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Original Research

Step-DAWN: an Italian algorithm proposed for the management of inhaled corticosteroids in severe asthma

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ABSTRACT

Purpose of research: Biologics have transformed the management of severe asthma, establishing clinical remission as a realistic treatment objective. Moreover, they offer the potential to reduce background treatment with inhaled corticosteroids (ICS). Although guidelines recommend ICS dose reduction in patients achieving disease control, they provide limited guidance on how to implement tapering. In this context, we developed Step-DAWN (De-escalation of ICS in Asthma With a Novel algorithm), a consensus-based protocol that guides ICS tapering in adults with severe asthma receiving biologic therapy.

Methods: Step-DAWN was ideated through a modified Delphi process; a Steering Committee consisting of two Italian specialists and two pharmaceutical Medical Affairs professionals drafted 30 statements, which were voted on by an Expert Panel comprising 12 specialists.

Results: Consensus was reached on 21 of 30 statements in the first round; three other statements reached consensus in the second round; six statements did not reach consensus. The Step-DAWN protocol was designed based on 24 statements that achieved consensus. Patients eligible for Step-DAWN should have maintained the four criteria of complete clinical remission (cCR) for at least 6 months. ICS dose should be reduced gradually, with follow-up assessments not exceeding 6 months. In case of loss of eligibility criteria, potential causes should

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be addressed before reattempting tapering. Fractional exhaled nitric oxide (FeNO) and blood eosinophil count (BEC) were identified as key biomarkers for monitoring airway inflammation.
Conclusion: Step-DAWN is the first consensus-based protocol designed by Italian specialists to provide guidance for ICS tapering in patients with severe asthma treated with biologics.

1. Introduction

Severe asthma (SA) is a complex airway disease requiring long-term management [1–4]. Approved biologics (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab and tezepelumab) are used as add-on therapies to background therapies with inhaled corticosteroids (ICS) combined with a long-acting beta2-adrenergic agonist (LABA) [2,4]. Owing to effective asthma symptom control, prevention of exacerbations and oral corticosteroid (OCS) use reduction, biologics have made remission a realistic goal [5–9].

Menzies-Gow and colleagues proposed the first definition of clinical remission (CR) in asthma [10]. The Severe Asthma Network Italy (SANI) group subsequently introduced definitions for partial (pCR) and complete CR (cCR) [10]. In both studies, CR requires the absence of OCS while continuing treatment with the biologic and background therapies [10,11]. While OCS withdrawal is strongly encouraged to minimize the risk of systemic side effects [2,4], adverse events (AEs) may also arise from ICS therapy; these include adrenal suppression, cardiovascular events, pneumonia, type 2 diabetes and osteoporosis [12–14]. Notably, adrenal suppression is a potentially life-threatening disorder with variable and non-specific symptoms, which may contribute to its underrecognition in routine practice [12,15]. Although short-term exposure to low-dose ICS has not been associated with an increased risk of AEs [13,14], the risk is observed at medium and high doses [13,15].

Evidence from clinical trials [16–22] and real-world studies [23–33] shows that biologics enable a reduction in ICS, without compromising asthma control. In the longest real-life study, patients treated with benralizumab for over 3 years significantly decreased their mean daily ICS dose, with the probability of dose reduction estimated at 37.4% [34]. Within this timeframe, 84.31% of patients achieved either pCR or cCR [28].

Although the reduction of ICS therapy appears to be feasible, limited data exist on real-life step-down implementation. While the decision to taper the ICS dose was likely guided by patients' treating physicians, reductions may also have resulted from poor patient adherence [24]. In the absence of standardized protocols, ICS reduction may have been carried out inconsistently. Against this background, the phase IV SHAMAL study pioneered the development of a structured algorithm for ICS reduction in patients treated with benralizumab [21]. The results were highly encouraging: 92% of patients reduced their ICS-formoterol dose, and 96% maintained the reduced regimen through week 48. However, patients who stepped down to ICS-formoterol as reliever-only therapy showed a decline in lung function, raising concerns about the long-term consequences of ICS withdrawal [21].

ICS-LABA withdrawal was also evaluated in a separate Phase II trial involving dupilumab-treated patients, albeit over a shorter follow-up period. In this study, dupilumab significantly reduced severe exacerbations, improved asthma control, and decreased FeNO levels despite the absence of background ICS or LABA therapy for at least 3 weeks [20]. These findings further support the potential for ICS reduction in select cases and reinforce the importance of cautious tapering, particularly given the variability of patient responses and limited long-term data.

Considering this evidence, the Global Initiative for Asthma (GINA) 2025 Report recommends reducing the ICS dose in patients with good disease control on biologics, although complete withdrawal is discouraged; yet, no practical guidance is provided on how the tapering should be implemented [2,4].

This study presents Step-DAWN (De-escalation of ICS in Asthma With a Novel algorithm), a novel protocol designed to guide ICS reduction in adults with SA receiving biologics. Developed by a panel of Italian pulmonologists, immunologists/allergologists, and industry representatives through a modified Delphi process, Step-DAWN recommends tapering ICS in patients who achieve cCR [11], and incorporates guidance on long-term follow-up, accounting for the potential loss of asthma control and including the option to re-initiate the de-escalation process.

2. Methods

2.1. The modified Delphi method

The consensus process was conducted using a modified Delphi approach, coordinated by a Steering Committee consisting of two Italian pulmonologists (one also specialized in immunology/allergology) and two representatives from the Medical Affairs department of the pharmaceutical industry sponsoring the initiative (AstraZeneca Italy). The two specialists have recognized national and international expertise in the management of SA, both in clinical research and routine practice. The industry representatives contributed by leveraging their knowledge derived from the protocol designed in the AstraZeneca-sponsored SHAMAL study, which remains to date the only trial that assessed the feasibility of reducing ICS therapy through a structured protocol in patients treated with benralizumab [21].

The Steering Committee defined the scope of the project, drafted preliminary statements, and oversaw the Delphi rounds. The statements were evaluated by an Expert Panel comprising 12 Italian specialists (pulmonologists and immunologists/allergologists). The panelists were selected by the two specialist members of the Steering Committee for their recognized clinical experience in SA; the industry representatives were not involved in their choice. Members of the Steering Committee did not take part in the voting. A methodologist supported the Steering Committee throughout the process.

2.2. Statement development

In June 2025, an initial online meeting was held with members of the Steering Committee and the Expert Panel to discuss the feasibility and components of a protocol to guide ICS tapering in patients treated with biologic therapies. The protocol was named “Step-DAWN”. Based on the discussion, the Steering Committee formulated a series of statements aimed at: (1) exploring the rationale and establishing preliminary considerations for developing an ICS tapering protocol, and (2) developing the Step-DAWN protocol.

Before drafting the statements on protocol design, participants reviewed the clinical workflow of ICS tapering, identifying the key decision points and assessment steps. This process allowed the Steering Committee to define four core areas forming the conceptual backbone of the protocol: (A) initial patient evaluation; (B) ICS tapering and follow-up; (C) loss of eligibility criteria; and (D) biomarker evaluation. Statements were developed for each area and subsequently evaluated through the Delphi process.

2.3. Voting system and rounds of voting

The statements were voted anonymously through an online survey platform. Panelists indicated their level of agreement using a 5-point Likert scale (1 = totally disagree, 2 = partially disagree, 3 = neither agree nor disagree, 4 = partially agree, 5 = totally agree). Consensus was defined *a priori* as agreement or disagreement (either partial or

total), expressed by at least 75.0% of the panelists.

After the first round of voting, descriptive statistics were calculated. The aggregated results were discussed during two online meetings involving members of both the Steering Committee and Expert Panel. Statements that did not reach consensus were revised and re-administered in a second round of voting.

2.4. Analysis of the results and design of the Step-DAWN protocol

Following completion of the Delphi process, the Steering Committee assembled the Step-DAWN protocol, incorporating only the statements that achieved formal consensus.

3. Results

A total of 30 statements were developed; of these, four addressed the background, rationale and preliminary considerations for developing an ICS tapering protocol, and 26 outlined the protocol structure. After the first round of voting, 21 out of 30 statements reached consensus (Table 1). The nine statements that did not reach consensus were rephrased and resubmitted for voting; of these, three statements reached consensus after the second round (Table 2).

3.1. Rationale and preliminary considerations for developing an ICS tapering protocol

Panelists agreed that ICS tapering can be considered in patients with SA treated with any biologic (Statement 1, 83.3% agreement, Table 1). They supported the development of a standardized protocol to guide ICS tapering (Statement 2, 91.7% agreement, Table 1), acknowledging that no such protocol exists (Statement 3, 100% agreement, Table 1). The protocol should aim to maintain the minimum effective dose, intended as the lowest ICS dose capable of maintaining good disease control, rather than pursue complete discontinuation (Statement 4, 75.0% agreement, Table 1).

3.2. Step-DAWN protocol development

The following 26 statements were organized around the four core areas of the Step-DAWN protocol described above. A total of three statements pertained to the initial patient assessment, four focused on ICS tapering, 12 described the management of patients in case of loss of eligibility criteria, and seven defined biomarker assessment requirements.

3.2.1. Initial patient evaluation

Panellists agreed that patients eligible for ICS tapering should meet all four criteria of cCR, as previously defined by the SANI group (Table 3) [10]; these should be maintained for at least 6 months (Statements 5 and 6, 83.3% and 91.7% agreement, respectively, Table 1). Only 41.7% of panelists agreed with statement 7, which proposed restricting ICS tapering to patients who did not require rescue therapy (Table 1). This statement was revised by allowing limited use of rescue therapies; however, agreement remained insufficient to reach consensus (Statement 7, 58.3% agreement, Table 2).

3.2.2. Tapering and patient follow-up

Overall, 91.7% of panelists agreed that the protocol should guide the tapering of total daily ICS dose in a gradual manner (Statements 8 and 9, Table 1). The first step down should be from high dose to medium dose according to the specific ICS used (doses reported for each ICS in the GINA guidelines) [4]. Patients should then be ideally re-evaluated every 6 months to check the maintenance of eligibility criteria, either to consider a further reduction of ICS dose from medium to low levels (Statement 10, 75% agreement, Table 1), or verify sustained asthma control in patients who have already reached the minimum ICS dose

Table 1
Results from the first round of voting.

N	Statement	% agreement
BACKGROUND, RATIONALE AND PRELIMINARY CONSIDERATIONS		
1	The reduction of ICS therapy can be considered in patients with severe asthma treated with any biologic therapy	**83.3%**
2	At present, no standardized and universally accepted protocol exists to guide ICS tapering in patients with severe asthma in clinical practice	**91.7%**
3	The availability and implementation of a protocol to guide ICS reduction in patients with severe asthma could be useful in clinical practice	**100%**
4	The ICS tapering protocol should guide towards the maintenance of a minimum effective dose, rather than requiring its complete discontinuation	**75.0%**
STEP-DAWN PROTOCOL DEVELOPMENT		
INITIAL PATIENT EVALUATION		
5	The ICS tapering protocol can be safely implemented in patients with SA receiving biologic therapy, provided they have met all four criteria for cCR as defined by the SANI group (absence of exacerbations, no use of OCS, symptom control documented by an ACT score ≥20 or an ACQ score ≤1.5, and stable lung function)	**83.3%**
6	The ICS tapering protocol can be safely implemented only in patients who have maintained all four cCR criteria (absence of exacerbations, no use of oral corticosteroids, symptom control documented by an ACT score ≥20 or an ACQ score ≤1.5, and stable lung function) for at least 6 months	**91.7%**
7	The ICS tapering protocol can be safely implemented only in patients who have not required rescue therapies (SMART or SABA) for at least 6 months	41.7%
ICS TAPERING AND PATIENT FOLLOW-UP		
8	The protocol should guide the gradual reduction of ICS dosage based on the patient's total daily dose (classified as high, medium, or low according to the specific ICS used, as outlined in the GINA guidelines), to minimize the risk of loss of asthma control	**91.7%**
9	In patients receiving high doses of ICS, the protocol should first indicate a reduction from high to medium doses, followed by a further reduction from medium to low doses	**91.7%**
10	In patients receiving high doses of ICS, the second reduction (from medium to low doses) should be carried out after at least 6 months of maintaining the cCR criteria	**75.0%**
11	Once the minimum ICS dose has been reached, patients should be reassessed periodically (every 6 months) to confirm maintenance of the cCR criteria	**91.7%**
LOSS OF ELIGIBILITY CRITERIA FOR ICS TAPERING		
12	The loss of at least one of the cCR criteria requires interruption of the ICS tapering process	58.3%
13	The loss of at least one of the cCR criteria requires stepping up the ICS to a higher dose	50.0%
14	If at least one of the cCR criteria is no longer met, the protocol should recommend the identification and evaluation of potential causes of deterioration	**100%**
15	The protocol should recommend the evaluation of treatment adherence in the event of loss of at least one of the cCR criteria	**100%**
16	The protocol should recommend investigating pre-existing and newly arising comorbidities in the event of loss of at least one of the cCR criteria	**100%**
17	The protocol should recommend investigating the patient's psychological condition (e.g., presence of anxiety, depression, etc.) in the event of loss of at least one of the cCR criteria	**91.7%**
18	The protocol should recommend evaluating the condition of the airways through imaging techniques (e.g., X-ray or CT scan) in the event of loss of at least one of the cCR criteria	50.0%
19	The protocol should suggest investigating the presence of mucus plugs through imaging techniques (e.g., CT scan) in the event of loss of at least one of the cCR criteria	41.7%
20	The protocol should recommend re-evaluating the pheno-endotypization of asthma in the event of loss of at least one of the cCR criteria	**83.3%**
21	The protocol should recommend performing blood tests (e.g., complete blood count, ESR, CRP) in the event of loss of at least one of the cCR criteria, to assess the presence of ongoing infectious processes	58.3%

(*continued on next page*)

Table 1 (*continued*)

N	Statement	% agreement
22	In the event of an exacerbation, the protocol should recommend performing laboratory investigations on an induced sputum sample, where feasible based on the availability of the necessary equipment, in order to characterize the nature of the exacerbation	50.0%
23	After identifying and correcting the causes of loss of cCR criteria, the protocol should allow for reattempting ICS tapering, provided the patient again meets the cCR criteria and sustains them for at least 6 months	**100%**
BIOMARKER EVALUATION		
24	The protocol should recommend measuring the main biomarkers of asthma-related inflammation during the initial patient assessment (before applying the ICS tapering protocol)	**100%**
25	The protocol should recommend measuring the main biomarkers of asthma-related inflammation during the patient's periodic follow-ups	**91.7%**
26	The protocol should recommend the measurement of FeNO as one of the main biomarkers of asthma inflammation	**100%**
27	The protocol should recommend the quantification of total serum IgE as one of the main biomarkers of asthma inflammation	41.7%
28	The protocol should recommend the measurement of BEC as one of the main biomarkers of asthma inflammation	**91.7%**
29	The protocol should recommend the measurement of eosinophil count in induced sputum, when feasible and depending on the availability of appropriate equipment	50.0%
30	Further studies are needed to provide evidence on biomarkers that can inform the safe initiation and continuation of ICS tapering	**91.7%**

Data are expressed as % of participants who expressed an agreement with each statement. Percentages in bold indicate consensus.
ACT: asthma control test; ACQ: asthma control questionnaire; BEC: blood eosinophil count; cCR: complete clinical remission; CT: computed tomography; FeNO: fractional exhaled nitric oxide; GINA: global initiative for asthma; ICS: inhaled corticosteroids; IgE: immunoglobulin E; OCS: oral corticosteroids; SA: severe asthma; SABA: short-acting β_2-agonist; SANI: severe asthma network in Italy; SMART: single maintenance and reliever therapy.

(Statement 11, 91.7% agreement, Table 1).

3.2.3. Loss of eligibility criteria

The loss of at least one cCR criterion was not considered sufficient to interrupt ICS tapering (statement 12, 58.3% agreement, Table 1) or increase ICS dose (statement 13, 50.0% agreement, Table 1). Consensus was reached after the statements were modified to emphasize that such decisions should be guided by the underlying causes of cCR loss and left to the clinician's discretion (statements 12 and 13, 100% and 83.3% agreement, respectively, Table 2). Panelists agreed that, if a patient loses even one cCR criterion, the protocol should recommend evaluation of the underlying causes (Statement 14, 100% agreement, Table 1), with particular attention to treatment adherence, comorbidities (Statement 15 and 16, 100% agreement, Table 1), and psychological conditions (Statement 17, 91.7% agreement, Table 1). Consensus was not reached regarding the use of imaging techniques for evaluation of airways and mucus plugs (Statements 18 and 19, 50.0% and 41.7% agreement, respectively, Table 1), even after the statements were rephrased (Statements 18 and 19, 66.7% and 41.7% agreement, respectively, Table 2). The need for asthma pheno-endotyping reassessment reached consensus (Statement 20, 83.3% agreement, Table 1), whereas the standardized use of blood tests was not endorsed (Statement 21, 58.3% agreement, Table 1). After modifying the statement, panellists supported the use of blood tests to help assess the causes of cCR loss, at the clinician's discretion (Statement 21, 83.3% agreement, Table 2). Conversely, sputum sample analysis was not considered essential (Statement 22, 50.0% and 41.7% agreement in the first and second rounds, respectively, Tables 1 and 2).

Panellsts agreed that the protocol should allow re-attempting ICS tapering, provided that patients have re-attained all four cCR criteria and maintained them for at least 6 months (Statement 23, 100% agreement, Table 1).

Table 2
Results from the second round of voting.

N	Statement	% agreement
STEP-DAWN PROTOCOL DEVELOPMENT		
INITIAL PATIENT EVALUATION		
7	The ICS tapering protocol can be safely implemented even in patients who have required rescue therapies (SMART or SABA) no more than once per week during the last 6 months	58.3%
LOSS OF ELIGIBILITY CRITERIA FOR ICS TAPERING		
12	The loss of at least one of the cCR criteria requires interruption of ICS tapering process, depending on the causes of the loss of cCR criteria, at the clinician's discretion	**100%**
13	The loss of at least one of the cCR criteria requires stepping up the ICS to a higher dose, depending on the causes of the loss of cCR criteria, at the clinician's discretion	**83.3%**
18	The protocol should recommend evaluating the condition of the airways through imaging techniques, depending on the causes of the loss of cCR criteria, at the clinician's discretion.	66.7%
19	The protocol should recommend investigating the presence of mucus plugs through imaging techniques, depending on the causes of the loss of cCR criteria, at the clinician's discretion.	41.7%
21	The protocol should recommend performing blood tests to investigate the causes of the loss of cCR criteria, at the clinician's discretion	**83.3%**
22	In the event of an exacerbation, the protocol should suggest performing laboratory investigations on an induced sputum sample, where feasible according to the availability of the necessary equipment, depending on the causes of the loss of cCR criteria, at the clinician's discretion	41.7%
BIOMARKER EVALUATION		
27	Among the main biomarkers of asthma-related inflammation, the protocol should suggest the quantification of total serum IgE	50.0%
29	Among the main biomarkers of asthma-related inflammation, the protocol should suggest the quantification of eosinophil count in induced sputum, where feasible depending on the availability of the necessary equipment, in order to monitor any change in the asthma pheno-endotype	58.3%

Data are expressed as % of panellists who expressed an agreement with each statement. Percentages in bold indicate consensus.
cCR: complete clinical remission; ICS: inhaled corticosteroids; IgE: immunoglobulin E; SABA: short-acting β_2-agonist; SMART: single maintenance and reliever therapy.

Table 3
The four criteria proposed by the SANI Group that define cCR in patients with SA.

cCR is defined by the following criteria:	
1	No further need to use OCS
2	Absence of asthma symptoms (ACT of 20/25 to 25/25; ACQ of $\leq$1.5)
3	Absence of asthma exacerbations or attacks
4	Stable lung function

ACT: asthma control test; ACQ: asthma control questionnaire; cCR: complete clinical remission; OCS: oral corticosteroids; SA: severe asthma; SANI: severe asthma network in Italy. Source: Data taken from Canonica et al. [10].

3.2.4. Biomarker evaluation

Panelists agreed that key airway inflammation biomarkers should be measured before and during ICS tapering (Statements 24 and 25, 100% and 91.7% agreement, respectively, Table 1). Consensus was reached for fractional exhaled nitric oxide (FeNO) (Statement 26, 100% agreement, Table 1) and BEC (Statement 28, 91.7% agreement, Table 1). Quantification of serum total IgE levels and sputum eosinophil count did not achieve consensus in either the first (Statement 27 and 29, 41.5% and 50.0% agreement, respectively, Table 1) or second round (Statement 27

and 29, 50.0% and 58.3% agreement, respectively, Table 2). Panelists underscored the need for further evidence to elucidate the use of biomarkers in the context of ICS tapering (Statement 30, 91.7% agreement, Table 1).

3.3. The consensus-based Step-DAWN protocol

The Step-DAWN protocol was crafted using the 24 statements that received consensus (Fig. 1). The algorithm begins with eligibility and biomarker checks before ICS de-escalation.

Once all four cCR criteria have been confirmed, patients may begin tapering their ICS dose in a stepwise manner. Patients should be re-evaluated every 6 months; if all cCR criteria persist, ICS tapering can continue until the minimum effective dose. The thresholds of high, medium, and low doses are molecule-specific and should be determined according to clinical guidelines [2,4].

Conversely, if the patient loses even one cCR criterion, physicians should investigate and address potential causes, performing clinical investigations as appropriate. The tapering may be interrupted, and/or the ICS dose may be increased at the physician's discretion.

ICS tapering may be re-attempted once the patient has regained all cCR criteria.

4. Discussion

This study introduces Step-DAWN, the first consensus-based protocol that guides ICS therapy de-escalation in clinical practice (Fig. 1). Step-DAWN is intended to maximize patient safety by promoting cautious tapering, not only allowing for the reduction of the overall pharmacological burden but also limiting ICS-associated AEs. Indeed, the risk of systemic AEs increases in a dose-dependent manner and becomes evident with medium ICS doses (from approximately 400-500 μg/day), after only a few months of continuous treatment [13,35]. Intriguingly, stepping up to high-dose ICS has also been linked with a higher incidence of asthma exacerbations and increased antibiotic courses [36]. Collectively, these findings support reducing ICS treatment to the lowest doses whenever clinically appropriate.

The advent of highly effective biologics has provided robust evidence supporting the feasibility of reducing corticosteroid exposure, both oral and inhaled [35]. Additional data will be provided by the ARRIVAL trial, which assesses whether tezepelumab enables safe ICS step-down while maintaining control and inducing CR [37].

Once asthma control is achieved with biologic treatment, uncertainty remains on optimal therapy adjustment [38]. While decreasing or interrupting biologic therapy is currently not recommended, reduction of background therapy seems feasible. By proposing a structured framework for ICS de-escalation, Step-DAWN helps address a substantial unmet need in clinical practice. The protocol's key innovation lies in its broad applicability across patients who achieve CR with any biologic therapy, and its comprehensive structure, which allows further attempts at ICS tapering. Owing to its clinical relevance, the development of Step-DAWN symbolically represents a “new dawn” in SA management.

Recently, a group of Spanish specialists proposed an algorithm for stepping down overall maintenance therapy, not limited to ICS but including withdrawal of LABA and other background agents, such as long-acting muscarinic antagonists (LAMA) and leukotriene receptor antagonists (LTRA), in biologic-treated patients with sustained asthma control (no exacerbations, no OCS use, symptom control, and stable lung function for 6–12 months). Similar to Step-DAWN, this algorithm also supports a stepwise approach to treatment de-escalation. However, the two protocols differ in their primary objectives. Step-DAWN specifically focuses on ICS tapering to minimize dose-dependent ICS-related AEs while maintaining disease control, whereas the algorithm proposed by Plaza et al. aims to guide de-escalation of the overall maintenance treatment regimen. Within the algorithm proposed by Plaza et al., patients receiving quadruple therapy are recommended to discontinue LTRA first, after which the algorithm branches into two alternative pathways based on either ICS reduction or LAMA withdrawal. Their algorithm further differs from Step-DAWN, as it does not clearly define management of patients in the event of loss of control and relies on fixed biomarker cut-offs, which may vary considerably depending on the biologic used. By contrast, Step-DAWN enables treatment adjustments according to the individual clinical response, incorporating treatment re-escalation when cCR criteria are no longer fulfilled and allowing ICS tapering to be re-attempted once cCR criteria have been re-established. Finally, the timing of ICS dose reduction differs between the two algorithms. The framework by Plaza et al. allows stepping down ICS after 3-6 months of sustained asthma control, whereas Step-DAWN requires maintenance of all cCR criteria for at least 6 months before each subsequent ICS dose reduction, prioritizing patient safety during ICS tapering while remaining aligned with the objective of minimizing ICS exposure in SA patients [39].

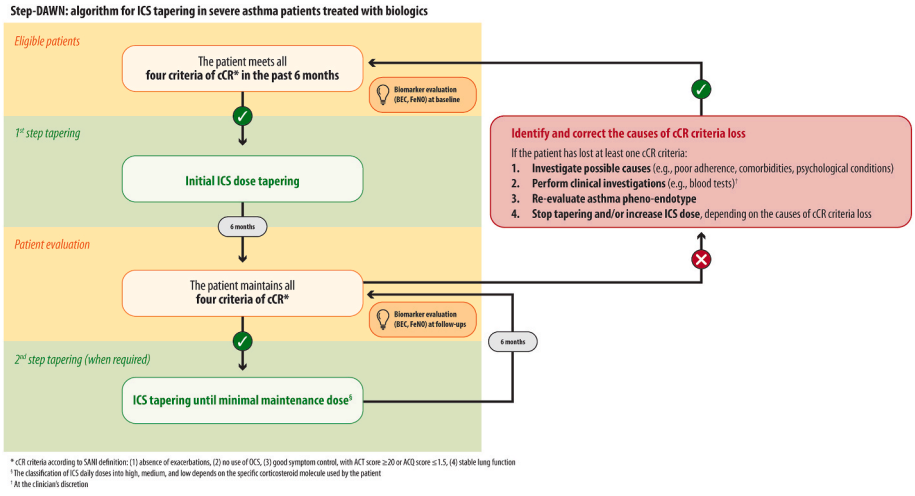

Fig. 1. The Step-DAWN protocol. ACT: asthma control test; ACQ: asthma control questionnaire; cCR: complete clinical remission; CT: computed tomography; FeNO: fractional exhaled nitric oxide; GINA: global initiative for asthma; ICS: inhaled corticosteroids; IgE: immunoglobulin E; OCS: oral corticosteroids; SABA: short-acting β_2-agonist; SANI: severe asthma network in Italy; SMART: single maintenance and reliever therapy.

4.1. Step-DAWN design

The proposed Step-DAWN protocol recommends maintaining ICS therapy at the lowest effective dose, consistent with GINA recommendations [2,4] and findings from the SHAMAL study [21].

4.1.1. Initial patient evaluation

Before initiating ICS tapering, patients must undergo a comprehensive evaluation and meet all four cCR criteria defined by the SANI group (Table 3) [11]. This rigorous approach restricts ICS reduction to the most stable patients, thereby minimizing the risk of loss of asthma control. Although the definition of cCR implies that criteria are sustained for 12 months [11], panellists considered this duration unnecessarily long for initiating ICS tapering. Evidence suggests that some patients can reduce their ICS dose after less than 6 months of biologic treatment [18,20,24,27,34]. Therefore, eligibility for the Step-DAWN protocol was defined as maintaining cCR criteria for at least 6 months.

Eligible patients are expected to have good asthma control and may not need rescue therapies. Nonetheless, the cCR criterion of an ACT score $\geq$20 reflects well-controlled, though not necessarily completely controlled, asthma, thereby allowing for minimal residual symptoms [40]. Consistently, limited use of rescue medications may be deemed acceptable. While the SHAMAL study permitted an average of up to eight ICS-formoterol inhalations per day during the 4 weeks preceding study initiation [21], in our study, consensus was not reached regarding the minimal acceptable dose of rescue therapy for patients initiating ICS tapering. Hence, this aspect was omitted from the protocol.

4.1.2. ICS tapering and patient follow-up

Loss of asthma control remains the primary concern during ICS tapering. To mitigate this risk, a gradual step-down approach was endorsed, from high to medium ICS daily doses and subsequently, from medium to low doses, following GINA recommendations [2,4]. Given that the risk of AEs becomes clinically relevant at medium ICS doses [13,15], tapering to low doses should also be considered in patients receiving medium-dose ICS who fulfil the Step-DAWN eligibility criteria. Patients should sustain all cCR criteria for at least 6 months before each dose de-escalation, with longer intervals potentially warranted.

Even after reaching the minimal effective dose of ICS (i.e., the lowest dose capable of maintaining cCR criteria), patients should undergo periodic reassessment. Although GINA guidelines recommend patient follow-up every 3-6 months [2,4], a 6-month follow-up interval was considered a pragmatic and feasible timeframe for monitoring patients in routine clinical practice.

While the protocol focuses on stepping down maintenance ICS therapy, reductions in LABA and LAMA exposure may occur when these agents are administered as part of fixed-dose combination inhalers. In patients receiving triple therapy, ICS dose reduction may require modification of the inhaled regimen, according to the available treatment formulations, patients' characteristics and clinical judgment. This approach is appropriate and consistent with current recommendations and with the tapering strategy adopted in the SHAMAL study design [4,21].

4.1.3. Loss of eligibility criteria for ICS tapering

Although Step-DAWN is designed to maintain long-term cCR, patients may still lose one or more of the four cCR criteria. For this reason, the protocol guides how to proceed in the event of cCR loss, with the first step being a thorough investigation of the underlying causes. As recommended by GINA, physicians should investigate patients' adherence to treatments, any change in their lifestyle, the impact of psychological conditions and comorbidities [2,4]. Physicians may also perform a range of investigations. However, the panel endorsed only the use of blood tests, which may help identify potential causes for the loss of cCR criteria, such as infection or progression toward systemic disease. In contrast, airway imaging was not broadly supported, as it may offer limited utility in certain scenarios (e.g., viral infections), where structural changes are unlikely to be informative. Assessment of mucus plugs and laboratory investigations on sputum samples were also excluded, primarily due to their technical complexity and limited availability [41–43]. Although these investigations have not been included, the panellists acknowledged their clinical value, recognizing that such assessments may contribute to a more refined re-evaluation of the patient's pheno-endotype and therapeutic management [44–47]. Therefore, their use may be considered when clinically appropriate. Implementation will depend on the availability and accessibility of these investigations, as well as the necessary technical resources within individual centres, and should be guided by the judgment of the treating physician.

In case of loss of cCR criteria, interrupting the tapering and incrementing the ICS dose are both plausible actions that the treating physician should consider. However, panellists did not identify specific scenarios where these actions should be applied. Such measures are recommended based on the distinct cCR criterion (or criteria) that have been lost and should be implemented only after the causes have been identified, at the physician's discretion. While the protocol does not list all the potential causes of cCR criteria loss or recommend corrective actions, physicians should evaluate all appropriate management strategies, including switching to another biologic therapy, in accordance with current guidelines [2,4]. Of note, Step-DAWN allows re-attempting ICS tapering, offering structured guidance for long-term treatment management.

4.1.4. Biomarker evaluation

Increasing attention has been given to biomarkers of asthma inflammation [48,49]. Among these, the panelists endorsed FeNO and BEC measurement to monitor type 2 inflammation; by contrast, measurement of total serum IgE was excluded. Unreliable results are obtained from patients treated with anti-IgE, as routine assays cannot discriminate between bound and free IgE [50]; moreover, total IgE levels do not consistently correlate with disease severity and fail to predict treatment response [48,51–53], limiting their clinical utility.

Similarly, the protocol does not recommend the measurement of eosinophil count in sputum samples, as this test requires technical expertise and specific equipment that limit its large-scale availability.

Importantly, FeNO and BEC measurements in case of loss of one or more cCR criteria should not be viewed as primary drivers of decision-making, but rather as complementary indicators of disease activity and the underlying inflammatory profile. At present, there are no universally established biomarker thresholds [51] that can reliably guide ICS tapering, dose re-escalation, or pheno-endotype reclassification. In addition, the interpretation of the direction and magnitude of biomarker fluctuations during treatment may vary according to the biologic agent used. Nevertheless, changes in FeNO and BEC should be regarded as complementary indicators of disease activity and the underlying inflammatory profile, supporting clinical assessment when interpreted in the context of symptom control, exacerbation history, lung function, comorbidities, and other relevant clinical characteristics. Future evidence identifying validated biomarker thresholds may influence this approach and contribute to the further development of the Step-DAWN protocol.

4.2. Strengths and limitations

The development of Step-DAWN represents a constructive collaborative effort between Italian specialists with expertise in SA and Medical Affairs representatives from industry. This partnership enabled the creation of a novel tool to guide the safe and standardized ICS tapering in clinical practice for the benefit of patients.

Despite its strengths, this work has limitations. First, the protocol was developed through a modified Delphi process involving a limited number of experts. This approach allowed interaction among participants, which may have reduced anonymity and increased the potential

for bias. As with all Delphi-based studies, the composition of the expert panel may have influenced the resulting recommendations. Although panelists were selected based on recognized expertise in severe asthma and biologic therapies and consensus was generated through a structured anonymous process, the possibility that a different panel composition might have yielded different conclusions cannot be excluded. While the involvement of two Medical Affairs representatives provided added value due to their in-depth knowledge of the SHAMAL study, their role was confined to statement drafting, without any influence or participation in the voting process.

A further limitation of Step-DAWN is its limited generalizability. By restricting ICS tapering to patients who have maintained all cCR criteria for at least 6 months, the protocol prioritizes safety but may exclude some biologic-treated patients who could potentially benefit from ICS reduction despite not fulfilling these stringent eligibility criteria. The clinical applicability, generalizability and safety of the Step-DAWN algorithm must be confirmed through prospective, multicenter studies across different biologic classes and healthcare systems. Subsequently, application of the protocol may facilitate the generation of comparable evidence on the outcomes of ICS tapering in biologic-treated patients. By providing a structured and standardized approach to ICS reduction, Step-DAWN may facilitate the interpretation and comparison of prospective studies, addressing the heterogeneity that currently characterizes real-world tapering practices. Further protocol refinements may be required based on emerging evidence, including the identification of validated biomarker thresholds for treatment adjustment and phenoendotype reassessment. Future studies should explore whether ICS tapering can be safely extended to broader patient populations beyond the eligibility criteria defined in Step-DAWN.

5. Conclusion

Unlike the SHAMAL study, which evaluated ICS tapering in patients treated with benralizumab, Step-DAWN provides a structured approach to step-down ICS in patients with SA controlled with any biologic therapy. It also promotes the reduction of overall corticosteroid exposure and the related risk of AEs [35]. The Step-DAWN protocol offers a detailed framework for the standardized implementation of ICS tapering in routine clinical practice. While the overarching principles underlying Step-DAWN are aligned with current GINA recommendations, the algorithm's unique contribution lies in translating these recommendations into a practical, stepwise algorithm. By specifying patient eligibility criteria, timing of each ICS dose reduction, monitoring, management of loss of cCR, treatment re-escalation, and re-attempting tapering after recovery of disease control, Step-DAWN addresses important operational gaps not covered by existing guidelines. As such, Step-DAWN may help reduce the heterogeneity that currently characterizes ICS tapering practices in the real world [4]. In Step-DAWN, ICS tapering can be initiated if all four cCR criteria are maintained for 6 months. This model marks a shift toward an era where remission is no longer viewed as the ultimate therapeutic endpoint, but rather as an opportunity to pursue optimal management by maintaining the lowest effective ICS dose.

Availability of data and materials

Data are available upon reasonable request.

Ethics and consent

Patients were not involved in the study; ethics and consent are not applicable.

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CRediT authorship contribution statement

Laura Pini: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Bianca Beghe':** Formal analysis, Investigation, Writing – review & editing. **Matteo Bonini:** Formal analysis, Investigation, Writing – review & editing. **Marco Caminati:** Formal analysis, Investigation, Writing – review & editing. **Giovanna Elisiana Carpagnano:** Formal analysis, Investigation, Writing – review & editing. **Carlotta Facchini:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Manuela Latorre:** Formal analysis, Investigation, Writing – review & editing. **Laura Malerba:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Andrea Matucci:** Formal analysis, Investigation, Writing – review & editing. **Pierachille Santus:** Formal analysis, Investigation, Writing – review & editing. **Nicola Scichilone:** Writing – review & editing. **Gianenrico Senna:** Formal analysis, Investigation, Writing – review & editing. **Antonio Spanevello:** Formal analysis, Investigation, Writing – review & editing. **Pierluigi Paggiaro:** Formal analysis, Investigation, Writing – review & editing. **Francesco Blasi:** Formal analysis, Investigation, Writing – review & editing. **Giorgio Walter Canonica:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: FB reports grants and/or personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Grifols, Insmed, Menarini, OM Pharma, Pfizer, Vertex, and Zambon.

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GEC has nothing to declare.

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