to treatment.[3,7,20-22]

In the treatment of UC, it is possible to identify agents that induce response and clinical remission (induction agents) and those used to maintain clinical remission (maintenance agents), although many of these drugs can be used in both situations.

2.1 INDUCTION OF REMISSION

Recommendations

The first-line therapy for mild-to-moderate left-sided colitis is the combination of oral and topical mesalazine. A daily dose > 2 g/day is effective and safe for inducing remission in patients with mild-to-moderate ulcerative colitis. Patients with moderate activity of the disease can benefit from an initial dose ≥ 4 g/day. (A) HIGH-QUALITY EVIDENCE

In distal colitis (distal margin < 60 cm from the anal border), the use of rectal 5-ASA (suppositories of 500 mg/day and 1000 mg/day for proctitis or enema of 1–3 g/day for distal colitis) is superior to that of rectal corticosteroids in inducing symptomatic improvement and remission. (A) HIGH-QUALITY EVIDENCE

There are no differences in remission induction failure and rate of adverse events when comparing a single daily dose and conventional regimen. There are no differences in remission induction failure or adverse events when comparing various formulations of 5-ASA. (A) HIGH-QUALITY EVIDENCE

The use of 5-ASA (mesalazine) compared to SSZ does not have a significant difference in failure to induce global or clinical remission, but mesalazine is associated with fewer adverse events. (A) HIGH-QUALITY EVIDENCE

2.1.1 Distal colitis

In patients with distal colitis, topical therapy is the preferred treatment.[23-25] A study including 38 randomized controlled trials (RCTs) compared the use of rectal 5-ASA derivatives (suppository, enema, or foam) with a placebo or another active therapy in patients aged > 12 years and with mild-to-moderate disease, presenting a distal margin of the disease < 60 cm from the anal border or distal to the splenic flexure. This therapy was superior to placebo treatment in inducing symptomatic, endoscopic, and histological remission. The pooled odds ratios (PORs) were 8.3 (8 studies, 95% CI 4.28–16.12, p < 0.00001, NNT = 2–4) for symptomatic remission, 5.3 (7 studies, 95% CI 3.15–8.92, p < 0.00001) for endoscopic remission, and 6.3 (5 studies, 95% CI 2.74–14.40, p < 0.0001) for histological remission. The use of rectal 5-ASA was superior to that of rectal corticosteroids in inducing symptomatic improvement and remission, with a POR of 1.56 (6 studies, 95% CI 1.15–2.11, p = 0.004, NNT = 7–31) and 1.65 (6 studies, 95% CI 1.11–2.45, p = 0.01, NNT = 5–45), respectively[23] (A), and these results were confirmed in another study[24] (A).

2.1.2 Proctitis

In mild-to-moderate proctitis therapy, suppositories are more adequate as they better target inflammation (only 40% of foam enemas and 10% of liquid enemas can be detected in the rectum after 4 h)[26] (B).

The use of suppositories compared to that of oral mesalazine shows on average a significantly higher improvement in disease activity indices (p < 0.001) and histological remission rates (p < 0.01) in patients with proctitis (≤ 15 cm from the anal border), with no significant differences in adverse events in an analysis of 2 and 4 weeks of treatment[27,28] (A). In patients with proctitis, oral Eudragit-S at doses of 2.4 g/day and 3.6 g/day was superior to oral microgranule mesalazine at a dose of 2.25 g/day in reducing the UC activity index that includes endoscopic data (UC-DAI)[29] (A).

In patients with distal UC (at least 5 cm above the anal border and < 50-60 cm), the combination of oral and rectal mesalazine produces earlier and more complete relief of rectal bleeding compared to oral or rectal therapy alone[30] (A).

In a meta-analysis that included 12 RCTs (761 patients), the authors compared oral and topical (enema or suppository) 5-ASA or the combination of oral and topical 5-ASA in adult patients with mild-to-moderate UC. There were no significant differences when comparing oral and topical use in the remission of active UC (4 studies, 214 patients), a result limited by a high statistical heterogeneity (I^2 = 64%). Oral and topical 5-ASA, compared to oral 5-ASA alone, reduced the risk of remission induction failure (RR = 0.65, 95% CI 0.47–0.91, NNT = 5) in 3–8 weeks in patients with active UC (4 studies, 322 patients), with no differences in the incidence of adverse events (RR = 0.77, 95% CI 0.55–1.09)[31] (A).

2.1.3 Left-sided ulcerative colitis

Most studies include patients with mild-to-moderate UC, and there is clear evidence of the efficacy of the use of both oral and topical mesalazine in left-sided UC compared to the use of a placebo[23,32] (A).

The first-line therapy for mild-to-moderate active left-sided UC is the combination of oral and topical mesalazine[25,30] (A).

A systematic review of 48 RCTs with a minimum treatment duration of 4 weeks evaluated the use of oral 5-ASA in inducing remission in 7,776 adults with mild-to-moderate active UC. Comparing the use of oral 5-ASA with that of a placebo, the 5-ASA derivative reduces the global or clinical remission induction failure rate as observed in the analysis of 8 clinical trials that included a total of 1,843 patients (RR = 0.86, 95% CI 0.81–0.91, NNT = 7–13). There was statistical significance only for 5-ASA derivatives at a dose ≥ 2 g/day, confirming the result of the previous study (RR = 0.91, 95% CI 0.85–0.98). There were no differences regarding adverse events in the analysis of 6 clinical trials (916 patients)[32] (A). Comparing the use of the 5-ASA derivative with that of SSZ, there were no differences in the global or clinical remission induction failure rate (RR = 0.9, 95% CI 0.77–1.04) in the analysis of 8 clinical trials (526 patients), but the use of the 5-ASA derivative is associated with a reduction in the number of adverse events (11 studies, RR = 0.48, 95% CI 0.37–0.63, NNT = 6–10)[32] (A). There were no statistically significant differences in the global and clinical remission induction failure rates (3 studies, 738 patients) and adherence failure rate to the treatment regimen (2 studies, 358 patients) when comparing daily use of one mesalazine dose and that of more than one mesalazine dose (conventional use). This comparison also showed no differences regarding adverse effects[32] (A). However, patients' preferences tend to favor once daily mesalazine. In a randomized trial in patients with active UC comparing once daily versus three times daily mesalazine, the vast majority of patients (313/380, 82%) preferred a once daily treatment schedule[22]. Only 2% preferred the three times daily schedule, and 14% had no preference. For 6 patients (2%) no data were available[22]. There were no statistically significant differences in the global and clinical remission induction failure rates (11 studies, 1,968 patients) and adverse events when comparing various formulations of oral 5-ASA[33] (A).

A mesalazine dose of 2–3 g/day is thus safe and effective in patients with mild-to-moderate UC[32] (A). Patients with moderate disease activity can benefit from an initial dose ≥ 4 g/day[33] (A).

2.2 MAINTENANCE OF REMISSION

Recommendations

SSZ is superior to 5-ASA in maintaining remission. However, when excluding studies with olsalazine – not available in Brazil – and including only studies with a 12-month evaluation, SSZ is as effective as 5-ASA. (A) HIGH-QUALITY EVIDENCE

There are no differences in efficacy or adherence to treatment between a 5-ASA daily dose (single total dose) and conventional regimen. However, patients more often prefer dosing regimens that require taking medication fewer times per day. (A) HIGH-QUALITY EVIDENCE

In the comparison of various formulations of oral 5-ASA, there are no differences in the relapse rates and frequency of adverse events. (A) HIGH-QUALITY EVIDENCE

Doses ≥ 2 g/day of 5-ASA derivatives in preventing relapse in patients with quiescent UC are more effective than doses < 2.0 g/day. (A) HIGH-QUALITY EVIDENCE

A systematic review of 38 RCTs with a minimum treatment time of 6 months evaluated the use of oral 5-ASA derivatives in patients with mild-to-moderate UC in remission (quiescent) (8,127 patients). The primary endpoint was failure to maintain clinical or endoscopic remission.[19] Compared with a placebo, the 5-ASA derivative reduced the relapse rate (7 studies with a total of 1,298 patients, RR = 0.69, 95% CI 0.62–0.77, NNT = 5–8). There were no significant differences regarding adverse events in the analysis of 4 studies (875 patients). Compared with SSZ, oral 5-ASA increased the relapse rate in the analysis of 12 studies, some of high quality but with heterogeneous results (1,655 patients) (RR = 1.14, 95% CI 1.03–1.27, NNT = 8–77). Restricting the analysis to studies with endpoints in a 12-month period (8 studies), there were no statistically significant differences between SSZ and 5-ASA (RR = 1.10, 95% CI 0.98–1.23). Similarly, when the analysis was restricted to 7 studies that did not use olsalazine (adverse effect of major diarrhea), there were no statistically significant differences between SSZ and 5-ASA[19] (A). There were no differences regarding adverse events in the analysis of 7 studies (1,138 patients). In the comparison of the single daily dose and conventional regimen, there were no significant differences in several parameters, including 6-month relapse rate in the analysis of 3 studies with 1,871 patients (including a high-quality RCT), 12-month relapse rate (7 RCTs, 2,826 patients), and failure to adhere to the therapeutic regimen (7 RCTs, 1,825 patients; a result limited by high heterogeneity)[19] (A). However, as it was the case in active UC[22], when patients were asked their preference, they preferred dosing regimens that required taking medication fewer times per day (e.g., once daily)[34-36] (A). This discrepancy reinforces the complicated and multifactorial nature of adherence[21,37]. Adherence with medication in clinical trials is generally greater than in clinical practice since participants are usually those more likely to be collaborative and adherent to drug regimens[37]. Furthermore, adherence is continuously reinforced during the clinical trial process. Thus, it may be difficult to detect differences in adherence between once daily and multiple dose regimens in this setting[37]. Future research should reevaluate the determinants of adherence in large-scale community-based studies, taking into account not only medication regimens, but also other potential components of adherence such as patient-physician relationship, open communication, and mutual agreement regarding the value of treatment, among others[21,35,37]. Comparing various formulations of oral 5-ASA, there were no significant differences in the 12-month relapse rate (5 RCTs, 457 patients) and frequency of adverse events (4 studies, 365 patients)[19] (A).

A systematic review evaluated the dose of 5-ASA (7 RCTs, 1,534 patients) in preventing relapse in patients with UC in remission (quiescent) and showed that doses ≥ 2.0 g/day were more effective than those < 2.0 g/day (RR = 0.79, 95% CI 0.64–0.97, NNT = 5–33)[32] (A).

Another systematic review that included 9 RCTs, with methodological limitations, evaluated the use of rectal 5-ASA in 484 patients with distal UC in remission. Compared to placebo treatment, the use of rectal 5-ASA is associated with improved rates of maintenance of clinical remission up to 12 months in the analysis of 4 studies (301 patients) (RR = 2.22, 95% CI 1.26–3.9, NNT = 2–13). There were no significant differences in the frequency of adverse events (2 studies, 160 patients), and the most common adverse events were anal irritation and abdominal pain. Comparing the use of rectal 5-ASA with that of oral 5-ASA, there were no statistically significant differences in clinical (2 studies, 69 patients) or endoscopic (2 studies, 91 patients) remission[38] (A). However, a second systematic review shows that the use of intermittent topical 5-ASA was superior to that of oral 5-ASA (3 studies, 129 patients), with a reduction in the relapse rate in patients with quiescent UC (RR = 0.64, 95% CI 0.43–0.95, NNT = 4)[31] (A).

Comparing different doses, there were no statistically significant differences between the use of 4 g/day and 2 g/day enema (1 study, 29 patients) or 1 g/day and 500 mg/day suppository (1 study, 76 patients)[38] (A).

2.3 PREVENTION OF COLORECTAL NEOPLASIA

A systematic review evaluated the efficacy of 5-ASA derivatives in preventing colorectal neoplasia in patients with UC (7 studies, 1,508 cases, 20,193 patients with UC). 5-ASA derivatives reduced the risk of colorectal neoplasia (OR = 0.63, 95% CI 0.48–0.84), especially in patients with higher mean daily doses (SSZ ≥ 2.0 g/day, mesalazine ≥ 1.2 g/day) (OR = 0.51, 95% CI 0.35–0.75)[39] (A). It should be noted that control of intestinal inflammation, regardless of the drug used, is the most important element in the prevention of dysplasia/colorectal cancer.[40]

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3. TREATMENT WITH CORTICOSTEROIDS

3.1 INDUCTION OF REMISSION

Recommendations

Outbreaks of acute UC that are unresponsive to 5-ASA derivatives require corticosteroids to induce remission. (A) HIGH QUALITY EVIDENCE

Prednisone displays a dose-response effect between 20 and 60 mg/day, with 60 mg/day being slightly more effective than 40 mg/day but carrying more adverse effects. (B) MODERATE QUALITY EVIDENCE

Prednisone at a dose of 40–60 mg/day is maintained until significant clinical improvement is noted; thereafter, a dose reduction of 5–10 mg/week must be performed until a daily dose of 20 mg is reached; from this point, the dose should be reduced to 2.5–5.0 mg/week. (C) LOW QUALITY EVIDENCE

There is no evidence to support the clinical use of oral budesonide (standard formulation) to induce remission in cases of active UC, with mesalazine being superior in such cases. (A) HIGH QUALITY EVIDENCE

There is no evidence to support the use of a dose greater than 60 mg/day of methylprednisolone; furthermore, treatment duration is usually limited to 7–10 days; longer-duration treatment provides no additional benefit. (A) HIGH QUALITY EVIDENCE

All patients hospitalized with severe UC should be assessed to confirm the diagnosis and exclude concomitant infection with *Clostridium difficile* or cytomegalovirus. (C) LOW QUALITY EVIDENCE

The absence of improvement after 3–5 days of IV steroids is an indication to initiate rescue therapy. (B) MODERATE QUALITY EVIDENCE

Long-term therapy with systemic steroids is not indicated. (C) LOW QUALITY EVIDENCE

The use of corticosteroids at the time of surgery in patients with IBD is associated with a higher risk of total postoperative complications and infectious diseases. (A) HIGH QUALITY EVIDENCE

In the majority of cases involving ulcerative colitis (UC), acute disease outbreaks can be controlled with 5-aminosalicylic acid (5-ASA) derivatives[1] (A). Patients who do not respond to 5-ASA derivatives require corticosteroids for the induction of remission[2] (A).

Among patients requiring corticosteroids, approximately 70% respond favorably to the first course; however, at the end of 1 year of treatment, only half of the patients maintain corticosteroid-free remission, while 22% develop dependence[3] (C).

The evidence that indicates the benefit of oral corticosteroid therapy in UC with mild to moderate activity comes from two studies that included patients with extensive UC. The first study compared the use of oral prednisolone with oral sulfasalazine—both associated with the use of hydrocortisone enema—and reported an induction of remission in 76% of patients in the prednisolone group and only 52% of the sulfasalazine group after 2 weeks of treatment[4] (B). The second study also showed that therapy with oral steroids together with rectal steroids was better than the isolated use of either medication[5] (B).

Prednisone has a dose-response effect between 20 and 60 mg/day; the dose of 60 mg/day is slightly more effective than the dose of 40 mg/day but carries the expense of more adverse effects[5,6] (B).

No randomized studies to date have evaluated the timing and method for reducing steroid therapy. The majority of the recommendations suggests starting with a dose of 40–60 mg/day orally until significant clinical improvement is noted and that treatment should not exceed 4 weeks. This should be followed by a reduction of 5–10 mg/week until a daily dose of 20 mg is reached. At that point, the dose should be reduced to 2.5–5.0 mg/week[7] (D).

Among five randomized clinical trials (RCTs) including a total of 445 adults with UC, one assessed the effectiveness of various glucocorticoids (beclomethasone, fluticasone, prednisone, prednisolone) *versus* placebo. The rate of remission achieved with glucocorticoids in the individual studies was 13–80%. The glucocorticoids significantly reduced the "non-remission" rate; however, these results are very limited owing to the high degree of heterogeneity among the studies (relative risk [RR] = 0.65; 95% confidence interval [CI], 0.45–0.93; $I^2 = 81$; $p < 0.001$). The number needed to treat (NNT) for glucocorticoids to achieve remission in one patient was 3 (95% CI, 2–9). In absolute numbers, the rate of adverse events (infection, weight gain, hyperglycemia, acne, hirsutism, and hypertension) was higher in the glucocorticoid group than in the placebo group, but the difference was not statistically significant (RR = 1.69; 95% CI, 0.30–9.62)[2] (A).

Other authors evaluated the use of oral budesonide (standard formulation) for inducing remission in patients with active UC. A study of 72 patients compared the use of oral budesonide 10 mg/day *versus* oral prednisolone 40 mg/day with subsequent gradual reductions over 9 weeks; after 9 weeks, mean endoscopic scores improved significantly in both groups (mean decrease was 1.20 in the budesonide group versus 1.36 in the prednisolone group; P=0.12). However, endoscopic and histological improvement in the distal colon was in favor of prednisolone, perhaps indicating a suboptimal release of budesonide in this region. Another study (n = 343 patients) compared the use of oral budesonide 9 mg/day (pH-dependent corticosteroid release) with oral mesalazine 3 g/day. The primary endpoint was clinical remission at week 8. Fewer patients achieved the primary endpoint with budesonide *versus* mesalazine (70/177 [39.5%] versus 91/166 [54.8%]) with a difference in proportions of - 15.3% (95% CI [- 25.7%, - 4.8%]; P=0.520 for non–inferiority). The authors concluded that mesalazine was superior to oral budesonide for achieving clinical remission in mild-to-moderately active UC. Thus, the objective of demonstrating non-inferiority for oral budesonide 9 mg/day versus oral mesalazine 3 g/day was not achieved.[8] (A).

Corticosteroids are the basis of therapy for severe active UC[9] (A). Steroids are administered intravenously (IV) as methylprednisolone (60 mg/day) or hydrocortisone (100 mg/6-8 hours). There is no evidence to support the use of a methylprednisolone dose higher than 60 mg/day since higher doses do not reduce colectomy rates. The treatment duration is usually limited to 7–10 days; continuing treatment beyond this period does not provide additional benefits[10] (A).

One RCT (N = 66 patients) had inadequate statistical power to exclude small differences compared the use of methylprednisolone (1 mg/kg/day; maximum dose, 60 mg/day) injected as a bolus twice daily with the same dose as a continuous infusion in patients hospitalized with severe UC. There was no significant intergroup difference in the analysis of the outcomes, including clinical remission after 7 days of treatment, rate of colectomy, or drug-related adverse events[11] (A).

All patients hospitalized with severe UC should be assessed to confirm the diagnosis and disease activity and exclude possible concomitant infection with *Clostridium difficile* or cytomegalovirus[12] (D).

A systematic review including 32 studies and a total of 1,991 patients (1,948 adults) evaluated therapy with IV corticosteroids (hydrocortisone, methylprednisolone, or betamethasone) in patients with UC and severe activity. For adult patients, without comparison with a control group, the rates of global response to steroids, short-term colectomy (up to 2 months after admission), and mortality were 67% (95% CI, 65–69%), 27% (95% CI, 26–29%), and 1% (95% CI, 0.7–1.6%), respectively[10] (A).

One RCT including only 30 patients with severe UC compared monotherapy with cyclosporine 4 mg/kg/day IV with methylprednisolone 40 mg/day IV. After 8 days, 53% (8/15) patients who received prednisolone demonstrated a clinical response to therapy *versus* 64% (9/14) treated with cyclosporine without a statistically significant difference. There were no cases of severe drug-related toxicity in any group[13] (A).

The persistence of a high number of daily bowel movements, presence of blood in the stool, and elevated serum C-reactive protein levels after the third day of intensive treatment with corticosteroids are the main factors associated with corticoid-refractory colitis, with a risk of colectomy of up to 85%[14] (C). The absence of improvement after 3–5 days of treatment with IV steroids is an indication to start another rescue therapy[1] (B).

A systematic review and meta-analysis of 11 observational studies evaluated the postoperative complications of 2,976 patients with inflammatory bowel disease (IBD) who underwent abdominal surgery. The use *versus* non-use of corticosteroids at the time of surgery was associated with a significant increase in the risk of total postoperative complications (odds ratio [OR], 1.41; 95% CI, 1.07–1.87; seven analyzed studies), including an increased risk of infectious complications (OR, 1.68; 95% CI, 1.24–2.28; five analyzed studies). Patients who received high doses of oral steroids preoperatively (>40 mg/day) were at a higher risk of total complications (OR, 2.04; 95% CI, 1.28–3.26; two analyzed studies)[15] (A).

In a case-control study that included 3,522 patients with incident IBD (age ≥ 66 years; mean follow-up, 4.4 years), the incidence of severe infections was reportedly 3.7/100 person-years (N = 564). The recent use of oral corticosteroids compared with the non-use of medication increased the risk of serious infections in these patients[16] (A).

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4. TREATMENT WITH THIOPURINES

4.1.INDUCTION OF REMISSION

Recommendation

The use of thiopurines in the induction of remission is limited owing to their slow onset of action (B). MODERATE-QUALITY EVIDENCE
Azathioprine (AZA) at a dose of 1.5–2.5 mg/kg per day is effective in patients who do not respond to or who cannot be weaned from corticosteroid therapy (B). MODERATE-QUALITY OF EVIDENCE

Randomized controlled trials (RCTs) with a small number of patients[1,2] (B) and uncontrolled studies[3,4] (C) have shown that azathioprine (AZA) at a dose of 1.5–2.5 mg/kg per day is effective in nonresponsive patients or when patients cannot be weaned from corticosteroid therapy[5]. Corticosteroid dependence has been defined as a relapse of the disease within 30 days after discontinuation of the medication or during dose reduction, preventing its discontinuation for more than 1 year[6] (C). A study of 80 patients identified no benefit of AZA 2.5 mg/kg/day when added to oral corticosteroid therapy for the treatment of active ulcerative colitis. There was no statistically significant difference in the remission rate over a period of 1 month between patients who received AZA plus corticosteroid and those who received corticosteroid plus placebo (78% vs. 68%, p=ns)[7] (A). Another study with 20 patients included patients with active ulcerative colitis and compared the use of AZA 2.5 mg/kg/day with the use of sulfasalazine, and no significant differences in clinical and endoscopic improvement were found in a 3-month analysis ($p<0.05$)[8] (B). For induction therapy, AZA has limited use owing to its slow onset of action and 3–6 months of treatment may be required to achieve an optimal effect[9] (B).

4.2. MAINTENANCE OF REMISSION

Recommendation

Thiopurines should be used to maintain remission; however, a therapeutic response may not occur within 3 months (A). HIGH-QUALITY EVIDENCE.
Thiopurines are effective as long-term therapy (A). HIGH-QUALITY EVIDENCE

Thiopurines (AZA and 6-mercaptopurine, 6-MP) have been studied as effective agents for the prevention of relapse. Two systematic reviews (SR), which included studies with methodological limitations (inadequate blinding or allocation and small sample size) evaluated the efficacy of AZA for the maintenance of remission in patients with ulcerative colitis.[10,11]

A total of 286 patients were included in a study comparing oral AZA or 6-MP with placebo for at least 12 months or with the conventional therapy (e.g. mesalazine). Four RCTs (232 patients) compared AZA with placebo and found an increase in the maintenance of remission (RR=1.47, 95% CI 1.16–1.85, NNT 4–11, failure to maintain remission in 65% of patients in the placebo group). There was no difference in the maintenance of remission when compared with sulfasalazine in one RCT with 25 patients (RR=1.52, 95% CI 0.66–3.50). In an analysis of five RCTs, AZA was found to result in a higher number of adverse events (pancreatitis, bone marrow suppression, hepatitis, and jaundice), although this was not statistically significant (RR=2.82, 95% CI 0.99–8.01)[10] (A). Based on pooled data, treatment with thiopurines (AZA/6-MP) was associated with an almost three-fold increase in the risk of any adverse event (RR=2.82, 95% CI 0.99–8.01) compared with patients not exposed to this therapy (bone marrow suppression 4% and acute pancreatitis in 2% - more frequent)[10] (A).

Authors compared thiopurine analogs (AZA and 6-MP) with a placebo or with no treatment in adults with ulcerative colitis. Five RCTs evaluated the use of AZA in 257 patients. An analysis of 2 RCTs (130 patients), which included patients with active disease, showed that AZA did not increase the incidence of remission compared with placebo (RR=0.85; 95% CI 0.71–1.01). The other three RCTs included 127 patients with quiescent ulcerative colitis and revealed a reduction of the relapse rate in the AZA group compared with placebo (RR=0.6, 95% CI 0.37–0.95)[11] (A).

Limited data are available on the predictive factors of response to AZA and there is uncertainty with regard to the duration of treatment. A study evaluated data from 346 patients with ulcerative colitis for a follow-up period of 30 years (1968–1999). In this study, the overall remission rate with AZA was 58%, which increased to 87% in patients treated for more than 6 months. Over a 5-year period, this rate was 62% when a strict definition of relapse was applied, or 81% when allowing a short relapse with a short corticosteroid treatment. After interruption of AZA treatment, the mean relapse time was 18 months[12] (C). A study conducted by our colleagues evaluated 42 patients with steroid-dependent ulcerative colitis who were treated with AZA[13] (C). This study showed that AZA promoted sustained clinical remission without steroids for up to 3 years and patients with an earlier onset of ulcerative colitis were more likely to achieve remission without using steroids.

In the evaluation of 6-MP *vs.* 5-aminosalicylate *vs.* methotrexate in patients with corticosteroid-dependent inflammatory bowel disease (ulcerative colitis and Crohn's disease), the analysis of the subgroup of 34 patients with ulcerative colitis found that remission was maintained in 50% of the patients treated with 6-MP *vs.* 8.3% with methotrexate (p=0.031, NNT=3) and in 50% of those treated with 6-MP *vs.* 0% with 5-aminosalicylate (p=0.019, NNT=2)[14] (B).

In 105 patients with refractory ulcerative colitis that were continuously treated with 6-MP for a long time, the rate of complete remission was 65%. Of those with complete response who continued to use 6-MP, 35% showed relapse, although complete remission was restored in 88%, with most requiring no systemic corticosteroids. Of those with complete response who interrupted treatment with 6-MP, 87% subsequently showed relapse[15] (C).

4.3 ADVERSE EVENTS

Recommendation

A higher incidence of myelosuppression occurs in the first 8 weeks of thiopurine therapy and may justify more frequent monitoring during this period (B). MODERATE-QUALITY EVIDENCE

Dose-dependent adverse events include bone marrow suppression and hepatic injury. Low TPMT activity is associated with high levels of thioguanine nucleotides (6-TGN) and active metabolites of AZA and 6-MP, which increase the risk of bone marrow toxicity (C). LOW-QUALITY EVIDENCE

Increased levels of 6-methylmercaptopurine (6-MMP) may be associated with the development of hepatotoxicity (C). LOW-QUALITY EVIDENCE

There is an increased association with non-melanoma skin cancer, high-grade cervical dysplasia and cervical cancer, urinary tract cancer, but no correlation with the risk of developing solid tumors (B). MODERATE-QUALITY EVIDENCE.

Treatment with AZA/6-MP is associated with a potential risk of lymphoma, with a positive correlation between lymphoma and Epstein-Barr virus infection (A). HIGH-QUALITY EVIDENCE

Deficiency of the enzyme thiopurine S-methyltransferase (TPMT), caused by mutations in the *TPMT* gene, is a metabolic disorder that increases the risk of occurrence of adverse events in patients treated with thiopurines. Low TPMT activity is associated with high levels of thioguanine nucleotides (6-TGN) and active metabolites of AZA and 6-MP, which increases the risk of bone marrow toxicity. In addition, increased levels of 6-methylmercaptopurine (6-MMP) may be associated with the development of hepatotoxicity[16] (C). TPMT levels determine enzyme activity and can be measured before treatment with thiopurines is started, allowing the identification of rare patients who are at risk of developing of severe myelotoxicity and optimization of the drug dosage[17] (D).

There is currently insufficient evidence to support the routine use of the TPMT genotyping test to measure enzyme activity and it should be noted that the TPMT test does not predict the long-term risk of myelosuppression or idiosyncratic adverse events, such as fever, arthralgia, and pancreatitis[18] (A).

To assess the relevance of monitoring AZA and 6-MP metabolite levels, it is necessary to perform controlled prospective evaluations before recommending routine use of these drugs, such as evaluation of the benefits of the traditional routine monitoring through complete blood count, liver examination, and clinical response[19] (D).

Two studies evaluated the co-prescription of allopurinol in the dose reduction of AZA/6-MP, as well as toxicity and lack of response. One of the studies included 110 patients with inflammatory bowel disease (IBD) who received thiopurine and allopurinol, and identified the occurrence of hepatotoxicity, other adverse events, inadequate response with low TGN/high methylated metabolites, and an adverse metabolic profile for a good clinical response with the monotherapy. Patients receiving dual primary therapy owing to high TPMT were also included. Dose adjustment of thiopurines was based on TGN/MMP levels. With a mean follow-up of 16 months, the combination therapy was successful in a significant number of patients (clinical remission in 76% of patients). Some limiting adverse effects were found[20] (C). Another study included 77 patients with IBD receiving thiopurine therapy who experienced hepatotoxicity and/or resistance to therapy or other adverse events. Thiopurine metabolite levels were determined during monotherapy and up to 4–8 weeks after the combination therapy was started. The thiopurine dose was adjusted to achieve intra-erythrocyte 6-TGN levels of 230–400 pmol/8 × 10^8. The mean follow-up was 19 months and the combination therapy was effective and well-tolerated in the long term: there was a reduction in the thiopurine dose ($p<0.001$); liver function was normalized in 81% of patients, and for up to 60 months, 65% of patients continued with the combination therapy[21] (C).

Treatment with AZA/6-MP is associated with a potential risk of lymphoma. A retrospective analysis of data (2001–2011) included 36,891 patients diagnosed with ulcerative colitis and a follow-up of 6.7 years (median). A total of 4734 patients with ulcerative colitis (13%) were treated with thiopurine (median 1 year). Patients treated with thiopurines had a four-fold higher probability of developing lymphoma (HR, adjusted for age, gender, and race = 4.2, 95% CI 2.5–6.8, $p<0.0001$) compared with those who did not receive thiopurines. This probability increased gradually with successive years of therapy and was reduced with the interruption of therapy[22] (A). This study confirmed the result of a previously published meta-analysis[23] (A).

The CESAME study included 19,486 patients with IBD (Crohn's disease, ulcerative colitis, or unclassified disease) with a median follow-up period of 35 months. The probability of developing lymphoproliferative diseases was five times higher in patients who used thiopurines compared with those who never used them (adjusted HR=5.28, 95% CI 2.01–13.9, $p=0.0007$)[24] (B).

The data analysis of 17,834 patients with IBD identified 44 cases of lymphoma, 19 of which were in patients that were exposed to AZA/6-MP. There was a positive correlation between lymphoma, Epstein-Barr virus infection, and AZA/6-MP therapy[25] (C).

A low rate of myelotoxicity was reported in patients with IBD and AZA/6-MP therapy. Despite limitations due to heterogeneity, a systematic review of 35 studies with 9,103 patients per year of follow-up showed the following results: an incidence of drug-induced myelotoxicity per patient and year of treatment of 3%; mortality risk due to myelotoxicity of 0.98%; incidence of severe myelotoxicity <1% per patient and year of treatment; and risk of mortality with severe myelotoxicity <0.1%[26] (B). Previous exposure to thiopurines increased

the risk of myeloid disorders by up to seven-fold among patients with IBD[27] (B). There was a higher incidence of myelosuppression in the first 8 weeks of therapy, which may justify more frequent monitoring during this period[28] (C).

A systematic review of observational studies (four cohort studies and four case-control studies) evaluated the association between the use of thiopurines (AZA/6-MP) and the risk of non-melanoma skin cancer in 60,351 patients with IBD. In an analysis of all studies, comparison of the use and the non-use of thiopurines indicated that these drugs were associated with an increase in the number of non-melanoma skin cancers (HR=2.28, 95% CI 1.50–3.45), although with high heterogeneity (I^2=76%), but without evidence of publication bias[29] (B).

An increased risk of high-grade cervical dysplasia and cervical cancer in women with IBD was described with thiopurine use (OR 1.34; 95% CI, 1.23-1.46, for patients on immunosuppressive medications in general [i.e., steroids, immunomodulators, or biologics], with an OR of 3.45 for thiopurine use specifically)[30]. It is thus recommended that special attention must be paid to women with cervical abnormalities, and strong consideration given to thiopurine discontinuance in the setting of advancing dysplasia or recurrence after erradication.[30] Also, some authors have shown an association of thiopurine use and urinary tract cancer (RR, 2.40; 95% CI, 1.24-6.54).[30] This risk was greatest in men older than 65 years[30] (B).

In the last four decades, the use of thiopurines was not correlated with the risk of developing solid tumors[31] (B). A data analysis of the CESAME cohort, already mentioned above, evaluated the development of colorectal cancer (CRC) among patients with IBD, and showed that patients with extensive and long-term colitis had a higher probability of developing the disease, but this was lower among patients who were treated with thiopurines compared with those who were never treated with these drugs (HR adjusted for high-grade dysplasia and CRC=0.28, 95% CI 0.1–0.9, p=0.03)[32] (B).

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5. TREATMENT WITH METHOTREXATE

Recommendations

Currently, there is insufficient evidence to support the use of methotrexate (MTX) to induce remission in patients with active cortico-dependent ulcerative colitis or even oral MTX in the maintenance of remission in patients with ulcerative colitis (B). MODERATE QUALITY EVIDENCE
There is no evidence that different doses and routes of administration of MTX may have different impacts on remission rates of ulcerative colitis (B). MODERATE QUALITY EVIDENCE

Methotrexate (MTX), a folate antagonist, is an immunosuppressive drug with anti-inflammatory properties that is used to treat various inflammatory diseases, including Crohn's disease and ulcerative colitis. MTX is an inhibitor of the enzyme dihydrofolate reductase; thus, it interferes with the biosynthesis of purines and pyrimidines, preventing the synthesis of DNA, RNA, and proteins. In addition to these cytotoxic effects, MTX can also have anti-inflammatory effects related to inhibition of the synthesis of eicosanoids and other cytokines.

5.1. REMISSION INDUCTION

There is currently insufficient evidence to support the use of MTX to induce remission in patients with active cortico-dependent ulcerative colitis[1] (A). A comparative study of MTX 12.5 mg/week *versus* placebo, orally, in the induction of remission in 67 patients with moderate to severe ulcerative colitis showed no significant difference (relative risk [RR], 0.96; 95% confidence interval [CI], 0.58–1.59) in the clinical remission rate, total suspension of steroids, and mean time to first remission (4.1 months in the MTX group and 3.4 months in the placebo group). The exclusion of patients due to adverse events did not differ significantly between groups (RR, 2.47; 95% CI, 0.23–25.91), Three patients were withdrawn from the study for suspected side effects: transient leukopenia, migraine, and a severe rash. The first two patients were administered methotrexate and the third patient was administered placebo[2] (B).

In a comparative study, 34 steroid-dependent ulcerative colitis patients were stratified into groups according to the use of 6-mercaptopurine (6-MP) (group A, 1.5mg/Kg/day, orally), MTX (group B, 15mg/week, orally), and 5-aminosalicylic acid derivatives (group C, 3g/day, orally). They were followed up over a period of 30 weeks. Regarding achieved remission, a significantly higher (P<0.05) rate existed for ulcerative colitis patients in group A (78.6%) than in group C (25%), with no statistical differences in group B (58.3%) *versus* C. With regard to maintaining remission, ulcerative colitis patients in group A (63.6%) presented significantly higher rates (P<0.0015 and P<0.001, respectively) versus 14.3% in group B and none in group C. Noticeable side effects appeared in 13.3% of patients from group A and 11.5% from group B (for the whole group of ulcerative colitis and Crohn's disease patients). Adverse events related to MTX use were nausea and dyspepsia, mild alopecia, a small increase in aspartate aminotransferase levels, peritoneal abscess, hypoalbuminemia, skin rash, and atypical pneumonia[3] (B).

A series of small studies revealed heterogeneity in the conceptualization of response at the time of follow-up with the dose of MTX used (7.5–25 mg/week) and the route of administration (orally, subcutaneously, intramuscularly).[1,4-6]

One study analyzed data of 91 patients with cortico-dependent or refractory ulcerative colitis who received MTX orally (mean 14 mg/week) or parenterally (mean 25 mg/week) and demonstrated that 37% (25/68) of the patients in the oral MTX group were able to successfully taper their corticosteroid therapy compared with 30% (7/23) of the parenteral group at up to 12 months of follow-up[4] (B). It was impossible to establish the impact of administration dose or route on remission rates in ulcerative colitis[5] (D).

MTX (25 mg/week, intramuscularly or subcutaneously) has also been studied in a multicentre trial including 111 patients with steroid-dependent ulcerative colitis (METEOR trial)[7]. The primary endpoint, steroid-free remission at week 16 (defined as a complete Mayo score ≤ 2 with no item >1 and complete withdrawal of steroids and no use of another immunosuppressive [IS] or anti -TNF therapy or colectomy), was achieved in 31.7% of patients assigned to MTX and in 19.6% of patients who received placebo (a difference of 12.1% [95% CI: - 4.0% to 28.1%]; P=0.15, n.s.). The rate of steroid-free clinical remission at week 16 (defined as a Mayo clinical subscore ≤ 2 with no item >1, without steroids, IS and anti-TNF agents or colectomy) was 41.7% for MTX and 23.5% for placebo (a difference of 18.2% [95% CI: 1.1% to 35.2%]; P=0.04). The proportion of patients with steroid-free endoscopic healing (endoscopic Mayo subscore of 0 or 1) at week 16 were 35% in the MTX group versus 25.5% in the placebo group (a difference of 9.5% [95% CI: - 7.5% to 26.5%]; P=0.28, n.s.). More patients receiving placebo discontinued the study due to adverse events (47.1%), mostly caused by ulcerative colitis, than patients receiving MTX (26.7%; P=0.03). A higher proportion of patients in the MTX group had nausea and vomiting (21.7%) than in the placebo group (3.9%; P=0.006).

5. 2 REMISSION MAINTENANCE

MTX did not demonstrate a well-established role in maintaining remission in patients with ulcerative colitis (lack of evidence)[6] (A). The use of oral MTX (12.5 mg/week) in patients with ulcerative colitis to maintain remission was compared with the use of placebo in 67 patients with active ulcerative colitis. The subgroup of 32 patients with clinical remission was followed for 9 months or until the occurrence of the first recurrence. In the MTX group, 64.3% relapsed compared with 44.4% in the placebo group with no significant difference (RR=1.45; 95% CI=0.76-2,76; n.s.)[2,6] (B). Another study compared oral MTX 15 mg/week with placebo in patients with quiescent ulcerative colitis (N=26), and also found no difference between MTX and placebo (RR= 0.12; 95% CI=0.01-2.18; n.s.)[8] (B) and no benefit with the grouping of the two randomized controlled trials was found (RR=0.59; 95% CI=0.04-7.90)[6] (A). However, this result may be compromised due to the significant heterogeneity between the two studies (I^2 = 70%).[6]

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6. TREATMENT WITH CALCINEURIN INHIBITORS

INTRODUCTION

Ulcerative colitis is a chronic colitis of unknown origin. Patients with severe forms of the disease should be hospitalized. Intravenous corticosteroids are the first treatment option, with a response rate of approximately 60%. Failure to respond to corticosteroid treatment after 4–7 days without surgical indications involves rescue therapy with cyclosporine, tacrolimus, or infliximab.[1-3] Cyclosporine leads to an initial positive response in approximately 80% of cases.

Cyclosporine is a macrolide immunosuppressant that inhibits the production of interleukin-2 activated by T-lymphocytes through a calcineurin-dependent pathway and the synthesis of other inflammatory cytokines.[4]

Tacrolimus, a calcineurin inhibitor like cyclosporine, has a similar mechanism of action.[1-3]

6.2. CYCLOSPORINE

Recommendations

Patients with severe corticosteroid-refractory ulcerative colitis and no surgical indications are candidates for rescue therapy with cyclosporine or infliximab. The efficacy of cyclosporine 2 mg/kg/day continuous infusion is equivalent to that of cyclosporine 4 mg/kg/day. There is no clear evidence of the advantage of using cyclosporine over infliximab, and both drugs can be used in severe cases of corticosteroid-refractory ulcerative colitis. (A) HIGH-QUALITY EVIDENCE

Serum cyclosporine levels (150–250 ng/mL for 2 mg/kg/day and 250–450 ng/mL for 4 mg/kg/day) must be monitored. (C) LOW-QUALITY EVIDENCE

The previous use of azathioprine results in lower response rates to cyclosporine. The association with azathioprine as a maintenance treatment after the induction of remission with cyclosporine IV reduces the colectomy rate by 40–50%.

Prophylactic treatment for *Pneumocystis jiroveci* (*carinii*) infection is recommended during the triple immunosuppressive intervals (oral corticosteroid, azathioprine, and oral cyclosporine) following the intravenous cyclosporine phase. (B) MODERATE QUALITY EVIDENCE

Two studies established the efficacy of intravenous cyclosporine as rescue therapy in patients with severe ulcerative colitis who were non-responders to intravenous corticosteroid treatments.[5,6] (A)

The first study included 11 patients who received intravenous cyclosporine (4 mg/kg/day continuous infusion) and 9 who received a placebo. Two of the 11 patients in the cyclosporine IV group did not respond to the treatment (no induction of remission) compared to all patients in the placebo group (relative risk [RR] = 0.18; 95% confidence interval [CI], 0.05–0.64). There was no statistically significant difference in the colectomy rate between the treatment and placebo groups during a follow-up of less than 1 month (3/11 and 4/9, respectively; RR = 0.6; 95% CI, 0.18–2.06). Of all patients in the placebo group, 5 migrated to the cyclosporine IV group and responded to cyclosporine.[5] (A)

In the second study, 15 patients were treated with cyclosporine IV (4 mg/kg/day continuous infusion) and the other 5 were treated with methylprednisolone (40 mg/day). After the eighth day of treatment, 5 of the 15 patients in the cyclosporine group showed no induction of remission, as did 7/15 of the steroid IV group (RR = 0.71; 95% CI, 0.29–1.75) with no statistically significant difference. The colectomy rate (RR = 1.0; 95% CI, 0.24–4.18) was similar between groups. During a follow-up of 1 year, 7 of 9 responders to cyclosporine remained in remission versus 4 of 8 in the steroid group ($p > 0.05$).[6] (A)

In a controlled randomized double-blind study of 73 patients who received different doses of intravenous cyclosporine (doses of 4 mg/kg/day, n = 38; 2 mg/kg/day, n = 35), evaluation of the response on the eighth day showed no significant differences (83% and 82%, respectively; number needed to treat = NS). In the short term (14 days), the colectomy rates were 9% and 13% for the groups of 2 and 4 mg/kg/day, respectively. Therefore, cyclosporine 2 mg/kg/day became the standard in clinical practice (lower toxicity).[7] (A) Serum cyclosporine levels (150–250 ng/mL using 2 mg/kg/day and 250–450 ng/mL using 4 mg/kg/day) must be monitored.[1-3] (D)

Combining the results of the clinical trials, the cyclosporine IV response rate was 76–85%[5-7] (A), with a mean response time of 4 days.[7] (A)

Regarding long-term efficacy, several case series have evaluated the need for colectomy in patients treated with cyclosporine. An initial response to cyclosporine was observed in 83% of 113 patients treated with cyclosporine; colectomy was avoided during this hospitalization. However, 33% of these patients required colectomy in the first year, 54% in 5 years, and 88% in 7 years.[8] (B) This study also showed that the previous use of azathioprine resulted in lower response rates to cyclosporine. The colectomy rate in patients who previously used azathioprine was 59% versus 31% in those who started using azathioprine at the time they started responding to cyclosporine.[8] (B) On the other hand, the association with azathioprine as a maintenance treatment after remission is achieved with cyclosporine, reduces the colectomy rate by 40–50%.[8] (B)

Cyclosporine does not increase the rate of postoperative complications in patients who undergo proctocolectomy.[9-11] (C) Serious adverse events (0–17%) related to the use of cyclosporine in ulcerative colitis include hypertension, nephrotoxicity, infection, and seizures (particularly in patients with hypocholesterolemia or hypomagnesemia). Less severe (31–51%) although more common adverse events include paresthesia, hypertrichosis, headache, abnormal liver function, hyperkalemia, and gingival hyperplasia.[12] (C) The mortality rate with the use of cyclosporine in ulcerative colitis is approximately 1.8–3.5%.[12] (C)

Prophylactic treatment for *Pneumocystis jiroveci* (*carinii*) infection is recommended during the triple immunosuppressive treatment interval (oral corticosteroid, azathioprine, and oral cyclosporine) following the use of intravenous cyclosporine.[1-3] (D)

A meta-analysis of six retrospective studies (historical cohort) analyzed the results obtained with rescue therapy in patients with severe corticosteroid-refractory ulcerative colitis (N = 321) using cyclosporine (n = 142) or infliximab (n = 179). There were no differences in the colectomy rates between the groups at 3 months of treatment (odds ratio [OR] = 0.86; 95% CI, 0.31–2.41; p = 0.775) or at 12 months (OR = 0.60; 95% CI, 0.19–1.89; p = 0.381). The number of adverse reactions (OR = 0.76; 95% CI, 0.34–1.70; p = 0.508) and postoperative complications (OR = 1.66; 95% CI, 0.26–10.50; p = 0.591) did not differ significantly between the groups.[13] (A)

A non-blinded clinical trial (N = 115) that was not included in the above meta-analysis compared cyclosporine and infliximab and showed no differences between treatments in efficacy against severe corticosteroid-refractory ulcerative colitis, with a clinical response seen on the 7th day of treatment of about 85% in both groups (p = 0.50). There was also no difference in the colectomy rate after 3 months of treatment (cyclosporine 18% *vs* infliximab 21%, p = 0.66) or in the number of severe adverse events (p = 0.23).[14] (B)

Another comparative study of cyclosporine and infliximab treatments included 83 patients with severe corticosteroid-refractory ulcerative colitis (45 in the cyclosporine group, 38 in the infliximab group). Cyclosporine increased the risk of colectomy by 20% (number needed to harm [NNH] = 5; 95% CI, 2–2116) in the first 3 months and by 21% (NNH = 5; 95% CI, 2–215) in the first year.[15] (B)

6.3. TACROLIMUS

Recommendation

Oral tacrolimus may reduce disease activity in severe corticosteroid-refractory ulcerative colitis. (A) HIGH-QUALITY EVIDENCE

Tacrolimus is also a calcineurin inhibitor with a mechanism of action similar to that of cyclosporine.[1-3]

The use of tacrolimus was evaluated in a study that included 62 patients hospitalized with moderate to severe corticosteroid-refractory ulcerative colitis by comparing its use with that of placebo for 2 weeks. Clinical response rates (50% *vs* 13%, p = 0.003), mucosal healing (44% *vs* 13%, p = 0.012), and clinical remission (9% *vs* 0%, p = 0.238) were higher in the tacrolimus group than in the placebo group, respectively.[16] (A)

In another study, 63 patients with active corticosteroid-refractory ulcerative colitis were treated with tacrolimus at different doses (10–15 ng/mL or 5–10 ng/mL) or placebo twice daily for 2 weeks. The initial tacrolimus dose was 0.025 mg/kg twice daily, which was then adjusted to maintain pre-established blood levels. Comparison of 10–15 ng/mL *vs* 5–10 ng/mL *vs* placebo revealed that disease activity score improved by 68% *vs* 38.1% *vs* 10% (p < 0.001 for high dose vs placebo; other comparisons were not significant); clinical remission rates in up to 2 weeks were 20% *vs* 10.5% *vs* 5.9% (not significant); and mucosal healing rates in up to 2 weeks were 78.9% *vs* 44.4% *vs* 12.5% (not significant).[17] (B)

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7. TREATMENT WITH BIOLOGICAL AGENTS

INTRODUCTION

The pharmacological treatment of ulcerative colitis (UC) aims to reduce the inflammatory process and maintain the remission of symptoms[1,2]. Despite therapeutic progress, the treatment options for moderate to severe active UC remain limited as only partial control is obtained with conventional therapies (sulfasalazine, aminosalicylates, glucocorticoids, and immunosuppressants) in a substantial proportion of patients, and owing to the presence of adverse events. Currently, the drugs of choice for these patients are anti-tumor necrosis factor alpha (anti-TNF-α) agents, infliximab (IFX), adalimumab (ADA), and golimumab, and, more recently, the anti-integrin agent vedolizumab, a selective antagonist of this adhesion molecule in the intestine.

7.1 INDUCTION OF REMISSION

Recommendations

All biological agents (ADA, golimumab, IFX, and vedolizumab) result in superior clinical response, clinical remission, and mucosal healing than placebo in the induction of remission. (A) HIGH QUALITY EVIDENCE
Combination therapy with IFX with azathioprine in patients with moderate to severely active UC who had not previously used anti-TNF-α, is more effective than monotherapy with IFX for the remission induction rate. (B) MODERATE QUALITY EVIDENCE
Cyclosporine and IFX may be used as rescue therapy in patients with severe uncontrolled UC that is unresponsive to corticosteroids. (B) MODERATE QUALITY EVIDENCE
When used as rescue therapy in patients with severe acute or fulminant colitis, IFX is effective in the short term (3 months) and long term (3 years) to reduce the need for colectomy. (B) MODERATE QUALITY EVIDENCE
IFX and golimumab displayed comparable efficacy in the induction of remission. (B) MODERATE QUALITY EVIDENCE

7.1.1 INFLIXIMAB

7.1.1.1 Monotherapy/combination therapy

Several studies have compared IFX together with azathioprine *versus* IFX associated with placebo and azathioprine associated with placebo, whereas others have compared IFX with placebo.

Studies such as the ACT 1 and ACT 2 trials, which involved patients with moderate to severe UC (Mayo score 6–12) who were refractory to corticosteroids alone or in combination with azathioprine or 6-mercaptopurine (ACT 1) or with 5-aminosalicylates (ACT 2), were performed to assess the clinical response after 8 weeks. Patients with prior use of anti-TNF-α agents were excluded. The clinical response was better in patients treated with IFX (5 mg/kg IV) than in the placebo group (69% *vs* 37% in ACT 1, $p < 0.001$) and (65% *versus* 29% in ACT 2, $p < 0.001$). Patients taking IFX also had a higher clinical response rate at Week 30 ($p \leq 0.002$ in both studies)[3] (A).

Patients with cortico-refractory UC were randomized to receive IFX (5 mg/kg IV) or placebo in Weeks 0 and 2. The rate of remission (score of symptoms of UC less than 2) was 39% in the IFX group and 30% in the placebo group until Week 6, with a non-statistically significant difference of 9% between groups (95% CI 19%–34%; $p = 0.76$). During this period, the quality of life related to health, as measured with the Inflammatory Bowel Disease Questionnaire (IBDQ) and EQ-5D instruments, was not significantly different between the groups ($p = 0.22$ and 0.3, respectively)[4] (A).

In the UC-SUCCESS study, 239 patients with moderate to severe UC (Mayo score 6–12), without prior therapy with TNF inhibitors, were randomized to the different study treatments. At Week 16, there was an increased rate of corticosteroid-free clinical remission (Mayo score ≤ 2) with the combination of IFX and azathioprine (39.7%) compared with IFX alone (22.1%; $p = 0.0170$) or azathioprine alone (23.7%; $p = 0.813$). The largest improvements in quality of life measured using the IBDQ and SF-36 from the beginning of the study were observed for the combination of IFX and azathioprine ($p < 0.05$ compared with the use of azathioprine or IFX alone)[5] (A).

7.1.1.2 Rescue therapy

Patients diagnosed with severe acute and fulminant colitis should be hospitalized and treated with high doses of intravenous corticosteroids. For those who do not respond to treatment after a period of 48 to 72 hours, some type of rescue therapy should be implemented before a surgical treatment is indicated. Despite intensive treatment, approximately 50% to 60% of patients are subjected to surgical treatment and colectomy. The authors concluded that IFX would be indicated as rescue therapy for the treatment of patients with moderate and severe colitis in order to reduce the number of colectomies[6] (B). If intravenous corticosteroids failed to control symptoms, patients with severe colitis were randomized to receive either IFX (N = 24) or placebo (N = 21). There was a significant reduction in the number of patients receiving a colectomy and a single dose of IFX (5 mg/kg body weight) compared with those receiving placebo (IFX = 29% *versus* placebo = 67%; odds ratio (OR) = 4.9, 95% CI 1.4–17, $p = 0.017$) over a 3-month follow-up period[6] (B). After randomization, there were more patients who received IFX in the group with a previous diagnosis of UC than in the group of patients who presented with the disease for the first time (21 vs 9). Therefore, we can conclude that patients with greater tissue damage (secondary to the disease) over time belonged to the IFX group.

Nevertheless, after multivariate analysis, the number of patients who had the disease for the first time and were consequently administered treatment was larger than the number

of patients in the placebo group who benefited from the use of IFX (OR = 3.6; 95% CI 1.0–13.7). The results of the same patient cohort were evaluated 3 years after treatment[7] (B). Approximately 50% of patients treated with IFX did not require surgery, and the majority remained in remission without the use of corticosteroids. However, 76% of patients recruited for the placebo group were colectomized (p = 0.012)[7] (B). We can conclude, therefore, that the benefit of salvage treatment with IFX is maintained over the long term[7] (B).

7.1.1.2.1 IFX ***versus*** cyclosporine

Several authors compared the results of cyclosporine *versus* IFX as rescue therapy in patients with severe UC unresponsive to corticosteroids. Six retrospective studies were included (historical cohort), with a total of 321 patients analyzed (142 in the cyclosporine group *versus* 179 in the IFX group). There was no difference between the groups in the rate of colectomy at 3 months (OR = 0.86; 95% CI 0.31–2.41; p = 0.775) and at 12 months (OR = 0.60; 95% CI 0.19–1.89; p = 0.381). No difference was found in the number of adverse reactions (OR = 0.76; 95% CI 0.34–1.70; p = 0.508) or postoperative complications (OR = 1.66; 95% CI 0.26–10.50; p = 0.591)[8] (B).

A randomized controlled clinical trial (N = 115), which aimed to compare cyclosporine with IFX, revealed no difference between drugs in relation to efficacy in severe UC unresponsive to corticosteroids. The clinical response on Day 7 was approximately 85% in both groups (p > 0.50). There was also no difference in the colectomy rate at 3 months (cyclosporine 18% *versus* IFX 21%, p = 0.66) and in the number of severe adverse events (p = 0.23)[9] (B).

Another open clinical study compared the efficacy between the two drugs. Patients with severe cortico-refractory UC (N = 83) received cyclosporine (n = 45) or IFX (n = 38). Cyclosporine increased the risk of colectomy by 20% (NNH = 5; 95% CI 2–2116) for up to 3 months and by 21% (NNH = 5; 95% CI 2–215) for up to 1 year[10] (B).

7.1.2 ADALIMUMAB

The ULTRA 1 study evaluated the efficacy of ADA for the induction of remission for up 8 weeks in patients with moderate to severe UC unresponsive to corticosteroids and/or immunosuppressants, including 186 patients (mean age = 37 years) who were randomized for the use of subcutaneous ADA (160 mg in Week 0, 80 mg in Week 2, and then 40 mg every 2 weeks) *versus* placebo. Another 390 patients were randomized, following an amendment to the protocol, for high-dose subcutaneous ADA (160 mg in Week 0, 80 mg in Week 2, and then 40 mg every 2 weeks) *versus* low-dose subcutaneous ADA (80 mg in Week 0 and then 40 mg every 2 weeks) *versus* placebo. No patients in this study had received previous treatment with anti-TNF-α. The outcomes assessed were: clinical remission (Mayo score ≤ 2, without individual subscores exceeding 1 and ≥ 1 reduction of rectal bleeding in 8 weeks) and clinical response (reduction of the Mayo score ≥ 3, ≥ 30% reduction of the initial value, and reduction of rectal bleeding subscore ≥ 1 or subscore of absolute rectal bleeding of 0 or 1). In this study, 18.5% of the patients in the ADA 160 mg initial dose group (p = 0.031 *versus* placebo, number needed to treat (NNT) = 11) and 10% in the ADA 80 mg initial dose (not significant *versus* placebo) went into remission in Week 8, compared with 9.2% in the placebo group. The clinical response in Week 8 was 54% with an initial ADA dose of 160 mg (not significant *versus* placebo) and 51.5% with an initial ADA dose of 80 mg (not significant *versus* placebo), compared with 44.6% of patients receiving placebo[11] (A).

The second study (ULTRA 2), in which 40% of the patients had received previous anti-TNF treatment, found a higher rate of clinical remission in patients treated with ADA than in those treated with placebo at Week 8 (16.5% *vs.* 9.3%; p = 0.019)[12] (A).

The incidence of adverse events was similar for ADA or placebo in the ULTRA 1 study (50.2% vs 48.4%, respectively). The most frequent adverse event was worsening or flare-up of UC (ADA 3.6% *versus* placebo 4.0%). Most of the adverse events were of mild to moderate severity[11] (A).

A meta-analysis, which included ULTRA 1 and ULTRA 2, examined the rates of remission in Week 8 of treatment, showed a clinically relevant effect with ADA, with relative risk (RR) of 1.85 (95% CI 1.26–2.72); I^2 = 0%, and NNT = 13 (95% CI 7–42). Although the remission rate was 17.2% (65/378) in the ADA group, the rate for the placebo group was 9.3% (35/376)[13] (A).

Another double-blind clinical trial assessed the use of ADA in the induction and maintenance of 273 patients with moderate to severe UC unresponsive to corticosteroids and/or immunosuppressants without prior use of anti-TNF-α[14]. The patients were randomized to receive subcutaneous ADA (160 mg in Week 0, 80 mg in Week 2, and then 40 mg every 2 weeks, or 80 mg in Week 0 and then 40 mg every 2 weeks) or placebo. Before Week 8, there was no significant difference in the rate of remission, but most patients treated with an initial ADA dose of 160 mg had a clinical response compared with the placebo group (50% *versus* 35%; p = 0.044)[14] (A).

7.1.3 GOLIMUMAB

The PURSUIT-SC clinical trial evaluated the efficacy of golimumab in the induction period of remission of moderate to severe UC[15] (A).

This was an integrated clinical trial that included a double-blind, Phase 2, dose-finding trial and Phase 3 dose-confirmation trials, which evaluated subcutaneous golimumab therapy in TNF-α antagonist-naïve patients with moderate-to-severe UC despite conventional treatment (Mayo score 6–12 and endoscopic subscore ≥ 2 points). In the dose confirmation study, the rate of clinical response at Week 6 was 51% for patients treated with 200 mg golimumab followed by 100 mg, and 30.3% for patients in the placebo group; this difference was statistically significant (p < 0.0001). Golimumab was also associated with a significantly higher rate of remission than the placebo (17.8% compared with 6.4%; p < 0.0001)[15] (A).

7.1.4 VEDOLIZUMAB

Vedolizumab was found to be effective for the induction of remission in adults with UC in four randomized clinical trials (RCT)[16]. The rate of induction of clinical remission with vedolizumab between 4 and 6 weeks (77%) in 606 adults with UC was superior to that in the placebo group (92%); RR = 0.86 (95% CI 0.8–0.91); NNT = 6–12; I^2 = 0%. Vedolizumab also resulted in a lower rate of failure in the clinical response (48%) within 6 weeks, in an analysis of three RCTs (N = 601 adults), than that observed in the placebo group (72%) RR = 0.68 (95% CI 0.59–0.78); NNT = 4 to 7; I^2 = 0%. The clinical recurrence before 52 weeks was 56.7% in the vedolizumab group, compared with 84.1% in the placebo group ($p < 0.0001$, NNT = 4), in 1 RCT (N = 373 adults). There was no statistically significant difference for adverse events (any or severe) between the groups[16] (A).

Vedolizumab remission induction therapy (300 mg intravenous dose) was compared with placebo in 6 of 374 patients with active UC in Cohort 1 of the GEMINI 1 study[17]. The response rate was 47.1% in the vedolizumab group *versus* 25.5% in the placebo group ($p < 0.001$). Clinical remission occurred in 16.9% of patients in the vedolizumab group and 5.4% of patients in the placebo group ($p = 0.001$). In this cohort, 42.2% of the patients had previously used anti-TNF-α[17] (A).

7.2 REMISSION MAINTENANCE

Recommendations

In remission maintenance, golimumab and IFX showed similar efficacy in clinical remission, sustained clinical remission, and mucosal healing. (B) MODERATE QUALITY EVIDENCE

7.2.1 IFX

In patients who respond to treatment for induction of remission, IFX should be used in remission maintenance. In the ACT 1 trial, clinical response up to Week 54 occurred in 46% of patients who received IFX 5 mg/kg IV compared with 20% in the placebo group ($p < 0.001$). There was a significant improvement in the quality of life with the use of IFX compared with placebo. There was no difference between the proportions of patients that experienced adverse events in the IFX and placebo groups; however, more adverse events occurred among the patients that received IFX in the ACT 1 study than in the ACT 2 trial (87.6% compared with 81.8%). The most common adverse events in ACT 1 and ACT 2 were worsening of UC (IFX 19.0% *versus* placebo 33.1%) and headache (IFX 15.7% *versus* placebo 14.6%), respectively. There were more severe adverse events in the placebo group in both RCTs (ACT 1: IFX 21.5% *versus* placebo 25.6%; ACT 2: IFX 10.7% *versus* placebo 19.5%). Treatment was interrupted in more patients owing to adverse events in the placebo group in both RCTs[3] (A). For long-term analysis, the ACT-1 and ACT-2 *Extension* trials included 229 of 489 patients treated in the ACT-1 and ACT-2 trials and these patients were followed for up to 3 years, with an average follow-up period of 113 weeks. Sixteen patients (7%) had an IFX dose optimized to 10 mg/kg every 8 weeks. Of the 229 patients, IFX was discontinued in 70 (30.6%) patients: 24 (10.5%) due to adverse effects; 11 (4.8%) due to loss of efficacy; 1 (0.4%) required colectomy; and 34 (14.8%) for other reasons, including withdrawal of informed consent, loss to follow-up, and non-adherence of the patient. At Week 104, 67.9% (108 out of 159) of the patients who were still being followed had no signs of disease activity[18] (B).

7.2.2 Adalimumab

The ULTRA 2 study, in which 40% of the patients had been previously treated with anti-TNF-α, revealed a higher rate of clinical remission at Week 52 in patients treated with ADA than in those treated with placebo (17.3% *versus* 8.5%; $p = 0.004$). This difference was also favorable to ADA, for up 1 year, among patients without prior treatment with anti-TNF-α (22% *versus* 12.4%; $p = 0.029$; NNT = 11) and with prior anti-TNF-α therapy (10.2% *vs* 3%; $p = 0.039$; NNT = 14). Of the patients who were in remission at Week 8, 8.5% of patients in the ADA group and 4.1% of patients in the placebo group remained in remission at Week 52 ($p = 0.047$)[12] (A).

The incidence of adverse events was similar with ADA or placebo in the ULTRA 2 trial (82.9% vs. 83.8%). The most frequent adverse event was the worsening or flare-up of UC (ADA 22.6% *versus* placebo 29.2%). Most of the adverse events were of mild to moderate severity. Treatment was interrupted for more patients in the placebo group owing to an adverse event (13.1%) than patients in the ADA group (8.9%)[11,12] (A).

In a study by Suzuki et al., which assessed the use of ADA for induction and maintenance therapy in 273 patients with moderate to severe UC unresponsive to corticosteroids and/or immunosuppressants, without prior use of anti-TNF-α, more patients in maintenance therapy with ADA compared with placebo displayed clinical response (31% *versus* 18%; $p = 0.021$) and remission (23% *versus* 7%; $p = 0.001$) at Week 52. There was no difference in the number of severe adverse events between the groups[14] (A).

In the long-term analysis, an extension of the ULTRA 1 and 2 trials evaluated the efficacy of the use of ADA until the fourth year of follow-up. From Week 52, 600 of 1094 patients included in the ULTRA 1 or 2 trials received ADA 40 mg every 2 weeks or required dose readjustment to 40 mg weekly (141 patients). Intention-to-treat analysis was performed. Of these patients, 199 were still in follow-up at the end of 4 years. The rate of remission based on the partial Mayo score (without endoscopy criteria), the remission by the IBDQ score, the healing of the mucosa, and the discontinuation of corticosteroids on Week 208 was 24.7%, 26.3%, 27.7%, and 59.2%, respectively. Considering that only the population of patients who went on to be accompanied in the period called ULTRA 3 (from Week 52), remission measured by the partial Mayo score was 63.6% and mucosal healing was 59.9% (non-responder imputation)[19] (B).

7.2.3 Golimumab

In the PURSUIT-M trial, which aimed to assess the efficacy of golimumab for remission maintenance, patients who responded to induction therapy in two previous trials (including PURSUIT-SC) were randomized to receive golimumab sc 50 mg, golimumab subcutaneous (sc) 100 mg, or placebo. The clinical response was maintained for 54 weeks in 47.0% of patients in the golimumab 50 mg group, 49.7% in the 100 mg group, and 31.2% in the placebo group ($p = 0.010$ and $p < 0.001$, respectively)[20]. The percentage of patients who were in remission in both Weeks 30 and 54 was higher in the golimumab 100 mg group (27.8%) and in the golimumab 50 mg (23.2%) group than in the placebo group (15.6%; $p = 0.004$ and $p = 0.122$, respectively), although the difference between golimumab 50 mg and placebo was not statistically significant. The number of adverse events was similar in both the 50 mg and 100 mg groups. However, among the patients in the golimumab 50 mg group, 8.4% of patients had one severe adverse event and 5.2% were discontinued from treatment owing to an adverse event, compared with 14.3% and 9.1%, respectively, in the 100 mg group. However, the main cause of interruption of treatment, was clinical worsening of the disease[20] (A).

7.2.4 Vedolizumab

A meta-analysis that included four randomized clinical trials assessed the efficacy of vedolizumab for the induction of remission at Weeks 4 and 6, also evaluated its efficacy at the end of the first year. Clinical recurrence at Week 52 was 56.7% in the vedolizumab group and 84.1% in the placebo group ($p < 0.0001$, NNT = 4) in 1 RCT (N = 373 adults). There was no statistically significant difference for adverse events (any or severe) between the groups[16] (A).

The GEMINI 1 study, mentioned above, also included a Cohort 2, in which 521 patients participated and which evaluated open-label vedolizumab. The patients in Cohort 1 and Cohort 2 who displayed clinical response to vedolizumab in Week 6 (n = 373) were randomized to receive 300 mg vedolizumab (once every 8 weeks *versus* 4 weeks) EV or placebo for up to 52 weeks. Only 56% completed the treatment and all patients were included in the intention-to-treat (ITT) analysis. There was clinical remission at Week 52 in 41.8% with vedolizumab 8/8 weeks ($p < 0.001$ *versus* placebo, NNT = 4); 44.8% with vedolizumab 4/4 weeks ($p < 0.001$ *versus* placebo, NNT = 4) and 15.9% with placebo. Clinical response continued through Week 52 in 56% with vedolizumab 8/8 weeks ($p < 0.001$ *versus* placebo, NNT = 3), 52% with vedolizumab 4/4 weeks ($p < 0.001$ *versus* placebo, NNT = 4), and 23.8% with placebo. Vedolizumab 8/8 or 4/4 weeks was associated with increased mucosal healing ($p < 0.001$ for both comparisons with placebo). There was no significant difference when comparing the two vedolizumab therapy groups with the placebo group[17] (A).

7.3 GOLIMUMAB *VERSUS* IFX *VERSUS* ADALIMUMAB *VERSUS* VEDOLIZUMAB

To counter the lack of direct comparative studies between the various biological agents for the treatment of moderate to severe UC, a meta-analysis to indirectly compare these agents (network meta-analysis). Five RCTs were included that evaluated the efficacy of golimumab (1 RCT), IFX (2 RCTs), and ADA (2 RCTs) in the treatment of moderate to severe active UC in adult patients without prior use of anti-TNF-α therapy. The evaluated outcomes included clinical response, clinical remission, mucosal healing after induction therapy (6–8 weeks), maintenance therapy (1 year), as well as sustained clinical response and remission (induction with maintenance)[21] (B).

No statistically significant differences were found between golimumab and ADA or between golimumab and IFX for induction therapy. The use of IFX was significantly superior to the use of ADA in the induction for all outcomes considered. Golimumab and IFX displayed similar efficacy for the maintenance of remission, in both clinical remission and sustained clinical remission, whereas ADA was not significantly superior to placebo for sustained clinical remission[21].

Golimumab and IFX also displayed similar efficacy to achieve maintenance, clinical response, sustained clinical response, and mucosal healing. At a dose of 50 mg and 100 mg, golimumab was significantly superior to ADA for clinical response and sustained clinical response, and golimumab 100 mg was also superior to ADA for mucosal healing. Therefore, this network meta-analysis (indirect evidence) suggested that IFX was significantly superior to ADA for induction, and that golimumab was significantly superior to ADA for the sustained outcomes. IFX and golimumab were comparable in terms of efficacy[21] (B).

Another network meta-analysis of 7 RCTs with patients presenting the same characteristics as the previous meta-analysis, which included one RCT comparing vedolizumab with placebo, showed that all biological agents (ADA, golimumab, IFX, and vedolizumab) presented greater clinical response, clinical remission, and mucosal healing than placebo for induction therapy. It was also suggested that IFX was more effective than ADA for the induction of clinical response (OR = 2.36; 95% CI 1.22–4.63) and in mucosal healing (OR = 2.02; 95% CI 1.133–3.59). There were no other indirect comparisons with statistical significance[22] (B).

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8. TREATMENT WITH JANUS KINASE (JAK) INHIBITORS

RECOMMENDATIONS

In ulcerative colitis, tofacitinib is superior to placebo in terms of clinical response, clinical remission, and mucosal healing in the induction of remission, regardless of previous exposure to anti-TNF agents. (A) HIGH QUALITY EVIDENCE

For the maintenance of remission in ulcerative colitis, tofacitinib is superior to placebo in terms of clinical remission, and mucosal healing, regardless of previous exposure to anti-TNF agents. (A) HIGH QUALITY EVIDENCE

JAK inhibitors have already been incorporated into the management of immune-mediated diseases such as rheumatoid arthritis (in Brazil, since late 2014).[1] Tofacitinib (TOFA; CP-690,550) is an oral small-molecule drug (SMD) with a molecular weight of 312.3 Da. It inhibits JAK1, JAK3, and, to a lesser extent, JAK2.[2-5] This inhibition ends up blocking signals for several inflammatory cytokines such as interleukin (IL)-2, IL-4, IL-6, IL-7, IL-9, IL-15, IL-21 and interferon-gama, among others.[2-5] These cytokines are involved in the pathogenesis of IBD and play a role in many immune signaling routes including lymphocyte activation, function, and proliferation.[2-6] The drug was approved by ANVISA for the treatment of moderate to severe UC in March 2019.[7]

The initial favorable results of TOFA in a phase II multicenter randomized trial in UC,[8] prompted a phase III program (OCTAVE) investigating the efficacy and safety of induction and maintenance therapy in patients with moderately to severely active UC.[9] In the OCTAVE induction 1 trial (n=476 in the TOFA group; n=122 in the placebo group) remission at 8 weeks (defined as a total Mayo score of ≤2, with no subscore >1 and a rectal bleeding subscore of 0) was 18.5% in the TOFA group (10 mg twice daily, oral) versus 8.2% in the placebo group (P=0.007). In the OCTAVE induction 2 trial, with similar methodology, remission at 8 weeks was observed in 16.6% in the TOFA group versus 3.6% with placebo (P<0.001).[9] An interesting observation was that in both trials the treatment effects were similar between those who had received previous treatment with a TNF antagonist and those who had not.[9] In the OCTAVE sustain trial, two maintenance doses, 10 mg twice daily (n=197) and 5 mg twice daily (n=198) were compared with placebo (n=198) for 52 weeks in patients who completed the OCTAVE 1 or 2 trials and had a clinical response defined as a decrease in the total Mayo score of at least three points, with an accompanying decrease in the rectal bleeding subscore of at least one point or an absolute rectal bleeding subscore of 0 or 1. Remission at 52 weeks was 34.3% and 40.6% in the 5 mg and 10 mg TOFA groups, respectively, compared with 11.1% in the placebo group (P<0.001for both comparisons with placebo).[9] In the OCTAVE induction 1 and 2 trials, the key secondary endpoint of mucosal healing, defined as a Mayo endoscopic subscore ≤1, at 8 weeks, occurred in significantly more patients in the TOFA group (10 mg) than in the placebo group (OCTAVE 1: 31.3% TOFA x 15.6% placebo; P<0.001; OCTAVE 2: 28.4% TOFA x 11.6% placebo; P<0.001).[9] Again, previous treatment with a TNF antagonist seemed not to influence the results. In the OCTAVE sustain trial, mucosal healing at 52 weeks was 37.4% and 45.7% in the 5 mg and 10 mg TOFA groups, respectively, versus 13.1% in the placebo group (P<0.001 for both comparisons).[9] These findings emphasize that patients with previous exposure to biological agents, mainly anti-TNFs, can still have TOFA as an important option, since both remission and mucosal healing can be observed in 30%-45% of patients.[9]

A numerically higher rate of herpes zoster infection (usually less than 1.5%) was observed in the TOFA groups in the maintenance trial, mainly with the higher dose (10 mg twice daily). No case of herpes zoster infection was considered serious or resulted in discontinuation of the drug.[9] Thus, herpes zoster vaccination may be considered before treatment with TOFA. Across the three trials,[8,9] lipid levels (i.e., cholesterol levels, LDL and HDL) increased with TOFA (usually in less than 30% of patients) and the increased plateaued after approximately 4 weeks.[9] Among patients with rheumatoid arthritis or psoriasis, TOFA has also been associated with an increase in lipid levels without an enhanced risk of cardiovascular events.[5,9] Also, more cases of non-melanoma skin cancer occurred with TOFA (5 cases) than with placebo (1 case) across the OCTAVE trials.[9] All of them had previous exposure to thiopurines. No cases of tuberculosis were reported in the three trials.[8,9] Data from the ongoing open-label extension trial (OCTAVE open) of TOFA in UC may further elucidate the long-term safety profile of this drug.[9]

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9.TREATMENT WITH PROBIOTICS

RECOMMENDATIONS

The probiotic VSL#3 increases the response rates and clinical remission of active RUC. (B) MODERATE QUALITY EVIDENCE
Some probiotics, especially *Escherichia coli* Nissle 1917, can be as effective as 5-ASA derivatives for the maintenance of clinical remission in patients with RUC in remission. (B) MODERATE QUALITY EVIDENCE
The probiotic VSL#3 is effective for maintaining remission in chronic pouchitis and preventing pouchitis after ileal pouch–anal anastomosis for RCU. (B) MODERATE QUALITY EVIDENCE

INTRODUCTION

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" according to the Food and Agriculture Organization[1].

The use of probiotics has long been proposed with the aim of providing benefits to human health, but in recent years, there has been a growing interest in its use in inflammatory bowel disease (IBD) due to the role of microbiomes in the pathogenesis of this disease[2]. Because refractory ulcerative colitis (RUC) is associated with intestinal microbiota antigens and dysbiosis, the use of probiotics has been suggested to modulate the existing microbiota.

Several studies have evaluated the use of probiotic agents as adjuvant therapy in the treatment of RUC and Crohn's disease (CD). The different treatment approaches for these conditions can be divided into treatment during the acute phase (induction therapy) and treatment for the long-term control of symptoms (maintenance therapy).

9.1 INDUCTION OF REMISSION

A systematic review of 23 randomized controlled trials (RCTs) evaluated the effects of probiotics on the induction and maintenance of remission in RUC, CD, and pouchitis (N = 1,763 patients with IBD)[3]. In the subgroup analysis, 9 RCTs (n = 649 patients with RUC) evaluated the effects of probiotic supplementation *versus* placebo *versus* conventional treatment (e.g., sulfasalazine, 5-aminosalicylic acid (5-ASA) derivatives, corticosteroids, immunosuppressants) with or without placebo. Overall, there was a statistically significant benefit with probiotic supplementation for inducing a response or clinical remission in active RUC (relative risk [RR] = 1.51; 95% confidence interval [CI], 1.10–2.06, number needed to treat [NNT], 3–25), but with significant heterogeneity (I^2 = 65%, p = 0.004). In the sensitivity analysis, which sought to reduce heterogeneity, 2 studies in which the controls received 5-ASA derivatives instead of placebo were excluded. In this case, an analysis of the remaining 7 studies (n = 443 patients with RUC) showed that probiotics were generally superior to placebo for inducing a response or clinical remission in active RUC (RR = 1.80; 95% CI, 1.36–2.39) with satisfactory heterogeneity (I^2 = 4%, p = 0.39)[3] (A).

Another systematic review, with 7 RCTs compared the clinical remission rate treatment with probiotics *versus* non-probiotics in 399 patients with RUC. The authors showed a higher remission rate with probiotics compared to placebo (odds ratio [OR], 2; 95% CI, 1.35–2.96). Two RCTs evaluated the use of VSL#3 (described below) and suggested that it is beneficial. Comparing the use of probiotics with an active control, usually 5-ASA derivatives, the clinical remission rate did not differ significantly (OR, 1; 95% CI, 0.85–1.18)[4] (A).

A systematic review of 4 RCTs compared the use of probiotics *versus* conventional therapy for inducing remission in patients with active RUC and showed no significant intergroup differences in remission rate or clinical improvement (2 studies compared probiotics with placebo, 1 compared probiotics with mesalazine, and 1 compared probiotics with the 5-ASA derivative balsalazide)[5] (A).

Studies support the beneficial use of VSL#3 for inducing remission or clinical response in adult patients with mild to moderate RUC. A comparative study was conducted in 147 adult patients with moderate RCU using VSL#3 *versus* placebo twice daily orally for 12 weeks. In the intention-to-treat (ITT) analysis, in which 57% of the patients completed the study, a higher improvement rate (>50%) was observed in the ulcerative colitis disease activity index (UCDAI) at week 6 in the VSL#3 group compared with the placebo group (32.5% in the VSL#3 group *versus* 10% in the placebo group [p = 0.001, NNT = 5). The clinical remission rates in the probiotic and placebo groups at up to 12 weeks of observation were 42.9% and 15.7%, respectively (p < 0.001, NNT = 4)[6] (B).

The association between VSL#3 with the oral 5-ASA derivative and/or immunosuppressants (azathioprine or 6-mercaptopurine) may reduce disease activity indices in patients with mild to moderate RUC with frequent relapses. Comparing the use of VSL#3 *versus* placebo for up to 8 weeks of observation, a decrease of 50% or more in the UCDAI was observed in 63.1% of the patients in the probiotic group and 40.8% in the placebo group (per protocol [PP], p = 0.01; ITT, p = 0.031, NNT = 5), with a reduction greater than or equal to 3 points in the UCDAI of 60% *versus* 43.9%, respectively (PP, p = 0.017; ITT, p = 0.046; NNT = 7). Reduced rectal bleeding (PP, p = 0.014; ITT, p = 0.036) was also observed. However, no intergroup difference in the clinical remission rate (UCDAI ≤ 2 points [scale, 0–12]) (47.7 vs 32.4%, p = 0.07) or endoscopic scores (PP, p = 0.086; ITT, p = 0.366) was noted[7] (B).

9.2 MAINTENANCE OF REMISSION

Three studies compared the use of probiotics and mesalazine and found no differences in relapse rates (analysis of 3 RCTs of 555 patients: OR, 1.33; 95% CI, 0.94–1.90) and

adverse events (analysis of 2 RCTs of 430 patients). An RCT of 32 patients compared probiotics with placebo and found no differences in the relapse rates up to 1 year (75% vs. 92%; OR, 0.27; 95% CI, 0.03–2.68) but similar numbers of adverse events in the two groups[8] (A).

A systematic review of 23 RCTs (N = 1,763 patients with IBD) showed that probiotics may have a similar effect to 5-ASA derivatives without additional adverse events[3] (A). An analysis of 5 RCTs (N = 729) showed no advantages in maintenance treatment with probiotics compared to control (probiotics *versus* 5-ASA, probiotics plus 5-ASA *versus* 5-ASA only, or probiotics plus 5-ASA *versus* placebo plus 5-ASA [RR = 0.89; 95% CI, 0.66–1.21; I^2 = 35%]). However, an analysis of 3 RCTs (N = 505 patients with RUC in remission) compared probiotics and 5-ASA derivatives and showed that the efficacy of probiotics was comparable to that of the 5-ASA derivative in the maintenance therapy in patients with RUC in remission (RR = 0.96; 95% CI, 0.76–1.19; I^2 = 0%), especially with the probiotic *Escherichia coli* Nissle 1917[3]. Treatment with probiotics associated with a 5-ASA derivative showed no advantages over the placebo associated with a 5-ASA derivative in patients with RUC in remission, but the high heterogeneity of the studies should be noted (RR = 0.67; 95% CI, 0.33–1.38; I^2 = 78%). In the sensitivity analysis, there was no significant difference in the maintenance of remission with *Escherichia coli* Nissle 1917 (3 RCTs that compared probiotic *versus* 5-ASA or probiotic plus 5-ASA *versus* placebo plus 5-ASA; N = 513) or with *Lactobacillus* (1 RCT that compared probiotic *versus* 5-ASA alone or *versus* 5-ASA plus probiotic; N = 187). However, VSL#3 was associated with a significant increase in the maintenance of remission in one study (1 RCT that compared probiotic plus 5-ASA *versus* placebo plus 5-ASA) of 29 pediatric patients with RUC in remission (RR = 0; 95% CI, 0.10–0.83). An analysis of 6 RCTs showed no differences in the number of adverse events between the probiotics and control groups (5-ASA derivatives, placebo; RR = 0.99; 95% CI, 0.67–1.44, I^2 = 43%)[3] (A).

9.3 POUCHITIS

Total proctocolectomy with an ileal pouch–anal anastomosis may be necessary in some patients with RUC due to drug treatment failure or the secondary development of dysplasia or cancer. Pouchitis is a non-specific idiopathic inflammation of the ileal reservoir that occurs in 30–50% of patients with RUC who have an ileal pouch[9] (B).

In a systematic review, 11 RCTs evaluated interventions for the treatment or prevention of pouchitis in adult patients with RUC after ileal pouch–anal anastomosis and 5 RCTs evaluated probiotics. Regarding the induction of remission in acute pouchitis, there was no statistically significant difference between *Lactobacillus* GG and placebo in a study of 20 patients[9] (B). In the maintenance of remission in cases of chronic pouchitis, VSL#3 was effective in an analysis of 2 RCTs of 76 patients (OR, 25; 95% CI, 10–62; NNT = 2 to prevent 1 relapse)[9] (B). For the prevention of pouchitis, VSL#3 was effective compared to placebo in a study of 40 patients (20% vs. 40%, p = 0.03, NNT = 5) and showed no differences in 1 open-label study of 28 patients (0% vs. 8.3%, p = 0.25)[9] (B). Thus, VSL#3 is effective for maintaining remission in chronic pouchitis and preventing pouchitis after ileal pouch–anal anastomosis for RUC[3,10] (B).

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10.SURGICAL TREATMENT

10.1. EMERGENCY SURGERY

Recommendations

One should consider emergency surgery for patients with worsening severe UC despite clinical treatment or in whom no significant improvement is seen after 48–96 hours of appropriate medical treatment. (C) LOW QUALITY EVIDENCE
In cases of toxic megacolon, surgery is indicated if the patient does not improve in 48–72 hours. (C) LOW QUALITY EVIDENCE
The surgical decision should not be postponed (>5 days of intensive therapy), as doing so may increase morbidity and mortality rates. (C) LOW QUALITY EVIDENCE
In emergent cases, subtotal colectomy with terminal ileostomy should be considered the first step in the surgical treatment of severe UC. (C) LOW QUALITY EVIDENCE

One should consider emergency surgery for patients with worsening severe ulcerative colitis (UC) despite clinical treatment or in whom no significant improvement is noted after 48–96 hours of appropriate medical treatment[1] (D). In cases of toxic megacolon, surgery is indicated if the patient does not improve in 48–72 hours[2,3] (D). Other indications for surgery include perforation and massive colorectal hemorrhage[4] (D). Postponing the surgical decision may increase morbidity and mortality rates[1] (D)[5] (C).

Among patients undergoing emergency surgery due to clinical treatment failure, higher mortality rates are observed in those in which the intervention was postponed for more than 5 days after non-response to therapy with intravenous (IV) corticosteroids compared to those in whom surgery was performed within 5 days ($p = 0.03$)[5] (C). Another study showed a higher number of severe complications when surgery was postponed for more than 8 days after IV corticosteroid failure (29% with corticosteroid plus cyclosporine) at any point in a mean follow-up of 5.4 years[6] (B).

In emergent situations, subtotal colectomy with an terminal ileostomy should be considered the first step in the surgical treatment of severe UC, allowing the patient to recover their general health, normalize nutrition, and provide time to consider total proctocolectomy with ileo–anal anastomosis and an ileal pouch or, perhaps, permanent ileostomy[7] (B). There is evidence of the safety of minimally invasive surgery or laparoscopy in emergency subtotal colectomy in patients with severe UC[8,9] (C). Reconstructive surgery is best performed 6 months after primary surgery[10] (D).

The use of immunosuppressive agents (azathioprine and 6-mercaptopurine) are not associated with increased complications after colectomy[11,12] (B). Several studies have shown that the use of cyclosporine does not increase the rate of postoperative complications in patients undergoing proctocolectomy[13,14] (C); in contrast, the use of corticosteroids in patients with inflammatory bowel disease substantially increases the risk of postoperative infections[15] (A).

Uncertainty persists regarding the risk of postoperative complications in patients with UC who received infliximab preoperatively. A meta-analysis of 13 observational studies found no association between the use versus non-use of infliximab preoperatively and the total number of early postoperative complications (odds ratio [OR], 1.09; 95% confidence interval [CI], 0.87–1.37; $I^2 = 28\%$) or infectious complications (OR, 1.10; 95% CI, 0.51–2.38; $I^2 = 67\%$) and non-infectious complications (OR, 1.10; 95% CI, 0.76–1.59; $I^2 = 31\%$). However, these results should be interpreted with caution due to several limitations such as significant heterogeneity when combining studies in the analysis of infectious complications[16] (B).

The mortality rate is higher in cases of emergency colectomy than in those of elective surgery[17] (C).

10.2 ELECTIVE SURGERY

Recommendations

The indications for elective surgery in UC include: intractability; documented carcinoma, high-grade dysplasia, a dysplasia-associated lesion or mass, adenoma-like lesions with dysplasia in the surrounding flat mucosa; stenosis; slow growth; physical disability; psychosocial dysfunction; or intolerable adverse medication effects. (C) LOW QUALITY EVIDENCE
Controversy persists regarding the approach to be used after a diagnosis of low-grade dysplasia in the flat mucosa. (C) LOW QUALITY EVIDENCE
Proctocolectomy with ileostomy may be considered the first-line procedure for patients at significant risk of pouch failure, such as those with an anal sphincter muscle deficiency, prior anoperineal disease, or limited physiological reserves secondary to comorbidities. (A) HIGH QUALITY EVIDENCE
Total proctocolectomy with ileo-anal pouch formation is the elective surgery more commonly used in patients with UC; it can be performed via an open or minimally invasive approach. (A) HIGH QUALITY EVIDENCE
Protective ileostomy in restorative proctocolectomy reduces the risk of anastomotic fistula. (A) HIGH QUALITY EVIDENCE
Postoperative complications in restorative proctocolectomy include anastomotic fistula, pelvic sepsis and/or abscess, anastomotic stenosis, and intestinal obstruction. (A) HIGH QUALITY EVIDENCE
Long-term morbidities of IPAA include infertility, sexual dysfunction, and pouchitis. (A) HIGH QUALITY EVIDENCE

The indications for elective surgery in UC include: intractability; documented carcinoma, high-grade dysplasia, presence of non-adenoma–type lesion or mass dysplasia, adenoma-like

lesion with dysplasia in the surrounding flat mucosa; stenosis; slow growth; physical disability, psychosocial dysfunction; and intolerable adverse effects of medication[1,3] (D).

Controversy persists regarding the approach that should be adopted after a diagnosis of low-grade dysplasia in the flat mucosa is made. Some studies demonstrated that the progression rate of low-grade dysplasia to high-grade dysplasia or carcinoma is approximately 55%; however, other studies reported lower rates of progression[18-21](B).

Rarely, surgery is required to control extraintestinal manifestations[22,23](D). Some of the manifestations that respond best to surgery include episcleritis, erythema nodosum, aphthous ulcerations, and arthropathy of the large joints. The manifestations less likely to respond to surgery include those that are hepatic, vascular, hematological, cardiopulmonary, or neurological[1,3] (D).

Whatever the indication for surgery, patients should be informed about the different options available. Proctocolectomy with permanent ileostomy can still be regarded a first-line procedure for patients who choose not to undergo restorative proctocolectomy[24] (D) or those at significant risk of pouch failure due to comorbidities such as anal sphincter muscle deficiency, anterior anoperineal disease, or limited physiological reserves secondary to comorbidities[25] (B). The most common complications of this surgery regardless of minimally invasive or open technique are stomal stenosis or prolapse[26] (C), intestinal obstruction, infection/fistula, persistent pain, delayed perineal wound healing, sexual or urinary dysfunction, and infertility[27,28] (C).

Total proctocolectomy with ileo pouch–anal anastomosis (IPAA) is the elective surgery more commonly used in patients with UC; this can be performed via an open or minimally invasive procedure[29] (A) in one, two, or three procedures according to the patient's clinical condition.

A study (N = 1,500) that compared restorative proctocolectomy with and without protection ileostomy reported similar functional outcomes between the two procedures but a higher risk of anastomotic fistula in the group without the proximal transit diversion (without ileostomy; OR, 2.37; p = 0.002). Reoperation was required in 30% of patients who underwent IPAA due to postoperative complications, fistula, pelvic sepsis and/or abscess, stenosis of the anastomosis, and intestinal obstruction[30] (A).

Patients who undergo IPAA may also present long-term morbidities such as an increased risk of infertility[31] (A), sexual dysfunction induced by pelvic innervation lesions[32] (A), and pouchitis, which can occur in up to 50% of patients in the long term[33] (D).

Ileorectal anastomosis (IRA) is a simpler option for transit reconstruction after subtotal colectomy[34-37] (C). However, one must consider this option only in special situations[34] (C). IRA may be indicated in young women desiring future pregnancy, patients with a short disease history, those with a poor sphincter apparatus, and those with indeterminate or Crohn's colitis. However, for IRA to be indicated, the remaining rectum must have good complacency and the inflammation must be easily controlled by topical 5-ASA[34] (C). Despite a lower risk of postoperative complications, a patient undergoing IRA should be evaluated periodically with rectoscopy since the surgery is more closely associated with cancer of the remaining rectum[36] (C).

Given the difficulty associated with dissecting the last centimeters of the rectum and the need to use several surgical stapling firings to close the rectal stump before anastomosis with the ileal pouch, some English authors described a technique used in rectal cancer surgery adapted for UC surgery: transanal total mesorectal excision[38] (D). There are several advantages of the technique compared to conventional abdominal proctocolectomy: technical ease in the narrow male pelvis; ease in obese patients; and no need for double stapling for the anastomosis, a fact that is related to an increased risk of anastomotic fistula and pelvic sepsis and consequent pouch loss[39] (D). The technique evolved in the last year with the adaptation of the transanal minimally invasive surgery (TAMIS) for the procedure[40] (D). Surgeons from the University of Leuven in Belgium recently described the benefit of proctocolectomy with rectal resection using TAMIS, with preservation of the mesorectum and primary anastomosis and no need for protective ileostomy[40] (D). Therefore, proctocolectomy can also be performed via perineal with advantages in some special clinical situations[38-40](D).

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REMICADE®/Bio-Manguinhos Infliximabe **(infliximabe). Observação importante: Consulte a bula completa antes de prescrever o medicamento.FORMA FARMACÊUTICA E APRESENTAÇÕES:** Pó liofilizado para solução concentrada para infusão em embalagem com 1 frasco-Ampola contendo 100 mg de infliximabe. Uso único. **USO INTRAVENOSO. USO ADULTO E PEDIÁTRICO ACIMA DE 6 ANOS. INDICAÇÕES:** Artrite Reumatoide (AR), Espondilite Anquilosante (EA), Artrite Psoriásica (AP), Psoríase em placa, Doença de Crohn (DC) adulto e pediátrico, Doença de Crohn (DC) Fistulizante, Colite ou Retocolite ulcerativa adulto e pediátrico. **CONTRAINDICAÇÕES:** Hipersensibilidade aos componentes do produto ou a proteínas murinas; infecções graves (tuberculose (Tb), sepse, abscessos e infecções oportunistas); insuficiência cardíaca (IC) moderada/grave. **ADVERTÊNCIAS E PRECAUÇÕES:** *Infecções:* Recomenda-se cautela ao considerar o uso de REMICADE®/Bio-Manguinhos Infliximabe em pacientes com infecção crônica ou com histórico de infecção recorrente. *Tuberculose:* Avaliar pacientes quanto aos fatores de risco para Tb, incluindo contato próximo com uma pessoa com Tb ativa e testados para a presença de Tb latente antes de iniciar o tratamento com REMICADE®/Bio-Manguinhos Infliximabe. O tratamento da Tb ativa ou latente deverá ser iniciado antes do tratamento com REMICADE®/Bio-Manguinhos Infliximabe. Deve-se considerar tratamento em pacientes com fatores de riscos significativos para Tb que tenham teste negativo para Tb latente. Pacientes em tratamento devem ser cuidadosamente monitorados para sinais e sintomas de Tb ativa durante e após o tratamento, incluindo pacientes com resultado negativo para Tb latente. Interromper REMICADE®/Bio -Manguinhos Infliximabe se o paciente desenvolver infecção séria ou sepse. *Reações à infusão:* Reações de hipersensibilidade (tipo 1) podem ocorrer durante ou dentro de 2 horas após a infusão. Medicamentos para tratamento de reações de hipersensibilidade devem estar disponíveis. Reduzir a velocidade da infusão também pode diminuir reações à infusão. O tratamento profilático prévio para as reações à infusão pode reduzir a ocorrência de reações subsequentes. *Reações à infusão após readministração de REMICADE®/Bio-Manguinhos Infliximabe:* Considerar risco-benefício da readministração de REMICADE®/Bio-Manguinhos Infliximabe após longo período sem tratamento (2 a 4 anos), acompanhando sinais e sintomas de hipersensibilidade tardia. *Administração concomitante de inibidor de TNF-α e anacinra, abatacepte ou outros biológicos* não é recomendada. *Substituição entre drogas modificadoras da doença (DMARDs) biológicas:* Ao substituir uma DMARD biológica por outra, monitorar sinais de infecção. *Reações hematológicas:* Cautela em pacientes tratados com REMICADE®/Bio-Manguinhos Infliximabe que apresentam ou apresentaram previamente citopenias significativas. *Vacinações:* recomenda-se atualizar todas as vacinas antes de iniciar REMICADE®/Bio-Manguinhos Infliximabe. *Vacinas de vírus vivos/Agentes terapêuticos infecciosos:* não é recomendado o uso concomitante com REMICADE®/Bio-Manguinhos Infliximabe. *Processo autoimune:* Se o paciente desenvolver sintomas sugestivos de síndrome semelhante ao lúpus com REMICADE®/Bio-Manguinhos Infliximabe deve-se descontinuar o tratamento. *Eventos neurológicos:* REMICADE®/Bio-Manguinhos Infliximabe e outros inibidores de TNF-alfa têm sido associados a um maior risco de ocorrência de distúrbios neurológicos. Cuidado ao considerar o uso de REMICADE®/Bio-Manguinhos Infliximabe e avaliar sua descontinuação em pacientes que apresentem ou desenvolvam esses distúrbios. *Malignidades:* Durante os estudos clínicos e no início da comercialização de REMICADE®/Bio-Manguinhos Infliximabe houve relatos de malignidades como linfomas, leucemia, cânceres de pele, de colo do útero e outras malignidades que não linfomas. O potencial papel da terapia com bloqueador de TNF-alfa no desenvolvimento de malignidades não é conhecido. Deve-se ter precaução adicional ao considerar a terapia em pacientes com histórico de malignidade ou ao continuar o tratamento em pacientes que desenvolveram malignidade. *Insuficiência cardíaca:* usar REMICADE®/Bio-Manguinhos Infliximabe com extrema cautela e somente após considerar outras opções de tratamento. *Eventos hepatobiliares:* avaliar pacientes com sinais ou sintomas de disfunção hepática para evidência de dano hepático. Se houver desenvolvimento de icterícia e/ou aumento da ALT(alanina aminotransferase) ≥ 5 vezes o limite superior dos valores normais, descontinuar REMICADE®/Bio -Manguinhos Infliximabe e realizar investigação completa da anormalidade. Avaliar e monitorar portadores crônicos da hepatite B antes, durante e após descontinuação do tratamento. **POPULAÇÕES ESPECIAIS:** *Idosos:* recomenda-se cautela ao se tratar pacientes idosos devido a maior incidência de infecções nessa população em geral. *Pacientes pediátricos:* REMICADE®/Bio-Manguinhos Infliximabe não foi estudado em crianças com DC, colite ou retocolite com menos de 6 anos de idade. Segurança e eficácia em AR juvenil não foram estabelecidas. *Gravidez (Categoria B) e lactação:* Não se sabe se REMICADE®/Bio-Manguinhos Infliximabe causa dano fetal quando administrado em gestantes ou se afeta a capacidade reprodutiva. Administrar em gestantes somente se realmente necessário. Crianças expostas in utero ao infliximabe podem apresentar risco de infecções aumentado, inclusive generalizada, que pode ser fatal. Não se sabe se REMICADE®/Bio-Manguinhos Infliximabe é excretado no leite humano ou absorvido sistemicamente após ingestão. **INTERAÇÕES MEDICAMENTOSAS:** Não é recomendada a administração concomitante de REMICADE®/Bio-Manguinhos Infliximabe com agentes terapêuticos infecciosos ou biológicos utilizado para tratar as mesmas condições que REMICADE®/Bio-Manguinhos Infliximabe, incluindo anacinra e abatacepte. **REAÇÕES ADVERSAS:** *Essenciais:* reações anafiláticas, distúrbios desmielinizantes do Sistema Nervoso Central (esclerose múltipla, neurite óptica), acidentes vasculares cerebrais, isquemia/infarto do miocárdio (alguns fatais) e arritmia (até 24 horas após a infusão), perda visual transitória (durante ou dentro de 2 horas após a infusão): reações no local da injeção, vasculite (principalmente cutânea), linfoma de célula T hepatoesplênica (a grande maioria em DC e colite ulcerativa, principalmente em adolescentes e adultos jovens), linfoma, malignidades pediátricas, leucemia, melanoma, carcinoma de células de Merkel, câncer de colo de útero, mialgia, artralgia; dermatose bolhosa IgA linear; pustulose exantemática generalizada aguda (PELA). *Comuns:* erupção cutânea, prurido, urticária, sudorese aumentada, pele seca, dermatite fúngica, onicomicose, eczema, seborreia, alopecia, cefaleia, vertigem, tontura, náusea, diarreia, dor abdominal, dispepsia, estenose intestinal, vômito, constipação, infecção do trato respiratório superior e inferior, dispneia, sinusite, pleurisia, edema pulmonar, fadiga, dor no tórax, edema, ondas de calor, dor, calafrios/rigidez, infecção viral, febre, abscesso, celulite, moniliase, reação tipo sarcoide, rubor, tromboflebite, equimose, hematoma, hipertensão, hipotensão, anemia, leucopenia, linfadenopatia, neutropenia, trombocitopenia, insônia/sonolência, aumento de transaminases, função hepática anormal, ITU, conjuntivite, palpitação, bradicardia, autoanticorpos. **POSOLOGIA:** Uso IV em adultos (≥18 anos) para todas as indicações de bula e em crianças e adolescentes (entre 6 e 17 anos) somente para DC e colite ou retocolite ulcerativa. *AR**:3 mg/kg nas semanas 0, 2 e 6. Manutenção a cada 8 semanas. *EA:* 5 mg/kg, nas semanas 0, 2 e 6. Manutenção a cada 6 a 8 semanas. *AP e Psoríase em placas:* 5 mg/kg nas semanas 0, 2 e 6. Manutenção a cada 8 semanas. *DC adulto e pediátrico***DC fistulizante, Colite ou Retocolite Ulcerativa em adultos e pacientes pediátricos:* 5 mg/kg nas semanas 0, 2 e 6. Manutenção a cada 8 semanas. *AR usar sempre em combinação com metotrexato (MTX). ***DC pedriátrica:* deve ser administrado concomitantemente com imunomoduladores, incluindo 6-mercaptopurina (6-MP), azatioprina (AZA) ou MTX. **Ajuste de dose:** Para AR considerar ajuste de dose até 10 mg/kg ou administração de 3 mg/kg a cada 4 semanas. Para DC moderada a grave adulto e pediátrico, considerar ajuste de dose de até 10 mg/kg. Para Colite ou Retocolite Ulcerativa em pacientes adultos, considerar ajuste de dose de até 10 mg/kg. Para maiores informações sobre ajuste, otimização de dose e readministração: consultar bula completa. **SUPERDOSE:** Em caso de superdose, acompanhar os pacientes para sinais e sintomas de reações ou eventos adversos e instituir tratamento sintomático apropriado imediatamente. Em caso de intoxicação, ligue para 0800 722 6001. **ARMAZENAMENTO:** Conservar sob refrigeração (entre 2 e 8°C). Se a reconstituição e a diluição forem realizadas em condições assépticas, a solução de infusão de REMICADE®/Bio-Manguinhos Infliximabe poderá ser utilizada dentro de 24 horas se armazenada entre 2 e 8° C. Não congelar. **USO RESTRITO A HOSPITAIS. VENDA SOB PRESCRIÇÃO MÉDICA.** Uso restrito a hospitais. REMICADE®. **JANSSEN-CILAG FARMACÊUTICA LTDA. MS 1.1236.3403.** Informações adicionais para prescrição: vide bula completa. SAC 0800 701 1851 – www.janssen.com.br – **Cód. CCDS 1812 VPS13.** Bio-Manguinhos Infliximabe - **Fundação Oswaldo Cruz. Instituto de Tecnologia em Imunobiológicos -Bio-Manguinhos. MS1.1063.0142.** SAC 0800 021 0310. Versão 07. Versão correspondente a VPS13. **Os medicamentos REMICADE® e Bio-Manguinhos infliximabe são parte de uma Parceria para o Desenvolvimento Produtivo (PDP), desta forma as informações de segurança e eficácia dos produtos são as mesmas. O infliximabe sendo produzido pela PDP utiliza a mesma tecnologia e o mesmo processo produtivo do Remicade inovador, tendo inclusive a mesma célula mãe.**

Contraindicação: Não use REMICADE®/Bio-Manguinhos Infliximabe caso tenha uma infecção grave, incluindo tuberculose.

Interação Medicamentosa: A combinação de infliximabe e anacinra não é recomendada.

Os medicamentos REMICADE® e Bio-manguinhos infliximabe são parte de uma Parceria para o Desenvolvimento Produtivo (PDP), desta forma as informações de segurança e eficácia dos produtos são as mesmas. O infliximabe sendo produzido pela PDP utiliza a mesma tecnologia e o mesmo processo produtivo do Remicade® inovador, tendo inclusive a mesma célula mãe.

Referências: 1. Chebli JM, Gaburri PD, Chebli LA, da Rocha Ribeiro TC, Pinto AL, Ambrogini Júnior O, et al. A guide to prepare patients with infl ammatory bowel diseases for anti- TNF-α therapy. Med Sci Monit. 2014 Mar;26(20):487-98. **2.** Bula de Remicade 2017. **3.** Rutgeerts P, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 8;353(23):2462-76. PubMed PMID: 16339095. **4.** Singh S, et. al. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. Aliment Pharmacol Ther. 2018 Jan;47(2):162-175. PubMed PMID: 29205406. **5.** US. FOOD & DRUG ADMINISTRATION. Drugs@FDA: FDA Approved Drug Products, de US.FOOD & DRUG ADMINISTRATIONS Site: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=10377212.

REMICADE® e BIO-MANGUINHOS INFLIXIMABE: o mesmo produto, uma nova embalagem.

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Material educacional exclusivo para o profissional de saúde responsável técnico das clínicas de infusão cadastradas no Programa de Pacientes da Janssen. Impresso em agosto/2019. Cód. CP-104862

INFOC Informações Científicas – infoc@janbr.jnj.com

XELJANZ® É O PRIMEIRO MEDICAMENTO ORAL INIBIDOR DA JAK APROVADO NO BRASIL PARA O TRATAMENTO DA COLITE ULCERATIVA[1,2]

XELJANZ® é uma pequena molécula da classe dos inibidores de JAK que age dentro das células[4]

XELJANZ® inibe as vias de sinalização mediadas por JAK que regulam a produção de várias citocinas pró-inflamatórias envolvidas na patogênese da RCU[4]

Como uma molécula pequena, não se espera que o XELJANZ® seja imunogênico[5]

POSOLOGIA[5]

Todos os pacientes	Manhã	Noite
Indução (8 semanas)	10mg	10mg
Manutenção	5mg	5mg

Armazene em temperatura ambiente (entre 15 e 30°C)[5]

Administrado por via oral, com ou sem alimento[5]

DOSE ORAL[5]

- Sem injeções[5].
- Sem infusões[5].
- Sem jejum[5].

Referências bibliográficas: **1.** Diário Oficial da União - Nº 52, segunda-feira, 18 de março de 2019. **2.** Sandborn, W. J., Su, C., Sands, B. E., D'Haens, G. R., Vermeire, S., Schreiber, S., ... & Friedman, G. (2017). Tofacitinib as induction and maintenance therapy for ulcerative colitis. New England Journal of Medicine, 376(18), 1723-1736. **3.** Hanauer, S., Panaccione, R., Danese, S., Cheifetz, A., Reinisch, W., Higgins, P. D., ... & Quirk, D. (2019). Tofacitinib induction therapy reduces symptoms within 3 days for patients with ulcerative colitis. Clinical Gastroenterology and Hepatology, 17(1), 139-147. **4.** Danese, S., Grisham, M., Hodge, J., & Telliez, J. B. (2015). JAK inhibition using tofacitinib for inflammatory bowel disease treatment: a hub for multiple inflammatory cytokines. American Journal of Physiology-Gastrointestinal and Liver Physiology, 310(3), G155-G162. **5.** Bula do medicamento. https://www.pfizer.com.br/sites/g/files/g10044511/f/product_attachments/Xeljanz_PS.pdf. Acessado em 02/10/2018.

INTERAÇÃO MEDICAMENTOSA: NÃO UTILIZAR O PRODUTO EM COMBINAÇÃO COM MEDICAMENTOS BIOLÓGICOS E IMUNOSSUPRESSORES POTENTES COMO AZATIOPRINA OU CICLOSPORINA. CONTRAINDICAÇÃO: HIPERSENSIBILIDADE AO XELJANZ® OU A QUALQUER COMPONENTE DE SUA FORMULAÇÃO.

XELJANZ® (citrato de tofacitinibe). Indicações: Pacientes adultos com artrite reumatoide ativa moderada a grave que apresentaram uma resposta inadequada a um ou mais DMARDs; para o tratamento de pacientes adultos com artrite psoriásica ativa que apresentaram uma resposta inadequada ou intolerância ao metotrexato ou a outros medicamentos modificadores do curso da doença (DMARDs); e para pacientes adultos com colite ulcerativa ativa moderada a grave com uma resposta inadequada, perda de resposta ou intolerância a corticosteroides, azatioprina (AZA), 6 mercaptopurina (6-MP) ou antagonistas do fator de necrose tumoral (TNF). Contraindicações: Hipersensibilidade ao XELJANZ® ou a qualquer componente da formulação. Advertências e Precauções: Não iniciar XELJANZ® em pacientes com uma infecção ativa, incluindo infecções localizadas. Considerar terapia antituberculose antes da administração de XELJANZ® em pacientes com uma história de tuberculose latente ou ativa, e para pacientes com um teste negativo para tuberculose latente, mas que possuem fatores de risco para uma infecção por tuberculose. Monitorar o desenvolvimento de sinais e sintomas de infecção, incluindo tuberculose, durante e após o início do tratamento com XELJANZ®. Interromper o tratamento se o paciente desenvolver infecção grave, infecção oportunista ou sepse. Cautela ao tratar idosos e diabéticos devido à maior incidência de infecções. O risco de herpes zoster parece ser maior em pacientes japoneses e coreanos tratados com XELJANZ®. Cautela nos pacientes com maior risco de perfuração gastrintestinal. Não é recomendado iniciar o tratamento com XELJANZ® em pacientes com contagem baixa de linfócitos (ou seja, menos de 500 células/mm3) devido a uma maior incidência de infecções. Não é recomendado iniciar o tratamento com XELJANZ® em pacientes com CAN menor do que 1000 células/mm3. Se CAN persistente de 500-1000 células/mm3, interromper a administração até que CAN seja maior do que 1000 células/mm3. Não é recomendado iniciar o tratamento com XELJANZ® em pacientes com Hb<9 g/dL. Interromper o tratamento quando Hb< 8 g/dL ou quando Hb diminuir >2 g/dL durante o tratamento. O tratamento com XELJANZ® foi associado a aumentos nos parâmetros lipídicos. Aumentos no colesterol total e LDL associados a XELJANZ® podem ser reduzidos aos níveis pré-tratamento com uso de estatinas. O tratamento com XELJANZ® foi associado com um aumento da incidência de elevação das enzimas hepáticas. A maioria destas anormalidades ocorreu em estudos com base na terapia DMARD. A monitorização hepática de rotina e pronta investigação das causas da elevação das enzimas são recomendadas. Se houver suspeita de lesão induzida por drogas, interromper a administração de XELJANZ®. Reações como angioedema e urticária que podem refletir a hipersensibilidade ao medicamento foram observadas em pacientes que receberam Xeljanz®. Alguns eventos foram graves. Muitos desses eventos ocorreram em pacientes com histórico de alergias múltiplas. Se ocorrer uma reação de hipersensibilidade grave, interrompa prontamente o uso de tofacitinibe enquanto avalia a causa ou as causas potenciais da reação. Recomenda-se que vacinas vivas atenuadas não sejam administradas concomitantemente com XELJANZ®. O tratamento com XELJANZ® não é recomendado no comprometimento hepático grave. A segurança e eficácia de XELJANZ® em crianças desde neonatos até menores de 18 anos de idade não foram estabelecidas. Gravidez: Categoria de Risco C: Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista. Lactação: Mulheres não devem amamentar durante o tratamento com XELJANZ®. Dirigir veículos e operar máquinas: não há estudos sobre este tipo de efeito. Este medicamento contém lactose. Reações adversas: Reações adversas mais comumente relatadas na população com Artrite Reumatoide (que ocorreram em ≥2% dos pacientes tratados com Xeljanz® em monoterapia ou em combinação com DMARDs): cefaleia, infecções do trato respiratório superior, nasofaringite, hipertensão, náusea e diarreia. Reações adversas mais comumente relatadas na população com Artrite Psoriásica: bronquite, diarreia, dispepsia, fadiga, dor de cabeça, nasofaringite e faringite. Além dessas, foram relatas como comuns: pneumonia, herpes zoster, infecção do trato urinário, aumento de peso, dor abdominal, vômitos, gastrite, artralgia, anemia, pirexia, edema periférico, insônia, tosse, rash cutâneo e hipersensibilidade ao medicamento. Interações: Evitar combinação com DMARDs biológicos e imunossupressores potentes tais como azatioprina e ciclosporina devido à possibilidade de imunossupressão aumentada e risco aumentado de infecção. Reduzir dose de XELJANZ® para 5 mg duas vezes ao dia se o paciente estiver tomando 10 mg duas vezes ao dia, ou para 5 mg uma vez ao dia se o paciente estiver tomando 5 mg duas vezes ao dia, quando em uso de inibidores potentes de CYP3A4 (ex: cetoconazol) e em pacientes que recebem uma ou mais medicações concomitantes que resultem na inibição moderada da CYP3A4 e inibição potente da CYP2C19 (ex: fluconazol). A coadministração com indutores potentes de CYP pode resultar em perda ou redução da resposta clínica (ex: rifampicina). Posologia para o tratamento da Artrite Reumatoide: XELJANZ® pode ser usado como monoterapia ou em combinação com metotrexato ou outros DMARDs não biológicos. A dose recomendada é 5 mg, via oral, duas vezes ao dia. Posologia para o tratamento da Artrite Psoriásica: A dose recomendada de Xeljanz® é de 5 mg administrada duas vezes ao dia, em combinação com DMARDs sintéticos convencionais (csDMARDs). Posologia para o tratamento da colite ulcerativa: a dose recomendada de Xeljanz é de 10 mg administrada oralmente duas vezes ao dia para indução por pelo menos 8 semanas e 5 mg administradas duas vezes ao dia para manutenção Nenhum ajuste de dose é necessário em pacientes com 65 anos de idade ou mais, em pacientes com comprometimento renal leve e em pacientes com comprometimento hepático leve. A dosagem de Xeljanz® deve ser reduzida para 5 mg duas vezes ao dia se o paciente estiver tomando 10 mg duas vezes ao dia e a dose de Xeljanz® deve ser reduzida para 5 mg uma vez ao dia se o paciente estiver tomando 5 mg duas vezes ao dia em pacientes com comprometimento renal moderado ou grave e em pacientes com comprometimento hepático moderado. Pacientes submetidos à hemodiálise devem receber a dose de XELJANZ® após a sessão do dia. Caso essa tenha sido administrada antes do procedimento de diálise, doses suplementares não são recomendadas no período pós-dialítico. VENDA SOB PRESCRIÇÃO MÉDICA. SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO. MS – 1.0216.0235. Para informações completas, consulte a bula do produto (XELCOR_35). Documentação científica e informações adicionais estão à disposição da classe médica mediante solicitação. Laboratórios Pfizer Ltda. Rua Alexandre Dumas, 1.860, São Paulo - SP - CEP 04717-904 Tel.: 0800-7701575. www.pfizer.com.br.

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PENTASA® mesalazina

ÚNICA MESALAZINA COM EXCLUSIVA TECNOLOGIA DE MICROGRÂNULOS[1]

EFICÁCIA EM CURTO PRAZO - Pentasa 4 g* - 1x/dia[2]

52% dos pacientes atingiram remissão clínica e endoscópica em **8 SEMANAS**.

EFICÁCIA A LONGO PRAZO - Pentasa 2 g - 1x/dia[3]

70,9% dos pacientes atingiram remissão clínica com melhor aderência ao tratamento.

COMPRIMIDO
500 mg
cx. com 50 compr.

SACHÊ
1 g
cx. com 30 sachês

SACHÊ
2 g
cx. com 30 sachês

SUPOSITÓRIO
1 g
cx. com 28 sup.

ENEMA LÍQUIDO
1 g em 100 mL
cx. com 7 frascos

*2 sachês de 2 g ou 4 sachês de 1 g.

Referências bibliográficas: 1. Bula do produto conforme registro na ANVISA Nº MS 1.2876.0002 http://www.anvisa.gov.br/datavisa/fila_bula/frmVisualizarBula.asp?pNuTransacao=19814652016&pIdAnexo=3652396 - acesso em 13/12/2018. **2.** Flourié B, Hagège H, Tucat G et al. MOTUS study investigators. Randomised clinical trial: once vs. twice-daily prolonged-release mesalazine for active ulcerative colitis. Aliment Pharmacol Ther, 2013; 37(8): 767-75. PMID: 23451806. **3.** Dignass AU, Bokemeyer B, Adamek H, Mross M, Vinter-Jensen L, Böner N, Silvennoinen J, Tan G, Pool MO, Stijnen T, Dietel P, Klugmann T, Vermeire S, Bhatt A, Veerman H. Mesalamine once daily is more effective than twice daily in patients with quiescent ulcerative colitis. Clin Gastroenterol Hepatol. 2009 Jul;7(7):762-9.

Pentasa® - mesalazina - **Comprimidos: USO ADULTO E PEDIÁTRICO (acima de dois anos de idade). Enema, Sachê e Supositórios: USO ADULTO. INDICAÇÕES: Comprimidos, Enema e Supositórios:** Doença Inflamatória Intestinal (Doença de Crohn e Retocolite Ulcerativa). **Sachê:** Retocolite Ulcerativa. **CONTRAINDICAÇÕES**: hipersensibilidade à mesalazina ou aos salicilatos ou a qualquer componente das formulações; em casos de doenças renais ou hepáticas severas. **ADVERTÊNCIAS E PRECAUÇÕES**: pacientes alérgicos à sulfassalazina devem ter cautela com uso de Pentasa; descontinuar em caso de reações de intolerância aguda, cólicas abdominais, dor abdominal aguda, febre, dor de cabeça severa e erupção cutânea, discrasia sanguínea, mio e pericardite. Usar com cautela quando coexistir asma, função hepática ou renal prejudicada. **USO DURANTE A GRAVIDEZ E LACTAÇÃO**: Pentasa® deve ser utilizado com cautela durante a gravidez e lactação. **USO EM IDOSOS, CRIANÇAS OU OUTROS GRUPOS DE RISCO: Comprimidos**: Não é recomendado o uso de Pentasa® em crianças com menos de dois anos de idade. **Enema, Sachê e Supositórios:** Não é recomendado o uso de Pentasa® em crianças. **Interações medicamentosas e com exames laboratoriais**: A terapia combinada de Pentasa® com azatioprina ou 6-mercaptopurina ou tioguanina mostra maior frequência de mielossupressão; raramente pode ocorrer alteração nas funções hepáticas e renais. **Interação com alimento: Comprimidos e Sachê:** O trânsito e a liberação de mesalazina após administração oral são independentes da coadministração de alimento, enquanto que a absorção sistêmica será reduzida. **Enema e Supositórios:** Não há dados disponíveis até o momento sobre a interação de Pentasa® com alimentos. **Reações adversas:** diarreia, náusea, dor abdominal, cefaleia, vômitos, eczema e erupção cutânea; reações de hipersensibilidade; como prurido, desconforto retal e urgência podem ocorrer. **POSOLOGIA: Comprimidos:** Retocolite Ulcerativa – Adultos: Tratamento agudo: Dose individual de até 4 gramas divididas ao longo do dia. Tratamento de manutenção: Dose inicial recomendada de 2 g uma vez ao dia; Retocolite ulcerativa - Crianças com mais de dois anos de idade: Tratamento agudo e de manutenção: Dose individual recomendada de 20 a 30 mg/kg de peso corpóreo ao dia, em doses divididas; Doença de Crohn - Adultos: Tratamento agudo e de manutenção: dosagem individual de até 4 g ao dia, em doses divididas; Doença de Crohn - Crianças com mais de dois anos de idade: Tratamento agudo e de manutenção: Dose individual recomendada de 20 a 30 mg/kg de peso corpóreo ao dia, em doses divididas. **Enema:** Para adultos: Um enema ao deitar. **Sachê:** Retocolite Ulcerativa – Adultos (em pacientes acima de 18 anos de idade): Tratamento agudo: Dose individual de até 4 gramas por dia a ser tomada uma vez ao dia (4 sachês de 1g ou 2 sachês de 2g) ao mesmo tempo pela manhã; ou em doses divididas duas vezes ao dia (2 sachês de 1 g ou 1 sachês de 2 g) tomados pela manhã e à noite. Tratamento de manutenção: Dose inicial recomendada de 2 g uma vez ao dia (2 sachês de 1g ou 1 sachê de 2g). **Supositórios:** Proctite ulcerativa - Adultos: Um supositório, uma a duas vezes ao dia por 4 semanas. / **VENDA SOB PRESCRIÇÃO MÉDICA** / Material de uso exclusivo à classe médica / **SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.** / Reg. MS: 1.2876.0002 / Farm. Resp.: Silvia Takahashi Viana - CRF/SP: 38.932 - Laboratórios Ferring Ltda. Praça São Marcos, 624 - 05455-050 - São Paulo – SP / CNPJ: 74.232.034/0001-48. (CCDS 2017/12_v16)

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

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