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CROHN'S DISEASE GUIDELINES

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 DOENÇA DE CROHN (DC).[5,6**]

INDUÇÃO: redução significativa dos subescores de **dor abdominal e evacuações líquidas ou muito moles** a partir da **PRIMEIRA DOSE** em pacientes virgens de anti-TNF.[7++]

CICATRIZAÇÃO DE MUCOSA: 67% dos pacientes alcançaram **cicatrização endoscópica de mucosa#** em **12 meses** de tratamento.[8]

MANUTENÇÃO: 95% de **resposta** e **89%** de **remissão clínicas+** ao longo de **5 anos** de tratamento.[9]

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

#Cicatrização endoscópica de mucosa definida como ausência de úlceras e/ou erosões.

+Análise as *observed* considera o número de pacientes em resposta ou remissão clínicas sobre o número de casos observados na visita do estudo. Resposta clínica definida como queda de ≥ 3 pontos no índice Harvey-Bradshaw (HBI); Remissão clínica definida como HBI ≤ 4. O método de estatística descritiva foi utilizado para avaliação de efetividade clínica.

++Os dois componentes do escore de índice de atividade da doença de Crohn (CDAI) relatados pelos pacientes - subescores de dor abdominal e número de evacuações líquidas ou muito moles - foram avaliados.

**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).

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 Crohn's disease (CD): a GEMINI 2 Post Hoc Analysis. World Congress of Gastroenterology at ACG 2017. Poster #1271. **8.** Dulai PS, *et al.* The Real-World Effectiveness and Safety of Vedolizumab for Moderate-Severe Crohn's Disease: Results From the US VICTORY Consortium. Am J Gastroenterol. 2016;111(8):1147-55. **9.** Vermeire S, *et al.* Long-Term Effectiveness And Safety Of Vedolizumab In Patients With Crohn's Disease: 5-Year Cumulative Exposure Of Gemini 2 Completers Rolling Into The Gemini Open-Label Extension Study. Gastroenterology. 2017;152(5): S601. Abstract Su1931.

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.
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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).

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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.

Journal articles in electronic format: Author(s). Title of article. Abbreviated title of periodical [support]. Publication date [date accessed with the expression "Cited: "]; volume (number): pages initial-final [or approximate number of pages]. Electronic address with the expression "Available from:" Pavezi N, Flores D, Perez CB. Proposição de um conjunto de metadados para descrição de arquivos fotográficos considerando a Nobrade e a Sepiades. Transinf. [Internet]. 2009 [Cited: 2010 Nov 8];21(3):197-205. Available from: http://revistas.puccampinas.edu.br/transinfo/search.php?op=search&query=metadados&limit

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Randomized trials use guideline CONSORT
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International Journal
of Inflammatory
Bowel Disease

In this edition of the official GEDIIB journal, readers will find the Crohn's disease treatment guidelines that were developed by the GEDIIB, aimed at providing orientation based on scientific evidence and on the experience of specialists in order to assist the reasoning and decision-making processes around its treatment in our country.

They are guidelines that address the use and results of several classes of drugs and some important aspects of surgical treatment, with their respective degrees of recommendation, supporting an understanding of the strength of scientific evidence for each of the options.

The choice of therapy in Crohn's disease is usually based on the phase of activity, the location of the disease, its phenotype, previously used medications, and adverse effects, respecting the individualization of the treatment to be shared with the patient.

Its appropriateness takes optimizing our prescriptions, increasing medication efficacy, and reducing the structural and psychological damages common to the evolution of the disease into account.

However, while these serve as guidelines, the autonomy of the physician in making therapeutic decisions prevails. On the other hand, they are by definition references to facilitate the implementation of treatment protocols together with the Health Ministry and the State and Municipal Health Secretariats.

Focused on a better understanding of the parameters of clinical activity, phenotypes, locations, and concepts, such as clinical improvement, clinical remission, sustained remission, among others, which are present in all guidelines, we start this issue with a chapter dedicated to the indices or concepts that will be used in the efficacy evaluation of each medication, thus making the read more user-friendly.

A lot of discipline, time commitment, and learning about guideline-building techniques occurred throughout the process and it is important that we recognize the dedication of all those involved in each step.

We all end up winning!

Cyrla Zaltman

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GUIDELINE

CROHN'S DISEASE GUIDELINES

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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 Crohn's disease.

1.3 INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease of multifactorial etiopathogenesis that can affect any part of the gastrointestinal tract in a segmental, asymmetric and transmural manner with variable intensity (D). The most affected segments are ileum, colon and perianal region. It can present a great variety of extra intestinal manifestations, being the most frequent the cutaneous, articular, ocular, as well as systemic symptoms (D). Although clinical manifestations begin more commonly in young adults, in the 2nd and 3rd decades of life, it can occur in any age group. Normally the most frequent symptoms that make patients seek medical attention are persistent diarrhea, abdominal pain and weight loss. The diagnosis of the disease is based on the set of information obtained by anamnesis and adequate physical examination, laboratory tests (serological and fecal biomarkers), radiological, endoscopic and anatomopathological examinations.[3]

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The assessment of disease activity can be performed by using the CDAI - *Crohn's Disease Activity Index* - CDAI.[4] (D) This index uses clinical data referring to the last seven days prior to consultation, weight and hematocrit, and its result will be the sum of eight components which have an input value that will be multiplied by a "weight" factor, giving the final result for each component. The total sum of the values obtained for each parameter will classify the disease in: remission (up to 150 points); mild activity (151-219 points); moderate activity (220-450 points) and severe activity (> 450 points).[5](B)

The inflammatory activity also can be assessed using a more simplified index, called the Harvey-Bradshaw Index, which has the advantage of evaluating single day data. (16).[4] (B)

For a uniform CD description, according to location and behavior, it must be used The Montreal Classification, which includes age at diagnosis, location (ileal, colonic, ileocolic, isolated upper GI disease) and behavior (not stenosing, non-penetrating, stenosing; penetrating and the perianal disease modifier).[6]

For to evaluate postoperative endoscopic recurrence (right ileocolectomy), at the level of the colonic ileus anastomosis and neo-ileus, it can be used the Rutgeerts score, which has a predictive character of symptomatic recurrence.[7]

1.4 CONCEPTS

These concepts are important for reading the recommendations of the CD guidelines, considering the follows aspects:

1. Active disease - CDAI >150 or HB $\geq$ 5.[4,5]
2. In remission disease – CDAI < 150 or HB < 5.[4,5]
3. Clinical response – should be defined as a reduction in the score of CDAI $\geq$ 100 points.[8]
4. Relapse or reactivation - Crisis of disease activity in a patient who was in remission, and should be confirmed with laboratory, radiological and endoscopic methods, regardless of the therapy used. In clinical studies, may be use an increase of 70 points in the CDAI with the same being above 150.[9]
5. Relapse - It can be frequent when it happens twice; continue when there is persistence of symptoms without period of remission.[10]
6. Early relapse - relapse within three months after achieving remission with treatment.[10]
7. Corticosteroid-dependent (cortico-dependent) disease - failure to reduce corticosteroids below 10mg prednisone (or equivalent) without clinical relapse within 3 months after initiation or relapse within 3 months after its onset.[10]
8. Corticosteroid refractory disease absence of a clinical response despite a course of prednisone of 1mg/kg/ day (maximum dose of 40 to 60mg/d), for 2 to 4 weeks.[10]
9. Recurrence (postoperative) - reappearance of radiological and/or endoscopic lesions after surgical resection.[11]
10. Clinical recurrence - recurrence of symptoms in the presence of new lesions confirmed by imaging methods.[12]
11. Localized disease – disease involvement less than 30 cm of extension.[10]
12. Extensive disease – disease involvement superior of 100 cm in extent, not necessarily in contiguity.[10]

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Attachment 1.

1. CLINICAL DOUBTS

a. What is the role (effectiveness and safety) of aminosalicylates in treatment of Crohn's Disease?
b. Which is the roll (damages and benefit) of corticosteroids in treatment of Crohn's Disease?
c. What is the role (damage and benefit) of thiopurines in treatment of Crohn's disease?
d. What is the role (damage and benefit) of methotrexate in treatment of Crohn's disease?
e. The calcineurin inhibitors (cyclosporine and tacrolimus) are effective and safe in the treatment of Crohn's Disease?
f. What is the role (damage and benefit) of biological drugs in treatment of Crohn's disease?
g. What is the role (damage and benefit) of probiotics, prebiotics and symbiotics in the treatment of Crohn's disease?
h. When is surgical treatment effective and safe in CD?

2. STRUCTURED QUESTION

Q: Crohn's Disease
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 - (Crohn Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn´s Disease OR Inflammatory Bowel Disease 1 OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis)
#2 - (Salicylates OR Aminosalicylic Acids OR Mesalamine OR 5-Aminosalicylate OR 5-ASA OR Sulphasalazine) OR Sulfasalasine AND Aminosalicylic Acid OR Mesalazine OR Mesalamine OR 5-aminosalicylic acid OR 5-aminosalicylate)
#3 - Random*

1st RECOVERY = #1 AND #2 AND #3 = 789

(Crohn Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn´s Disease OR Inflammatory Bowel Disease 1 OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis) AND (Salicylates OR Aminosalicylic Acids OR Mesalamine OR 5-Aminosalicylate OR 5-ASA OR Sulphasalazine) OR Sulfasalasine AND Aminosalicylic Acid OR Mesalazine OR Mesalamine OR 5-aminosalicylic acid OR 5-aminosalicylate) AND Random*

b. Corticosteroids

1 - (Crohn Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn´s Disease OR Inflammatory Bowel Disease 1 OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis)
#2 - (Adrenal Cortex Hormones OR Steroids OR Cortisone OR Hydrocortisone OR Prednisone OR Prednisolone OR Methylprednisolone OR Dexamethasone OR Budesonide)
3 - Random*

1st retrieval = # 1 AND # 2 AND # 3 = 461

(Crohn Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn´s Disease OR Inflammatory Bowel Disease 1 OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis) AND (Adrenal Cortex Hormones OR Steroids OR Cortisone OR Hydrocortisone OR Prednisone OR Prednisolone OR Methylprednisolone OR Dexamethasone OR Budesonide) AND Random*

c. Thiopurines

1 - (Crohn Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn´s Disease OR Inflammatory Bowel Disease 1 OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis)
#2 - (Purines OR Thiopurine OR Antimetabolites OR Immunosuppressive Agents OR 6-Mercaptopurine OR 6-MP OR Azathioprine OR AZA)
#3 - Random*

1st RECOVERY = #1 AND #2 AND #3 = 480

(Crohn Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn´s Disease OR Inflammatory Bowel Disease 1 OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis) AND (Purines OR Thiopurine OR Antimetabolites OR Immunosuppressive Agents OR 6-Mercaptopurine OR 6-MP OR Azathioprine OR AZA) AND Random*

d. Methotrexate

1 - (Crohn Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn´s Disease OR Inflammatory Bowel Disease OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis)
2 - (Immunosuppressive Agents OR Methotrexate)
3 - Random*

1st RECOVERY = #1 AND #2 AND #3 = 378

Crohn Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn´s Disease OR Inflammatory Bowel Disease OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis) AND (Immunosuppressive Agents OR Methotrexate) AND Random*

Attachment 1.

e. Calcineurin (cyclosporine and tacrolimus)

Crohn Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn´s Disease OR Inflammatory Bowel Disease 1 OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis) AND (Immunosuppressive Agents OR Calcineurin OR Calcineurin Inhibitors OR Calcineurin Antagonists OR Calcineurin Blockers OR Cyclosporine OR Ciclosporin OR Tacrolimus OR Cyclosporins) AND (Therapy/narrow [filter] OR Prognosis/narrow [filter] OR Comparative study OR Comparative studies)

f. Biological drugs

1 - (Crohn´s Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn's Disease OR Inflammatory Bowel Disease 1 OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis)
2 - (Antibodies, Monoclonal OR Tumor Necrosis Factor-alpha OR Interferon-alpha OR Leukocyte Interferon OR alpha Interferon)
1 - (Crohn Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn's Disease OR Inflammatory Bowel Disease 1 OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis)
2 - (Antibodies, Monoclonal OR Tumor Necrosis Factor-alpha OR Interferon-alpha OR Leukocyte Interferon OR alpha Interferon)
3 - Random *

1st RECOVERY = #1 AND #2 AND #3 = 575

(Crohn Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn's Disease OR Inflammatory Bowel Disease 1 OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis) AND (Antibodies, Monoclonal OR Tumor Necrosis Factor-alpha OR Interferon-alpha OR Leukocyte Interferon OR alpha Interferon) AND Random*

g. Probiotics, prebiotics and synbiotics

1 - (Crohn Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn´s Disease OR Inflammatory Bowel Disease 1 OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis)
2 - Probiotic* OR Prebiotic* OR Synbiotic
3 - Random*

1st RECOVERY = #1 AND #2 AND #3 = 105

(Crohn Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn´s Disease OR Inflammatory Bowel Disease 1 OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis) AND (Probiotic* OR Prebiotic* OR Synbiotic*) AND Random

h. Surgical treatment

Without method filter: (Crohn Disease OR Crohn's Enteritis OR Regional Enteritis OR Crohn's Disease OR Crohn's Disease OR Inflammatory Bowel Disease 1 OR Granulomatous Enteritis OR Granulomatous Colitis OR Terminal Ileitis OR Regional Ileitis) AND (Surgery).

4. RECOVERED WORKS

The evidence obtained to be used for analyzing the effectiveness and damage from use probiotics, prebiotics or symbiotic in the treatment of Crohn's disease followed the steps of: preparing the clinical question, the question structure, evidence search, critical evaluation and selection of evidence, expose of results and recommendations.

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.

a. Aminosalicylates: The number of jobs recovered to the last date of search (04.24.2017) with the final search strategy was 691.
b. Corticosteroids: We retrieved studies 461 until the last search date (10.09.2017) with the end search strategy.
c. Thiopurines: The number of jobs recovered to the last date of search (09.24.2017) with the final search strategy was 480.
d. Methotrexate: The number of jobs recovered to the last date of search (04.24.2015) with the final search strategy was 378.
e. Calcineurin (cyclosporine and tacrolimus): The number of jobs recovered to the last date of search (07.12.2015) with the final search strategy was 607.
f. Biological drugs: The number of jobs recovered to the last date of search (22.10.2017) with the final search strategy was 575.
g. Probiotics, prebiotics and synbiotics: The number of jobs recovered to the last date of search (01.10.2017) with the final search strategy was 105.
h. Surgical treatment: We retrieved works with the search 13.263 (16.08.2015) strategy used for scientific information databases.

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

Attachment 1.

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.

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 medium 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.

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

Study data	**Sample Calculation**
Reference, Study design, JADAD[2], 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

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. AMINOSALICYLATES

2.1 INTRODUCTION

Aminosalicylates are drugs derived from the salts of aminosalicylic acid (ASA), and mainly composed of sulfasalazine and derivatives of 5-ASA. Their mechanisms of action are similar to those of nonsteroidal anti-inflammatory drugs; they inhibit cyclooxygenase (COX)-1 and COX-2 enzymes, reducing the synthesis of inflammatory prostaglandins. Sulfasalazine is a drug derived from the combination of a sulfonamide with a salicylate, while mesalazine is obtained through the bonding of two 5-ASA molecules via a diazo linkage.[1] These drugs have therapeutic effects in the intestinal lumen and are available as different formulations, thereby allowing better distribution in specific sites of action.[1,2] To achieve this effect, there are slow-release formulations, as well as pH-dependent extended-release formulations. [2]

2.2 INDUCTION OF REMISSION

Recommendation

- **The use of mesalazine at low doses (1.0 to 2.0 g/day) was not superior to that of placebo with respect to the induction of clinical remission in patients with active Crohn's disease (B).**
- **The use of mesalazine at high doses (3.0 to 4.0 g/day) provided higher induction rates of clinical remission in patients with mild to severe active Crohn's disease. The effectiveness of mesalazine was not superior to that of placebo in terms of induction of remission (B).**

The use of mesalamine at low doses (1.0 to 2.0 g/day) was not superior to that of placebo with respect to the induction of clinical remission in patients with active Crohn's disease (B).

The use of mesalazine at high doses (3.0 to 4.0 g/day) provided higher induction rates of clinical remission in patients with mild to severe active Crohn's disease. The effectiveness of mesalazine was not superior to that of placebo in terms of Induction of remission (B).

Numerous studies have evaluated the ability of aminosalicylates to induce clinical remission compared to that of placebo[3-6](B). A multicenter study involving patients with active Crohn's disease (Crohn's disease activity index (CDAI): 151-400) who were randomized for treatment with mesalazine (at doses of 1.0, 2.0, or 4.0 g/day divided into four daily doses) or placebo and followed up for a 16-week period, indicated that the use of mesalazine at a dose of 4.0 g/day was associated with a significant decrease in CDAI score to a greater extent than that of placebo (average reduction of 72 and 21 points, respectively) (B). Clinical remission was detected in 43% of patients treated with mesalazine at 4.0 g/day, and in 18% of patients treated with placebo (ARR=0.252; CI95%: 0.096 to 0.384; NNT=4) (B). However, the reductions in CDAI score in patients treated with mesalazine at 1.0 and 2.0 g/day were not different from those in the placebo group[3](B). A different controlled study that included a small number of patients (n=38) with active Crohn's disease (CDAI: 150-450) indicated that after a 16-week follow-up, individuals randomized for treatment with mesalazine at a dose of 3.2 g/day presented higher rates of complete disease remission than those in the placebo group (p=0.042) [4](B).

Recommendation

- **Aminosalicylates are not inferior to corticosteroids (budesonide and 6-methylprednisolone), antibiotics, or in inducing clinical remission (B).**

Aminosalicylates are not inferior to corticosteroids (budesonide and 6-methylprednisolone), antibiotics, or in inducing clinical remission (B).

Studies have also compared the efficacy of aminosalicylates *versus* corticosteroids and antibiotics in inducing clinical remission. A study involving patients with active Crohn's disease (CDAI > 150) treated with aminosalicylate (4.5 g/day) or 6-methylprednisolone (48, 32, 24, 20, 16, 12, or 8 mg/day) for 8 weeks indicated that basal CDAI values in randomized patients in the aminosalicylate group showed higher mean reduction (reduction of 85 *versus* 122 points), although the decrease was not significant when compared to the 6-methylprednisolone group[7](B). In the same context, a study evaluating patients with active Crohn's disease (CDAI: 200–400) who were randomized for a 16-week treatment with budesonide (9.0 mg/day) or mesalazine (2.0 g twice a day) verified that both treatments were associated with an improvement in quality of life, which was significantly higher in the budesonide group (at the 2nd, 8th, 12th, and 16th week of treatment) than in the mesalazine group [8](B).

In a study involving patients with active Crohn's disease (CDAI: 200-400) in the terminal ileum and/or the ascending or distal colon who were randomized for treatment with budesonide (9 mg/day), mesalazine (4.5 g/day), or placebo, no significant difference was noted in clinical remission between the budesonide and mesalazine groups (69.5 and 62.1%, respectively) (ARR=-0.074; CI 95%: -0.184 to 0.039)[9](B).

To compare the conflicting data presented previously, a systematic review analyzing 19 controlled trials was included in these guidelines. In this study, the use of mesalazine at low (1.0 to 2.0 g/day) and high doses (4.0 g/day) did not present a better effect than that of placebo in inducing clinical remission (RR=1.46; CI 95%: 0.89 to 2.40 *vs*. RR=2.02; CI 95%: 0.75 to 5.45, respectively), and it was even less effective than treatment with corticoids[10](A).

Furthermore, no difference in clinical remission rate of Crohn's disease was observed between patients randomized for a 6-week treatment with mesalazine (4.0 g/day) and those treated with ciprofloxacin (1.0 g/day) (ARR=0.018; CI95%: -0.910 to 0.468)[11](B).

2.3 MAINTENANCE OF REMISSION

Recommendation

- **Evidence of effect associated with the use of aminosalicylates on the maintenance of clinical remission, as observed for pharmacotherapy or surgical treatments, is controversial (A).**
- **Therapy with mesalazine a lower efficacy in controlling postoperative recurrence than therapy with anti-tumor necrosis factor drugs (TNFs) (B).**

Evidence of effect associated with the use of aminosalicylates on the maintenance of clinical remission, as observed for pharmacotherapy or surgical treatments, is controversial (A).

Therapy with mesalazine presented a lower efficacy in controlling postoperative recurrence than therapy with anti-tumor necrosis factors (TNFs) (B).

Controlled studies were conducted to analyze the efficacy of aminosalicylates in maintaining drug- or surgery-induced

clinical remission in patients with Crohn's disease (B). Some of these trials compared the efficacy of various oral doses of mesalazine with that of placebo in patients with Crohn's disease in clinical remission (CDAI < 150) by pharmacotherapy. At the end of a 4-month follow-up period, patients treated with extended-release 5-ASA (2.0 g/day) showed no difference in clinical recurrence rate from that of patients treated with placebo (ARR=0.062; CI 95%: -0.264 to 0.386)[12](B). Similar results were noted for patients with Crohn's disease in clinical remission (Harvey-Bradshaw index < 4) that were randomized for treatment with mesalazine (1.0 g/day) or placebo; The use of mesalazine , including in higher doses (4.0 g /day) showed no benefit over placebo after a 12-month follow-up (ARR=-0.270; CI 95%: -0.487 to 0.025)13(B) and (ARR=0.143; CI 95%: -0.870 to 0.626)14(B), respectively. In another study, no difference in clinical recurrence rate was observed between patients in clinical remission (CDAI < 150) treated for 48 weeks with mesalazine (3.0 g/day) and those treated with placebo (ARR=0.113; CI95%: -0.011 to 0.230)[15](B). However, according to a subgroup analysis, females or individuals with ileocecal/colon disease have lower recurrence rate when treated with mesalazine, presenting a significant difference in comparison to placebo, 21% *versus* 41% (p=0.018), 19% *versus* 41% (p=0.003)[15](B). In another study, 117 patients with Crohn's disease in corticosteroid-induced clinical remission were randomized for treatment with 5-ASA (3.0 g/day) or placebo, and then corticosteroid was gradually withdrawn for up to 6 weeks. After a 12-month follow-up period, no difference in disease recurrence rate was observed between the groups (ARR=-0.047; CI 95%: -0.212 to 0.120) [HZ1][16](B).

However, a different multicenter clinical trial, which involved individuals with Crohn's disease in clinical remission (CDAI < 150) randomized for treatment with aminosalicylates (2.4 g/day) or placebo, showed a lower clinical recurrence rate in patients treated with aminosalicylates than in those treated with placebo after a 12-month follow-up period (ARR=0.218; CI95%: 0.028 to 0.392 and NNT=4)[17](B).

According to a systematic review that included seven randomized clinical trials, aminosalicylates, more specifically 5-ASA, was not superior to placebo in maintaining drug-induced clinical remission[18](A).

2.4 PREVENTION OF POSTOPERATIVE RECURRENCE

An analysis of patients diagnosed with Crohn's disease in clinical remission indicated that after surgical treatment, there was no difference in clinical recurrence rate (CDAI > 150) between patients treated with mesalazine (3.0 g/day) and those with placebo[19](B). Endoscopic recurrence rate was also analyzed in this study, and a lower rate was observed in mesalazine group. Additionally, endoscopic recurrence was less severe in patients randomized for treatment with mesalazine[19](B). Another study, which involved individuals in surgically induced clinical remission randomized for treatment with mesalazine (3.0 g/day), did not indicate a significant difference in disease recurrence rate between the mesalazine and placebo groups (ARR=0.098; CI95%: -0.061 to 0.252)[20](B). A similar result was observed in a study where mesalazine at 4.0 g/day was applied and compared to placebo (ARR=0.064; CI95%: -0.040 to 0.164)[21](B). Nevertheless, a retrospective analysis indicated a significant reduction in clinical recurrence rate in patients with isolated small bowel Crohn's disease treated with mesalazine more than that in those treated with placebo (21.8 ± 5.6 *versus* 39.7 ± 6.1%, respectively) (p=0.02)[21](B). Despite limited literature, endoscopic recurrence rate in patients with Crohn's disease in clinical remission after surgical treatment, as verified in a study, showed clinical benefit in individuals randomized for treatment with mesalazine (2.4 g/day) (ARR=0.306; CI 95%: 0.086 to 0.499 and NNT=3)[22](B).

To clarify the previous data, a systematic review composed of six controlled studies with patients with Crohn's disease in clinical remission after surgical treatment (n=834) was performed with subsequent meta-analysis, where it was possible to verify that the use of mesalazine was associated with the reduction in the clinical recurrence rate (RR=0.80; CI 95%: 0.70 to 0.92)[23](A). Another systematic review, which consisted of seven studies that compared the efficacy of aminosalicylate with that of placebo, reported a lower recurrence rate in patients treated with mesalazine than in those with placebo (OR=0.68; CI95%: 0.52 to 0.90)[24](A). Nevertheless, the combined analysis of these data should be carefully interpreted, given that well-designed studies did not indicate any difference between the groups[24](A).

The efficacy of aminosalicylates in preventing clinical recurrence in patients who achieved remission with drug or surgical treatment was compared with those induced by other active drugs (corticosteroids, thiopurines, or biological drugs). The efficacy of pH-dependent-release mesalazine (3.0 g/day) was compared with that of extended-release budesonide (6.0 mg/day) in cortico-dependent patients with Crohn's disease in clinical remission (CDAI < 150). After a 12-month follow-up period, only 17% of the patients randomized for treatment with mesalazine remained in the study, whereas 23 participants discontinued the treatment because of therapeutic failure. In this study, the use of budesonide was associated with a long period of clinical remission, as well as a significantly lower annual recurrence rate when compared to mesalazine (55% *versus* 82%, respectively; CI95%: 12.4% to 41%; p=0.045)[25](B).

In a another study, patients with Crohn's disease in remission (CDAI ≤ 150) were treated with azathioprine (2.0 mg/kg/day) or mesalazine (3.0 g/day), and after a 24-month follow-up period, recurrence risk was similar between the groups (ARR=0.113; CI95%: -0.038 to 0.246) and no significant difference in postoperative relapse was observed (ARR=0.041; CI95%: -0.058 to 0.115) [26](B). During the study period, 21.7% of patients randomized for treatment with azathioprine abandoned the treatment because of adverse events, whereas 8.5% of those treated with mesalazine (p=0.04)[26](B).

In a study involving patients who underwent ileocolic resection and were randomized for treatment with 6-mercaptopurine (6-MP; 50 mg/day), mesalazine (3.0 g/day), or placebo, endoscopic recurrence occurred (Rutgeerts score > i1) in 43%, 63%, and 64% of patients in the 6-MP, mesalazine, and placebo groups, respectively, at the 24th week 27(B). The clinical recurrence rates were 50, 58, and 77%, respectively, for the 6-MP, mesalazine, and placebo groups, with no difference verified between the mesalazine and placebo groups[27](B).

Patients with Crohn's disease who underwent surgical resection and ileocolonic anastomosis with no evidence of active disease (CDAI < 200) were randomized for a 12-month treatment

with azathioprine (2.0 to 2.5 mg/kg/day) or mesalazine (4.0 g/day). A CDAI score of ≥ 200, or an increase in CDAI score by > 60 points from the initial score, was less frequent among patients randomized for treatment with azathioprine than among those treated with azathioprine; However, no significant difference in clinical recurrence was observed between the groups (ARR=0.108; CI 95%: -0.014 to 0.108)[28](B).

Medication discontinuation due to adverse events was more frequent among patients randomized for treatment with azathioprine than among those treated with mesalazine (ARR=-0.220; CI 95%: -0.220 to -0.057)[28](B).

With the introduction of biologics in the therapeutic arsenal against Crohn's disease, studies were conducted to analyze the clinical and endoscopic recurrence rates of patients who achieved remission by ileocolectomy with ileocolonic anastomosis. A comparative study with a 2-year follow-up involving patients using adalimumab (160, 80, or 40 mg every 2 weeks), azathioprine (2.0 mg/kg/day), and mesalazine (3.0 g/day) verified that one of the 16 patients (6.3%) treated with adalimumab exhibited endoscopic recurrence (i2, i3, or i4 in the Rutgeerts score), whereas in the azathioprine and mesalazine groups, respectively, only 11 of 17 patients (64.7%) (OR=0.036 with CI95%: 0.004 to 0.347) and (83.3%) (15/18) patients (OR=0.013 with CI95%: 0.001 to 0.143) [29](B) showed endoscopic recurrence. In addition, clinical recurrence (as measured by the Hanauer Scale) occurred in two of the 16 patients (12.5%) treated with adalimumab, 11 of the 17 treated with azathioprine (OR=0.078 with CI95%: 0.013 to 0.464), and nine of the 18 treated with mesalazine (OR=0.143 with CI95%: 0.025 to 0.819)[29](B).

A non-randomized prospective study included 26 patients in clinical remission (CDAI < 150) in use of mesalazine (3 g/day) after ileocolonic resection with patients with Crohn's disease that presented endoscopic recurrence in the neoterminal ileum, after 6 months of surgery. In the following 6 months, 10 patients maintained the treatment with mesalazine (3 g/day), eight treated with azathioprine (50 mg/day), and eight with infliximab (5 mg/kg every 8 months). During the last 6 months, none, three (38%), and seven (70%) patients in the infliximab, azathioprine, and mesalazine groups, respectively, developed clinical recurrence (p=0.01). In the same period, endoscopic activity improved in 75, 38, of patients in the infliximab and azathioprine groups, respectively, with no improvement in mesalazine group (p=0.006). Therefore, therapy with infliximab showed efficacy in controlling the clinical and endoscopic activity of Crohn's disease[30](C).

In a prospective, pilot, open-label, non-randomized, multicenter study, 43 patients with ileocolonic Crohn's disease underwent curative surgery with no ostomy, and ileocolonoscopy 6 months after the surgery. In total, 24 of 43 patients were diagnosed with endoscopic recurrence (Rutgeerts ≥ i2), 13 of whom were treated with infliximab (5 mg/kg IV in induction and maintenance schemes) and 11 of whom were treated with mesalazine at 800 mg three times a day. Ileocolonoscopy was performed at the 54th week, when among patients treated with mesalazine, none had reached endoscopic remission and two presented clinical recurrence within 8 and 9 months after surgery. In the group treated with infliximab, 54% of patients showed endoscopic remission at the 54th week (p=0.01), 69% showed improved endoscopic score, and none exhibited clinical recurrence. In conclusion, treatment with infliximab of postoperative endoscopic lesions was superior to that with mesalazine[31](B).

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3. CORTICOSTEROID

3.1 INDUCTION OF REMISSION

Recommendation

- **The use of budesonide at the dose of 9mg daily is recommended as a primary therapy in patients with mild to moderate CD who have active disease restricted to the ileum and / or the right colon. (A)**
- **Treatment with budesonide is not indicated for severe disease or severe exacerbations of CD. (A)**
- **Initial treatment of severe ileal CD includes oral corticosteroids (prednisolone or prednisone), or parenteral corticosteroid (hydrocortisone) equivalent to 40-60mg/day of prednisone. (D)**
- **Systemic corticosteroids, such as prednisolone or equivalent, are effective to induce clinical remission in active colonic CD. (A)**
- **In cases of extensive small bowel CD, treatment with systemic corticosteroids and the early introduction of concomitant immunomodulators is considered appropriate. (D)**
- **Mild esophageal or gastroduodenal CD can be treated with a proton pump inhibitor alone. Severe or refractory disease requires additional systemic corticosteroids, immunosuppressive therapy, or anti-TNF-based strategy management. (D)**
- **Corticosteroids are not effective to treat patients with perianal CD. (D)**

Oral budesonide, at a dose of 9mg/day, is the treatment of choice to induce clinical remission in mild active CD, located in the ileocecal region, being superior to placebo (relative risk [RR] 1.93, 95% IC: 1.37-2.73; in an analysis of 3 randomized controlled trials [ECRs] with a total of 379 adult patients). Although being inferior to conventional steroids (RR 0.85, 95% IC: 0.75-0.97; analysis of 8 ECRs with 750 adults or children), especially in the presence of severe disease (CDAI> 300) (RR 0,52, 95% IC: 0.28-0.95), it has fewer side effects (RR 0.64, 95% IC 0.54-0.76, analysis of 6 ECRs with 703 adults or children)[1] (A). Approximately 50-60% of patients with mild ileocecal CD achieve remission at 8 weeks with budesonide[2-6] (A).

Therefore, oral budesonide at a dose of 9mg/day is recommended as a primary therapy in patients with mild to moderate active CD who have the disease restricted to terminal ileum and/or right colon.

Conventional systemic corticosteroids (prednisone, prednisolone, methylprednisolone) are highly effective but have a higher risk of side effects compared to budesonide[1] (A).

A systematic review of 8 ECRs, with methodological limitations, evaluating systemic corticosteroids for induction of remission in patients with active CD, compared corticosteroid with placebo in 2 ECRs and with 5 ASA derivatives in the other 6 ECRs. In comparison to placebo, systemic corticosteroids had higher rates of remission (267 patients; RR = 1.99, 95% IC 1.51-2.64, NNT 2-7, remission of 31% in the placebo group). However, there were more patients excluded due to the adverse effects of systemic corticosteroids in the analysis of the 2 ECRs, but not statistically significant (267 patients; RR 4.57, 95% IC 0.75-27.83.) While comparing systemic corticosteroids with 5-ASA derivatives, it was observed a greater frequency of induction of remission in the first group while analyzing 3 of the 6 ECRs (N = 322 patients with a follow-up of more than 15 weeks (RR = 1.65, 95% IC 1.33-2.03, NNT 3-8)[7] (A).

To date, there are no adequate studies evaluating different corticosteroid therapy regimens in CD. Prednisone is usually used at a dose of 0.5-0.75mg / kg (or 40-60mg/day as a single dose in the morning) for a period of 7-28 days. Doses greater than 60mg/day are not recommended for adults whereas doses greater than 40mg/day are associated with small clinical benefit, but accompanied by a significant increase of adverse effects. Weaning should be started as soon as a clear clinical response occurs (e.g., 5-10mg/week up to 20mg and then 2.5-5mg/week, until cessation of therapy)[8-10] (D).

Response to corticosteroids is defined in several studies as a clinical improvement following high-dose oral corticosteroid therapy (40-60mg prednisone/day) within 30 days, or a clinical improvement after treatment with high-dose parenteral corticosteroids within 7-10 days[11] (D),[12](C). On the other hand, patients who do not respond to corticosteroids within this time frame are defined as steroid-refractory or steroid-resistant[11](D). Patients who are unable to reduce corticosteroid therapy below the equivalent of 10mg/day of prednisolone (or budesonide below 3mg/day) within 3 months of onset without recurrence, or who relapse within 3 months after discontinuing corticosteroid use are defined as steroid-dependent[9] (D).

Systemic corticosteroids, such as prednisolone or equivalent, are effective to treat active colonic CD[13,14] (A). Initial treatment of severe ileal CD includes prednisolone or parenteral corticosteroid (hydrocortisone) equivalent to 40-60mg/day of prednisone in a divided dose or in continuous infusion[9,10] (D).

The inflammatory intensity and the level of malabsorption are greater in cases of extensive impairment (> 100 cm) than when the disease is located in the small bowel. In this scenario, treatment with systemic corticosteroids and the early introduction of immunomodulators are considered appropriate[9] (D).

Mild esophageal or gastroduodenal CD can be treated with a proton pump inhibitor alone. Severe or refractory disease requires additional systemic corticosteroids or a strategy based on anti-TNF agents[9] (D). However, corticosteroids are not effective in treating patients with CD and perianal fistulas [10] (D).

3.2 MAINTENANCE OF REMISSION

Recommendation

- Corticosteroids are not recommended to maintaining CD remission. (A)

Exposure to corticosteroids should be minimized, although it´s the main support for the initial treatment of active disease[9] (D).

A meta-analysis evaluating conventional systemic corticosteroids, such as prednisolone, to maintain clinical remission that included 3 studies and 403 patients showed no significant difference between corticosteroids and placebo at 6, 12 or 24 months[15] (A).

Two other systematic reviews with meta-analysis[16,17] (A) evaluated the use of budesonide (6mg/day) to maintain clinical

remission and confirmed the conclusion that "modest benefits related to lower CDAI scores and a longer period of time to recurrence are offset by higher rates of treatment-related adverse events"[9] (D). Therefore, prolonged use of corticosteroids should be avoided, and the introduction of immunosuppressive therapy, such as azathioprine or 6-mercaptopurine, should be preferred[18-20] (A).

Following ileocolic resection, systemic corticosteroids and budesonide 6mg/day are not effective to reduce the likelihood of symptomatic recurrence[10] (D).

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4. THIOPURINES

4.1 INTRODUCTION

The 6-Mercaptopurine (6-MP) and its prodrug azathioprine (AZA) are purine analogs that competitively interfere with the metabolism of the nucleic acid.[1,2] Consequently, both drugs reduce cell proliferation and have immune modulating properties. The purine antimetabolites inhibit the synthesis of ribonucleotides, but at least one immunomodulatory mechanism is to induce apoptosis of T cells, modulating cellular signaling (Rac1);[3] were also demonstrated changes in subpopulations of T cells.[4] AZA is metabolized non-enzymatic manner, mercaptopurine, which are subsequently metabolized to 6-thioguanine nucleotide (6-TGN), which is the active moiety of the drug.

4.2 INDUCTION OF REMISSION

Recommendation

- **Patients without previous therapy with immunosuppressants and cortico-dependent should be treated with a thiopurine. (A)**
- **It was not demonstrated superiority of azathioprine when introduced at the beginning of CD evolution, compared with conventional therapy. (A)**
- **Combination therapy of azathioprine (AZA)with infliximab (IFX) is more effective in inducing remission of free corticosteroids in comparison to monotherapy (IFX or AZA) in patients without previous use of immunosuppressive or biological therapy. (A)**

A systematic review and meta-analysis evaluating the results of five studies of induction of remission, included 380 adult CD patients (N) and a 12-17 weeks. The authors failed to identify significant differences in clinical remission rates (CDAI <150 and HBI ≤ 3) between the use of purine analogues (AZA or 6-MP) and placebo.[5] **(A)**. Clinical remission (primary endpoint) with thiopurines was obtained in 48% of patients (95/197) and 37% (68/183) placebo (RR = 1.23 95% IC: 0.97 to 1.55)[5] (A). In this analysis, no heterogeneity was detected for this comparison (p = 0.35, I2 = 9%) and GRADE[6] test indicated that the quality of the evidence for the primary endpoint (clinical remission) was moderate[5] (A). The response rate (clinical remission or improvement) was higher in four randomized controlled trials (ECRs) that lasted more than 16 weeks (RR 1:59, 1:05 to 2:41 95%) owing to the delay in onset of drug action. The thiopurines group showed greater "steroid sparing effect" (final dose of prednisone <10mg/day) analysis of 4 trials with the total de143 adult patients (RR 1.34; 95% IC: 1.02 to 1.77; 3-109 NNT occurring corticosteroid-sparing effect by 46% in the placebo group)[5] (A). With respect to EAS, there was no significant difference between groups related to exclusion adverse events [RR 1.7, 95% IC 0.94 to 3.08] in 8 ECRs analysis with a total of 510 adults, and serious AEs [RR 2:57, 95% IC 0.92 to 7.13], in the analysis of compounds 2 ECRs with 216 adults CD patients[5] (A).

In the SONIC randomized, double-blind trial, the efficacy of infliximab monotherapy, azathioprine monotherapy, and the two drugs combined was evaluated in 508 CD adults with moderate-to-severe activity, who had not undergone previous immunosuppressive or biologic therapy. Patients were randomized to receive an intravenous infusion of IFX 5mg/kg at weeks 0, 2 and 6, and after 8/8 weeks plus daily oral placebo capsules; oral AZA 2.5mg/kg/day plus placebo infusion; or combination therapy with the two drugs. The patients received study medication until the 30th week and could continue in a blind extension until the 50th week. The combined therapy (IFX plus AZA) was better than IFX monotherapy to induce corticosteroid-free remission at week 26 (57% *vs* 45%, respectively; p <0.05; NNT= 4 to 55). Monotherapy AZA therapy was less effective for inducing free remission corticosteroids (30%) at week 26 p <0.01 *vs* both schemes based on IFX). The mucosal healing defined as the disappearance of ulcers was greater in the combination therapy group (AZA + IFX) compared to the other two groups. Serious infections occurred in 3.9% of patients in the combined therapy group, 4.9% in IFX group and 5.6% in the AZA group (no statistical significance for any of the comparisons, NNT = NS)[7,8] (A).

A network meta-analysis confirms that IFX or combination of IFX plus AZA are more effective than placebo in inducing remission in adult CD patients[9] (A).

Early treatment with IFX ("top-down strategy") was compared with a conventional approach (corticosteroids and immunomodulators - "step-up strategy") in an open-label. multicenter ECR. It was included 133 adult patients with active CD (CDAI score> 200 points for at least two weeks prior to randomization) of recent onset (without prior therapy with corticosteroids, anti-metabolites or IFX), that were randomized into two groups: a group with IFX plus AZA as initial therapy, or corticosteroids and AZA. Additional treatment with IFX was permitted and, if necessary, corticosteroids, to control disease activity. Although remission rates at 1 year were similar between the two groups (77% *vs* 64%, respectively, p = 0.15), 19% of the patients in the strategy "step-up" were still with corticosteroids, compared with 0% in the "top-down" strategy (p <0.001). Endoscopic remission was higher in approach "top-down". There was no significant difference between the two groups regarding the number of SAEs[10] (A).

The Diamond Study, a multicenter, randomized, open-label study compared the use of adalimumab (ADA) monotherapy (160mg at week 0, 80mg at week 2 and then 40mg weekly to 52nd) with ADA plus azathioprine (AZA) (25 -100mg/day) in immunosuppressant-naïve CD patients with moderate to severe activity (CDAI ≥220) for 52 weeks. The rate of clinical remission (CDAI score <150) did not differ between the group ADA monotherapy and combination therapy group at week 26 (71.8% *vs* 68.1%, respectively, OR, 0.84; p = 0, 63). There endoscopic improvement at week 26, higher in the combined group (84.2%, n = 57) than in the monotherapy group ADA (63.8%, N = 58) (p = 0.019)[11] (A).

4.3 MAINTENANCE OF REMISSION

Recommendation

- **Combined therapy (IFX plus AZA) has greater efficacy in maintenance ateroid-free remission compared to monotherapy (IFX or AZA) in patients with no prior use immunosuppressant or biological. (A)**
- **If the remission was achieved with the combined therapy (anti-TNF-α and thiopurines) in the treatment of naïve patients it is recommended to maintain the same regimen. (D)**
- **The continuous use of AZA after obtaining clinical remission in CD is associated with reduced risk of relapse as compared to its suspension. (A)**
- **In patients with moderate to severe activity with an evolution of at least three months, without the use of biological therapy or thiopurines, the use of combination therapy (ADA plus AZA) has the same efficacy as monotherapy with ADA for clinical remission but an endoscopic improvement was higher in combination therapy. (A)**

A systematic review and meta-analysis involving six ECRs (a total of 489 patients with age superior to 18 years with quiescent CD) showed that AZA (1.0 to 2.5mg/kg/day) was significantly better than placebo in maintaining remission period during 6 to 18 months, but with poor quality criteria assessed by the evidence GRADE[6], and the expense of increased rate of adverse effects. Seventy-three percent of patients of AZA group remained in remission compared with 62% of patients in the placebo group (RR 1.19, 95% IC 1.05 to 1.34; I2 = 0%; NNT= 9). In this review, the low quality of evidence makes impossible to obtain a clear conclusion when comparing the thiopurines with budesonide, mesalazine or other[12] (A).

Two ECRs showed no superiority of AZA when introduced at newly diagnosed CD disease. The first study showed that AZA (2.5mg/kg/day) within 6 months after the CD diagnosis may not increase the remission time compared to the conventional treatment, in selected cases of adult patients at high risk for disease "disabling" (≥ 2 of the following parameters: age <40 years, active perianal injury and corticosteroids within 3 months after diagnosis). Conventional treatment consisted of AZA only in the presence of cortico-dependence, active disease with frequent relapses, poor response to corticosteroids or in the presence of severe perianal disease. In following three years, comparing AZA *versus* conventional therapy, median of trimesters in remission was 67% *vs* 56%, respectively (not significant)[13] (B). The second ECR included adult patients with newly diagnosed of CD (less than 8 weeks) of CD. Patients were randomized to AZA (2.5mg/kg/day, N = 68) or placebo (N = 63). Only corticosteroids were permitted in concurrent use for the control of disease activity. There was no difference in the number of patients in sustained remission between groups, without the use of corticosteroids up to 18 months (difference of -7.6%; 95% IC -9.2% to 24.4%, p=48, NNT = NS)[14] (A).

A systematic review and meta-analysis concluded that continued use of AZA or 6-mercaptopurine (6-MP), for up to 18 months after clinical remission, can reduce the relapse rate in CD patients with. In this review were included three studies, being 2 cohorts and 1 ECR, with total of 334 patients [AZA 218 and 126 patients with placebo or no treatment]). There were 45 (20.6%) patients that relapsed in AZA group and 46 (36.5%) in the control group showing that continuous AZA treatment significantly decreased the likelihood of relapse (OR = 0.35, 95% IC: 0.21 -0.6); I2 = 0, NNT= 6)[15] (A). Another meta-analysis of 3 ECRs (1 included in the meta-analysis cited above) consists of the total 163 patients, evaluated the AZA withdrawal in remission patients for 5 to 7.5 years and compared with continued therapy. Continued AZA was associated with reduced risk of relapse compared to the withdrawal (RR = 0,39, IC 95% 0,21 to 0,74; $I^2 = 0$; NNT = 4 (IC95% 3-14)[16] (A).

Analogs of thiopurine (AZA, 6-MP) can reduce the need for surgical resection in CD patients, according systematic review that included 17 observational retrospective studies (N=21 632 CD patients). It was observed a reduction of the risk of surgical resection when compared the use and non-use of thiopurines (HR = 0.59, 95% IC 0.48 to 0.73). The analysis of 10 studies (N = 12 586 patients), however, the results has high heterogeneity. The use of thiopurines for more than 6 months compared to the non-use or use for less than 6 months (study 3) also reduced the risk of surgery[17] (B).

4.4 FISTULIZING PERIANAL CROHN'S DISEASE

Recommendation

- **In simple fistulizing refractory or recurrent disease not responsive to antibiotics, thiopurines can be used as second-line therapy. (D)**
- **In complex perianal fistulizing disease , AZA may be used as combination therapy with anti-TNFα in order to increase the effect of the biological therapy. (D)**

There are no ECRs that assess the effect of AZA or 6-MP on the closing perianal fistulas as a primary outcome in CD. A meta-analysis of five ECRs evaluated closing perianal fistula, as secondary endpoint, yielding response in 54% of cases *vs* 21% in placebo group (odds ratio, 4:44 [95% 1:50 to 13:20])[19] (B). Other studies showed improvement of perianal disease with prolonged use of purine derivatives[20,21] (D). In simple fistulizing refractory or recurrent disease does not respond to antibiotics, thiopurines can be used as second-line therapy. In complex perianal fistulas can consider the combined treatment of anti-TNF-α with thiopurines, in order to increase the effect of anti-TNF-α[22] (D).

4.5 PREVENTION OF POSTOPERATIVE RECURRENCE

Recommendation

- The treatment based on the risk of clinical recurrence with early colonoscopy and step up treatment for recurrence is better than only conventional therapy in preventing CD postoperative recurrence. (A)
- Prophylactic treatment is recommended after ileal bowel resection in patients with at least one risk factor for recurrence and thiopurines is one of the treatments of choice. (A)

A recent randomized multicenter study showed that treatment according to the evaluation of the risk of clinical recurrence with early colonoscopy and introduction of the *step up* treatment for recurrence it´s better than just conventional therapy in the prevention of postoperative recurrence of CD[23] (A).

A prophylactic treatment is recommended after ileal bowel resection in patients with at least one risk factor for recurrence. To prevent post-operative recurrence the drugs of choice are thiopurines[22] (D).

A systematic review and meta-analysis (2 ECRs and 168 patients evaluated at 1 - 2 years), comparing the thiopurines (AZA or 6-MP) to placebo in patients with CD surgically induced remission identified significant reduction in relapse rates clinic in the group of thiopurines. In this analysis, 48% of thiopurines group relapsed compared to 63% of subjects treated with placebo (RR = 0.74; 95% IC 0.58 to 0.94). No heterogeneity was detected for this comparison (p = 0.53, I2 = 0%). However, there was clinical and methodological heterogeneity between the two studies, with regard to the choice of purine analogue, and the use of other drugs. Conducting assessment of the quality of evidence through GRADE[6] instrument, it´s observed that the overall quality of the evidence for this result was low, due to the high risk of bias. However, sensitivity analysis using the random model (*random-effect*) showed significant difference in the clinical recurrence rates, favoring the use of purine analogues (RR = 0.76; 95%

IC 0.61 to 0.95; NNT = 4-32). With respect to EAS not logged difference between the use of thiopurines and the use of placebo, but 15% of patients treated with purine analogues discontinued its use because of AEs compared to 11% in the placebo group (RR = 1.33 [95% IC 0.59 to 2.98])[24] (A). This review also compares the use of the thiopurines with aminosalicylates (5-ASA) and found no significant difference in the clinical relapse rate, at 1 or 2 years ("random-effects" RR = 1.14, 95% IC 0.93 to 1.41; 5 ECRs analysis of 425 patients). In this comparison AZA was associated with an increased dropout of therapy due to AEs (RR = 2.07; 95% IC 1.26 to 3.39; 5 ECRs analysis with 423 patients)[23] (A). One study (n = 33) showed reduction of clinical relapse (RR 5.18, 95% IC 1.35 to 19.83) and endoscopic recurrence (RR 10.35, 95% IC 1.50 to 71.32) favoring ADA on the use of AZA[25] (B). There was insufficient evidence to compare AZA to IFX[24] (A).

In another meta-analysis, the pooled analysis, the thiopurines were more effective than the control group (placebo or without antibiotic induction therapy or mesalazine) in the prevention of clinical recurrence at 1 year (NNT = 13) and preventing endoscopic recurrence serious in one year, but they haven´t been effective in preventing very severe postoperative recurrence in one year. If only comparing placebo studies were considered, the effectiveness of thiopurine analogs would be superior to placebo for clinical and endoscopic recurrence at 1 year (NNT = 7 and 4, respectively)[26] (A).

4.6 ADVERSE EVENTS

Recommendation

- **Treatment with thiopurines is associated with an increased risk of lymphoma and non-melanoma skin cancer, however, the absolute rates of these diseases remain low and the risk/benefit can be evaluated in shared decision with the patient. (A)**

Adverse events of immunosuppressants (AZA and 6-MP) can occur in up to 20% of cases, most often in the first 2-3 weeks and comprises mainly allergic reactions, leukopenia and hepatotoxicity[12,27] (A).

Therapy with thiopurines has been linked to increased risk of non-Hodgkin lymphoma[28,29] (A). A decision analysis study, using a Markov model, concluded that the AZA results in increased life expectancy adjusted for quality, especially in young patients with the lowest baseline risk of lymphoma and longer life expectancy in the absence of deaths related to CD[30] (A). Recent meta-analysis confirms these results and suggests that the risk decreases after discontinuation of AZA[31] (A).

The prospective study (CESAME study) cited above, included 19.486 IBD patients (CD, UC disease or unclassified), with a follow up of 35 months (median). The probability of lymphoproliferative disease was 5-fold higher in patients using thiopurines compared to those who have never used (adjusted HR = 5.28, 95% IC 2.01 to 13.9, p = 0.0007)[29] (A).

Data analysis of 17,834 patients with IBD identified 44 cases of lymphoma, and 19 had previously been exposed AZA / 6-MP. There was a positive correlation between lymphoma, *Epstein-Barr* virus and AZA / 6-MP[32] (C).

It is reported lower myelotoxicity rate in IBD patients using AZA/6-MP. Systematic review limited by the heterogeneity of 35 trials including 9103 person-years showed: an incidence of drug-induced myelotoxicity of 3% per patient year of treatment; risk of mortality from myelotoxicity of 0.98%; incidence of severe myelotoxicity <1% per patient year of treatment and risk of mortality in severe myelotoxicity <0.1%[33] (A). Among patients with IBD the thiopurines increases the risk of myeloid disorders up to 7 times[34] (B). A greater incidence of myelosuppression for the first 8 weeks of therapy may justify a more frequent monitoring this period[35] (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. Comparing use with non-use of thiopurines, the thiopurines were associated with increase of the number of non melanoma skin cancer in all studies (HR = 2.28; 95% IC 1.50 to 3.45), however with high heterogeneity I^2 = 76%), but no evidence of publication bias [36] (A).

Considering the last four decades, the use of thiopurines shows no evidence of risk of developing solid tumors[37] (B). Data analysis of the CESAME study cohort, already mentioned above, evaluated the development of colorectal cancer (CRC) among patients with IBD, showing that patients with extensive colitis, and disease of long duration are more likely in this instance, however, this is less among patients receiving therapy with thiopurine compared with those who have never received this treatment (adjusted HR for high grade dysplasia and CRC = 0.28; 95% IC 0.1 to 0.9; p = 0.03)[38] (B).

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5. METHOTREXATE

Recommendation

- **The weekly therapy with methotrexate 25mg IM or SC is effective at inducing remission in adults with refractory Crohn's disease. For maintenance of remission the dose can be reduced to 15mg (oral or IM). weekly**
- **The combination of methotrexate IM with prednisone allows clinical improvement, reducing the need for corticosteroids in patients with active disease.**
- **There is no benefit in the addition of methotrexate to infliximab therapy for induction of remission.**
- **The combination therapy of methotrexate 15-25mg/week parenteral to anti-TNF drug reduces the formation of antibodies and can improve the long-term results.**

Methotrexate (MTX), the second most commonly used immunosuppressive agent for IBD being effective in Crohn's disease[1] (B). MTX acts by inhibiting dihydrofolate reductase and interfere with pyrimidine and purine biosynthesis by preventing the synthesis of DNA, RNA and cellular proteins. With these cytotoxic effects it may have anti-inflammatory effects by inhibiting the synthesis of cytokines and other eicosanoids[2](B).

5.1 INDUCTION OF REMISSION

A systematic review that included seven ECRs (n = 495), all with methodological limitations (allocation with uncertain concealment, lack of blinding and high loss rate), compared oral or parenteral MTX to placebo or other drugs in adult patients with refractory CD. The heterogeneity of the population, interventions and outcomes analyzed prevented meta-analysis[3] (A).

One ECR (n = 141) compared IM MTX in steroid-dependent patients at a dose of 25mg/week to placebo and showed that MTX significantly increased free remission corticosteroids (39% *vs* 19%; p = 0.025; NNT = 5); reduced the prednisone (P = 0.026), but increased the abandonment of treatment for adverse events (17% *vs* 2%; *p* = 0.012; NNH = 6), between 16 weeks[4] (B). Two other studies including adults with refractory disease (n = 85) compared oral MTX (12.5 to 15mg/week) to placebo, and no significant difference in induction of remission or abandonment by adverse events, was observed at week 16[5,6] (B).

In comparison with oral or parenteral MTX, thiopurines showed no significant difference in remission rate on weeks 24-36 (n = 143 three studies)[6-8] (B). One study (n = 54) compared parenteral and oral MTX to azathioprine and showed a higher rate of adverse events in the MTX group (63% *vs* 26%, p <0,05/NNH=2)[8] (B).

The combination therapy of MTX and infliximab did not increase the remission rate at weeks 14-24 on an analysis of two ECRs[9,10] (B).

5.2 MAINTENANCE OF REMISSION

A systematic review that included five ECRs evaluated the use of MTX in the maintainance of remission in 333 adult patients with CD. Remission was defined as a CDAI score ≤ 150, with or without the corticosteroid [11] (B). 65% of the MTX group (IM) maintained remission compared to 39% in the placebo group (RR 1.67, 95% IC 2.67 to 1:05). The other ECR showed that 90% of patients with oral MTX maintained remission when compared to 67% with placebo (RR 1.67, 95% IC 2.67 to 1:05).

In a blind ECR of unspecified allocation, 76 adult patients with active CD who achieved remission with MTX 25mg / IM weekly for 16-24 weeks were randomized to 15mg/week (n = 40) *versus* placebo (N = 36) for 40 weeks. At week 40, the remission rate was 65% in the MTX group and 39% in the placebo one (p = 0.04; NNT = 4 with a 95% NNT 2-23). It was necessary to use prednisone due to relapse in 28% *vs* 58% (p = 0.01; NNT = 4) for MTX and placebo groups, respectively. There was no difference between groups in the total rate of AE and the number of serious ones[12] (B).

Another ECR (n = 22) compared MTX 12.5mg weekly orally to placebo and no statistically significant difference was observed in remission rate at week 36 of treatment (90% *vs* 66.7%, respectively, RR = 1.67, 95% 2.67 1.05 The IC95%) [6] (B).

An analysis of two ECRs 8.9 (B) consisting of CD patients with small bowel and colon involvement (N = 50) compared oral MTX to 6-mercaptopurine, showing no difference in the maintenance of remission rates between the two groups (77% *vs* 57%, respectively; RR = 1,36; CI95% 0.92 to 2.00)[11] (B).

Two ECRs (n = 145)[9,10](B), which included patients with small bowel and colonic CD treated with combination therapy (MTX associated with IFX) *versus* IFX monotherapy for 36-48 weeks showed no significant difference in remission rates between the groups (54% *vs* 54%, respectively; RR = 1.02, 95% IC 0.76 to 1.38)[11] (B). However, MTX reduced the formation of anti-infliximab (anti-TNF-α)[10] (B), suggesting that combination therapy can increase the durability of anti-TNFα therapy). The findings of another study favor this same case, when it was found that combination therapy of anti-TNF-α and MTX at weekly doses of 15-25mg IM was superior in maintenance of clinical remission compared with MTX alone at lower doses[13] (B).

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6. CALCINEURIN INHIBITORS

Recommendation

- **There is no evidence to support the use of cyclosporine and tacrolimus in the induction and maintenance of remission in patients with active Crohn's disease. (A)**
- **The oral tacrolimus in minimum blood concentration of 10 to 15 ng/ml, can be used as a therapy in severe and refractory CD to anti-TNF agents. (A)**
- **Topical tacrolimus may be recommended for patients with perianal ulcers related to Crohn's disease. (B)**
- **Tacrolimus may be effective in perianal penetrating Crohn's disease refractory to anti-TNF therapy. (B)**

6.1 CYCLOSPORINE

6.1.1 INDUCTION OF REMISSION

A systematic review of four randomized controlled trials (ECRs)[1-4] (n = 740) evaluated the use of cyclosporine orally for at least 12 weeks therapy to placebo for induction of remission of active CD (CDAI> 150) with or without corticosteroids, showing no efficacy.

Two ECRs evaluated the use of cyclosporine 5mg/kg/day orally *vs* placebo (n = 176) and after 16 weeks of treatment no statistically significant difference was shown in clinical remission rates (odds ratio [OR] = 1.96 95% IC 0.97 to 3.93)[5] (A).

A ERC (n = 71) comparing different doses of oral cyclosporine (median 7.6mg/kg/day) *vs* placebo showed clinical improvement with the use of cyclosporine after 12 weeks (59.5% *vs* 32.4%; p = 0.024, NNT = 4), however, the clinical criteria was not validated.[1] (B).

Three ECRs (n = 399) with cyclosporine use showed a statistically significant increasement in AEs and abandon rates of treatment compared to placebo (62.6% *vs* 8% ciclosporin placebo; p <0.0001, NNH = 1.8). The adverse effects associated with cyclosporine include paresthesia, hypertrichosis, dyspepsia, hypertension, rash, dizziness, diarrhea, headache, mouth ulcers, ocular photosensitivity, nausea, vomiting, epigastric pain, tremor, back pain, weight gain, gingival hyperplasia, renal failure and increased serum creatinine level[5] (A).

6.1.2 MAINTENANCE OF REMISSION

Another ECR (n = 118) compared oral cyclosporine (5mg/kg/day) to placebo for one year in maintenance of remission of adults with quiescent CD. It showed no significant difference in clinical relapse rate (RR = 0.96; 95% IC 0.77 to 1.2), with only 20% of remission maintenance rate in each group[4,6] (A).

6.2 TACROLIMUS

6.2.1 INDUCTION OF REMISSION

Penetrating Crohn's disease

An ECR assessed the use of oral tacrolimus in 48 patients with active CD and enterocutaneous or perianal fistulas (42 with perianal fistulas) that do not responded to antibiotics. Patients were randomized to use oral tacrolimus (0.2mg/kg/day), adjusted to serum levels of 10 to 20 ng/ml or placebo for 10 weeks. It was allowed stable doses of corticosteroids, immunosuppressants, aminosalicylates or oral antibiotics. An improvement of fistulas was achieved in 43% of patients using tacrolimus *vs* 8% in the placebo group (RR = 0.64 for no improvement, 95% IC 0.44 to 0.92 p = 0.004; NNT = 3), however no significant difference in relation to the complete closure of fistulas and maintained for more than 4 weeks was observed (10% *vs* 8%). The association with thiopurines or biological therapy as infliximab didn´t influence the clinical response. The small number of patients with enterocutaneous fistulas precludes an assessment of the effectiveness of the medication in this condition. Therefore, oral tacrolimus induces improvement in the drainage of the fistula, but does not promote its healing[7] (A). Nephrotoxicity occurred more frequently in patients treated with tacrolimus (p = 0.008). Other common AEs in the tacrolimus group were headache (p = 0.01), insomnia (p = 0.006), cramps in the lower limbs (p = 0.01), paresthesia (p <0.001) and tremor (p = 0.006)[7] (A).

Topical tacrolimus 1 mg/g (1 g - twice/day) for 12 weeks compared to placebo was evaluated in an ECR that included 19 patients with perianal CD (fistulas and 12 with 7 with ulceration). Concomitant therapy with oral aminosalicylates, corticosteroids, methotrexate, 6-MP or azathioprine was allowed and 6 patients received treatment with infliximab. Data were analyzed at 16 and 24 weeks. Three of four patients with ulcers treated with topical tacrolimus showed improvement according to the attending physician's assessment, 0/3 compared to the placebo group. Topical tacrolimus showed no benefit in patients with perianal fistula. Two patients treated with tacrolimus developed perianal abscesses after an improvement in the drainage of leaks. Adverse events were infrequent and mild.

Luminal disease

The use of oral tacrolimus as therapy in severe CD refractory to anti-TNF agents was evaluated in a retrospective study involving 24 patients, of which 37% were steroid-dependent or refractory, treated for 4 months (median). The response was defined as improvement after at least 7 days of treatment from one or more of the following signs or symptoms: bowel movement frequency, the output fistula, rectal bleeding, abdominal pain, extra-intestinal manifestations or welfare. Remission was considered when the patient achieved less than 3 bowel movements/day; absence of rectal bleeding, abdominal pain or extra-intestinal manifestations and increased welfare. Response and steroid-free remission rates were 67% and 21%, respectively, and lasted an average of four months. Only 42% of patients discontinued corticosteroid therapy and surgery was required 54%, about 10 months after the beginning of tacrolimus. Patients with serum levels between 10 to 15 ng/ml showed the highest response rate (86 5%) and remission (57%). The rate of adverse events was 75% and no death or irreversible side effects attributable to the tacrolimus was reported after 56 months[8] (C).

A systematic review to evaluate the use of tacrolimus in the DC[15] included eleven studies, two ECRs[11,12] and nine case series totaling 163 patients with CD, of which 127 received tacrolimus (102 patients orally or EV and 25 topical). In patients with luminal CD, the pooled rate of remission and clinical response to tacrolimus was respectively 44.3% (7% -69%) and 37.1% (14% -57%). The pooled perianal disease remission and response rate was respectively 28.6% (0% -64%) and 38.8% (0% -57%). The combined data from the two studies with topical tacrolimus 13.16 (n = 14) showed that 35.7% of patients achieved remission and 28.6% parcial response[9] (C).

Cutaneous Crohn's disease

A number of cases that included 20 patients with cutaneous CD evaluated the use of tacrolimus 0.1% ointment to the affected areas 1x/day for 3 months (maximum total dose of 90 g). Seventeen patients completed 3-month treatment and 15 showed improvement on a severity scale prepared for this study and not validated. In the 3 months evaluation, 4 patients showed marked improvement (51 to 75%); 10 slight improvement (1 to 25%) or moderate (25 to 50%) and was withdrawn from the study. Ten patients relapsed between 3-9 days after completion of treatment and were being excluded from the study. Patients with late recurrence (after 12 weeks) had the option to continue the study with topical tacrolimus 0.1% for up to 12 months. Patients with perianal injury were those who responded better to the therapy, although only two of them have sustained remission. The most frequent complaints with the topical use of tacrolimus were local irritation, with burning and itching. Systemic absorption was not detected in any of the patients during the study[10] (C).

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7. BIOLOGICAL DRUGS

7.1 ANTI-TNF-α THERAPY

7.1.1 *INFLIXIMAB*

Recommendation

- Infliximab is effective in inducing and maintaining remission in patients with moderate to severe Crohn's disease refractory to conventional therapy (B).
- Infliximab is effective in fistulizing CD (B).
- Infliximab is effective in preventing recurrence of Crohn's disease in patients undergoing ileocolectomy (A).
- Combination therapy of infliximab with azathioprine induces better clinical outcomes when compared to infliximab or azathioprine monotherapy (A).

Infliximab (IFX) is an anti TNF drug consisting of the union of the variable binding regions of murine monoclonal antibody specific for human tumor necrosis factor (A2) and the constant regions of human IgG1 immunoglobulin.

INDUCTION OF REMISSION

The first study (multicenter, double-blind) evaluating the use of IFX in patients (N = 108) with moderate to severe CD refractory to aminosalicylates and steroids was published in 1997 by Targan et al.[1], showing that the drug was effective when compared to placebo in a single infusion at a dose of 5 mg/kg, 10 mg/kg or 20 mg/kg, with no difference between these doses. Comparing IFX with placebo up to four weeks, the clinical response rate was 64% in patients treated with 5-20 mg/kg IFX *vs.* 17% [NNT = 1.6]) and the remission rate was 33 *vs.* 4% (NNT = 4), respectively. Adverse effects (AEs) rates were similar between the groups.[1] (B)

In 1999, Present et al. demonstrated that infusions of IFX (5 mg/kg [n = 31] and 10 mg/kg [n = 32]) at weeks 0, 2 and 6 were superior to placebo (n = 31) for abdominal or perianal fistula closure, when the patients were followed up for 18 weeks. The number of patients with ≥50% reduction in the number of fistulas with active drainage was 62% in the IFX group (5-10 mg/kg) *vs.* 26% in the placebo group (NNT = 3). The apparent cure was followed by abscess formation in 11% of patients treated with IFX due to occlusion of the fistulous orifice in the cutaneous plane, with the maintenance of the opening in the gastrointestinal tract. The most common IFX AEs were headache, abscess, upper respiratory tract infection and fatigue[2] (B).

MAINTENANCE OF REMISSION

One of the main studies using IFX as an effective drug in the maintenance of remission was the multicenter, double-blind, randomized controlled trial (RCT) ACCENT I (*Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulizing Crohn's Disease*), which included 573 patients with luminal CD (CDAI between 220 and 400) who received IFX (5.0 mg/kg EV). They were evaluated for response to the treatment at the end of two weeks. At this stage, 58% of the patients responded to the first dose with a 70-point decrease in the CDAI from baseline and decrease of at least 25% in the total score. Patients who responded to IFX were randomized into three groups: group I - placebo intravenous infusions at weeks 2 and 6 and every 8 weeks up to 46 weeks; group II: 5.0 mg/kg IFX at these same intervals and group III: 5.0 mg/kg IFX at weeks 2 and 6 followed by 10 mg/kg every eight weeks until the end of follow-up[3] (B). Thirty-nine percent of patients from group II, 45% of group III patients and 21% of group I patients were in clinical remission with CDAI lower than 150 at week 30, and this difference was significant (absolute risk reduction (ARR) = 0.18 with 95% CI: 0.05 to 0.277 and NNT = 5 compared to group I and II, and ARR = 0.23 with 95% CI: 0.106 to 0.354 and NNT = 4 compared to groups I and III, respectively). After week 54, 40% of the IFX group achieved clinical remission with corticosteroid withdrawal *versus* 15% of the placebo group, with no significant differences between the two doses of 5 mg/kg or 10 mg/kg. The incidence of severe infections was similar among all treatment groups[4] (B).

A multicenter, double-blind, randomized, placebo-controlled study (ACCENT II, 2004) evaluated the efficacy of IFX maintenance therapy in 306 adult patients with CD and one or more abdominal or perianal fistulas with active drainage for at least three months. Patients received IFX 5 mg/kg intravenously at weeks 0, 2 and 6. One hundred ninety-five patients that responded at weeks 10 and 14, and 87 unresponsive patients were then randomized to receive placebo or IFX 5 mg/kg intravenously every 8 weeks (at weeks 14, 22, 30, 38 and 46). They were followed until the week 54. Among respondents, loss of response time was significantly longer for patients receiving IFX maintenance therapy than for those receiving placebo maintenance (more than 40 weeks *vs.* 14 weeks, p <0.001); 42% *vs.* 62% lost the response (NNT = 5). Among the non-responders, 21% and 16% had subsequent response when IFX and placebo were compared, respectively, but without statistical significance (p = 0.6). IFX did not reduce the risk of new fistula-related abscess in 54 weeks (ARR = 5.1%, 95% CI -0.32 to 0.13, NNT = NS). It should be noted that the type of fistula (abdominal and perianal fistulas) was not stratified in this study, compromising the analysis of the results. Patients in the IFX maintenance group were more than twice as likely to have antinuclear antibodies and almost four times as likely to have antibodies to double-stranded DNA than placebo maintenance patients. There was no difference in the number of patients with adverse effects between the two groups (NNT = NS)[5] (B).

COMBINATION THERAPY

In the double-blind RCT *SONIC study*, the efficacy of IFX monotherapy, azathioprine (AZA) monotherapy and the two drugs combined were evaluated in 508 adult patients with moderate to severe CD without prior exposure to immunosuppressive or biological therapy. Patients were randomly assigned to receive an intravenous infusion of IFX 5 mg/kg at weeks 0, 2 and 6 and then every 8 weeks combined with daily placebo capsules; Oral AZA 2.5 mg/kg/day, combined with placebo infusion; or combination therapy with the two drugs. Patients were given study medication by the week 30 and could continue until the end of the 50-week double-blind extension period. Combination

therapy (IFX with AZA) was superior to IFX monotherapy for induction of corticosteroid-free remission at week 26 (57% *vs.* 45%, respectively, p <0.05, NNT = 4 to 55). AZA monotherapy was the least effective (30% corticosteroid-free remission at week 26, p <0.01 *vs.* both IFX based regimens). Mucosal healing (defined as the disappearance of ulcers) was higher in the combined treatment group (AZA with IFX) when compared to the other two groups. Serious infections occurred in 3.9% of the combination therapy group patients, 4.9% in the IFX group and 5.6% in the AZA group, with no statistical significance for any of the comparisons (NNT = NS)[6,7](A).

A network meta-analysis confirms that IFX or the combination of IFX and AZA are more effective than placebo in inducing remission in CD in adult patients[8] (A).

In another study, 113 corticodependent (luminal relapse after corticosteroid reduction for at least two times) adult patients with moderate to severe CD (CDAI = 220-400) were randomized to receive an infusion of IFX 5 mg/kg or placebo in weeks 0, 2 and 6. All patients received AZA at a dose of 2-3 mg/kg/day or 6-mercaptopurine (6-MP) 1-1.5 mg/kg/day. Clinical success (remission, without the use of corticosteroids) was defined as CDAI <150 without corticosteroids. Benefit and increase in clinical remission rate for the combined therapy group was observed at week 24 (ARR = 27.5%; 95% CI: -44% to -10%, NNH = 4)[9] (A).

Early treatment (top-down approach) with IFX was compared to the conventional approach (immunomodulators + corticosteroids, step-up strategy) in multicenter, open-label RCTs. A total of 133 adult patients with active CD (CDAI score >200 for a minimum of 2 weeks prior to randomization) were randomized into two groups: initial therapy with IFX and AZA, or corticosteroids, and later AZA. Further treatment with IFX and, if necessary, corticosteroids could control disease activity. Although remission rates at 1 year were similar (77% *vs.* 64%, respectively, p = 0.15), in 19% of the cases in the step-up strategy the use of corticosteroid was necessary compared to 0% in the top-down approach (p <0.001). Endoscopic healing rate was higher in the top-down approach. There was no difference between the two groups in terms of number of serious adverse events[10] (A).

PREVENTION OF POSTOPERATIVE CLINICAL RECURRENCE

The efficacy of IFX in preventing postoperative recurrence in CD was evaluated in 297 adult patients in a multicenter, placebo-controlled RCT (mean age = 36 years) undergoing ileocolonic resection within 45 days (mean = 36 days) before randomization. One group used IFX 5 mg/kg infused every eight weeks *versus* placebo for 208 weeks. IFX was not superior to placebo in preventing clinical recurrence at week 76 but reduced endoscopic recurrence. A smaller proportion of patients in the IFX group had clinical recurrence (CDAI ≥ 200 and ≥ 70-point increase in the CDAI from baseline), as well as endoscopic recurrence (Rutgeerts score ≥ i_2, new fistula, return of drainage or abscess) until the week 76 compared to the placebo group, with no statistical significance (12.9% *vs.* 20.0%; absolute risk reduction [ARR] with IFX, 7.1%; (95% CI: -1.3% to 15.5%, p = 0.97). A significantly lower proportion of patients in the IFX group had endoscopic recurrence compared to the placebo group (30.6% *vs.* 60.0%, RAS with IFX, 29.4%, 95% CI: 18.6% to 40.2%; NNT = 4; p <0.001). Furthermore, a significantly lower proportion of patients in the IFX group had endoscopic recurrence, based only on Rutgeerts scores[3] ≥ i_2 (22.4% *vs* 51.3%, ARR with IFX, 28.9%, 95% CI: 18, 4% to 39.4%, p <0.001). This RCT was interrupted early (104 weeks) because there was no difference in the primary outcome (clinical recurrence). However, this rule was not predefined[10] (A).

7.1.2 ADALIMUMAB

Recommendation

- **Adalimumab is effective in inducing and maintaining remission of Crohn's disease in patients with moderate to severe Crohn's disease refractory to conventional therapy (B).**
- **Adalimumab may be effective in fistulizing Crohn's disease (B).**
- **Adalimumab is effective in preventing recurrence of Crohn's disease in patients undergoing ileocolectomy (B).**
- **There is no evidence of clinical benefit in the combination of adalimumab and azathioprine in patients with moderate to severe Crohn's disease (A).**

Adalimumab (ADA) is a fully human recombinant IgG1 monoclonal antibody that binds to soluble TNF-α.

INDUCTION OF REMISSION

The first double-blind placebo-controlled RCT published with ADA for CD patients was the CLASSIC I study (2006). CD adult patients with moderate to severe disease CD (CDAI = 220-450) (N=299) were randomized into 4 groups and followed up for 4 weeks. The groups were: subcutaneous placebo (SC) at week 0 and week 2; ADA 40 mg at week 0 and 20 mg at week 2; ADA 80 mg at week 0 and 40 mg at week 2; and ADA 160 mg at week 0 and 80 mg at week 2. The majority (95%) of patients completed the study. Comparing placebo *vs* ADA initial dose of 40 mg *vs* 80 mg *vs* 160 mg the study showed: remission rate (CDAI score <150) up to 4 weeks was 12% *vs* 18% (not significant) *vs.* 24% (p = 0.06) *vs.* 36% (p = 0.001, NNT = 5); decrease in CDAI score ≥ 100 points up to 4 weeks occurred in 25% *vs* 34% *vs* 40% *vs* 50% (p <0.05; NNT = 4). The incidence of adverse events was similar between groups, except for reaction at the site of application when ADA 160/80 mg doses were used. Therefore, doses of 160/80 mg of ADA (SC) showed higher rates of clinical remission and improvement of symptoms compared to other doses and placebo (ideal dose in inducing remission)[12] (A) .

The GAIN study (2007) evaluated the use of ADA as induction therapy in patients (n = 325) with moderate to severe CD (CDAI = 220 - 450) who had loss of response or intolerance to IFX treatment. Patients were randomized to treatment with subcutaneous ADA (SC) at doses of 160/80 mg or placebo at weeks 0 and 2. This study included 301 patients (93%), and, in the week 4, 21% of the patients (34/159) randomized to ADA had clinical remission (CDAI< 150) compared to 7% (12/166) of those treated with placebo. This difference was significant (ARR = 14.2%, 95% CI: -0.217 to -0.067 and NNT = 7). There were fewer adverse events in the ADA group (ARR = 15.7%, 95% CI 0.05 to 0.26, NNT = 6) and there was no difference between ADA *vs.* placebo for infection risk (NNT = NS)[13] (B).

MAINTENANCE OF REMISSION

The CLASSIC II study included 55 patients in clinical remission at the end of the CLASSIC I study, in order to establish the effectiveness of ADA in treatment maintenance. Patients were eligible for CLASSIC II randomization if they were in clinical remission at week 0 (week 4 in CLASSIC I) and week 4. At week 4, those in remission were randomly assigned to receive maintenance treatment with ADA 40 mg SC 14/14 days, ADA 40 mg 7/7 days, or placebo from week 4 to week 55. Patients with activity at both times entered an open cohort receiving 40 mg 14/14 days. All patients were followed until the end of the week 56. Clinical remission at the end of the week 56 occurred in 79% (15/19) in the ADA group 14/14 days, 83% (15/18) in the weekly ADA group and 44% (8/18) in the placebo group; (p <0.05 for each ADA group *versus* placebo). Among non-randomized patients, 46% were in remission at week 56. Maintenance treatment with ADA was well-tolerated. Rates of serious adverse events were low in ADA-treated and placebo-like patients. No patient developed severe infectious adverse events, opportunistic infections, tuberculosis, lupus, demyelinating neurological diseases or lymphoma; and no patient died[14] (B).

The randomized, double-blind, multicenter CHARM study established ADA efficacy in patients with moderate to severe luminal and fistulizing CD (CDAI = 220-450) for at least 4 months, at a follow-up of 56 weeks. Participants used ADA induction therapy (80 mg at week 0 and 40 mg at week 2), and at week 4, patients were stratified by the response (70-point decrease in the CDAI from baseline) and randomized into 3 groups: ADA 40 mg weekly, ADA 40 mg at 14/14 days and placebo. If patients had no response or had relapses after week 12, they could switch to open treatment with ADA. The primary outcome evaluated was the percentage of randomized responders who achieved clinical remission (CDAI <150) at weeks 26 and 56. The percentage of randomized responders in remission was significantly higher in ADA 40 mg weekly and 40 mg 14/14 days *versus* placebo at week 26 (40%, 47% and 17%, respectively, p <0.001) and at week 56 (36%, 41% and 12%, respectively, p <0.001). An increase in remission was observed at week 26 compared to placebo, both in ADA 14/14 days and ADA weekly (ARR = 25.8% with 95% CI: 0.150 to 0.36 and NNT = 4 and ARR 27.8% with 95% CI: 0.167 to 0.380 and NNT = 3, respectively). there was no difference between ADA weekly treatment or 14/14 days in the week 56 evaluation. However, remission rate in ADA-treated patient groups was greater than that in the placebo group (ARR = 25.4% with 95% CI: 0.154 to 0.343 and NNT = 4 and ARR = 31.4 with 95% CI: 0.209 to 0.407 and NNT = 3, respectively)[15] (A). This study also showed that in patients who had not undergone biological therapy before, the ADA remission rate was higher than those with previous use of IFX compared with placebo (ARR = 30.6%; 95% CI -0.41 to -0.19; NNT = 3) [15] (B). The subgroup of patients who did not respond to IFX responded better (remission rate) to ADA compared to placebo (ARR = 20.5%; 95% CI -0.31 to -0.09, NNT = 5) [15] (B). Adverse events occurred in 59% of the patients (507 of 854) during the induction period. However, only 5.3% of the cases were severe, and only one case was of multiple sclerosis[15] (A).

Patients entered an open-label extension study after 56 weeks participating in the CHARM study (ADHERE - *Adiditional long-term Dosing with Humira to Evaluate Sustained Remission and Efficacy in CD*). The patients that were still on blind therapy at the end of the CHARM study received ADA 40 mg 14/14 days after entry into ADHERE. Patients undergoing open therapy for ADA every two weeks or weekly continued adopting the same regimen. During ADHERE, patients with ADA 14/14 days could migrate to weekly doses in the event of relapse or non-response to treatment. Almost half of the participants had previous treatment with another TNF inhibitor. Among the 382 patients who completed the study, clinical remission rates (CDAI <150) at 2 years (by the original randomization) were 37.6% in those randomized to placebo, 41.9% in patients receiving ADA 14/14 days, and 49.8% in patients receiving weekly ADA. Moreover, there was a reduction in the rate of hospitalizations and the need for surgical treatment, associated with an improvement in the quality of life[16] (B).

The long-term (4-year) results of the CHARM and ADHERE studies show that less than one-third of patients using ADA maintain remission, and the same proportion of patients may discontinue treatment due to adverse events[17] (B).

Effectiveness of ADA for maintenance of remission was confirmed in the CHARM study[15], with some interesting data on mucosal healing available on the EXTEND study (*Extend the Safety and Efficacy of Adalimumab Through Endoscopic Healing* [RCT, double-blind]) which included 135 patients (age = 18 -75 years) with moderate to severe ileocolonic CD for ≥ 4 months and who were treated on an ADA induction regimen at a dose of 160mg SC at week 0 and then 80mg at week 2. Patients (n = 129) were randomized into groups with ADA 40 mg or placebo 14/14 days from week 4 to week 52. ADA (open study) was given to relapsed patients or those who did not respond to treatment, starting at week 8. Mucosal healing was reevaluated by ileocolonoscopy at weeks 12 and 52. The comparison of ADA *versus* placebo at week 12 showed: clinical remission (CDAI <150) in 47% *vs.* 28% (p = 0.021, NNT = 6); endoscopic remission in 52% *vs.* 28% (p = 0.006, NNT = 5) and mucosal healing (based on ileocolonoscopy) in 27% *vs* 13% (p = 0.056). The same comparison at week 52 showed: Clinical remission in 33% *vs* 9% (p = 0.001, NNT = 5); remission in 28% *vs.* 3% (p <0.001, NNT = 4) and mucosal healing in 24 *vs* 0% (p <0.001, NNT = 5). Therefore, maintenance therapy with ADA, immediately after ADA induction, may increase endoscopic remission rates at weeks 12 and 52 in patients with active CD[18] (B). At 52 weeks, there was a lower hospitalization rate in patients who maintained a healed mucosa. In this study, ADA was associated with five severe adverse events, including three opportunistic infections[18] (B).

FISTULIZING DISEASE

In the CHARM study, results of 117 patients with CD fistulas, 2/3 of them with a single lesion and 1/3 with more than one pathway treated with ADA in combined groups (N = 70) or placebo (47) were analyzed. Thirty-percent of the patients undergoing ADA maintenance therapy (combined groups) achieved complete fistula closure at week 26, increasing to 33% at week 56, *versus* 13% in the placebo group (ADA *vs.* placebo at weeks 26 and 56 with significant difference, p = 0.43 and p = 0.016, respectively)[15] (A).

An extension of the CHARM (open-label extension) study, evaluating long-term results (approximately 2-year follow-up), showed that 60% (22/37) of the patients treated with ADA maintained fistula healing, while the responders that were excluded

from the study (loss of efficacy, adverse effects, protocol violation), have reached the significant mark of 31%[19] (B).

In the GAIN study, 45 of 325 included patients had perianal fistula. There was no significant difference between groups in the clinical response or lesion remission to the 160/80mg induction regimen at weeks 0 and 2 or placebo[13] (B).

A multicenter, prospective, open, observational study, including patients with previous use of IFX for the same reasons as the 22 patients with fistulizing disease, and using the same dosage and control schedule of 4 weeks, showed fistula remission (complete closure of all fistulas that were draining from the baseline) in 5 patients (23%) and partial fistula response in nine (41%) (≥ 50% decrease in the number of fistulas that were draining from baseline) at week 4[20] (C).

The open-label, single-arm, multicenter, phase IIIb CHOICE study evaluated the safety and efficacy of ADA in patients with moderate to severe CD non-responsive or loss of response to IFX. Of the 88 patients with at least one fistula with drainage from baseline, 83 had data available at the last visit (the last visit dates ranged from week 4 to week 36). Fistula drainage decreased by 41.3% at the last visit compared to the baseline, when approximately 40% of the patients (34/88 patients) had complete healing of the fistula[21] (C).

COMBINATION THERAPY

The open, multicenter, controlled, open-label DIAMOND study (-*Deep Remission of Immunomodulator and Adalimumab Combination Therapy for Crohn's Disease*) evaluated the efficacy of ADA associated or not with azathioprine in patients (N = 177) with moderate to severe CD (CDAI ≥ 220), who have never used biological and immunomodulatory drugs (AZA, 6-MP, methotrexate, tacrolimus, or cyclosporin). Patients were randomized to ADA(SC) 160 mg at week 0, 80 mg at week 2, and thereafter 40 mg 14/14 days until the week 52 (monotherapy group, n = 92), or ADA associated with AZA (25-100 mg / day) (combined group, n = 85) for 52 weeks. The primary endpoint analyzed was clinical remission (CDAI <150) at week 26. The intention-to-treat analysis with non-responder imputation (NRI) showed that the clinical remission rate at week 26 was not different between the monotherapy group and the combined group (71.8% *vs.* 68.1%, OR = 0.84, 95% CI 0.44 to 1.61, p = 0.63). The analysis by protocol also showed no difference between the two groups for this outcome. The endoscopic improvement rate at week 26 was significantly higher in the combined group (84.2%) than in the monotherapy group (63.8%, p = 0.019). However, the clinical remission and endoscopic improvement rates at week 52 were not significantly different between the two groups (79.6% *vs.* 69.8%, p = 0.36). Over the course of 52 weeks, 19 patients (22.3%) in the monotherapy group and 22 patients (24.2%) in the combined group were excluded due to adverse events, with no significant difference between the groups. Therefore, this study suggests that AZA does not contribute to improving the efficacy of ADA treatment, as it does for the improved efficacy of treatment with IFX[22] (A).

PREVENTION OF POSTOPERATIVE CLINICAL RECURRENCE

Patients (With CD submitted to íleocolonic resection (N:51)) were randomized to treatment with ADA(SC) 160/80 mg and maintenance with ADA(SC) 40 mg 14/14 days, AZA 2.0 mg/kg/day or oral mesalazine 3.0 g/day. The treatment was initiated 2 weeks after surgery and patients were followed up for 2 years. After this period, 6.3% of the ADA group had endoscopic recurrence compared to 64.7% and 83.3% of the AZA group patients and the mesalazine group, respectively. The difference found is significant and favors individuals treated with ADA (ARR = 0.585 with 95% CI: 0.207 to 0.699 and NNT = 2, and ARR = 0.771 with 95% CI: 0.407 to 0.883 and NNT = 1 for treatment with ADA compared to the use of AZA and mesalazine, respectively)[23] (B). A total of 12.5% of the ADA group patients had clinical recurrence compared to 64.7% and 50% of the patients undergoing treatment with AZA and mesalazine, respectively, with significant differences (ARR = 0.522 with 95% CI: 0.132 to 0.719 and NNT = 2 and ARR = 0.375 with 95% CI: 0.001 to 0.568 and NNT = 3, for ADA group patients compared to AZA group patients and mesalazine group patients, respectively)[23] (B). Therefore, ADA is superior to thiopurines and mesalazine in preventing recurrence of postoperative CD.

7.1.3 *CERTOLIZUMAB PEGOL*

Recommendation

- **Certolizumab is effective in inducing and maintaining remission in patients with moderate to severe Crohn's disease refractory to conventional therapy (A).**
- **Certolizumab may have clinical benefits when used in patients with moderate to severe Crohn's disease with failure or intolerance to infliximab (B).**

Certolizumab pegol (CZP) consists of a TNF-alpha humanized monoclonal antibody fragment expressed in *Escherichia coli* and conjugated to two polyethylene glycol (PEG) molecules and is administered subcutaneously. CZP, unlike the other anti-TNFs, does not contain the Fc portion of immunoglobulin and thus does not induce complement activation, antibody-dependent cytotoxicity, and apoptosis. Furthermore, it does not cross the placental barrier since it is not an IgG1 immunoglobulin as the other anti-TNFs[24,25].

Certolizumab pegol (CZP) is a Fab' fragment of a humanized antibody recombined against tumor necrosis factor alpha (TNF-α),

INDUCTION OF REMISSION

A multicenter, double-blind, placebo-controlled RCT evaluated the efficacy of CZP therapy in 439 adults (18-75 years) with moderate to severe CD (CDAI = 220- 450) without prior anti-TNF therapy. Patients were stratified according to serum C-reactive protein (CRP) concentration at baseline (<10 mg/L and ≥10 mg/L). Patients were randomized to receive CZP (400 mg SC, N = 223) or placebo (N = 215) at weeks 0, 2 and 4. The primary outcome evaluated was the clinical remission rate (CDAI ≤ 150 points) at week 6. The clinical response (reduction ≥ 100 points of the CDAI score at week 0) at weeks 2, 4, and 6 was considered a secondary outcome. There was no difference in the clinical remission rate between the CZP group *vs.* placebo group at week 6 (p = 0.174; NNT = NS), as well as in the

clinical response rate (p = 0.179; NNT = NS). Serious adverse events occurred in 5% and 4% of CZP and placebo groups, respectively[26] (A).

The controlled, randomized, multicenter, double-blind, placebo-controlled trial study PRECiSE 1 (*PEGylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy 1*) included adult patients with, moderate to severe CD (CDAI = 220-450) (N = 662), , without disease control for at least three months, on the use of corticosteroids, immunosuppressants or the association of these two drugs. These patients were randomized to treatment with CZP (SC) 400 mg or placebo at weeks 0, 2 and 4 weeks and every four weeks until the week 24, were evaluated between the week 6 and 26[26] (A). The aim was to analyze clinical response rates (reduction greater than 100 points in the baseline CDAI) and clinical remission (CDAI ≤ 150). The study showed a clinical response rate of 37% in the CZP group and 26% in the placebo group at week 6 (p <0.05). Twenty-two percent of patients in the CZP group responded to treatment responded in the placebo group at weeks 6 and 26 (composite outcome) (p = 0.05). CZP was superior to placebo in inducing clinical remission at week 4 and at week 26 (p <0.05 for both comparisons), but not at other periods evaluated. CZP induction and maintenance therapy was associated with modest improvement in response rates, compared with placebo, but without significant improvement in remission rates. The incidence rate of adverse events was similar between the groups. Headache, nasopharyngitis and abdominal pain were the most prevalent events in the CZP group (18%, 13%, and 11%, respectively)[24] (A).

MAINTENANCE OF REMISSION

The randomized, double-blind, placebo-controlled PRECiSE 2 study evaluated the efficacy of CZP maintenance therapy in adults with moderate to severe active Crohn's disease for at least 3 months (CDAI 220-450). Forty hundred mg of CZP (SC) was administered at weeks 0, 2 and 4 as induction therapy. Patients with clinical response (more than 100-point decrease in the CDAI from baseline) at week 6 were stratified according to their initial RCT level and randomized to receive either 400 mg CZP or 4/4 week placebo until the week 24 with follow-up until the 26th week. Among patients responding to induction therapy at week 6, remission (defined by a CDAI ≤ 150) at week 26 was achieved in 48% of patients in the CZP group and 29% in the placebo group (CZP *vs.* placebo ARR = 19.3% with 95% CI -0.285 to -0.097 and NNT = 5; p <0.001). Sixty-three percent of patients in the CZP (intent-to-treat analysis) group maintained response at week 26 *versus* 36% of the patients in the placebo group (p <0.001). Serious infectious adverse events, including one case of pulmonary tuberculosis, occurred in 3% of patients receiving CZP and in less than 1% of patients receiving placebo[25] (A).

Patients who completed PRECiSE 2 were eligible to enter into PRECiSE 3, an extension of PRECiSE 2. A prospective and open study in which patients received CZP 400 mg SC every four weeks for 54 weeks with no option of increasing their dose. One-hundred-forty one of 215 patients who received CZP and 100 of 210 who received placebo were eligible for this study. The aim was to analyze the results of continuous treatment with CZP compared to discontinuation of treatment after drug induction therapy. The response rate (Harvey-Bradshaw index) at the 26th week of PRECiSE 2, corresponding to week 0 of the PRECiSE 3 study, was 56.3% (121/155 patients) in the continuous therapy group and 37.6% (79/210 patients) in the group that interrupted the use of CZP[25] (B). Although the reduction in response was evident over time in the continuous therapy and discontinuation groups, substantial response rates were sustained in both groups, being 62.8% and 47.1% for the weeks 52 and 80 weeks respectively, among individuals undergoing continuous therapy. The corresponding values in the interrupt group were 63.3% and 45.6%, respectively)[25] (B). CZP was well-tolerated in this study, and the incidence of AEs was similar among the groups studied[27](B).

An additional dose or re-induction with CZP may help achieve clinical response at 12 months in patients previously non-responders. This is the conclusion of the PRECiSE 4 study, which is based on an extension of the PRECiSE 2 study that included 124 patients who relapsed before week 26 in the original study. Forty-nine patients in the PRECiSE 2 continuous therapy group received an additional dose of CZP 400 mg followed by maintenance with CZP 400 mg 4/4 weeks. Another 75 patients in the PRECiSE 2 placebo group received CZP 400 mg at weeks 0, 2 and 4, followed by maintenance with CZP 400 mg 4/4 weeks. Fifty-five patients (44%) were withdrawn from the study for 52 weeks, mainly due to AAS, lack of improvement or worsening of the disease. Comparing the continuous and reinduction groups at week 4 there was a response rate of 63% *vs.* 65%, respectively, and 55 *vs.* 59% at 1 year[28] (B).

The multicenter WELCOME study aimed to evaluate the clinical efficacy of CZP in patients with moderate to severe CD (CDAI = 220-450) who had loss of response or were intolerant to IFX (secondary failures). In this study, all patients received induction with CZP 400 mg at weeks 0, 2 and 4, and were then evaluated at week 6. Only individuals who showed clinical response (decrease in CDAI ≥100) were randomized to maintenance treatment CZP 400 mg every two or every four weeks (329/539 patients, 61%), until the week 24, and then evaluated at the week 26. One-hundred-fifty patients (46%) with a high dropout rate completed the study. A clinical response of 37% *vs.* 40% (not significant) and clinical remission of 30% *vs.* 29% (not significant) was observed comparing CZP group every 2 weeks *versus* CZP group every 4 weeks[29] (B).

FISTULIZING CROHN'S DISEASE

In the PRECiSE 1 study, 107 patients had fistulas with drainage from baseline. At week 26, 30% of the CZP group and 31% of the placebo group achieved fistula remission[24] (C).

A subgroup analysis of the PRECiSE 2 study, including patients with draining fistulas who responded to treatment after induction therapy and were randomized to CZP 400 mg (N = 28) or placebo (N = 30) 4/4 weeks, showed that 36% of patients in the CZP group had complete fistula closure at week 26, compared to 17% in the placebo group (p = 0.038; NNT = 5). However, partial fistula closure (≥ 50% closure at two consecutive visits after the baseline, ≥ 3 weeks apart) was not statistically different (p = 0.069), reaching 54% and 43% of patients treated with CZP and placebo, respectively, at 26 weeks. Therefore, CZP increases

the rate of fistula closure by up to 26 weeks in patients with DC who have responded to 6-week induction therapy[25] (B).

7.1.4 ADVERSE EFFECTS

Maintenance therapy with anti-TNF-α is not associated with an increased overall rate of severe infection in pivotal studies. However, opportunistic infections, such as tuberculosis or fungal infections, may occur as a direct consequence of the use of these drugs. Failure to observe an increased rate of these infections in the trials may be secondary to the relatively short follow-up[30] (A).

A systematic meta-analysis review including 22 RCTs compared anti-TNF-α *versus* placebo in 7,054 patients with IBD and found that anti-TNF-α therapy doubled the risk of opportunistic infections in these patients (RR = 2.05, 95% CI 1.10-3.85, NNH = 500; 95% CI 200-1567). The increase found did not show statistical significance in the analysis of 15 studies including 4,566 patients (RR = 2.34, 95% CI 0.98 to 5.57, NNH = NS)[30] (A).

Another systematic review including 8 historical cohort studies compared therapy with IFX up to 3 months after abdominal surgery *versus* no treatment in 1,641 patients with CD. Comparing preoperative IFX *versus* non-treatment, therapy with IFX was associated with a moderately increased risk of infectious complications (6 studies, N = 1,159, OR = 1.50, 95% CI 1.08-2.08, NNH = 6-41), mainly occurring distant from the surgical site (OR = 2.07, 95% CI, 1.30-3.30). There was no difference in the rate of noninfectious complications in the analysis of 4 studies including a total of 834 patients[31] (A).

Anti-TNF-α therapy may be associated with a small or non-increased risk of neoplasia (melanoma) compared to the general population, but the risk may be increased when combined with immunomodulatory therapy (thiopurines or methotrexate)[32,33] (A).

A systematic meta-analysis review (6 RCTs - CLASSIC I and II, CHARM, GAIN, EXTEND and ADHERE), including data from 1,594 patients (3,050 patients per year of exposure) with CD, compared ADA associated with immunomodulator *versus* ADA monotherapy to assess the risk of malignancy. Immunomodulators were defined as any immunomodulator (thiopurine or methotrexate), or thiopurine alone. Comparing ADA monotherapy *versus* expected incidence in the general population, there was no significant difference in the incidence of non-melanoma skin cancer or other types of cancer. Combination therapy was associated with an increased incidence of non-melanoma skin cancer (standardized incidence rate 3.04, 95% CI 1.66-5.1) and increased incidence of other malignancies (standardized incidence rate [SIR] 4.59, 95% CI 2.51-7.7) compared to the general population. ADA in combination therapy was also associated with increased risk of non-melanoma skin cancer (RR = 3.46, 95% CI 1.08-11.06, for combination therapy *vs.* any immunomodulator and corrected RR = 4.01, 95% CI 1.24-13 for combination therapy *vs.* thiopurine alone) and increased risk of other neoplasms (RR = 2.82, 95% CI 1.07-7.44, for combination therapy *vs*. any immunomodulator, corrected RR = 2.61; 95% CI 0.93-7.31 [not significant] for combination therapy *vs* thiopurine only)[32] (A).

A systematic meta-analysis review (9 RCTs, 3 cohorts and 14 case series) evaluated the non-Hodgkin's lymphoma (NHL) rate in patients with adult CD who received anti-TNF therapy and compared that rate with that of a population registry of CD patients treated with immunomodulators (8,905 patients with 21,178 patient/year of follow-up). Of the 26 studies included, 22 were on treatment with IFX, 3 on ADA, and 1 on CZP. An average of 66% of patients was on concomitant use of immunomodulators. Thirteen NHL cases (6.1 per 10,000 patients-year) were reported among those who used TNF inhibitors and most had previous exposure to the immunomodulator (6-MP or AZA). Compared with the expected NHL rate in the *Surveillance Epidemiology and End Results* (SEER) database, [1.9 per 10,000 patient-years], TNF inhibitors were associated with increased risk of NHL (SIR = 3.23, 95% CI 1.5-6.9). On the contrary to the NHL rate in patients treated with isolated immunomodulators (4 per 10,000 patient-years), TNF-α inhibitors were not associated with increased risk of NHL (SIR = 1.7, 95% CI 0.5-7.1). There was significant heterogeneity in the NHL rate in all studies. Therefore, the use of anti-TNF-α agents with immunomodulators is associated with an increased risk of NHL in adult patients with CD, but the absolute rate of these events is low[33] (A).

A historical cohort study compared 4,554 patients with inflammatory bowel disease (IBD) exposed to TNF-α inhibitors with 16,429 patients with unexposed IBD, in a follow-up of 5 years. TNF-α inhibitors have been associated with increased risk of central demyelinating disease (including multiple sclerosis, optic neuritis, transverse myelitis and other central demyelinating diseases) in patients with inflammatory bowel disease (hazard ratio 2.19, 95% CI 1.02-4.71)[34] (A).

7.2 VEDOLIZUMAB

Recommendation

- **Vedolizumab is effective in inducing and maintaining remission of Crohn's disease in patients with moderate to severe Crohn's disease refractory to conventional therapy and prior therapy with anti-TNF-α (B) biologicals.**
- **Vedolizumab may be effective in perianal fistulizing CD (B).**

Vedolizumab (VDZ) is a recombinant humanized monoclonal antibody that identifies the α4β7 integrin present on the surface of lymphocytes, inhibiting the migration of these cells from the bloodstream to the intestinal mucosa through the vascular endothelium. Its mechanism of action consists in causing selective immunosuppression for the gastrointestinal tract.

GEMINI II[35] and III RCTs are phase III, multicenter, double-blind, placebo-controlled, with no description of allocation trials to assess the efficacy and safety of VDZ in moderate to severe CD including patients without prior use of anti-TNF-α and patients who had an inadequate response, loss of response or intolerance to immunomodulatory or anti-TNF-α agents.

GEMINI II[35] was designed to evaluate the efficacy and safety of VDZ as induction treatment (dose at weeks 0 and 2 with evaluation at week 6) and maintenance treatment (at weeks 6-52). In contrast, GEMINI III was designed to assess the efficacy and safety of VDZ only as an induction treatment with doses at weeks 0, 2 and 6 and evaluation at weeks 6 and 10.

The GEMINI II study[35] had two cohorts. Cohort 1 was randomized to the induction assay, while cohort 2 received open induction and was randomized to maintenance evaluation. Cohort 1

received VDZ 300 mg or placebo, respectively, at week 0 and 2, and cohort 2 received 300 mg VDZ openly at week 0 and week 2. Response to therapy was evaluated at week 6. Respondents in both cohorts were randomized to VDZ 300 mg 8/8 weeks, VDZ 300 mg at 4/4 weeks or placebo. The non-responders in the treatment arm received VDZ at 4/4 weeks. The placebo arm of the induction experiment received placebo during the maintenance period.

Induction of remission

Thirty-six patients (mean age = 37 years) with active CD for ≥ 3 months (CDAI = 220-450), non-responders or intolerant to steroids, imunossupressors or anti-TNF were included. At week 6, the remission rate (CDAI ≤ 150) was 14.5% *vs.* 6.8%, respectively (p = 0.02, NNT = 13) and the CDAI-100 response (decrease ≥ 100 points) was 31.4% *vs.* 25.7%, respectively (non-significant) when comparing VDZ *versus* placebo. In cohort 2, 747 patients who received open-label VDZ had remission in 17.7% and CDAI-100 response in 34.4%. There was no statistically significant difference in the clinical remission rate in patients with prior failure in the treatment with anti-TNF-α, being 4.3% in the placebo group and 10.5% in the VDZ group) (ARR 6.2%, 95% CI: -1.4-13.7, p = 0.11). Moreover, the CDAI-100 score in patients with prior failure in the treatment with anti-TNF-α did not reach a statistically significant difference, reaching 22.9% in the placebo group compared to 23.8% in the VDZ group (ARR 1.0%; 95% CI: -11.8-13.7, p = 0.88). Therefore, induction therapy with VDZ may increase the remission rate in CD patients[35] (B).

Maintenance of remission

A total of 119 patients from the induction (randomized) phase described above and 674 patients from the cohort with open-label therapy who responded to treatment (70-point decrease in the CDAI from baseline) for VDZ at 6 weeks were randomized to VDZ 300 mg EV 8/8 weeks or 4/4 weeks *versus* placebo for 1 year. Treatment was discontinued by 52% of patients, mainly due to lack of efficacy, but all were included in the intention-to-treat analysis.

The remission rates at 52 weeks were: 39% VDZ group 8/8 weeks (p <0.001 *versus* placebo, NNT = 6); 36.4% VDZ group 4/4 weeks (p = 0.004 *versus* placebo, NNT = 7) and 21.6% placebo group[35](B).

The CDAI-100 response rates at 52 weeks were: 43.5% VDZ group 8/8 weeks (p = 0.01 *versus* placebo, NNT = 8); 45.5% VDZ group once 4/4 weeks (p = 0.005 *versus* placebo, NNT = 7) and 30.1% placebo group[35](B).

The clinical remission rate was statistically significant in patients with anti-TNF-α therapeutic failure with 12.8% of the placebo group compared to 28.0% in the 8/8 week VDZ group (ARR 15.2%, 95% CI: 3.0–27.5, p = 0.01) and 27.3% in the VDZ 4/4 week group (ARR 14.5%, 95% CI: 2.0–26.9; p=0.02)[35] (B).

There was no significant difference between groups for durable remission (remission in ≥ 80% of study visits, including the final visit)[35] (B).

The most common adverse events with VDZ included nasopharyngitis, infections, and severe infections (no p-value reported)[35] (B). Therefore, maintenance therapy with VDZ may improve symptoms in patients with a previous response to VDZ induction.

GEMINI III RCT is a multicenter, double-blind, placebo-controlled study of VDZ induction therapy for patients with CD (CDAI = 220-400) and previous anti-TNF-α therapy failure (i.e., an inadequate response, loss of response or intolerance to ≥1 anti-TNF-α). Patients (N = 315) were randomized 1:1 for induction with VDZ 300 mg EV at weeks 0, 2 and 6 or placebo. The primary outcome was clinical remission at week 6 and the secondary outcomes were clinical remission at week 6 in the general population (N = 416; patients with anti-TNF-α failure [N = 315] and those without prior use of anti-TNF-α [N = 101], clinical remission at week 10 in both populations, long-term clinical remission (defined as remission at weeks 6 and 10 in both populations), and CDAI-100 score at week 6 in patients with previous failure of treatment with anti-TNF-α. This study showed no significant difference for the primary outcome. However, the secondary outcome, clinical remission in the general population (with no prior use of anti-TNFα; N = 416) at week 6, reached statistical significance with 26.6% in the VDZ group, compared with 12.1% in the placebo group p = 0.001)[36] (B). At week 10, a greater proportion of patients that failed prior therapy with anti-TNF-α and received VDZ had remission (26.6%) compared with those receiving placebo (12.1%) (p = 0.001, RR = 2.2, 95% CI, 1.3-3.6). Moreover, there was a higher rate of patients with previous failure of treatment with anti-TNF-α receiving a score of 100 on CDAI at week 6 compared to placebo group (39.2% *vs.* 22.3%; p = 0.001; RR = 1.8; 95% CI 1.2-2.5)[36] (B). VDZ is effective in inducing clinical remission at week 10, but not at week 6, in patients with moderate to severe CD and prior failure of treatment with anti-TNF-α. It is also effective in inducing clinical response (CDAI-100) at weeks 6 and 10 in patients with moderate to severe CD and prior failure of treatment with anti-TNF-α. Better results can be obtained in patients without prior use of anti-TNF-α. The rate of adverse events was similar among all groups.

Post-hoc analysis of data on treatment efficacy in 516 patients with no prior use of anti-TNF-α and 960 patients with prior failure of treatment with anti-TNF- α in the GEMINI 2 and GEMINI 3 trials was performed at weeks 6, 10, and 52. Clinical remission (CDA ≤ 150), clinical response (reduction of ≥100 points in CDAI), long-term clinical remission (remission in ≥ 80% of study visits, including final visit) and remission without corticosteroids were evaluated. Among patients responding to induction with VDZ at week 6, 48.9% without prior use of anti-TNF-α and 27.7% of those with prior failure of treatment with anti-TNF-α were in remission with VDZ at week 52 (*versus* 26.8% and 12.8% with placebo, p <0.05 for all comparisons). Clinical efficacy was similar to the number or type of anti-TNF-α previously used. The safety profiles were similar in both subpopulations[37] (B).

Patients in C13004 studies (Phase II), GEMINI 2 and GEMINI 3 (both phase III) and patients with no prior use of VDZ were included in the GEMINI LTS[38] (GEMINI long-term safety [LTS]), an extension, open-label, phase III and single-arm study, whose main aim was to evaluate the safety profile of VDZ 300 mg IV treatment every 4 weeks in the long-term. The clinical response and remission results were scored according to the Harvey-Bradshaw Index (scores ranging from 0 to ≥ 18 with higher scores indicating greater disease activity) and health-related quality of life (HRQOL) and were assessed for up to 152 weeks of treatment. Provisional data for up to 100 weeks of treatment with

VDZ in GEMINI LTS are reported here with a total follow-up of approximately 3 years (152 weeks of exposure) for patients who completed the 52-week GEMINI 2 study[38].

Among the patients with available data (analysis *as observed*) continuously using VDZ and that responded at week 6 in the GEMINI 2 study, 83% (100/120) and 89% (62/70) were in remission after 104 and 152 weeks, respectively. The increase in dose frequency from 8 weeks (GEMINI 2) to every 4 weeks (GEMINI LTS) improved outcomes in patients who had been withdrawn from GEMINI 2. Forty-seven percent (27/57) showed clinical response and 32% (18/57) showed clinical remission at week 52 of the GEMINI LTS study. Patients' previous exposure to anti-TNF-α did not alter the benefits, including the long-term benefits of HRQOL[38] (C).

We conclude that the clinical benefits of VDZ continued in the long-term treatment, regardless of anti-TNF exposure. Moreover, increased dose frequency (every 4 weeks) may improve outcomes in patients who lose response or remission with the conventional dose every 8 weeks[38] (C).

Fistulizing Crohn's disease

Subgroup analysis of the GEMINI 2 study was performed to evaluate fistulas closure in patients with draining fistulas from the baseline until week 52. There was an increase in the number of fistulas without drainage in response to the use of VDZ 8/8 weeks compared to placebo at 52 weeks (41.2% *vs.* 11.1%, respectively – ARR = 30.1%; 95% CI 2.6 - 57.6%, NNT = 3, 95% CI 2–39). The power of the present study (subgroup analysis) in identifying a 30% difference between the placebo and VDZ groups, every 8 weeks, with a level of significance of 5% (95% CI), is only 53.2%. There was no difference between the VDZ group 4/4 weeks and the placebo group (NNT = NS)[35] (B).

Adverse effects

Individual data of 2,932 patients with ulcerative colitis or CD from 4 RCTs and 2 extension studies comparing VDZ *vs.* placebo were analyzed without considering study quality. The rate of serious adverse events found in the analysis of 1,723 patients using VDZ in four trials was: 25.1 events / 100 persons-year (95% CI: 22.9-27.4), compared to a rate of 31.8 events / 100 persons-year (95% CI 21.5-42) found in the analysis of 355 patients using placebo in 2 trials. The rate of severe infection or infestation found in the analysis of 1,723 patients using VDZ in 4 trials was: 5.6 events / 100 persons-year (95% CI: 4.6-6.5), compared to a rate of 3 events / 100 persons-year (95% CI: 0.1-6) in the analysis of 355 patients using placebo in 2 trials. Therefore, VDZ does not appear to increase the risk of serious adverse events or infection in patients with CD[39] (B).

7.3 USTEKINUMAB

Recommendation

- Ustekinumab is effective in inducing and maintaining remission of Crohn's disease in patients with moderate to severe disease refractory to conventional therapy, including patients who did not respond to anti-TNF-α therapy (A).

Ustekinumab (UTQ) is a human monoclonal antibody directed against IL-12 and IL-23, two important proinflammatory cytokines in the pathophysiology of CD.

INDUCTION OF REMISSION

Our systematic meta-analysis review included 6 RCTs evaluating the efficacy and safety of anti-interleukin-12/23p40 monoclonal antibodies (including UTQ) in 2,324 patients with moderate to severe active CD. Four RCTs evaluated UTQ[40,41,] The outcomes assessed were clinical response (defined by an increase of ≥ 100 points in the CDAI), and clinical remission (CDAI score <150 points). UTQ reduced the risk of failure in inducing clinical response up to 6 weeks in the analysis of 4 RCTs including 1,947 patients (RR = 0.77, 95% CI 0.69 to 0.87, NNT = 5-11, failure in inducing clinical response in 76% of patients in the placebo group). It also reduced the risk of failure in inducing clinical remission up to 6 weeks in the analysis of 4 RCTs with 1,947 patients, but with a confidence interval including a difference that may not be clinically important (RR = 0.91, 95% CI 0.86 to 0.95, NNT = 9-23, failure in inducing remission in 88% of patients in the placebo group). There was no difference in the number of serious adverse events between the two groups (UTQ *versus* placebo) in the analysis of 4 RCTs (N = 2,023 patients).

Therefore, UTQ increases clinical response and may increase clinical remission rate in patients with moderate to severe Crohn's disease[42] (A).

MAINTENANCE OF REMISSION

An RCT (IM-UNITI trial) included 397 adult patients (mean age = 43 years) with moderate to severe CD clinically which responded to induction therapy with UTQ in 8 weeks in UNITI-1 and UNITI-2 RCTs. Patients were randomized to 1 of 3 subcutaneous maintenance regimens with UTQ for 40 weeks and followed up to week 44: UTQ 90 mg 8/8 weeks, UTQ 90 mg 12/12 weeks or placebo. Blinding was maintained by administering treatments every 4 weeks and using placebo between active treatments. Patients meeting the criteria for loss of response (CDAI ≥220 and ≥100 points baseline increase) at weeks 8 - 32 received 90 mg UTQ 8 8 weeks. 2.3% of the patients were excluded from the analyses, due to the administration of the initial formulation of the drug with stability problems. Response and clinical remission outcomes were described in RS including the meta-analysis described above. Clinical response rates at week 44 were: 59.4% for UTQ 8/8 weeks (p = 0.02 *vs.* placebo, NNT=7); 58.1% for UTQ 12/12 weeks (p = 0.03 *vs* placebo, NNT=8) and 44.3% for placebo. Clinical remission rates at week 44 were: 53.1% for UTQ 8/8 weeks (p = 0.005 *versus* placebo, NNT= 6); 48.8% for UTQ 12/12 weeks (p = 0.04 *versus* placebo, NNT=8) and 35.9% for placebo. The AE rates were similar among the treatment groups (80.3% - 83.5%). The most common AEs were infections, arthralgia, headache, nasopharyngitis, abdominal pain and fever[40] (A).

Another RCT (CERTIFI Study) including 526 patients (mean age = 39 years) with moderate to severe CD activity randomized patients to induction therapy with UTQ EV (1 mg/kg *vs* 3 mg/kg *vs* 6 mg/kg) *versus* placebo 8/8 weeks. Mean values of baseline CDAI were significantly lower in the placebo and UTQ 1mg groups compared to the higher dose UTQ groups.

A group of 145 patients, all failing treatment with anti-TNF from baseline, and who had a clinical response to UTQ at week 6, were randomized to SC injections of UTQ 90 mg *versus* placebo at weeks 8 and 16 as maintenance therapy. The clinical response was defined as a decrease of ≥ 100 points in the CDAI score and clinical remission as CDAI <150.

Comparing UTQ 90 mg *vs.* placebo as maintenance therapy, UTQ 90 mg had higher clinical response rates at week 22 compared to placebo (69.4% *vs.* 42.5%, p <0.001, NNT = 38). Maintained response was defined as clinical response at each visit during the maintenance phase (55.6% *vs* 32.9%, p = 0.005, NNT= 5) and clinical remission (41.7% *vs.* 27.4%, p = 0.03 and NNT= 7). Therefore, we conclude that UTQ maintenance therapy can improve clinical response and remission at week 22 in patients with moderate to severe CD which had not responded to Anti-TNF but had an initial response to UTQ[43] (A).

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8. PROBIOTICS, PREBIOTICS AND SYMBIOTIC

Recommendation

- **Probiotics are not effective in the induction and maintenance of remission in patients with Crohn's disease (CD). (B)**
- **Probiotics do not prevent endoscopic recurrence in CD, defined according to the Rutgeerts score (≥1, ≥2 or ≥3). (B)**
- **There is no indication for the use of probiotics in the prevention of postoperative recurrence of CD (A).**
- **There is no evidence to support the use of probiotics in the treatment of active CD. (A)**
- **There is little evidence to support the use of symbiotic in active CD. (B)**

The intestinal flora is the set of microorganisms that exist in the human intestine. The intestinal microbiome concerns the genome of these organisms. These microorganisms have with the host one mutualistic relationship in which both contribute and benefit.

As greater insight into the influence of the intestinal microbiota, the host immune response is acquired, there is a need to explore ways to manipulate the microbiota or their function to modulate the host immune response and restore health. There have been many attempts to shape the intestinal microbial population with prebiotics and probiotics in patients with CD[1].

Probiotics are defined as "live or attenuated microorganisms which when administered in adequate amounts, confer health benefits on the host" in accordance with an agreement of the Food and Agriculture Organization of the United Nations (2001)[2].

The use of probiotics has been proposed in order to provide benefits to human health for a long time, but in recent years there has been a growing interest for its use in inflammatory bowel disease (IBD), due to the role of the microbiome in its pathogenesis.[3] Some probiotics appear to have anti-inflamatórias[4] properties, or the ability to modulate visceral hypersensitivity[5,6].

Several studies have been conducted on the use of probiotic agents as adjunctive therapy in the treatment of ulcerative colitis and Crohn's disease (CD). The treatment approaches to these conditions may be divided into treatment during the acute phase (induction therapy) for the treatment and long-term control of symptoms (maintenance therapy).

Prebiotics are food substances that remain undigested and can stimulate the growth or activity of bacteria, which are also beneficial to human health. Although there is no formal consensus on the specific definition of prebiotics, they include fructo-oligosaccharides (FOS) and inulin. Symbiotic are combinations of prebiotics and probiotics, with a potentially synergistic action.

8.1 PROBIOTICS

A systematic review and recent meta-analysis[7] **(A)** of high-quality (score AMSTAR [0 to 11, where 11 represents the highest quality] = 10) included only randomized controlled trials (ECRs) not combined data from studies evaluating the effectiveness of probiotic and symbiotic or data from studies that grouped adult and pediatric patients. ECRs included adult patients (> 90% over 16 years) with inflammatory bowel disease (IBD) confirmed by endoscopy, radiology or histology and compared probiotics with 5-aminosalicylates (5-ASAs) or placebo. The overall effectiveness of probiotics was evaluated for induction of remission in ulcerative colitis (UC) and active CD, maintenance of remission in ulcerative colitis or quiescent CD and relapse prevention of postoperative CD (primary endpoints). The incidence of adverse events occurring as a result of therapy were considered secondary outcome. Two studies evaluated the efficacy of probiotics for induction of remission in active CD[8,9] **(B)**; two effectiveness in preventing relapse in quiescent CD [10,11]**(B)** and four the efficacy in the prevention in prevention of relapse following CD surgical resection[12,13] **(B)**[14]**(A)**[15] **(B)**.

INDUCTION OF REMISSION

Two ECRs totalling 37 patients, evaluated the efficacy of probiotics (*Lactobacillus rhamnosus* GG[8], *Escherichia coli* Nissle 1917[9]) *versus* placebo for induction of remission in active CD[8,9]**(B)**. No study had low risk of bias. A total of six (31.6%) of 19 patients randomized to probiotics not achieved remission compared with 6 (33.3% of 18 placebo (relative risk (RR) for reference fails = 0.99, 95 0.57 to 1.72%, not statistically significant). There was heterogeneity between these two studies (I2 = 0%), while the power for that detection was low. Furthermore, few studies were included to assess publication bias.

Only one of these two studies[8] **(B)** reported AEs data, and none in the two treatment arms.

MAINTENANCE OF REMISSION

Only two ECRs[10,11]**(B),** no low risk of bias, totaling 195 patients, evaluated the efficacy of probiotics (Saccharomyces boulardii[12], VSL # 3[13]) *versus* placebo in preventing relapse in CD quiescent. A total of 52 (52.0%) patients allocated to 100 probiotics had recurrence of disease compared to 50 (52.6%) of 95 who received placebo (relapse of disease activity RR = 1.03; 95% IC = 0.70 to 1.51), with no statistical significance). There was no heterogeneity between the two studies (I2 = 27%), although again the power to this detection was low, and few studies to assess publication bias.

Only one of these ECR11 (B) reported AEs in 58.3% of patients (49/84) assigned to one or more probiotics with AEs, compared with 55.6% (45/81) in the placebo group (RR = 1 05, 95% IC 0.80 to 1.37; NNH = not significant [NS]).

PREVENTION OF POST-SURGICAL RECURRENCE

Four ECRs placebo controlled[12,13]**(B)**[14] **(A)**[15] **(B)**, in a total of 333 patients, evaluated the efficacy of probiotics (*Lactobacillus rhamnosus* GG14, *Lactobacillus johnsonii* LA1[15,16], VSL # 3[15]) *versus* placebo in preventing clinical relapse or endoscopic CD, with remission after surgical resection. One ECR showed low risk bias[14]. The clinical relapse endpoint was evaluated in three ECRs[12-14]. The total of 26.7% (28/105) patients allocated to treatment with probiotics showed clinical relapse, compared with 25.9% (28/108) who received placebo (RR clinical relapse of disease activity = 1.06 95% IC = 0.59 to 1.92; NNH = NS). There was heterogeneity among these three studies (I^2 = 37%, p = 0,20), and again been few studies to assess publication bias.

The all four ECRs[12-15] evaluated the efficacy of probiotics in the prevention of endoscopic recurrence of disease activity. All the assays used Rutgeerts score to define endoscopic[16] recurrence (B) with reported data with scores ranging from 1 to 4. The probiotics did not prevent endoscopic recurrence defined in accordance with the score of Rutgeerts score (≥1, ≥ 2 or ≥3). There was heterogeneity between studies when a score of ≥1 Rutgeerts was used to define the endoscopic recurrence (I^2 = 53%, p = 0,10), but there was heterogeneity in the other two tests (≥2 I^2 = 32%, p = 0,22 e ≥3 I^2 = 0%, p = 0,59).

Three ECRs[12,14,15] reported data on EAs. In total, 30.2% (39/129) patients allocated to treatment with probiotics (Lactobacillus rhamnosus GG14, *Lactobacillus johnsonii* LA1[14], VSL#3[15]) experienced at least one AE, compared to 38.8% (52/134) in the group placebo (RR = 0.81; 95% IC = 0.61 to 1.08; NNT = NS).

8.2 PREBIOTICS

INDUCTION OF REMISSION

An ECR-controlled double-blind placebo evaluated the use of fructooligosaccharides (FOS) in patients with active CD. The study included adults with an established diagnosis of CD for at least 3 months and CDAI ≥ 220, with an additional marker of inflammation (CRP elevation / sedimentation rate erythrocyte/platelet counting). Patients were randomized to 15 g FOS / day (n = 54) or placebo (n = 49) for 4 weeks. The primary endpoint was clinical response evaluated at week 4 (decrease in CDAI ≥ 70 points) in an intention to treat analysis. A loss of 17% of the total number of patients in *follow-up* of 4 weeks (FOS 14 [26%] 4 *vs* placebo [8%]; p = 0.018). There was no significant difference in the number of patients who achieved clinical response between the FOS and placebo groups in the intention-to-treat analysis (ARR = 16.6%, 95% IC -0.01 to 0.34, NNT = NS), up to 4 weeks[17] **(A)**.

At this time, there is no evidence to support the use of probiotics in the treatment of active CD. Additional studies are needed to explore whether probiotics may have a role as adjunctive therapy or maintaining remission.

8.3 SYMBIOTICS

INDUCTION OF REMISSION

Some studies included a combination of probiotics and prebiotics in the treatment of CD. A double-blind placebo-controlled ECR, randomized 35 adult patients with active CD (CDAI = 150-450) to compare *Bifidobacterium longum* to (2 x 10^9 CFU twice/day) growth substrate and inulin/oligofructose ("Synergy 1"6.0 g twice a day) [N = 19] or placebo [n = 16]. The symbiotic/placebo was taken just after breakfast and after the evening meal to minimize the antibacterial effects of gastric acid in the probiotic. All patients continued the conventional therapy and were followed for 6 months. The achievement of remission measured by CDAI (CDAI <150 points or decrease> 75 points from baseline) in symbiotic *versus* control group was considered as a secondary endpoint. The symbiotic group and the placebo group were not homogeneous, observing prognostic differences among the groups at baseline (serum levels of CRP and albumin and the CDAI score), which may have affected the results. There was also a significant number of patients lost to follow-up (almost half); however, patients who completed the study, 62% (8/13) in the treatment arm was in remission compared to 45% (5/11) in the placebo arm. Despite the major limitations of this study due to the high rate of loss of follow-up (randomized 35 and a loss of 46% in 6 months), and significant differences in baseline characteristics between the groups, the study raises the question of "whether the consumption symbiotic plays a role in active Crohn's disease." Lacking other ECRs evaluating the use of the symbiotic DC[18]**(B)**.

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9. SURGICAL TREATMENT

9.1 GENERAL INDICATIONS

Recommendation

- **Clinical treatment is the primary therapy for CD where as surgical treatment remains secondary. (B)**
- **Prolonged clinical treatment in the presence of stenosis, extra-intestinal manifestations or with known history of CD is greater than 5 years should be conducted with caution. (B)**
- **Cutaneous and ophthalmologic articular manifestations are common in colonic disease, are usually related to its activity, and may improve after colectomy. (B)**

Despite improvement in the therapeutic arsenal, indication for surgery remains high in Crohn's disease.[1] (D)

Indications for surgery in patients with CD include clinical intractability and complications of the disease or both. Clinical treatment is the primary therapy for CD while surgical treatment remains secondary and is indicated if the first and second line of therapies fail to induce remission in cases of severe disease. Surgery should also be considered prior to clinical treatment progression in cases of patients with severe or cortico-dependent disease, with limited disease extension, particularly in patients with stenosing behavior or in those with contraindications or with risk factors for continued clinical therapy. Prolonged clinical treatment in the presence of stenosis, extra-intestinal manifestations or known history of CD for more than 5 years should be administered with caution[2] (B). Despite the rising use of biological therapy, about one-third of patients do not respond adequately to drug treatment[3] (A).

Depending on the type of lesion and clinical situations, surgical indications in CD are as follows: intestinal obstruction and stenosis (54%), fistulas (28%), abscesses (7%), perforations refractory to clinical treatment (3.5%); extensive bleeding (2%) and colorectal cancer (1%). Other surgical indications are: toxic megacolon, symptomatic fibrotic stenosis, enterocutaneous fistulas with high output or stenosis, symptoms due to bypass formation (e.g. duodenal fistula / transverse colon), intestinal fistulas involving a large area of intact intestine, enterovesical fistulas unresponsive to conservative therapy and with repetitive urinary tract infection and retroperitoneal abscesses. The relative risk of colorectal cancer and small bowel cancer is significantly elevated in patients with CD[4] (D) Extra-intestinal manifestations (EIM) of CD constitute another indication for surgery and may occur in up to 25% of patients. Cutaneous, ophthalmologic and articular manifestations are common in colonic disease and are related to disease activity; improvement may occur after colectomy. However, other EIMs (hepatic, cardiovascular, hematological, pulmonary and neurological) occur independently of the presence of intestinal CD[5,6] (B).

Approximately 70% to 90% of patients with CD will need some kind of surgical procedure during their life, ranging from drainage of anal abscesses to complex intestinal segmental resections[7] (D).

Multiple specific surgical maneuvers are available and choosing the most appropriate depends on various factors related to the patient and the disease.

9.2 STENOSING PHENOTYPE

Recommendation

- **Acute obstructions, probably due to active inflammation, are often resolved with clinical treatment; however, chronic sub-occlusion, usually resulting from a fibrostenotic lesion, tends to require surgical treatment. Surgery usually involves resection of the affected intestinal segment, but other options include intestinal bypass, ileostomy or enteroplasty. (D)**
- **Recurrence rate tends to increase over time in patients with CD, and they may eventually require multiple resections, increasing the risk of short bowel syndrome with associated metabolic morbidities. (D)**

Intestinal obstructions are a frequent complication of small bowel involvement as a result of DC[8,9] (B) Acute obstructions, probably due to active inflammation, can be resolved with clinical treatment, but chronic sub-occlusion, usually resulting from a fixed fibrostenotic lesion, tends to require surgical treatment[10] (D). Surgery usually involves resection of the affected segment, but other options include intestinal bypass, ileostomy or enteroplasty. The recurrence rate tends to increase with the time of CD progression and may require multiple resections, increasing the risk of short bowel syndrome with associated metabolic morbidities[11] (D)

9.3 PENETRATING PHENOTYPE

Recommendation

- **Patients with short-extension high-output enterocutaneous fistulas with everted mucosa (labial) require surgical intervention; however, it should be postponed until clinical and nutritional status is improved. (D)**
- **Risk factors associated with poor postoperative outcome in penetrating CD include the presence of abscesses at the time of surgery, chronic use of corticoid and impaired nutritional status. (B)**

Fistulas with associated abscesses or stenosis are common complications of small bowel CD and necessitate surgery[9] (B). Patients with short-lived high-output enterocutaneous fistulas with everted mucosa (labial) require surgical intervention; however, this should be postponed until clinical and nutritional status is improved[12] (D). Patients with asymptomatic rectovaginal fistula or with mild symptoms may not need surgical treatment, and symptomatic patients should be treated with reparative local surgical, derivative ostomy or proctectomy. Opting for surgery will depend on the severity of symptoms, fistula classification, anal sphincter involvement and the patient's decision[13,14] (B).

Intracavitary abscesses are complications that can occur in approximately 25% of CD patients[15] (B). In these patients, non-surgical treatment (percutaneous aspiration with or without drainage) and primary surgical treatment (laparotomy

with or without intestinal resection) showed similar results concerning the rate of abscess recurrence and complications up to 5 years. Starting with anti-tumor necrosis factor and/or immunosuppressive therapy after resolution of the abscess may reduce the risk of recurrence of penetrating disease[16] (B). Several risk factors were associated with a worse surgical outcome in penetrating CD (defined as subacute perforation with abscess formation and chronic perforation with internal fistula formation), such as the presence of an abscess at the time of surgery, chronic use of corticoid, and nutritional impairment[17,18] (B).

9.4 PERIANAL DISEASE

Recommendation

- Asymptomatic perianal fistulas should not be treated, whereas symptomatic perianal fistulas could benefit from combined conservative and surgical treatment. (D)

Approximately 10% to 15% of patients with CD have symptoms limited to the anorectal region, but up to 90% have some clinical manifestations of the disease at this site[19] (D). In patients with perianal disease, drainage of abscesses is always indicated, as well as fistulotomy with or without seton placement in the most symptomatic cases. Asymptomatic perianal fistulas should not be treated, while symptomatic perianal fistulas may benefit from combined medical and surgical treatment. Proctectomy is indicated in cases of important suppuration associated with severe proctitis and anal incontinence. Aggressive procedures that may alter continence should be avoided[20] (D).

9.5 COMPLICATIONS OF Crohn'S DISEASE

Recommendation

- Specific surgical indications for colon disease include the development of dysplasia or cancer and toxic megacolon unresponsive to clinical treatment. (B)
- Old age at diagnosis of CD, disease duration (over 8 years), and disease extension (pancolitis) are considered risk factors for the development of dysplasia and adenocarcinoma. (B)
- Surgery is indicated for colonic CD when there is proven neoplasm or multifocal dysplasia regardless of degree. (D)
- Surgical indications associated to CD include megacolon toxic, perforation, lack of response to conservative treatment, fulminant colitis, massive hemorrhage and hemodynamic instability. (D)

Other indications for surgery, less common for small bowel and/or colonic CD, include perforation, hemorrhage, and cancer. Free bowel perforation is associated with a high mortality rate when untreated[21] (B).

Moreover, other surgical indications specific for CD of the colon include the development of dysplasia or cancer and toxic megacolon[22] (B). Older age at diagnosis of CD, duration of disease (over 8 years) and disease extension (pancolitis) are considered risk factors for the development of dysplasia and adenocarcinoma[23] (B). As in ulcerative colitis, surgery is indicated in colonic CD when there is proven neoplasia and multifocal dysplasia regardless of degree[24,25] (D). Surgical indications for toxic megacolon due to CD include perforation, lack of response to conservative treatment, fulminant colitis, massive hemorrhage and hemodynamic instability; in this case, subtotal colectomy with terminal ileostomy is the technique of choice[1] (D).

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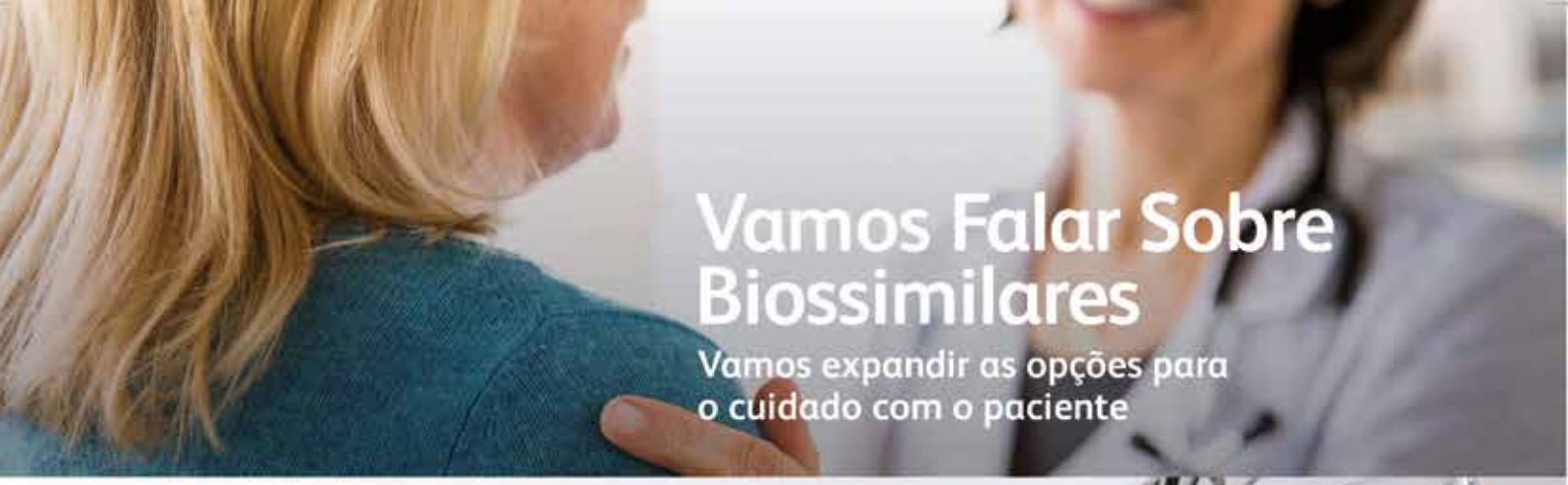


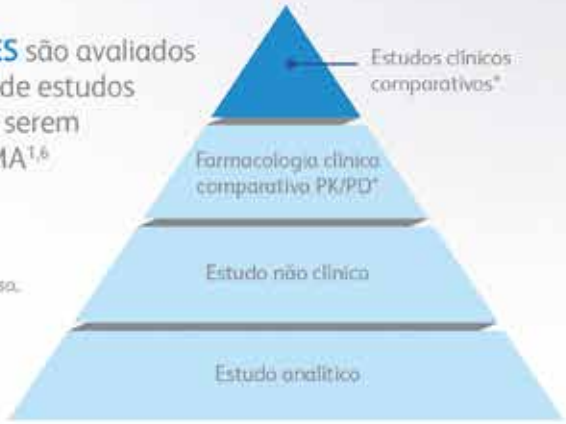
Vamos Falar Sobre Biossimilares

Vamos expandir as opções para o cuidado com o paciente

1 Para efeitos de segurança e eficácia, os **BIOSSIMILARES** são altamente similares aos medicamentos biológicos existentes, sem diferenças clínicas significativas[1]

2 Os **BIOSSIMILARES** são altamente complexos e seus biológicos de referência são criados a partir de células vivas e exigem competências significativas e tecnologia de ponta no desenvolvimento e na fabricação[2-5]

3 Os **BIOSSIMILARES** são avaliados em quatro etapas de estudos rigorosos antes de serem aprovados pelo EMA[1,6]



*A necessidade de dados clínicos comparativos será avaliada em cada caso, de acordo com a incerteza residual

4 Os **BIOSSIMILARES** podem oferecer uma série de possíveis benefícios às partes interessadas[7-9]

Melhorias no acesso e nos resultados[7-9]

Mais opções de tratamento[7-9]

Aumento do uso de produtos biológicos[7-9]

POTENCIAL SIGNIFICATIVO DE REDUÇÃO DE CUSTOS PARA O SISTEMA DE SAÚDE[14]

5 Os biossimilares reforçam o compromisso da Pfizer de oferecer tratamentos que podem melhorar a vida do paciente, aproveitando nossa presença global e conhecimento para oferecer biossimilares de alta qualidade[10-13]

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SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.

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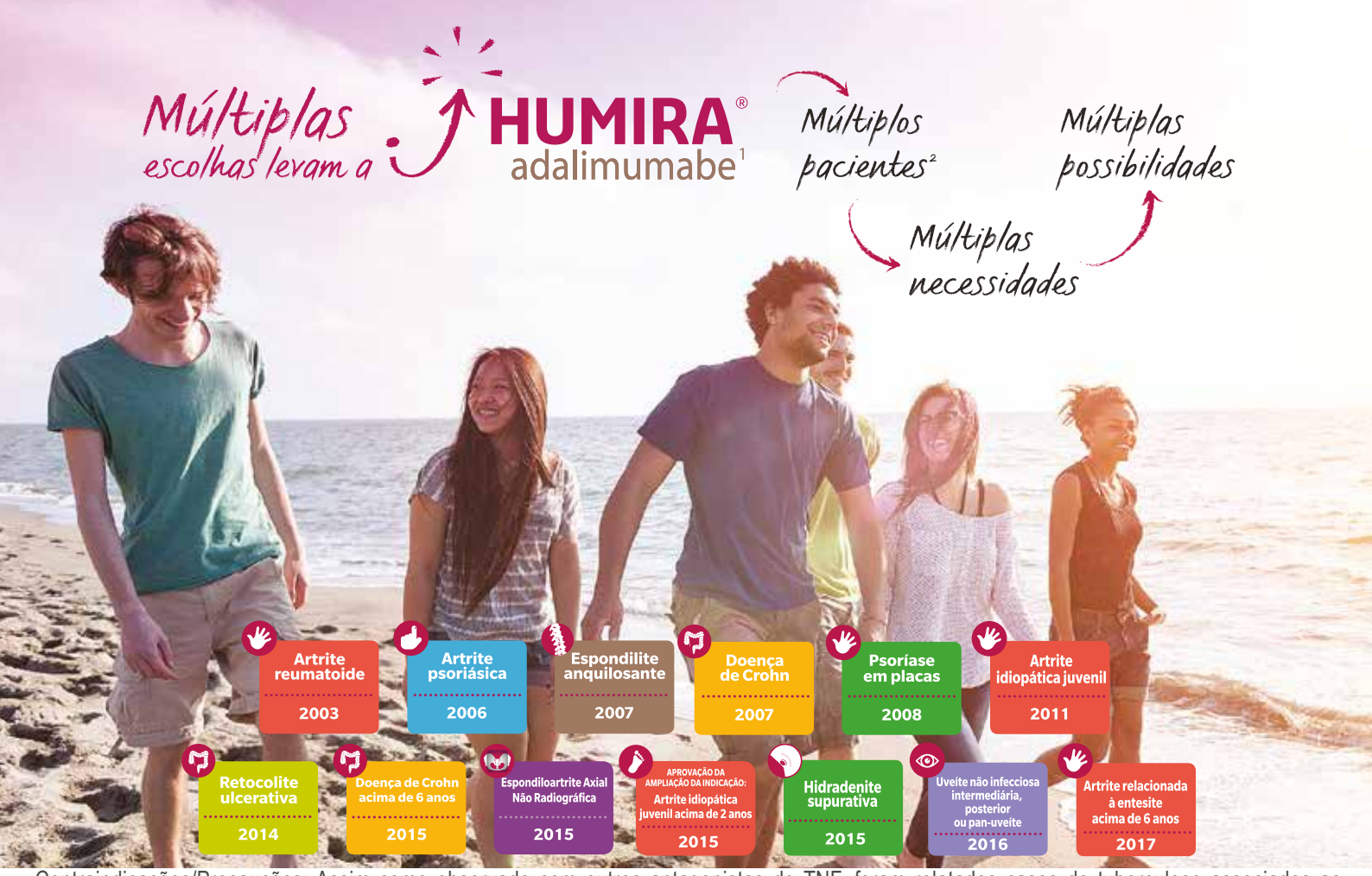

Contraindicações/Precauções: Assim como observado com outros antagonistas de TNF, foram relatados casos de tuberculose associados ao Humira® (adalimumabe). A administração concomitante de antagonistas de TNF e abatacepte tem sido associada a aumento do risco de infecções, incluindo infecções sérias,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

HUMIRA® (adalimumabe) – MS: 1.9860.0003. **Apresentações:** 40 mg em frasco-ampola de 0,8 mL (USO PEDIÁTRICO ACIMA DE 02 ANOS), 40 mg em seringa de 0,8 mL e 40 mg em caneta de 0,8 mL (USO ADULTO E PEDIÁTRICO ACIMA DE 06 ANOS). **Indicações:** Artrite Reumatoide, Artrite Psoriásica, Espondilite Anquilosante, Espondiloartrite Axial Não Radiográfica (Espondiloartrite Axial sem Evidência Radiográfica de EA), Doença de Crohn, Colite Ulcerativa ou Retocolite Ulcerativa, Psoríase em Placas, Hidradenite Supurativa, Uveíte Não Infecciosa Intermediária, Posterior ou Pan-uveíte, Artrite Idiopática Juvenil Poliarticular e Artrite relacionada à Entesite. **Contraindicações:** pacientes com conhecida hipersensibilidade ao adalimumabe ou quaisquer componentes da fórmula do produto, pacientes com Tuberculose ativa ou outras infecções graves, nomeadamente, sepsia e infecções oportunistas e pacientes com insuficiência cardíaca moderada a grave (classe III/IV da NYHA). **Advertências e Precauções:** Infecções: foram relatadas infecções graves devido a bactérias, micobactérias, fungos, vírus, parasitas ou outras infecções oportunistas. Pacientes que desenvolvem uma infecção fúngica grave são também advertidos a interromper o uso de bloqueadores de TNF até que a infecção seja controlada. O tratamento com HUMIRA® (adalimumabe) não deve ser iniciado ou continuado em pacientes com infecções ativas, até que as infecções estejam controladas. Recomenda-se cautela ao uso em pacientes com histórico de infecções de repetição ou com doença de base que possa predispor o paciente a infecções. Tuberculose: foram relatados casos de tuberculose incluindo reativação e nova manifestação de tuberculose pulmonar e extrapulmonar (disseminada). Antes de iniciar o tratamento todos os pacientes devem ser avaliados quanto à presença de tuberculose ativa ou inativa (latente). Se a tuberculose ativa for diagnosticada, o tratamento com HUMIRA® (adalimumabe) não deve ser iniciado. Se for diagnosticada tuberculose latente, o tratamento apropriado deve ser iniciado com profilaxia antituberculose. Reativação da Hepatite B: o uso de inibidores de TNF foi associado à reativação do vírus da hepatite B (HBV) em pacientes portadores crônicos deste vírus podendo ser fatal. Deve-se ter cautela ao administrar inibidores de TNF em pacientes portadores do vírus da hepatite B. Eventos neurológicos: com exacerbação de sintomas e/ou evidência radiológica de doença desmielinizante, deve-se ter cautela ao considerar o uso de HUMIRA® (adalimumabe) em pacientes com doenças desmielinizantes do sistema nervoso periférico ou central, de início recente ou preexistentes. A descontinuação do tratamento com HUMIRA® (adalimumabe) deve ser considerada na ocorrência de alguma destas desordens. Malignidades: foi observado maior número de casos de linfoma entre os pacientes que receberam antagonistas de TNF. Malignidades, algumas fatais, foram relatadas entre crianças e adolescentes que foram tratados com agentes bloqueadores de TNF. A maioria dos pacientes estava tomando concomitantemente imunossupressores. Casos muito raros de linfoma hepatoesplênico de células T foram identificados em pacientes recebendo adalimumabe. O risco potencial com a combinação de azatioprina ou 6-mercaptopurina e HUMIRA® (adalimumabe) deve ser cuidadosamente considerado. Devem ser tomadas precauções quando for usado um anti-TNF em pacientes com DPCO, bem como em pacientes com risco aumentado de doenças malignas devido a tabagismo intenso. Alergia: durante estudos clínicos, reações alérgicas graves foram relatadas incluindo reação anafilática. Se uma reação anafilática ou outra reação alérgica grave ocorrer, a administração de HUMIRA® (adalimumabe) deve ser interrompida imediatamente e deve-se iniciar o tratamento apropriado. Eventos hematológicos: raros relatos de pancitopenia, incluindo anemia aplástica. A descontinuação da terapia deve ser considerada em pacientes com anormalidades hematológicas significativas confirmadas. Insuficiência cardíaca congestiva: casos de piora da ICC também foram relatados. Processos autoimunes: pode ocorrer a formação de anticorpos autoimunes. Se um paciente desenvolver sintomas que sugiram Síndrome lúpus-símile, o tratamento deve ser descontinuado. **Cirurgia**: Um paciente que requeira cirurgia durante o tratamento com HUMIRA® (adalimumabe), deve ser cuidadosamente monitorado para infeções, e devem ser tomadas ações apropriadas. **Capacidade de dirigir veículos e operar máquinas:** HUMIRA® (adalimumabe) pode ter uma pequena influência na capacidade de dirigir veículos e operar máquinas. Após a administração de HUMIRA® (adalimumabe) podem ocorrer vertigens e distúrbios visuais. Uso em idosos: a frequência de infecções graves entre pacientes com mais de 65 anos de idade tratados com HUMIRA® (adalimumabe) foi maior do que para os sujeitos com menos de 65 anos de idade. Deve-se ter cautela quando do tratamento de pacientes idosos. Uso na gravidez: os resultados de estudos em mulheres grávidas não revelaram evidências de danos fetais decorrentes de HUMIRA® (adalimumabe). Este medicamento só deve ser usado durante a gravidez quando, na opinião do médico, os benefícios potenciais claramente justificarem os possíveis riscos ao feto. A administração de vacinas vivas em recém-nascidos expostos ao adalimumabe no útero não é recomendada por 05 meses após a última injeção da mãe durante a gravidez. **Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista.** Uso na lactação: HUMIRA® (adalimumabe) é excretado no leite humano em concentrações muito baixas e os efeitos sistêmicos do adalimumabe em uma criança lactente são improváveis. Os benefícios para o desenvolvimento e para a saúde provenientes da amamentação devem ser considerados juntamente à necessidade clínica da mãe de utilizar o adalimumabe. Devem ser considerados também quaisquer efeitos adversos potenciais sobre a criança lactente a partir de adalimumabe ou a condição materna subjacente. **Interações Medicamentosas:** metotrexato: não há necessidade de ajuste de doses de nenhum dos dois medicamentos. Outras: o uso concomitante de HUMIRA® (adalimumabe) e outros DMARDs (por exemplo, anacinra e abatacepte) não é recomendado. Vacinas vivas não devem ser administradas concomitantemente a HUMIRA® (adalimumabe). Não foram observadas interações com DMARDs (sulfassalazina, hidroxicloroquina, leflunomida e ouro parenteral), glicocorticoides, salicilatos, anti-inflamatórios não esteroidais ou analgésicos. **Reações Adversas:** infecções no trato respiratório, leucopenia, anemia, aumento de lipídeos, dor de cabeça, dor abdominal, náusea, vômito, elevação de enzimas hepáticas, rash, dor musculoesquelética, reação no local da injeção, infecções, neoplasia benigna, câncer de pele não-melanoma, trombocitopenia, leucocitose, hipersensibilidade e alergia, urticária, insuficiência renal, alterações da coagulação e distúrbios hemorrágicos, teste para autoanticorpos positivo, linfoma, neoplasia de órgãos sólidos, melanoma, púrpura trombocitopênica idiopática, arritmia, insuficiência cardíaca congestiva, oclusão arterial vascular, tromboflebite, aneurisma aórtico, doença pulmonar obstrutiva crônica, pneumopatia intersticial, pneumonite, pancreatite, aumento da bilirrubina, esteatose hepática, rabdomiólise, lúpus eritematoso sistêmico, pancitopenia, esclerose múltipla, parada cardíaca, cicatrização prejudicada. **Reações adversas de pós-comercialização:** diverticulite, linfoma hepatoesplênico de células T, leucemia, carcinoma de células de Merkel (carcinoma neuroendócrino cutâneo), anafilaxia, sarcoidose, doenças desmielinizantes, acidente vascular cerebral, embolismo pulmonar, derrame pleural, fibrose pulmonar, perfuração intestinal, reativação da hepatite B, insuficiência hepática, hepatite, vasculite cutânea, Síndrome de Stevens-Johnson, angioedema, novo aparecimento ou piora da psoríase, eritema multiforme, alopecia, Síndrome lúpus-símile, infarto do miocárdio, febre. **Posologia: ADULTOS:** Artrite Reumatoide, Artrite Psoriásica, Espondilite Anquilosante, Espondiloartrite Axial Não Radiográfica: a dose para pacientes adultos é de 40 mg, administrados em dose única por via subcutânea, a cada 14 dias. Doença de Crohn: início do tratamento - Semana 0: 160 mg por via subcutânea; Semana 2: 80 mg; Manutenção do tratamento: a partir da Semana 4, 40 mg a cada 14 dias. Colite Ulcerativa ou Retocolite Ulcerativa: início do tratamento - Semana 0: 160 mg por via subcutânea; Semana 2: 80 mg; Manutenção do tratamento: 40 mg a cada 14 dias. Psoríase: a dose para pacientes adultos é de 80 mg administrada por via subcutânea, seguida de 40 mg em semanas alternadas, uma semana após a dose inicial. Uma terapêutica continuada para além de 16 semanas, deve ser cuidadosamente reconsiderada em pacientes que não responderam dentro deste período de tempo. Após 16 semanas de tratamento, os pacientes que não apresentem uma resposta adequada podem se beneficiar de um aumento da frequência de dose para 40 mg por semana. Hidradenite Supurativa: 160 mg inicialmente, no Dia 1, seguida de 80 mg duas semanas depois, no Dia 15 (administrado em duas injeções de 40 mg em um dia). Duas semanas depois (Dia 29) continuar com uma dose de 40 mg por semana. Uveíte Não Infecciosa intermediária, posterior ou pan-uveíte: 80 mg inicialmente, seguida de 40 mg em semanas alternadas, começando na semana seguinte à dose inicial. **PEDIÁTRICOS:** Artrite Idiopática Juvenil Poliarticular: para pacientes entre 02 e 12 anos a dose é de 24 mg/m² de ASC, até uma dose única máxima de 20 mg para pacientes com idade entre 02 a < 04 anos e 40 mg para pacientes entre 04 e 12 anos, por via subcutânea a cada 14 dias. Para pacientes com idade superior a 13 anos a dose é de 40 mg, administrados em dose única por via subcutânea, a cada 14 dias. Artrite relacionada à Entesite: para pacientes acima de 06 anos a dose é de 24 mg/m² de ASC até um máximo de 40 mg administrados em dose única a cada 14 dias. Doença de Crohn: para pacientes pediátricos com 06 anos ou mais e com peso corporal menor que 40 kg, a dose inicial (Dia 01) é 80 mg por via subcutânea (duas injeções de 40 mg em um dia), seguidas por 40 mg após duas semanas (Dia 15). A dose de manutenção (Dia 29) para doença de Crohn ativa com intensidade grave é de 20 mg, a cada 14 dias e para doença de Crohn ativa com intensidade moderada é de 10 mg, a cada 14 dias. Para pacientes pediátricos com 06 anos ou mais e com peso corporal maior ou igual à 40 kg, a dose inicial (Dia 01) é 160 mg (quatro injeções de 40 mg em um dia ou duas injeções por dia por dois dias consecutivos), seguidas por 80 mg após duas semanas (Dia 15). A dose de manutenção (Dia 29) para doença de Crohn ativa com intensidade grave é de 40 mg, a cada 14 dias e para doença de Crohn ativa com intensidade moderada é de 20 mg, a cada 14 dias. O paciente pediátrico com doença de Crohn, cuja posologia for ≥ 40 mg de adalimumabe deve utilizar a apresentação em seringas preenchidas ou caneta. VENDA SOB PRESCRIÇÃO MÉDICA. Importado por: AbbVie Farmacêutica Ltda - Av. Guido Caloi, 1935, 1º andar, Bloco C - São Paulo - SP - CNPJ: 15.800.545/0001-50. AbbVie Line: 0800 022 2843. BU62.

Referências: 1. Bula do produto HUMIRA® (adalimumabe). **2.** Burmester GR, Panaccione R, Gordon KB, et al.Adalimumab: long-term safety in 23,458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis.* 2013;72(4):517-524.

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