Biological therapies in inflammatory bowel diseases: levels of evidence and methodological challenges

Terapias biológicas nas doenças inflamatórias intestinais: níveis de evidência e desafios metodológicos

Terapias biológicas en las enfermedades inflamatorias intestinales: niveles de evidencia y desafíos metodológicos

Letícia Isadora Alves da Silva Lima[1], Erica Nascimento Paranhos do Vale[2], Maria Eduarda Lima Reis[3], Rafaela Oliveira Ribeiro[4], Rossana Vanessa Dantas de Almeida Marques[5]

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1. Universidade Federal do Maranhão (UFMA). Imperatriz Maranhão, Brasil. https://orcid.org/0009-0004-7254-993X

2. Universidade Federal do Maranhão (UFMA). Imperatriz Maranhão, Brasil. https://orcid.org/0009-0003-8085-1859

3. Universidade Federal do Maranhão (UFMA). Imperatriz Maranhão, Brasil. https://orcid.org/0009-0003-8933-5607

4. Universidade Federal do Maranhão (UFMA). Imperatriz Maranhão, Brasil. https://orcid.org/0009-0000-4702-5297

5. Universidade Federal do Maranhão (UFMA). Imperatriz Maranhão, Brasil. https://orcid.org/0000-0001-8287-7137

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RESUMO

Introdução: As Doenças Inflamatórias Intestinais (DIIs), como a Doença de Crohn e a Colite Ulcerativa, causam inflamação recorrente e prejuízo funcional. As terapias biológicas ampliaram o manejo clínico, mas a literatura mostra variação metodológica que limita a força das evidências. **Objetivo**: Avaliar criticamente e discutir o nível de evidência na produção científica atual sobre o uso de terapias biológicas no tratamento da Doença Inflamatória Intestinal (DII), abordando a qualidade metodológica. **Metodologia**: Estudo observacional, quantitativo, descritivo e analítico. Foram incluídos artigos da base PubMed (2020–2025), avaliados pela metodologia GRADE. Os dados foram extraídos por avaliadores calibrados e analisados no software JAMOVI 2.5. **Revisão de Literatura:** Foram analisados 140 artigos. A maioria apresentou alto nível de evidência, embora 40% tenham sido de baixa qualidade. Metanálises e estudos observacionais predominaram. Eventos adversos foram relatados em 70% dos trabalhos, mais comuns em estudos de longa duração. Ensaios clínicos relataram randomização em 78% e cegamento em 63%. **Conclusão**: As terapias biológicas demonstram eficácia no tratamento das DIIs, mas ainda exigem maior rigor metodológico, padronização dos desfechos e acompanhamento prolongado para garantir segurança e efetividade.

Palavras-chave: Colite ulcerativa; Doença de Crohn; Doenças inflamatórias intestinais; Medicina baseada em evidências; Terapia biológica.

ABSTRACT

Introduction: Inflammatory Bowel Diseases (IBD), such as Crohn's disease and Ulcerative Colitis, cause recurrent inflammation and functional impairment. Biological therapies improved management, but methodological variations reduce the strength of evidence. **Objective**: To critically evaluate and discuss the level of evidence in scientific production on the use of biological therapies for IBD, addressing methodological quality. **Methods**: Observational, quantitative, descriptive, and analytical study. Articles from PubMed (2020–2025) were assessed with the GRADE methodology. Data were extracted by calibrated reviewers and analyzed with JAMOVI 2.5 software. **Literature Review**: A total of 140 articles were analyzed. Most showed high-level evidence, while 40% were low quality. Meta-analyses and observational studies predominated. Adverse events were reported in 70% of studies, more frequent in long-term designs. **Conclusion**: Biological therapies are effective for IBD, but require greater methodological rigor, standardized outcomes, and long-term monitoring to ensure safety and effectiveness.

Keywords: Biological Therapy; Crohn Disease; Evidence-Based Medicine; Inflammatory Bowel Diseases; Ulcerative Colitis.

RESUMEN

Introducción: Las Enfermedades Inflamatorias Intestinales (EII), como Crohn y Colitis Ulcerosa, causan inflamación recurrente y deterioro funcional. Las terapias biológicas mejoraron el manejo, pero la literatura muestra variaciones metodológicas que limitan la solidez de las evidencias. **Objetivo**: Evaluar el nivel de evidencia en estudios sobre terapias biológicas en EII, considerando la calidad metodológica. **Metodología**: Estudio observacional, cuantitativo y descriptivo. Se incluyeron artículos de PubMed (2020–2025), evaluados con la metodología GRADE. Los datos fueron analizados en el software JAMOVI 2.5. Revisión de la Literatura: Se revisaron 140 artículos. La mayoría mostró alto nivel de evidencia, aunque el 40% fue de baja calidad. Predominaron metaanálisis y estudios observacionales. Los eventos adversos se informaron en el 70%, con mayor frecuencia en estudios prolongados. **Conclusión**: Las terapias biológicas son eficaces en EII, pero requieren mayor rigor metodológico y seguimiento prolongado para garantizar seguridad y efectividad.

Descriptores: Colitis ulcerosa; Enfermedad de Crohn; Enfermedades inflamatorias intestinales; Medicina basada en evidencias; Terapia biológica.

REVISÃO

Introdução

Inflammatory Bowel Diseases (IBD), including Crohn's Disease (CD) and Ulcerative Colitis (UC), are chronic and multifactorial conditions affecting the gastrointestinal tract.[1] Their etiology involves genetic and environmental factors, resulting in abnormal immune response activation.[2,3] These diseases present with recurrent inflammation, which can lead to strictures, fistulas, and functional intestinal loss, impacting quality of life and increasing the burden on healthcare systems.[4]

The development of biological therapies represented a milestone in IBD treatment.[5] These agents act selectively on the immune response, showing superior efficacy to conventional treatments, such as corticosteroids and immunosuppressants, while reducing severe adverse effects.[6] However, the expansion of therapeutic options requires critical evaluation of available evidence to ensure safe and appropriate use.[7]

In this context, Evidence-Based Medicine (EBM) is essential for clinical decision-making, integrating scientific evidence, professional experience, and patient preferences.[8,9] In IBD management, EBM promotes individualized and effective interventions, highlighting the importance of consistent methodological analyses. This study aims to evaluate the level of evidence in recent publications on biological therapies, emphasizing methodological quality and clinical practice improvement.

Methodology

This observational, quantitative, descriptive, and analytical study was guided by the question: "What is the quality of scientific evidence regarding the use of biological therapies in the treatment of Inflammatory Bowel Diseases (IBDs), and how do they impact clinical practice?" To guide the analysis, the PCC strategy (Population, Concept, and Context) was applied: patients with Crohn's Disease and Ulcerative Colitis (Population), efficacy and safety of biological therapies (Concept), and methodological quality of studies and their outcomes (Context).

The search was conducted in PubMed using the following descriptors: (Biological Therapy) AND ((Inflammatory Bowel Diseases) OR (Crohn disease) OR (Ulcerative colitis)) NOT (Covid). Studies published between 2020 and 2025, classified as clinical, trials (randomized or not), meta-analyses, and observational studies were included. A total of 381 articles were identified, of which 140 composed the final sample after screening by title, abstract, and full text.

The quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, considering study type and duration, sample size, intervention used, blinding, randomization, outcomes, subgroup analyses, and adverse events. Data collection was performed by four calibrated evaluators, achieving near-perfect agreement (kappa = 0.812).

Statistical analysis was conducted using JAMOVI 2.5 software through descriptive statistics (means, standard deviations, absolute and relative frequencies) and the chi-square test, adopting a significance level of $p < 0.05$.

Results

The analyzed studies highlight essential aspects of biological therapies in IBD, summarized in tables with clinical and methodological data.

Table 1 provides an overview of the included studies, highlighting the evidence level according to the GRADE methodology, methodological diversity, and the main outcome assessment methods.

Table I - Sample characterization by evidence level, study type, adverse events, and outcome assessment method.

Variables	n	%
Evidence Level (GRADE)		
High	72	51,4
Moderate	12	8,6
Low	21	15,0
Very Low	35	25,0
Study Type		
Meta-analysis	51	36,4
Observational	48	34,3
Clinical trial	41	29,3
Adverse events reported		
Yes	98	70,0
No	20	14,3
Not Reported	22	15,7
Main outcome assessment method		
Clinical scores	88	62,9
Statistical analysis	38	27,1
Laboratory tests	8	5,7
Questionnaires	4	2,9
Imaging exams	2	1,4

Source: Authors (2025).

Table 2 highlights the representativeness of the approaches. In fifty-seven articles, study duration was not reported.

Table II – Study characterization, subgroup analyzed, and biological therapy used

Characterization	Mean ± SD	n	%

Sample size (patients)	249,0 ± 956,0	--	--
Study duration (weeks)	539,0 ± 660,0	--	--
Subgroup			
Crohn's Disease		61	43,6
Ulcerative Colitis		47	33,6
Crohn + Crohn's Disease		32	22,8
Biological therapy			
Monoclonal antibodies and immunobiologics		91	65,1
Fecal microbiota transplant		27	19,3
Stem cells		14	10,0
Therapeutic apheresis		3	2,1
Probiotics		2	1,4
Stem cells , monoclonal antibodies, immunobiologics		1	0,7
Fecal microbiota transplant, monoclonal antibodies, immunobiolo;		1	0,7
Fecal microbiota transplant, probiotics		1	0,7

Source: Authors (2025).

The methodological aspects of the analyzed clinical trials are described in Table 3.

Table III – Clinical trials characterization by blinding, blinding method, and randomization

Variables	**n**	**%**
Blinding		
Yes	26	63,41
No	15	36,59
Blinding method		
Double-blind	21	51,22
Single-blind	5	12,20
Not applicable	15	36,58
Randomization		
Present	32	78,04
Absent	9	21,96

Source: Authors (2025).

Table 4 shows evidence in the patterns of the results. Twenty-two articles did not report adverse events, and fifty-seven did not provide information on study duration.

Table IV - Association between adverse events and methodological variables

Methodological Variables	**Adverse Events Reported**				**p-value**
	Yes		No		
	n	%	n	%	
Study Duration					
Full year or more	42	60,87	4	28,57	0,027
Incomplete year	27	39,13	10	71,43	
Main Method Outcome assessment					
Clinical Scores	67	68,37	13	65,00	0,002
Statistical analysis	27	27,55	1	5,00	

Laboratory tests	2	2,04	3	15,0(	
Questionnaires	1	1,02	2	10,0(	
Imaging exams	1	1,02	1	5,00	
Study Type					
Meta-analysis	36	36,7	4	20,0(	
Observational	34	34,6	8	40,0(	0,330
Clinical trial	28	28,5	8	40,0(	
Subgroup					
Crohn's Disease	39	39,8(	13	65,0(	
Ulcerative Colitis	36	36,7	5	25,0(	0,107
Crohn's Disease and Ulcerative Colitis	23	23,4	2	10,0(	
Sample size					
1-500 patients	89	90,8	18	90,0(	
501-1000 patients	4	4,08	1	5,00	0,983
More than 1000 patients	5	5,10	1	5,00	

Source: Authors (2025).

Table 5 analyzed the associations between study types and methodological variables, elucidating the approaches employed.

Table V - Association between study type and methodological variables of the evaluated studies.

Variables	**Study Type**						**p-valu**
	Meta-analysis		Observational		Clinical Trial		
	n	%	n	%	n	%	
Study duration							
Full year or more	8	15,6	28	58,3	18	43,9(	0,090
Incomplete year	2	3,92	16	33,3	21	51,2	
Omitted	41	80,3	4	8,34	2	4,88	
Main outcome assessment method							
Clinical Score	14	27,4	38	79,1(	36	87,8(	
Statistical analysis	36	70,5	2	4,16	0	0,00	
Laboratory tests	0	0,00	5	10,4	3	7,34	<0,00
Questionnaires	1	1,97	2	4,16	1	2,43	
Imaging exams	0	0,00	1	2,11	1	2,43	
Subgroup							
Crohn's Disease (CD)	18	34,6	22	45,8	21	51,2	
Ulcerative Colitis (UC)	20	40,3	9	18,7	18	43,9(	0,004
CD and UC	13	25,0	17	35,4	2	4,89	
Sample size							
1-500	45	88,2	46	95,8	37	90,2	
501-1000	2	3,93	2	4,17	1	2,44	0,400
Mais de 1000	4	7,84	0	0,00	3	7,32	

Source: Authors (2025).

Discussion

The analysis of the available evidence on biological therapies for Inflammatory Bowel Diseases (IBD) revealed a heterogeneous literature, with studies of different methodological quality levels. Among the included studies, 51.4% (72) were classified as high-level evidence and 8.6% (12) as moderate, while 40% (56) presented low or very low levels, indicating advances but also limitations that reduce the strength of clinical recommendations.[11] The predominant study type was meta-analysis (36.4%; 51), followed by observational studies (34.3%; 48) and clinical trials (29.3%; 41). Although meta-analyses are robust synthesis tools, the high proportion of observational studies highlights the risk of bias and limits the generalizability of results.[12]

Regarding safety, adverse events were reported in 70.0% (98) of studies, a relevant finding given the immunomodulatory profile of these therapies. However, 15.7% (22) did not include this data, compromising the assessment of risk-benefit.[7] Moreover, longer studies reported more adverse events compared to shorter ones (p=0.027), reinforcing the need for prolonged follow-up, as highlighted by Selinger et al.[5]

In terms of outcome assessment methods, clinical scores predominated in 62.9% (88) of the studies, in contrast to the low use of laboratory tests (5.7%; 8) and imaging exams (1.4%; 2). Reliance on subjective parameters weakens the reliability of findings, as they may be influenced by patient and evaluator perception.[12] Feuerstein et al. recommend integrating biomarkers, such as fecal calprotectin, to increase precision and comparability between studies.[11]

In subgroup analysis, Crohn's Disease was more frequently investigated (43.6%) than Ulcerative Colitis (33.6%), reflecting its greater clinical complexity but limiting the representativeness of the findings.[13] Linhares et al. emphasize the need for comprehensive guidelines for both diseases, given the symptom overlap and therapeutic responses.[6] Regarding interventions, 65.1% evaluated monoclonal antibodies and immunobiologics, consolidating agents such as infliximab and adalimumab as pillars in the treatment of moderate-to-severe cases.[6] Emerging strategies, such as fecal microbiota transplantation (19.3%) and stem cell therapies (10.0%), are beginning to be explored, but the lack of methodological standardization and larger trials still limits their validation.[13]

Analysis of sample sizes and study duration revealed wide variability. Most studies included 1 to 500 participants, while studies with more than 1,000 participants were less frequent, restricting the generalization of findings.[17] Small and short-duration trials hinder the evaluation of robust outcomes and late events, whereas larger and longer studies, such as Sandborn et al.'s study on risankizumab over 52 weeks, provide more consistent results applicable to clinical practice.[14,4] These data reinforce the importance of long-term multicenter trials.

Among the evaluated clinical trials, 63.41% (26) used some form of blinding, with double-blind being predominant (51.22%; 21), while 36.59% (15) did not apply this strategy. Randomization was present in 78.04% (32) but absent in 21.96% (9), compromising the impartiality of findings.[32] Allocation concealment and blinding strategies are essential to reduce bias but are still not applied uniformly, as highlighted by Miola et al.[15]

Final Considerations

The analysis of evidence on Inflammatory Bowel Diseases (IBD) reveals a predominance of studies with high or moderate levels of evidence, although methodological challenges persist, such as heterogeneity of study designs and lack of standardization of outcomes. The scarcity of adverse event reporting and the short duration of some studies reinforce the need for prolonged follow-up to assess safety and efficacy. The predominant use of clinical scores highlights the importance of including biomarkers and imaging exams. Future research should prioritize randomized trials, representative samples, adequate blinding, and explore emerging therapies, such as fecal microbiota transplantation and stem cells, to consolidate their efficacy and safety.

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Correspondent author:
Letícia Isadora Alves da Silva Loma
Rua Senador Millet, 446, Bairro Maranhão Novo,
Cep: 65903-200.
Imperatriz, Maranhão, Brasil.
leticia.isadora@discente.ufma.br