J Bras Pneumol. 2024;50(1):e20240004
https://dx.doi.org/10.36416/1806-3756/e20240004

Asthma remission

Paul M O'Byrne[1]

The term "remission" is frequently used in medicine, particularly in the management of chronic inflammatory diseases and cancer. It is defined as the reduction or disappearance of signs and symptoms of a disease. A reduction is known as a partial remission, and disappearance as a complete remission. There is an important element of the time during which the signs and symptoms have disappeared, and this duration varies with the type of the chronic disease.

Importantly, remission does not imply absence of treatment for the disease, nor is it the same as a cure; however, complete remission of evidence of the presence of some cancers over a five-year time frame is considered evidence of a cure.

Asthma is the most common chronic respiratory disease, affecting more than 350 million patients worldwide.[1] There are effective medications for asthma treatment, most notably inhaled corticosteroids (ICS), alone or together with long-acting inhaled β_2 agonists (LABA).[2] The objective of asthma treatment is to obtain asthma control. The concept of asthma control has been in use for more that 20 years. It consists of (i) absence of daytime or nighttime asthma symptoms; (ii) absence of asthma exacerbations; (iii) normal lung function; (iv) normal activities of daily living. The amount of treatment needed to achieve asthma control has been used as an indicator of asthma severity. Asthma control can be achieved in most asthma patients by using inhaled medications.

There are, however, a minority of asthma patients (7-10%) who do not achieve asthma control, even with higher doses of inhaled ICS/LABA therapy.[3] These patients have more frequent severe asthma exacerbations, often reduced lung function, and major impact on their daily lives. Up to 70% of these severe asthma patients are recognized to have persisting eosinophilic airway inflammation, which is termed T_2-high severe asthma.[3] A range of monoclonal antibodies have been developed which target specific proteins associated with T_2-high asthma, which are collectively known as asthma biologics. These are antibodies which bind to IL-5 (mepolizumab and reslizumab)[4,5]; to the IL-5 receptor α (benralizumab)[6]; to the IL-4 receptor α (dupilumab)[7]; to IgE (omalizumab)[8]; or to thymic stromal lymphopoietin (tezepelumab).[9,10] Each of these biologics improves asthma control in severe T_2-high asthma by reducing exacerbations, improving symptoms, and improving lung function. Several asthma biologics have also been demonstrated to be oral corticosteroid sparing.[11-13]

A concept has been proposed that, by blocking cytokines important in the pathogenesis of asthma, biologics may have a greater likelihood of inducing asthma remission than conventional therapies.[14] This is not an unrealistic hypothesis. There are known clinical situations where an asthma cure has occurred. A cure would be identified not only by absence of symptoms, but also by the absence of the characteristic inflammatory biomarkers and physiological abnormalities of asthma, particularly airway hyperresponsiveness. This has been described in patients with occupational asthma to western red cedar; in these cases, early removal of the patients from the workplace has resulted in cure.[15] In addition, many children with asthma have a complete remission of their symptoms during adolescence,[16] although some have a recurrence of asthma later in life.

With regards to the use of asthma biologics, most studies have identified patients who have a greater clinical response, as measured by standard clinical outcomes, than the mean results for the study group. These patients have been called "super-responders."[17] While the concept of remission is different, neither the definition nor the period of remission has been agreed and differs in studies which have evaluated the benefits of asthma biologics in inducing partial remission (Table 1), and, not surprisingly, the percentage of patients considered to be in remission varies from 15% to 41%.[18-21] The most consistent features of partial remission in these studies are symptom control, the absence of need for oral corticosteroids, and the absence of asthma exacerbations for at least 1 year.

There is a high likelihood that the term "asthma remission" will become more widely used in studies examining the efficacy of asthma biologics. It will be important to come to a consensus on defining the term, particularly as comparisons will be made (often inappropriate) between studies where remission has been a clinical outcome. Several efforts have been made to provide a definition,[22-24] but have not yet become widely accepted. This definition of a complete asthma remission should include absence of asthma symptoms, absence of exacerbations and of the need for oral corticosteroids, and maintenance of the patients' best FEV_1 values, with no evidence of variability. These benefits should be maintained for at least 1 year. Occasional symptoms, the level of which is yet to be defined, and particularly if caused by external stimuli, such as exercise or atmospheric pollutants, may be acceptable to define a partial asthma remission.

While there are benefits in focusing on asthma remission as a clinical outcome, there are both unanswered questions and risks. The absence of a widely agreed definition has already been discussed, but there is also no information about the duration of time that a patient

1. Firestone Institute for Respiratory Health and the Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

Table 1. Definitions of asthma remission in patients on asthma biologics.

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
FEV_1	≥ 100 mL 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.

should remain on an asthma biologic once remission has been achieved or about the risks of recurrence of asthma symptoms if the biologic is discontinued. Also, if remission becomes a widely accepted clinical outcome for patients on asthma biologics, and a patient does not achieve remission while on one biologic, there will be the temptation to try another, and the benefits of this to patients has not been studied yet.

REFERENCES

1. Asher MI, García-Marcos L, Pearce NE, Strachan DP. Trends in worldwide asthma prevalence. Eur Respir J. 2020;56(6):2002094. https://doi.org/10.1183/13993003.02094-2020
2. Global Initiative for Asthma [homepage on the internet]. Bethesda: Global Initiative for Asthma; c2023 [cited 2024 Jan 2]. Global Strategy for Asthma Management and Prevention (2023 update). Available from: http://www.ginasthma.org
3. Chung KF, Wenzel S; European Respiratory Society/American Thoracic Society Severe Asthma International Guidelines Task Force. From the authors: International European Respiratory Society/American Thoracic Society guidelines on severe asthma. Eur Respir J. 2014;44(5):1378-1379. https://doi.org/10.1183/09031936.00120714
4. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma [published correction appears in N Engl J Med. 2015 Apr 30;372(18):1777]. N Engl J Med. 2014;371(13):1198-1207. https://doi.org/10.1056/NEJMoa1403290
5. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2011;184(10):1125-1132. https://doi.org/10.1164/rccm.201103-0396OC
6. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med. 2014;2(11):879-890. https://doi.org/10.1016/S2213-2600(14)70201-2
7. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med. 2013;368(26):2455-2466. https://doi.org/10.1056/NEJMoa1304048
8. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol. 2001;108(2):184-190. https://doi.org/10.1067/mai.2001.117880
9. Gauvreau GM, O'Byrne PM, Boulet LP, Wang Y, Cockcroft D, Bigler J, et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. N Engl J Med. 2014;370(22):2102-2110. https://doi.org/10.1056/NEJMoa1402895
10. Corren J, Parnes JR, Wang L, Mo M, Roseti SL, Griffiths JM, et al. Tezepelumab in Adults with Uncontrolled Asthma [published correction appears in N Engl J Med. 2019 May 23;380(21):2082]. N Engl J Med. 2017;377(10):936-946. https://doi.org/10.1056/NEJMoa1704064
11. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med. 2009;360(10):985-993. https://doi.org/10.1056/NEJMoa0805435
12. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P,et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med. 2017;376(25):2448-2458. https://doi.org/10.1056/NEJMoa1703501
13. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. N Engl J Med. 2018;378(26):2475-2485. https://doi.org/10.1056/NEJMoa1804093
14. Upham JW, James AL. Remission of asthma: The next therapeutic frontier?. Pharmacol Ther. 2011;130(1):38-45. https://doi.org/10.1016/j.pharmthera.2011.01.002
15. Malo JL, Chan-Yeung M. Occupational asthma. J Allergy Clin Immunol. 2001;108(3):317-328. https://doi.org/10.1067/mai.2001.116432
16. Vonk JM, Postma DS, Boezen HM, Grol MH, Schouten JP, Koëter GH, et al. Childhood factors associated with asthma remission after 30 year follow up. Thorax. 2004;59(11):925-929. https://doi.org/10.1136/thx.2003.016246
17. Upham JW, Le Lievre C, Jackson DJ, Masoli M, Wechsler ME, Price DB; et al. Defining a Severe Asthma Super-Responder: Findings from a Delphi Process. J Allergy Clin Immunol Pract. 2021;9(11):3997-4004. https://doi.org/10.1016/j.jaip.2021.06.041
18. McDowell PJ, McDowell R, Busby J, Eastwood MC, Patel PH, Jackson DJ, et al. Clinical remission in severe asthma with biologic therapy: an analysis from the UK Severe Asthma Registry. Eur Respir J. 2023;62(6):2300819. https://doi.org/10.1183/13993003.00819-2023
19. Oishi K, Hamada K, Murata Y, Matsuda K, Ohata S, Yamaji Y, et al. A Real-World Study of Achievement Rate and Predictive Factors of Clinical and Deep Remission to Biologics in Patients with Severe Asthma. J Clin Med. 2023;12(8):2900. https://doi.org/10.3390/jcm12082900
20. Pavord I, Gardiner F, Heaney LG, Domingo C, Price RG, Pullan A, et al. Remission outcomes in severe eosinophilic asthma with mepolizumab therapy: Analysis of the REDES study. Front Immunol. 2023;14:1150162. https://doi.org/10.3389/fimmu.2023.1150162
21. Menzies-Gow A, Hoyte FL, Price DB, Cohen D, Barker P, Kreindler J, et al. Clinical Remission in Severe Asthma: A Pooled Post Hoc Analysis of the Patient Journey with Benralizumab. Adv Ther. 2022;39(5):2065-2084. https://doi.org/10.1007/s12325-022-02098-1
22. Thomas D, McDonald VM, Pavord ID, Gibson PG. Asthma remission: what is it and how can it be achieved?. Eur Respir J. 2022;60(5):2102583. https://doi.org/10.1183/13993003.02583-2021
23. Lommatzsch M, Buhl R, Canonica GW, Ribas CD, Nagase H, Brusselle GG, et al. Pioneering a paradigm shift in asthma management: remission as a treatment goal. Lancet Respir Med. Epub online ahead of print. https://doi.org/10.1016/S2213-2600(23)00415-0
24. Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, et al. An expert consensus framework for asthma remission as a treatment goal. J Allergy Clin Immunol. 2020;145(3):757-765. https://doi.org/10.1016/j.jaci.2019.12.006