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Asthma Remission - Is it a Holy Grail?

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Resumo

O objetivo terapêutico da asma está mudando do simples controle dos sintomas para a busca ambiciosa da remissão, definida como um período sustentado de controle abrangente da doença. Historicamente, o foco exclusivo em beta-agonistas de curta duração (SABA) levou a resultados insatisfatórios, impulsionando a adoção de terapias combinadas e, mais recentemente, de medicamentos antiasmáticos modificadores da doença (DMAADs). A remissão é amplamente categorizada em clínica (ausência de exacerbações e uso de corticosteroides orais, melhora na qualidade de vida) e biológica (normalização de biomarcadores inflamatórios). A remissão em adultos é rara, o que ressalta a importância de identificar preditores (função pulmonar preservada, menor duração da doença).
Inspirado pela reumatologia, o foco na obtenção de baixa atividade da doença (BAD) visa prevenir danos pulmonares irreversíveis. No entanto, a aplicação do conceito é controversa, equilibrando o risco de tratamento excessivo em casos mais leves com a necessidade de terapia intensiva na asma grave. Um consenso sobre os critérios de remissão e a realização de estudos prospectivos são imprescindíveis para distinguir a doença ativa do dano pulmonar estabelecido e consolidar a remissão como uma meta clínica alcançável.

Palavras-chave: asma, remissão, medicamentos antiasmáticos modificadores da doença.

Abstract

The therapeutic goal for asthma is shifting from simple symptom control to the ambitious pursuit of remission, defined as a sustained period of comprehensive disease control. Historically, focusing solely on short-acting beta-agonists (SABA) led to poor outcomes, driving the adoption of combination therapies and, more recently, disease-modifying anti-asthmatic drugs (DMAADs).
Remission is broadly categorized into clinical (absence of exacerbations and oral corticosteroid use, improved quality-of-life) and biological (normalization of inflammatory biomarkers). Adult remission is rare, underscoring the importance of identifying predictors (preserved lung function, shorter disease duration).
Inspired by rheumatology, the focus on achieving low disease activity (LDA) aims to prevent irreversible lung damage. However, the concept's application is controversial, balancing the risk of overtreatment in milder cases against the need for intensive therapy in severe asthma. A consensus on remission criteria and the

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execution of prospective studies are imperative to distinguish active disease from established lung damage and solidify remission as an achievable clinical goal.

Key-words: asthma, remission, disease-modifying anti-asthmatic drugs.

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Introduction

In recent years, the development of novel therapeutic strategies in asthma has fostered an ambitious paradigm shift: the pursuit of remission. [1] In medical terminology, remission signifies a sustained period during which a patient experiences comprehensive disease control, effectively mitigating its burden on their lives.

The understanding and pursuit of remission are continually evolving across various diseases, driven by advancements in treatment. Consider the field of oncology, where remission refers to the period during which cancer is no longer detectable following treatment. [2] In chronic inflammatory diseases, it describes a phase characterized by low disease activity (LDA) alongside absent or minimal symptom burden. [3] Disease activity refers to biological pathways that cause end-organ damage but can be suppressed with pharmacological treatment. In rheumatoid arthritis, LDA is defined by assessing joint swelling and tenderness plus the systemic biomarker C-reactive protein (CRP); LDA is achieved if 0 or 1 joint is affected and the CRP is 1mg/dL. LDA is a treatment target for rheumatologists, providing an objective basis for treatment escalation if it is not achieved. Rheumatology guidelines have adopted an aggressive approach to achieving LDA early in the natural history of the disease in order to prevent end-organ damage such as joint destruction. End-organ damage can cause symptoms and disability; therefore, remission (which encompasses LDA plus a low symptom burden), is far more likely to be achieved if treatment has successfully prevented significant end-organ damage. Now, these concepts of LDA and remission are being applied to the management of asthma. [5]

Historically, the primary therapeutic objective in asthma has centered on symptom control, often represented by the intermittent use of short-acting beta-agonists (SABA). [6] However, SABA overuse is associated with higher rates of hospitalization and mortality, indicating inadequate anti-inflammatory treatment. [7] This realization spurred a paradigm shift towards combination therapies involving inhaled corticosteroids (ICS) and fast-acting bronchodilators being used as-needed, with the evolving goal of mitigating the future risk of exacerbation. [8]

In recent years, the advent of disease-modifying anti-asthmatic drugs (DMAADs) with potent anti-inflammatory properties has further propelled the

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aspiration of achieving comprehensive disease control and eliminating future risk. Consequently, treatment goals in asthma have evolved, with the concept of remission increasingly appearing in new clinical guidelines. [9] However, the precise implications of remission for patients, clinicians, and healthcare systems remain to be fully elucidated. This article describes the current understanding of this evolving concept, bridging the gap between research and its practical consequences in the daily management of asthma patients.

Types of Remission in Asthma

The term remission itself is controversial. An initial question is: What is the difference between a controlled patient and a patient in remission? The term remission could be regarded as a high level of asthma control, with current treatment achieving the absence of symptoms. The term remission attempts to represent control in a broader perspective for a longer period and includes concepts of clinical remission and biological remission. The former focuses on clinical assessment only, while the latter considers underlying biological pathways of disease activity.

The main components of clinical remission, recently described by several authors, are the absence of exacerbations, absence of oral corticosteroid (OCS) use, and improvement in quality-of-life tool scores such as the ACQ-5 and ACT, typically for 12 months (Table 1). When these three components are achieved, it is referred to as clinical remission, and a fourth criterion may be added: improvement or stabilization of lung function, considering FEV1. Some authors use three components, while others believe that all four are needed to define clinical remission.

Clinical remission can be on treatment (e.g., with biologic therapy) or off treatment (spontaneous remission). In asthma, the term remission is mainly applied to Global Initiative for Asthma (GINA) Step 5 patients using biologics. The term remission without treatment is possible but rarely used in asthma and refers to a patient who meets all components while no longer receiving treatment; this is commonly observed during teenage years. [12]

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Table 1 - Describes the different concepts recently reported by some authors. [11, 12]

Variable	Menzies-Gow et al. (21)	Pavord et al. (20)	Oishi et al. (19)	McDowell et al. (18)
ACQ-5/6	< 1.5 or ≤ 0.75	N/A	< 1.5	< 1.5
ACT	N/A	> 20	N/A	N/A
VEF1	≥100mL improvement	N/A	> 80% predicted	Above LLN or < 100 mL baseline value
OCS use	Zero	Zero	Zero	Zero
Asthma exacerbations	Zero	Zero	Zero	N/A
Duration	6 months	1 year	1 year	1 year
Patients with remission	15-23%	41%	31.5%	18%

ACQ: asthma control questionnaire; ACT: asthma control test; OCS: oral corticosteroids; and LLN: lower limit of normal.

Biological remission has also been described, defined by meeting biomarker-related criteria, such as a reduction of inflammatory biomarkers like serum eosinophils. Complete remission is achieved when both clinical and biological criteria are met. [12]

Predictors of Remission

In childhood asthma, it is not uncommon to observe spontaneous remission. In children, the strongest predictors are fewer and milder symptomatic episodes, improving or preserved lung function, and less airway hyperresponsiveness. In this scenario, the convergence of these three components is key for the remission in adulthood. [21]

Conversely, adult remission is rare, and identifying predictors of remission during treatment presents a challenge. The identification of such predictors can facilitate early intervention and modification of the disease course. Recently, numerous publications have addressed this topic. The primary factors described include preserved lung function, low hyperreactivity, short disease duration, absence of chronic rhinosinusitis with nasal polyps, and young age. [13, 14, 15, 16]

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Challenges and Controversies in Asthma Remission

A significant frontier in pulmonology lies in establishing a consensus on remission criteria to solidify it as a definitive treatment goal in asthma. For years, therapeutic objectives have centered on symptom control and the reduction of future risk. [17] Shifting this paradigm toward remission as a primary aim raises pertinent questions, particularly regarding potential increases in medication utilization, even in patients with milder disease (GINA Steps 1 and 2).

One of the principal controversies surrounding the concept of remission in asthma pertains to the long-standing acceptance that patients in GINA Steps 1 and 2 may not require regular controller medication, relying instead on reliever medications as needed for intermittent symptoms. [18] As complete remission is defined as the comprehensive control of both symptoms and underlying inflammation, then a paradox arises: can remission occur spontaneously or only in patients with more severe disease (GINA Steps 4 and 5) who are receiving intensive treatment? This situation carries the potential risk of overtreatment and the excessive use of expensive biologic therapies in milder cases. [19]

Conversely, the concept of early intervention with biologics to interrupt the inflammatory cascade and prevent progression to an end-stage disease state is gaining traction. [20] This paradigm shift has precedents in other specialties, such as rheumatology. However, clearly defined criteria are still needed to accurately identify the patients most likely to benefit from such early aggressive treatment before significant disease progression due to irreversible lung damage occurs. [5]

While remission represents an aspirational treatment goal, it could also be perceived as an elusive "holy grail" that currently lacks an evidence base. It is crucial to recognize that achieving remission under treatment signifies comprehensive control across all facets of the disease, but that this may not be an appropriate treatment goal for all patients. The presence of high levels of disease activity early in the natural history of the disease can identify individuals at high risk of rapid disease progression with end-organ damage. Targeting these high-risk individuals to achieve LDA and/or remission will prevent irreversible lung damage. [22]

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Further rigorous investigation is imperative to fully elucidate the real-world impact of remission on patients and healthcare providers. From a scientific perspective, prospective studies with remission as a primary endpoint are essential, as current evidence largely stems from post-hoc analyses. [5] Furthermore, a more complex approach will be needed in the future to distinguish between active disease processes and lung damage. Targeting disease activity is an achievable goal, but trying to achieve remission in individuals with significant lung damage may be an unrealistic treatment goal that will result in overtreatment.

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