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COMMENTARY

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SANI clinical remission definition: a useful tool in severe asthma management

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ABSTRACT

In the field of severe asthma, the concept of disease control has recently been integrated by the one of clinical remission. With this new concept, we move on to analyze the efficacy of therapy on multiple parameters simultaneously, starting with the mandatory discontinuation of the systemic glucocorticoids, to which is added the effect on exacerbations, respiratory function, and symptoms control. The Italian severe asthma registry SANI (Severe Asthma Network Italy) drafted criteria for the definition of disease remission, allowing patients to be classified into two groups, partial and complete remission. The greater dynamism of the definition, provided by SANI, allows us to hypothesize its practical use, concerning therapy management of severe asthma patients, starting from the level of remission, with the aim to facilitate the clinical decision on replacement, continuation or modulation of patients' therapy.

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Changing in outcome

Severe asthma is a condition affecting about 10% of asthmatic patients, the burden of which in clinical and economic terms is well known (1–3). Although this type of asthma is, by definition severe, it's nowadays more easily treatable, due to monoclonal antibodies, developed to control symptoms, as alternatives to systemic steroids, until two decades ago the main prescribed therapy (4–6). Studies, both clinical trials (RCTs) and real life (RL), of biologics were usually evaluating the efficacy of the drugs on a single primary endpoint at a time, once the effect on exacerbations (7–13), once on tapering of systemic glucocorticoid therapy (14–17), or on reducing symptomatology and improving quality of life.

A new paradigm for severe asthma management has emerged in recent years; we are facing a transition from a focus on single outcomes to a more comprehensive approach, centered on achieving *clinical remission* (18).

The fascinating challenge of the concept of clinical remission, which is still in its infancy, lies in trying to see the effectiveness of a therapy in a more holistic way, in fact that in the past the evaluation of treatment efficacy in severe asthma was primarily focused on conventional outcomes (*i.e.* symptom control, lung function improvement, OCS intake and exacerbation reduction); in contrast, the introduction of the concept of clinical remission is trying to revolutionize the effectiveness of biologics, observing its simultaneous effectiveness on several pre-established goals. The idea of clinical remission was already expressed in other fields of medicine, such as rheumatology, diabetology, oncology, to asthma as well (19,20).

Historically, remission has been thought of as spontaneous remission (21). In the context of asthma, off treatment clinical remission may be observed in asthmatic children during adolescence, or in some patients with occupational asthma after work cessation (22–24). Clinical remission is still outside the concept of cure, which would require a return to normal airway physiology, in terms of inflammation and remodeling, as well as complete symptom control, upon discontinuation of treatment. To date, the term clinical remission refers to the achievement of certain composite outcomes during treatment. Despite there is not a complete consensus of the definition of clinical remission, and we found several minimal differences in the various definitions, the real innovation of the concept of remission is the introduction of a multiple parameter evaluation, necessarily co-present, to define a drug treatment's efficacy. Another important feature of the concept of clinical remission is the achievement and persistence of the above outcomes over a long observation period (e.g. 1 or 2 years) (21). In addition, some other concepts are introduced, such as the one of quantification of the parameters needed to define the patient in remission. In fact rather than a control of symptoms, function and exacerbations, here is required a complete discontinuation of systemic corticosteroid intake, no exacerbations, ACT or ACQ value must obtain to reach a minimal cutoff, which in later parts of the manuscript is more fully described, and respiratory function that must be stable or, in some cases at least 80% FEV_1, all simultaneously. The second important concept introduced is that of observation time, generally 1 year, in some cases more than 1, to be able to define the patient in remission. Time factor that is also decisive in the timing of observations of the parameters required, in the field of remission after 1 or more year, indeed at each visit in the concept of disease control (25).

The following criteria for clinical remission were identified: the drug's effect on exacerbations, OCS intake, lung function, and symptom control of the disease. Several authors also indicate the effects of the drug on canonical biomarkers that are usually considered (peripheral eosinophils, eosinophils on sputum, and bronchial nitric oxide - FeNO) and, in some cases, also the effect on bronchial hyperreactivity (20,26–29). Remission is an interesting goal to achieve to consider a patient as perfectly responder to a therapy, till now not the only one, and in the manuscript we propose a use of this concept to manage patients. The possibility to change the paradigm of asthma control, using the concept of asthma remission, is so recognized that national and international documents and guidelines insert, despite with several differences, the concept of remission to be achieved by patients.

Remission definitions

Currently, there is no standard, shared definition of asthma remission.

In the different definitions, there are similarities, which are ineluctable, and others which are only indicated by some authors, both in terms of the parameters to be evaluated and the observation time. The cornerstones, present in all the different definitions are the discontinuation of systemic glucocorticoid therapy to control asthma, the absence of exacerbations, the evaluation of symptoms control, using questionnaires such as ACT or ACQ, and the positive

effect of treatment on lung function. It is precisely on this last point that the various authors are divided, with some considering the achievement, and subsequent maintenance, of FEV1 > 80% of predicted to be indispensable, while others indicate stabilization of the same functional parameter as a necessary outcome. In the following sections, we detail the similarities and differences of the clinical remission criteria proposed by different investigators.

OCS intake

A common point of all definitions, perhaps the only one on which all agree, is the discontinuation of systemic glucocorticoid therapy. It is well established that systemic glucocorticoid therapy can cause both long-term and short-term side effects (30). By contrast, an additional positive effect of biologics derives from the reduction, if not even discontinuation, acute (i.e. exacerbations) and chronic therapy of severe asthma. Therefore, a patient cannot be defined as not only in remission but also fully responsive to biological therapy if unable to discontinue systemic glucocorticoid therapy.

Exacerbations

The exacerbation rate is a canonical primary endpoint in all RCT and RL studies in patients with severe asthma treated with biologics and appears to be closely related to cyclic glucocorticoid intake, usually prescribed during acute episodes of disease. With this background, it seems easy to point out the role of reducing exacerbations in the concept of clinical remission of the disease considering the important role of exacerbations in the progression of the disease especially in terms of accelerated decline in FEV1 over time. Thus, a patient cannot be called in remission if they complain of acute disease episodes during the observation period. The absence of exacerbations during a certain period (e.g. 1 or 2 years) is a pivotal point in definitions of clinical remission (20,29,31).

Control of the disease

This point is certainly more controversial than the previous ones. The various definitions of clinical remission drive the use of questionnaires, such as ACT and ACQ, for defining disease control. Although validated and globally popular, they are burdened by a subjectivity that data such as respiratory function, number of exacerbations and OCS dosage, do not have. A patient might have an altered perception of their symptomatology, either in a positive or negative sense, also due to psychological mechanisms related to temporal adaptation, in which the decreased perception of symptoms is caused by a psychological change due to chronic obstruction and dyspnea (27). Despite this, it is essential to assess perceived symptom control, a value also stated in the ATS/ERS guidelines for defining asthma as uncontrolled (32). Regarding symptoms main guidelines and consensus use ACT or ACQ questionnaires, reaching values higher than 20 or 23 in ACT, and 0.75 or 1.5 about, main guidelines and consensus use ACT or ACQ questionnaires, reaching values higher than 20 or 23 in ACT and 0.75 or 1.5 in ACQ (31), or a more general absence of asthma symptoms.

Lung function

Respiratory function is a key point of the various definitions of disease remission, but there are some differences among the proposals of different groups of clinical investigators. Some authors believe it is necessary to reach at least 80% of FEV1 to define the patient as being in remission. In contrast, other authors consider crucial to have an improvement of 100 ml or 200 ml, or finally to maintain a stabilization of respiratory function values (19,20,26,28).

Time factor

Time is another important criteria on to consider in the evaluation of clinical remission. Some authors indicate 1 year as the minimum observation time, whereas it is necessary to evaluate the parameters for 2 years.

Summary, we can define a set of common parameters such as oral glucocorticoid intake, exacerbation, and disease control, and then the parameter of respiratory function that allows us to distinguish the various definitions into those that require stabilization from those that require achieving 80% FEV1.

Some authors have also proposed achieving a resolution of the inflammatory pattern, as an additional criterion to define a patient in remission. Menzies-Gow, in his 2020 manuscript, talks about "clinical" remission on treatment, referring to patients who have reached the criteria of clinical remission, based on the four endpoints previously mentioned, which, to reach a “complete remission” of disease, the normalization of biomarkers of inflammation, such as eosinophils on blood, on sputum or even that of exhaled nitric oxide values, must be added. The same group of investigators have also revised the challenging hypothesis of including the reduction of airway hyperresponsiveness among the clinical remission criteria. This fascinating

hypothesis raises clinical and ethical problems linked to the intrinsic difficulties of evaluating bronchial hyperresponsiveness in patients with severe asthma. Similarly, Thomas et al., in their proposal of complete remission, have suggested including the normalization of several biomarkers of inflammation such as blood eosinophils, FeNo, and bronchial hyperresponsiveness to histamine or methacholine (29). Another important question is if the effect of biologics, on other markers of asthma pathology (like remodeling indices, mucus plugs, etc), which may be measured by invasive or, better, with noninvasive imaging tests, may be considered as a demonstration of a real disease-modifying effects of these treatments. In addition, these authors have proposed to include the reduction of subepithelial thickness among the criteria of complete remission [25]. Finally, we should mention the recent proposal by the American Associations (33) to include the evaluation of other items such as work/school day absences.

Remission in guidelines

The concept of clinical remission has become so important in the management of patients with asthma that it has entered the 2023 guidelines in several national guidelines. The first scientific societies to include remission as a goal for patients with severe asthma were the Austrian [Austrian Society for Pediatrics and Adolescent Medicine (ÖGKJ), Austrian Society for Pneumology (ÖGP)] and the German Societies [German Respiratory Society (DGP] (34). These scientific societies included the absence of systemic glucocorticoid therapy and exacerbations, stable respiratory function, and symptom control as *sine qua non* criteria for clinical remission. Subsequently, those from Spain (Spanish Society of Pneumology and Thoracic Surgery (SEPAR)) distinguished patients in clinical remission, following the criteria described above for the German-Austrian societies, and complete remission of disease if, in addition to the previous criteria, normalization of bronchial hyperactivity and absence of bronchial inflammation are added. In both cases, the required observation time is 12 months (35).

The definition of clinical remission, provided by the Japanese Practical Guidelines for Asthma Management (PGAM) guidelines, includes similar and some slightly different goals than previously described. Similar to the previous definitions, full symptom control without systemic glucocorticoid therapy and no evidence of disease re-exacerbation is required. In addition, the minimum target of 23, as measured by ACT, is required to evaluate disease control. Regarding respiratory function, this is not listed among the parameters to be achieved (25,36).

SANI definitions

The criteria for defining severe asthma remission, drawn up by the Italian severe asthma registry SANI (Severe Asthma Network Italy), have recently been published. Two different levels of remission were identified: partial and complete. In both cases, the discontinuation of OCS and three major criteria are essential: absence of exacerbations, normal respiratory function and disease control. If all the criteria mentioned above are present at the same time, a patient can be defined as "complete remission"; in case only two of the three are present, it is defined as *"partial remission"* (28). Regarding disease control, the SANI definition requires an ACT value ≥ 20; concerning the respiratory function, the FEV_1 value must remain stable in the year of observation.

Certain biomarkers of disease, such as peripheral eosinophil number, and FeNO, which have been taken into account in some definitions of remission, were not included in the SANI-defined criteria. Finally, according to the SANI criteria, the patients must maintain the required criteria for one year of treatment.

Practical applications

Based on the concepts we have expressed so far, it seems clear that clinical remission, in its various aspects, will only become a composite outcome of certain interest, and a goal to be achieved by the drugs used in clinical practice or under investigation. Having clinical remission of disease as the goal, rather than simple disease control, clearly must be the paradigm of research in the near future (37,38). Starting with discontinuing systemic glucocorticoid therapy, seeking complete control of exacerbations, and focusing on achieving the drug's response on respiratory function will ensure a better therapeutic offer to patients. Obtaining these results could help the patient to slow the progression of the disease, even to modify it altogether (19,25). This new goal imposes a closer relationship between physician and patient, with a shared decision-making of the disease, starting from adherence to inhaled therapy, to biological therapy (including home self-administration) and self-monitoring of the patient considering no longer a single parameter, but a group of goals to be achieved.

The most controversial point among the clinical remission criteria seems to be the one involving respiratory function. Again, evaluating both

stabilization and improvement at an increase in FEV1 ≥ 80%, the achievement of this goal suggests the involvement of biologic drugs in bronchial wall remodeling, allowing the two concepts of disease remission and disease-modifying drugs to be associated. The effect of the drug, not only on reducing the impact of systemic glucocorticoids, but also on bronchial wall remodeling, is certainly of great interest first from a scientific point of view but also in daily clinical practice when choosing therapy for our patients (19,39).

Finally, the fact that some definitions of remission, divide the results into a complete and a partial form, can also help the clinician in the daily management of their patient, when this concept is associated with the choice of treatment.

Proposal for the SANI tool in clinical practice

Implementing what was initially suggested in the previous paragraph, we can hypothesize to use the definition of remission, as a guide for daily clinical practice, for the therapeutic management of our patients.

Indeed, one of the major points under discussion, in patients using biologic drugs, is that of assessing the response to therapy, and whether to continue, or switch to another drug. About this, the concept of clinical remission, is useful to more holistically evaluation of the effect of drugs, allowing a more complete indication regarding its efficacy, driving to the continuation or discontinuation of the drug.

Another point of discussion, regarding patients with severe asthma being treated with biologics, is the management of inhaled therapies taken concurrently with monoclonal antibodies. The literature shows a lack of complete adherence to inhaled treatments, both in asthmatics in general and in those being treated with biologics (40,41). This behavior, if not properly agreed and planned together with the physicians in charge of the patients, could lead to an increase in exacerbations and a progressive worsening of disease control. However, the possibility of modulating inhaled therapy, as recently demonstrated with Benralizumab by Jackson et al Lancet 2023, appears to be an appealing target and it should be explored further, both with clinical trials and in real life (42).

The possibility of defining a complete and a partial form of remission may help to manage these two points.

Following what we summarized in Figure 1, we would like to propose using the two steps of remission provided by SANI, *partial and complete*, to guide asthma management. In this regard, we can consider three types of treatment responses:

- One in which the patient *does not* achieve clinical remission.
- One in which the patient achieves *partial* remission.
- One in which the patient achieves *complete* remission.

We associate three therapeutic strategies with the three categories of response:

1. The patient who does not go into clinical remission will/might be a candidate for a therapeutic switch to another biologic.
2. The patient who achieves "*partial remission*" will be led to continue the treatments as they are in

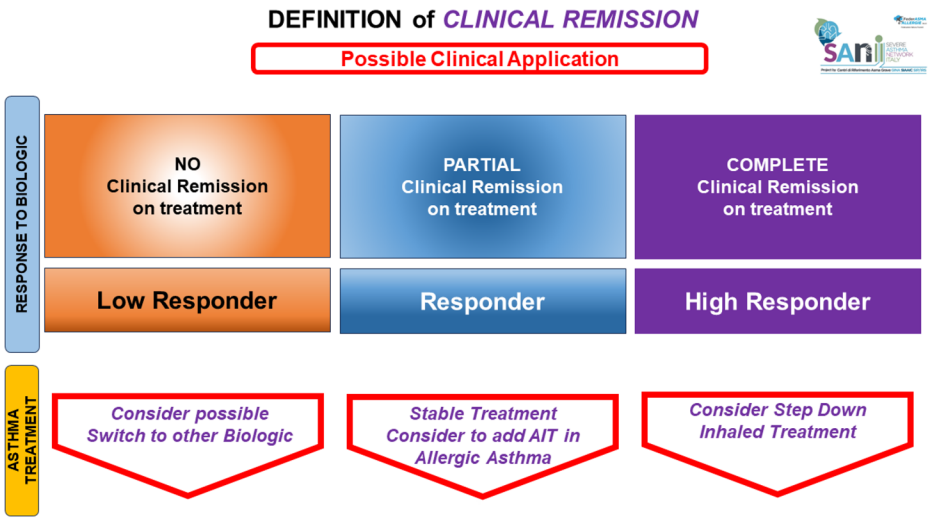

Figure 1. Purpose to clinical application of clinical remission in asthma.

place and, where possible and eligible, add allergen-specific immunotherapy (AIT) (43).

3. The patient in "*complete disease remission*", a therapeutic step down of inhaled treatment, could be evaluated/actuated (42).

Given the dynamic nature of the response time to treatment, and the possibility of moving from one stage of remission to another, it's appropriate for the patients to be reevaluated periodically, in order to categorize them into the proposed scheme and consequently modulate their ongoing treatments.

Concluding statements

Using the practical application of the SANI simple tool, it becomes apparent that the management of therapy for severe asthma patients could be easier and consistently used in different patients. So, using the SANI independent tool developed by Scientific Societies and Patients' associations could add value to Severe Asthma management.

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References

1. Scichilone N, Barnes PJ, Battaglia S, Benfante A, Brown R, Canonica GW, Caramori G, Cazzola M, Centanni S, Cianferoni A, et al. The hidden burden of severe Asthma: from patient perspective to new opportunities for clinicians. J Clin Med. 2020;9:1–27.
2. Loftus PA, Wise SK. Epidemiology and economic burden of asthma. Int Forum Allergy Rhinol. 2015;5 Suppl 1(S1):S7–S10. doi:10.1002/alr.21547.
3. López-Tiro J, Contreras-Contreras A, Rodríguez-Arellano ME, Costa-Urrutia P. Economic burden of severe asthma treatment: a real-life study. World Allergy Organ J. 2022;15(7):100662. doi:10.1016/j.waojou.2022.100662.
4. Kardas G, Panek M, Kuna P, Damiański P, Kupczyk M. Monoclonal antibodies in the management of asthma: dead ends, current status and future perspectives. Front Immunol. 2022;13:983852. doi:10.3389/fimmu.2022.983852.
5. Canonica GW, Blasi F, Paggiaro P, Senna G, Passalacqua G, Spanevello A, Aliberti S, Bagnasco D, Bonavia M, Bonini M, et al. Oral CorticoSteroid sparing with biologics in severe asthma: a remark of the Severe Asthma Network in Italy (SANI). World Allergy Organ J. 2020;13(10):100464. doi:10.1016/j.waojou.2020.100464.
6. Calzetta L, Aiello M, Frizzelli A, Bertorelli G, Rogliani P, Chetta A. Oral corticosteroids dependence and biologic drugs in severe asthma: myths or facts? A systematic review of real-world evidence. Int J Mol Sci. 2021;22(13):7132. doi:10.3390/ijms22137132.
7. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, Sproule S, Gilmartin G, Aurivillius M, Werkström V, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet. 2016;388(10056):2115–2127. doi:10.1016/S0140-6736(16)31324-1.
8. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012;380(9842):651–659. doi:10.1016/S0140-6736(12)60988-X.
9. Corren J, Katelaris CH, Castro M, Maspero JF, Ford LB, Halpin DMG, Rice MS, Radwan A, Deniz Y, Rowe PJ, et al. Effect of exacerbation history on clinical response to dupilumab in moderate-to-severe uncontrolled asthma. Eur Respir J. 2021;58(4):2004498. doi:10.1183/13993003.04498-2020.
10. Pavord ID, Hoyte FCL, Lindsley AW, Ambrose CS, Spahn JD, Roseti SL, Cook B, Griffiths JM, Hellqvist Å, Martin N, et al. Tezepelumab reduces exacerbations across all seasons in patients with severe, uncontrolled asthma (NAVIGATOR). Ann Allergy Asthma Immunol. 2023;131(5):587–597.e3. doi:10.1016/j.anai.2023.08.015.
11. Vultaggio A, Aliani M, Altieri E, Bracciale P, Brussino L, Caiaffa MF, Cameli P, Canonica GW, Caruso C, Centanni S, et al. Long-term effectiveness of benralizumab in severe eosinophilic asthma patients treated for 96-weeks: data from the ANANKE study. Respir Res. 2023;24(1):135. doi:10.1186/s12931-023-02439-w.
12. Bagnasco D, Nicola S, Testino E, Brussino L, Pini L, Caminati M, Piccardo F, Canevari RF, Melissari L, Ioppi A, et al. Long-term efficacy of mepolizumab at 3 years in patients with severe asthma: comparison with clinical trials and super responders. Biomedicines, 92023; 11: 2424. doi:10.3390/biomedicines11092424.
13. Solidoro P, Nicola S, Ridolfi I, Canonica GW, Blasi F, Paggiaro P, Heffler E, Bagnasco D, Patrucco F, Ribolla F, et al. Biologics in severe eosinophilic asthma: three-year follow-up in a SANI single center. Biomedicines. 2022;10(2):200. Jan 18 doi:10.3390/biomedicines10020200.
14. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, Ortega HG, Pavord ID. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371(13):1189–1197. doi:10.1056/NEJMoa1403291.
15. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, Barker P, Sproule S, Ponnarambil S, Goldman M. Oral glucocorticoid–sparing effect of benralizumab in severe asthma. N Engl J Med. 2017;376(25):2448–2458. doi:10.1056/NEJMoa1703501.
16. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, Zhu H, Hamilton JD, Swanson BN, Khan A,

et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med. 2018;378(26):2475–2485. doi:10.1056/NEJMoa1804093.
17. Wechsler ME, Colice G, Griffiths JM, Almqvist G, Skärby T, Piechowiak T, Kaur P, Bowen K, Hellqvist Å, Mo M, et al. SOURCE: a phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of tezepelumab in reducing oral corticosteroid use in adults with oral corticosteroid dependent asthma. Respir Res. 2020;21(1):264. doi:10.1186/s12931-020-01503-z.
18. Canonica GW, Varricchi G, Paoletti G, Heffler E, Virchow JC. Advancing precision medicine in asthma: evolution of treatment outcomes. J Allergy Clin Immunol. 2023;152(4):835–840. doi:10.1016/j.jaci.2023.07.009.
19. Lommatzsch M, Brusselle GG, Canonica GW, Jackson DJ, Nair P, Buhl R, Virchow JC. Disease-modifying anti-asthmatic drugs. Lancet. 2022;399(10335):1664–1668. doi:10.1016/S0140-6736(22)00331-2.
20. Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, Szefler SJ, Woodruff PG, de Giorgio-Miller A, Trudo F, et al. An expert consensus framework for asthma remission as a treatment goal. J Allergy Clin Immunol. 2020;145(3):757–765. doi:10.1016/j.jaci.2019.12.006.
21. Tai A, Tran H, Roberts M, Clarke N, Gibson A-M, Vidmar S, Wilson J, Robertson CF. Outcomes of childhood asthma to the age of 50 years. J Allergy Clin Immunol. 2014;133(6):1572–1578.e3. doi:10.1016/j.jaci.2013.12.1033.
22. Andersson M, Hedman L, Sundberg S, Bjerg A, Forsberg B, Rönmark E. Remission of childhood asthma in adolescence – A longitudinal study. Eur Respir J. 2011;38(Suppl 55):317.
23. Andersson M, Hedman L, Bjerg A, Forsberg B, Lundbäck B, Rönmark E. Remission and persistence of asthma followed from 7 to 19 years of age. Pediatrics. 2013;132(2):e435–e442. doi:10.1542/peds.2013-0741.
24. Van Den Toorn LM, Prins JB, Overbeek SE, Hoogsteden HC, De Jongste JC. Adolescents in clinical remission of atopic asthma have elevated exhaled nitric oxide levels and bronchial hyperresponsiveness. Am J Respir Crit Care Med. 2000;162(3 Pt 1):953–957. doi:10.1164/ajrccm.162.3.9909033.
25. Lommatzsch M, Buhl R, Canonica GW, Ribas CD, Nagase H, Brusselle GG, Jackson DJ, Pavord ID, Korn S, Milger K, et al. Pioneering a paradigm shift in asthma management: remission as a treatment goal. Lancet Respir Med. 2023;12(2):96–99.
26. Pavord I, Gardiner F, Heaney LG, Domingo C, Price RG, Pullan A, Oppenheimer J, Brusselle G, Nagase H, Chupp G, et al. Remission outcomes in severe eosinophilic asthma with mepolizumab therapy: analysis of the REDES study. Front Immunol. 2023;14:1150162. doi:10.3389/fimmu.2023.1150162.
27. Carpaij OA, Burgess JK, Kerstjens HAM, Nawijn MC, van den Berge M. A review on the pathophysiology of asthma remission. Pharmacol Ther. 2019;201:8–24. doi:10.1016/j.pharmthera.2019.05.002.
28. Canonica GW, Blasi F, Carpagnano GE, Guida G, Heffler E, Paggiaro P, Allegrini C, Antonelli A, Aruanno A, Bacci E, et al. Severe Asthma Network Italy Definition of Clinical Remission in Severe Asthma: A Delphi Consensus. J Allergy Clin Immunol Pract. 2023;11(12):3629–3637. doi:10.1016/j.jaip.2023.07.041.
29. 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. doi:10.1183/13993003.02583-2021.
30. Volmer T, Effenberger T, Trautner C, Buhl R. Early View Consequences of long-term OCS therapy and its side effects in severe asthma in adults-A focused review of the impact data in the literature Consequences of long-term OCS therapy and its side effects in severe asthma in adults-A focused review of the impact data in the literature. Eur Respir J. 2018;52(4):1800703. doi:10.1183/13993003.00703-2018.
31. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343–373. doi:10.1183/09031936.00202013.
32. Lugogo NL, Mohan A, Akuthota P, Couillard S, Rhoads S, Wechsler ME. Are we ready for asthma remission as a clinical outcome? Chest. 2023;164(4):831–834. doi:10.1016/j.chest.2023.04.028.
33. Blaiss M, Oppenheimer J, Corbett M, Bacharier L, Bernstein J, Carr T, Chipps B, Couillard S, Forno E, Grant T, et al. Consensus of an American college of allergy, asthma, and immunology, american academy of allergy, asthma, and immunology, and american thoracic society workgroup on definition of clinical remission in asthma on treatment. Ann Allergy Asthma Immunol. 2023;131(6):782–785. doi:10.1016/j.anai.2023.08.609.
34. Lommatzsch M, Criée CP, De Jong CCM, Gappa M, Geβner C, Gerstlauer M, Hämäläinen N, Haidl P, Hamelmann E, Horak F, et al. Diagnosis and treatment of asthma: a guideline for respiratory specialists 2023 - published by the German Respiratory Society (DGP) e. V. Pneumologie. 2023;77:461–543.
35. Plaza Moral V, Alobid I, Álvarez Rodríguez C, Blanco Aparicio M, Ferreira J, García G, Gómez-Outes A, Garín Escrivá N, Gómez Ruiz F, Hidalgo Requena A, et al. GEMA 5.3. Spanish Guideline on the Management of Asthma. Open Respir Arch. 2023;5(4):100277. doi:10.1016/j.opresp.2023.100277.
36. Lommatzsch M. Remission in asthma. Curr Opin Pulm Med. 2024;30(3):325–329.
37. 2023. GINA Main Report - Global Initiative for Asthma - GINA. Available from: https://ginasthma.org/2023-gina-main-report/ [last accessed 23 November 2023].
38. Upham JW, James AL. Remission of asthma: the next therapeutic frontier? Pharmacol Ther. 2011;130(1):38–45. doi:10.1016/j.pharmthera.2011.01.002.
39. Busse WW, Melén E, Menzies-Gow AN. Holy Grail: the journey towards disease modification in asthma. Eur Respir Rev. 2022;31(163):210183. doi:10.1183/16000617.0183-2021.
40. Caminati M, Vianello A, Andretta M, Menti AM, Tognella S, Degli Esposti L, Micheletto C, Bovo C, Senna G. Low adherence to inhaled corticosteroids/long-acting β2-agonists and biologic treatment in se-

vere asthmatics. ERJ Open Res. 2020;6(2):00017–2020. doi:10.1183/23120541.00017-2020.
41. Maddux JT, Inselman JW, Jeffery MM, Lam RW, Shah ND, Rank MA. Adherence to Asthma Biologics: implications for Patient Selection, Step Therapy, and Outcomes. Chest. 2021;159(3):924–932. doi:10.1016/j.chest.2020.10.050.
42. Jackson DJ, Heaney LG, Humbert M, Kent BD, Shavit A, Hiljemark L, Olinger L, Cohen D, Menzies-Gow A, Korn S. Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with benralizumab (SHAMAL): a randomised, multicentre, open-label, phase 4 study. Lancet. 2023;403(10423):271–281. doi:10.1016/S0140-6736(23)02284-5.
43. Bożek A, Fischer A, Bogacz-Piaseczynska A, Canonica GW. Adding a biologic to allergen immunotherapy increases treatment efficacy. ERJ Open Res. 2023;9(2):00639–2022. doi:10.1183/23120541.00639-2022.