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Expert Opinion and Evidence-Based Review on Maintenance Therapy Step-Down in Patients With Severe Asthma Controlled With Biologics

Vicente Plaza[a], Gregorio Soto Campos[b], Juan Carlos Miralles López[c], Alicia Padilla Galo[d], Eva Martínez Moragón[e], Fernando Rodríguez[f], Mar Mosteiro[g], Pilar Ausín[h], Pilar Cebollero[i], Santiago Quirce[j], Carlos Almonacid[k,*], on behalf of the Working Group on adjusting maintenance medication in severe asthma with biologics[1]

[a] *Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[b] *Hospital Universitario de Jerez, Jerez de la Frontera, Spain*
[c] *Hospital General Universitario Reina Sofía, Murcia, Spain*
[d] *Hospital Universitario Virgen de la Victoria, Málaga, Spain*
[e] *Hospital Dr. Peset, Valencia, Spain*
[f] *Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain*
[g] *Complejo Hospitalario Universitario de Vigo (CHUVI), Vigo, Spain*
[h] *Hospital del Mar-Research Institute, Universidad Pompeu Fabra, Barcelona, Spain*
[i] *Hospital Universitario de Navarra, Pamplona, Spain*
[j] *Department of Allergy, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain*
[k] *Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain*

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ABSTRACT

Introduction: Severe asthma (SA) management requires a comprehensive, individualized approach with continuous pharmacological treatment adjustments. In SA patients controlled with biologics, decisions on how to adjust maintenance therapy remain a clinical challenge, as current guidelines provide only general recommendations but lack specific practical guidance on how to implement step-down strategies.
Material and methods: A literature review about maintenance therapy step-down in SA patients was conducted, complemented by five regional expert meetings across Spain. A total of 87 allergists and pulmonologists from referral hospitals discussed four clinical questions: whether step-down is a potential therapeutic goal, the minimum clinical conditions required to initiate tapering, the duration of disease control needed, and the preferred sequence of therapy reduction. Quantitative insights were captured through televoting, complemented by structured discussions.
Results: Experts agreed that maintenance therapy step-down can be considered a potential therapeutic objective in patients with SA who achieve sustained control with biologics. Key conditions identified to start it included absence of exacerbations, nonuse of oral corticosteroids, adequate symptom control and preserved lung function for at least 6 or 12 months. A stepwise sequence for stepping-down maintenance therapy was established, prioritizing withdrawal of leukotriene receptor antagonists and high-to-low-dose reduction of inhaled corticosteroids, and finally withdrawal of long-acting beta-agonists, while maintaining low-dose inhaled corticosteroids.
Conclusions: Expert perspectives, together with clinical trial and real-world evidence, support a gradual, individualized approach guided by objective markers and close monitoring. The algorithm proposed will provide clinicians with a structured, evidence-informed framework to guide the safe and effective reduction of SA maintenance therapy in real-world practice.

* Corresponding author.
E-mail address: caralmsan@gmail.com (C. Almonacid).
[1] The list with the authors within the collaborative working group is disclosed in the Annex 1.

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Evidencia sobre la reducción progresiva del tratamiento de mantenimiento en pacientes con asma grave controlada con fármacos biológicos: revisión exhaustiva de la literatura y opinión de expertos

Palabras clave:
Asma grave
Biológico
Terapia de mantenimiento
Corticosteroides inhalados
Ajuste
Algoritmo

R E S U M E N

Introducción: El manejo del asma grave (AG) requiere un enfoque integral e individualizado, con ajustes continuos del tratamiento farmacológico. En pacientes con AG controlada mediante fármacos biológicos, la toma de decisiones sobre cómo ajustar la terapia de mantenimiento sigue siendo un reto clínico, ya que las guías actuales solo ofrecen directrices generales y carecen de recomendaciones específicas.
Material y métodos: Se realizó una revisión exhaustiva de la literatura sobre la reducción escalonada de la terapia de mantenimiento en pacientes con AG, complementada con cinco reuniones de expertos en distintas regiones de España. Un total de 87 alergólogos y neumólogos procedentes de hospitales de referencia debatieron cuatro cuestiones clínicas: si la reducción escalonada del tratamiento de mantenimiento es un objetivo terapéutico viable, las condiciones clínicas mínimas necesarias para iniciar la disminución, el tiempo requerido de control de la enfermedad y la secuencia óptima para reducir la terapia. Las opiniones cuantitativas se recogieron mediante una herramienta de televoto y se complementaron con debates estructurados.
Resultados: Los expertos coincidieron en que la reducción escalonada de la terapia de mantenimiento puede considerarse un objetivo terapéutico en pacientes con AG en quienes se logre un control sostenido con biológicos. Las condiciones clave identificadas para iniciar este proceso incluyen la ausencia de exacerbaciones, no precisar corticosteroides orales, control adecuado de los síntomas y función pulmonar preservada durante al menos 6 o 12 meses. Se estableció una secuencia escalonada para la reducción de la terapia de mantenimiento, priorizando la retirada de los antagonistas de los receptores de leucotrienos y la reducción de dosis, de altas a bajas, de corticosteroides inhalados, para finalmente retirar los beta-agonistas de acción prolongada, manteniendo corticosteroides inhalados a dosis bajas.
Conclusiones: Las opiniones de los expertos, junto con la evidencia procedente de ensayos clínicos y datos de vida real, apoyan un enfoque gradual e individualizado, guiado por biomarcadores objetivos y una monitorización estrecha. El algoritmo propuesto proporcionará a los clínicos un marco estructurado y fundamentado en la evidencia para guiar la reducción segura y eficaz de la terapia de mantenimiento en AG en la práctica clínica real.

Introduction

Severe asthma (SA) is defined as asthma requiring treatment with medications recommended in Global Initiative for Asthma (GINA) steps 4–5 during the previous year, systemic corticosteroids for ≥50% of the year to prevent loss of control, or asthma that remains uncontrolled despite this therapy.[1] Achieving control requires an intensive and individualized pharmacological approach; SA management includes high-dose inhaled corticosteroids (ICS) combined with long-acting β_2-agonists (LABA), long-acting muscarinic antagonist (LAMA), or leukotriene receptor antagonists (LTRA). For uncontrolled patients, biologics (omalizumab, mepolizumab, benralizumab, dupilumab, tezepelumab, reslizumab) oral corticosteroids (OCS) may be necessary.[2,3]

Clinical guidelines offer a structured algorithm for therapeutic decision-making. In the real world, however, SA management remains complex and constantly evolving. Patient heterogeneity, variable treatment response, and comorbidities often complicate adherence to standardized protocols. Additionally, many patients remain exposed to a high pharmacological burden despite appropriate therapy.[4,5]

Reducing maintenance therapy after achieving disease control with biologics has thus gained recent relevance and constitutes a practice to be considered, although no specific algorithms exist, in international guidelines such as GINA (Global Initiative for Asthma) 2025.[2,3] In addition, although some relevant previous structured frameworks were proposed and provided early guidance on medication adjustment following the principle of the minimum dose to ensure asthma control,[6] they predate the biologic era and may not fully apply to current treatment paradigms.[2,3] By combining the available evidence and expert opinions, this manuscript aim to inform on optimizing and safely reducing maintenance therapy in patients with SA who achieve sustained control with biologics.

Material and methods

Literature review

A targeted narrative literature review was conducted to provide evidence on maintenance therapy step-down in SA. Considering its comprehensive respiratory medicine coverage, PubMed was searched using MeSH and free-text terms related to SA, maintenance therapy, dose reduction/ICS reduction, step-down, and biologics (omalizumab, mepolizumab, benralizumab, dupilumab, tezepelumab, reslizumab). The search covered January 2015–June 2025, with selected exceptions based on expert judgement, and was cross-checked with additional sources resulting from manual reviewing of reference lists and key conference abstracts.

Aligning with methodologies followed in similar studies in the field,[7] this review focused on collecting key evidence to inform expert discussions, rather than to systematically appraise all available studies in this regard.

Expert meetings

Given the presented evidence gaps and the lack of specific recommendations in asthma guidelines, between December 2024 and March 2025, five regional scientific meetings were held across Spain to specifically explore expert perspectives on step-down of maintenance therapy in SA patients controlled with biologics. During these meetings, a literature presentation prepared on the basis of the results from the described literature review and an experts' discussion scheme was followed.

A total of 87 medical doctors (34 allergists, 53 pulmonologists) from referral hospitals representing each of the regions participated in these meetings. All recognized opinion leaders, participants from both medical specialties were selected by regional meeting coordinators from the Spanish SA Network, based on each participant's recognized expertise and leadership in SA management. The sessions covered four predefined scientific questions regarding which no conflict of interest was detected: (1) step-down as a potential therapeutic goal; (2) minimum conditions before initiating step-down; (3) required duration of control; and (4) preferred order of therapy reduction.

To complement discussion, televoting (Slido, Cisco Systems, Inc) captured quantitative opinions. Response rates ranged from 61 to 62, and all participants contributed either through voting or discussion. The presented results combine quantitative voting with qualitative insights.

Results

Evidence synthesis from literature review

Use of maintenance therapy in patients with SA

Disease control in SA usually requires substantial pharmacological intervention, including biologics. High-dose ICS are among the most widely prescribed maintenance therapies and are used at or above guideline-defined thresholds.[8] GEMA (from Spanish *Guía Española para el Manejo del Asma*) and GINA define high-dose ICS as budesonide > 800 μg/day or fluticasone propionate > 500 μg/day.[2,3]

Real-world data indicate that many patients receive high ICS doses.[4,5] In a Spanish real-world cohort, the median ICS dose was budesonide 993 μg/day in patients without biologics,[9] while international trials reported a mean dosage of 899 μg/day of fluticasone propionate or equivalent before biologic initiation.[4] In a Danish nationwide study, 24% of patients initiating biologics therapy used >1600 μg/day of a budesonide equivalent, a proportion unchanged after 12 months of biologic treatment.[5]

Comorbidities further increase pharmacological burden. In an international registry, ≈60% of adults had ≥3 comorbidities, most commonly nasal polyps, allergic rhinitis, chronic rhinosinusitis, and obesity, and were more likely to require high-dose ICS or long-term OCS.[10] Another study emphasized that obesity, chronic rhinosinusitis (with/without nasal polyps), and obstructive sleep apnoea contribute to persistent symptoms and higher ICS doses.[11]

In Spain, recent data confirm extensive use of ICS-based combinations in SA. In the ENEAS study, all uncontrolled SA patients received high-dose ICS/LABA for ≥12 months, per protocol.[12] The CHRONICON survey reported that 80% of SA patients, versus only 18.8% with non-severe disease, were prescribed fixed ICS/LABA combinations.[13] These data highlight high corticosteroid use in SA and the relevance of strategies to reduce maintenance therapy.

Risk–benefit profile of ICS and other maintenance therapies in SA

ICS act locally to reduce airway inflammation, but at high doses (considering GEMA ICS dosage thresholds)[2] these drugs may entail potential side effects due to clinically relevant systemic absorption. A meta-analysis by Maijers et al. found that the steroid-sparing effect of high-dose ICS in corticosteroid-dependent asthma is largely due to systemic bioactivity. Each fluticasone propionate 1000 μg increase reduced oral prednisolone by up to 4.9 mg, almost entirely explained by systemic absorption.[14]

High-dose ICS systemic effects are associated with adverse outcomes such as adrenal insufficiency, diabetes, cataracts, osteoporosis, increased risk of metabolic and infectious complications, and potential cognitive impairment.[14–18] In older adults, reduced bone mineralization has been linked to ICS with higher systemic bioavailability.[15]

Major clinical benefit is obtained with low-to-moderate doses according to the ICS dose-response curve proposed by Beasley et al.[19] Approximately 90% of maximal therapeutic effect is achieved with 100–250 μg/day of fluticasone propionate or equivalent, while higher doses offer small improvements but significantly increase systemic exposure.[19] A cohort study of 162,202 patients found that moderate-to-high-dose ICS were associated with an increased risk of major cardiovascular events (*hazard ratio* [*HR*] 4.63; 95% confidence interval [CI], 2.62–8.17), arrhythmias (*HR* 2.91; 95% CI, 1.72–4.91), pulmonary embolism (*HR* 3.32; 95% CI, 1.69–6.50), and pneumonia (*HR* 4.09; 95% CI, 2.98–5.60).[20] These data highlight the importance of using the lowest effective ICS dose to achieve asthma control and minimize systemic effects.

Despite the well-established risks associated with prolonged high-dose ICS use, asthma maintenance therapy is often continued without reassessment. This therapeutic inertia may cause adverse effects and highlights the need for routine evaluation of step-down of maintenance therapy, particularly in patients with sustained control with biologics.

Current perspectives of patients, clinicians, and scientific societies on maintenance therapy step-down in SA controlled with biologics

Poor patient education and delayed SA recognition often worsen polypharmacy issues.[21] Patients face emotional and practical burden associated with long-term, complex treatment regimens.[22] Daily use of multiple drugs and awareness of high corticosteroid doses can cause psychological stress and reinforce perceptions of severe disease.[23] When asthma is controlled with biologics, many patients prefer reducing maintenance treatments, including ICS doses, to minimize medication load and long-term side effects.[12,23–25]

Clinicians recognize the need to reassess maintenance strategies. Reducing corticosteroid exposure, including ICS, is now a priority in the biologic era to limit long-term adverse effects.[26]

Consistently, the American College of Allergy, Asthma and Immunology, the American Academy of Allergy, Asthma & Immunology, and the American Thoracic Society incorporated ICS reduction in the joint definition of clinical remission, which requires sustained symptom control, preserved lung function, no exacerbations, and only low–moderate ICS doses in line with the GINA guidelines.[27]

Asthma maintenance therapy adjustment after biologics: clinical trials and real-world evidence

Randomized clinical trials (RCTs) and real-world studies indicate that reducing maintenance therapy is feasible and safe in selected SA patients controlled with biologics. Real-world data confirm that reductions in ICS and other therapies are already applied in clinical practice with favourable outcomes.

Clinical trials. Data on maintenance therapy reduction from RCTs are scarce and incidental in trials designed to assess efficacy and safety.

In an omalizumab trial, 460 patients with moderate–severe allergic asthma were randomized to subcutaneous omalizumab or placebo plus a fixed dose of inhaled beclomethasone dipropionate (BDP). After 16 weeks of treatment and maintained asthma control, BDP tapering was initiated, reducing the baseline dose by 25% every 2 weeks for 8 weeks. The lowest BDP dose required for asthma control (227 μg/day [mean] and 335 μg/day [mean] in omalizumab and placebo arms, respectively), that corresponded to a low-dose ICS equivalent (≤200 μg/day fluticasone propionate),[2] was subsequently maintained for the final 4 weeks of the study, and was maintained until then without LABA combination. Omalizumab-

treated patients had fewer exacerbations vs placebo during the extension phase (0.60 and 0.83 exacerbations per patient, respectively; $p < 0.023$), despite significant ICS reduction.[28]

In a phase IIb dupilumab study, patients with persistent, moderate–severe asthma and elevated eosinophil count on stable ICS/LABA at enrolment received dupilumab or placebo for 12 weeks. At week 4, patients were instructed to discontinue LABA and to taper and discontinue ICS during weeks 6–9. Compared with placebo, dupilumab reduced exacerbations, improved lung function, and lowered Th2 inflammatory markers after LABA and ICS withdrawal.[29]

In contrast to the above, some clinical studies have been specifically designed to test step-down feasibility. The ANDHI-In Practice substudy included patients who had completed the double-blind phase of the ANDHI study and had already been receiving benralizumab for ≥4 months without exacerbations. Criteria for step-down were: (1) score < 1.5 on the Asthma Control Questionnaire (ACQ-6); (2) absence of exacerbations since the last visit; and (3) physician agreement. The reduction was conducted in stages, typically starting with discontinuation of LAMA, LTRA or xanthines, followed by ICS dose reduction. At week 80, 53.5% of patients had reduced at least one maintenance medication, and 41.9% had shifted to a lower GINA step. In controlled patients, high-dose ICS use decreased from 63.1% at baseline to 25.1% at the end of follow-up. Additionally, a high proportion of these controlled patients discontinued LAMA (65.2%), LTRA (52.4%), and LABA (19.9%).[30]

In the SHAMAL phase IV study, patients with eosinophilic SA controlled on benralizumab were randomized to two arms which maintained or reduced their ICS/formoterol regimen for 32 weeks, followed by a background period of 16 additional weeks. Eligibility required ACQ-5 score < 1.5 and use of high-dose ICS. Dose reductions were initiated when maintained asthma control had been achieved (no exacerbations since the previous visit, ACQ-5 score increase < 0.5, and no significant rise in ICS/formoterol reliever use). Patients meeting these criteria at the medium dose tapered their regimen in a stepwise fashion. The ICS/formoterol dose was reduced from medium (ICS 200 μg plus formoterol 6 μg for two inhalations twice per day as maintenance therapy, plus ICS 200 μg plus formoterol 6 μg as needed) to low dose (one inhalation per day) and then to ICS/formoterol reliever use only. At week 32, 92% of the patients had reduced their ICS/formoterol maintenance dose at the end of the reduction period, while 96% of them maintained this reduction afterwards, with a budesonide/formoterol mean total daily dose difference between arms of −819.82 μg at week 48.[31]

Similarly to SHAMAL, the ARRIVAL study with tezepelumab will assess the potential to reduce maintenance ICS in patients with an ACQ-5 score < 1.5 and no exacerbations or in patients with low biomarker levels (blood eosinophil counts < 150 cells/μL, FeNO level < 25 ppb) and ACQ-5 score ≤ 2 with no exacerbations.[32]

Real-world evidence on maintenance therapy adjustment in SA. Even not designed for step-down assessment, several retrospective studies have reported reductions in ICS and other controllers in routine care.

In a retrospective study of 63 patients on omalizumab, mepolizumab, dupilumab or benralizumab, 41% achieved complete asthma remission and 61% transitioned from GINA therapeutic step 5 to step 3 even when a significant number of them (45–59%) were identified as non-adherent to inhaled and oral asthma therapy, indicating substantial treatment simplification while maintaining disease control.[33]

Consistent findings have emerged in studies focusing specifically on benralizumab. A cross-sectional study in Spain observed a reduction in mean ICS from 993 ± 485 μg/day to 693 ± 343 μg/day of budesonide or equivalent after 12 months of treatment with benralizumab.[9] A multicentre cohort of 139 SA patients on benralizumab reported a reduction of high-dose ICS use from 83.3% at baseline to 57.6% at 12-month, with a shift to low–moderate dose ICS use and a decrease in LAMA (from 65.5% to 45.9%) and LTRA use (from 50.4% to 39.9%).[34] Similarly, an observational study in 21 patients with severe eosinophilic asthma on benralizumab found that 95% reduced their ICS requirements over a one-year period without loss of asthma control.[35] In the 36-month Italian SANI retrospective analysis of 108 patients with severe eosinophilic asthma treated with benralizumab 20.55% decreased their mean daily ICS dose. At 36 months, low dose ICS use (<500 μg/day) had risen from 9.20% at baseline to 32.86%. The chance of requiring high-dose ICS at 36 months decreased by 85% compared to baseline. This reduction was accompanied by the significant discontinuation of short-acting β_2-agonists and LAMA, without any deterioration in exacerbation rate, asthma control, or lung function.[36] A secondary analysis categorized patients by ICS dose (<500, 500–1000, >1000 μg fluticasone/equivalent). Thirty percent of patients moved to a lower category, with almost three times more patients receiving <500 μg/day at 36 months. No baseline differences were found between stable and decreasing ICS subgroups.[37]

Lastly, in a retrospective physician panel-based review of 394 patients treated with mepolizumab, it was observed that 21% of patients reduced or discontinued ICS during a one-year follow-up. The proportion of patients requiring high-dose ICS decreased by 18%, and use of short-acting β_2-agonists was reduced by 45% during the follow-up period.[38] Interestingly, 63% of ICS reductions were a shared decision between patients and their healthcare professionals, 33% by the healthcare professional, and only 4% by the patient themselves.

Current strategies for adjusting maintenance therapy in SA

Asthma management guidelines consistently emphasize that asthma therapy should be titrated to the minimum effective dose required to maintain control, but clear algorithms and concrete recommendations are still lacking, and some differences that illustrate the current lack of universal consensus exist, therefore highlighting the need for further research and harmonization across clinical opinions. The GINA 2025 update does acknowledge the possibility of adjusting controller therapy once asthma is well controlled on biologics but offers limited operational guidance. The document recommends reviewing treatment every 3–6 months and emphasizes minimizing or discontinuing OCS as a high priority in patients who have responded to type 2 inflammation-targeted therapy. If asthma remains well controlled, clinicians may consider discontinuing LAMA while maintaining an ICS/LABA scheme that could be dose-reduced, or switching to an ICS/formoterol as-needed regimen, based on sustained stability.[3] Similarly, the Spanish national asthma guidelines (GEMA) recognize that a reduction in asthma maintenance treatment (including ICS/LABA tapering) can be considered in patients with good control and the goal is to minimize pharmaceutical load; but no specific guidance is provided for those receiving biologics.[2]

Recent expert reviews and position papers have begun to propose practical frameworks for step-down of maintenance therapy in patients with SA treated with biologics in routine clinical practice. Wechsler et al. propose several strategies for optimizing treatment in patients who are well controlled on biologics, including the discontinuation of OCS, which is broadly recognized as a primary goal, and the reduction of maintenance therapies (ICS, LABA, LAMA, LTRA) based on available evidence. However, they did not establish a specific stepwise protocol on how to implement this tapering. They emphasize reassessing disease control every 3–6 months before each step.[7] Merrell and colleagues similarly advocate for OCS withdrawal as a priority and suggest relying

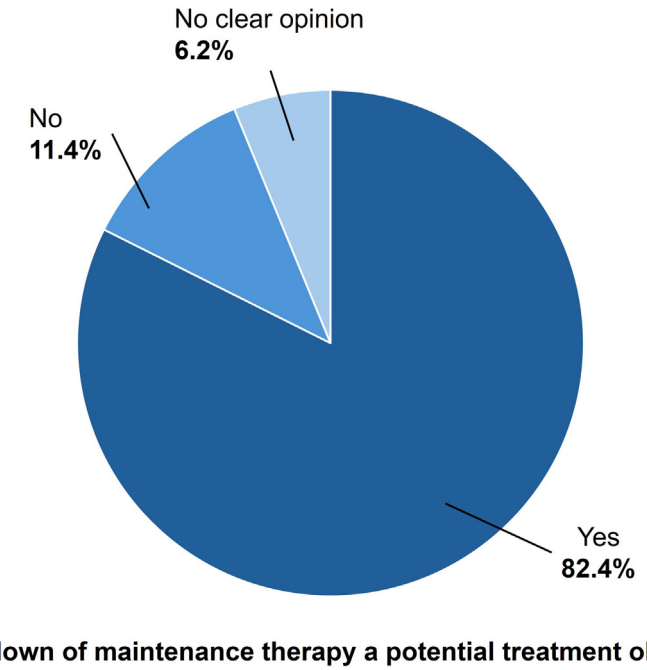

Fig. 1. Participants' opinion on the question "Is maintenance therapy step-down a potential treatment objective?" ($n = 62$).

on objective indicators, such as symptom scores, exacerbation history, and lung function, before reducing ICS/LABA.[39] Menzies-Gow et al. also support this sequence and propose OCS tapering as the first target, followed by inhaled therapy reduction only if clinical stability is maintained without recent exacerbations.[40]

Expert perspectives on maintenance therapy step-down in SA

In the context of evidence reinforcing the possibility of safe adjustment of asthma maintenance treatments after achieving control with biologic therapy in SA, and in the absence of clear algorithms or robust recommendations on such practice, the insights of experienced clinicians are essential to guide decisions regarding step-down strategies.

The results and discussion presented here come from a series of structured expert meetings held to explore these critical aspects of step-down. Each session centred on four predefined clinical questions: whether step-down of maintenance therapy should be considered a therapeutic goal; the minimum clinical conditions needed to initiate tapering under biologic therapy; the duration of disease control required before starting; and the preferred sequence for reducing maintenance treatments. Importantly, no mentions to specific biologic alternatives were made and all the discussions were independent on the biologic that a patient could be receiving and that is the responsible of the patient's asthma control.

Step-down of maintenance therapy as a therapeutic goal

The responses to the question asked in this regard through the televoting system described in Methods showed that the vast majority (82.4%) of the participating experts agreed that reducing asthma maintenance therapy can be considered a potential therapeutic objective in patients with SA controlled with biologics (Fig. 1). Upon experts' discussion, it was stated that the principal reason justifying starting maintenance therapy step-down was the reduction of corticosteroid-related adverse effects, particularly those associated with high-dose ICS and other chronic therapies. Second, minimizing overall treatment burden could enhance therapy adherence, especially among patients motivated by their perceived improvement under biologic therapy. Third, maintenance therapy step-down is already a reality in routine clinical practice in specialized asthma units in Spain but it is based on clinical experience and judgement rather than a standardized protocol. In this sense, step-down of maintenance therapy may be considered a consequence of achieving asthma control with biologics, and also a secondary goal to reduce treatment burden, as long as key outcomes such as symptom control and prevention of exacerbations are preserved. Participants emphasized the importance of individualized decisions, particularly in patients who show a significant response to biologic therapy and in whom treatment minimization may be appropriate even in the absence of systemic side effects.

Minimum conditions to initiate step-down of maintenance therapy

Through televoting, experts ranked the minimum conditions for asthma maintenance therapy step-down once control is achieved following biological treatment. They agreed that treatment step-down could be considered when clinical control of SA is achieved, dependent on the absence of exacerbations and no requirement for OCS (Fig. 2). After these, other parameters should be considered, including adequate symptom control, preserved lung function (based on spirometry), and minimal need for rescue medication. The same parameters were considered essential for monitoring and follow-up of patients after initiating step-down of maintenance therapy to ensure that SA control is maintained and to identify any need for therapeutic modification.

Other factors such as bronchial provocation testing, FeNO levels, blood eosinophil counts, adherence to therapy, and patient quality of life were considered important but less determinant for taking the decision to start step-down and guiding the follow-up during the step-down process. The importance given to each parameter might vary across regions because of the limited availability of such tools in routine care and their more complementary role in evaluating disease control.

Adherence to treatment was widely discussed within experts' debates. While it ranked lower in priority, it was recognized as essential to determine whether maintenance therapy is truly needed or if patients have independently discontinued it. Several experts highlighted that even if adherence was not rated among

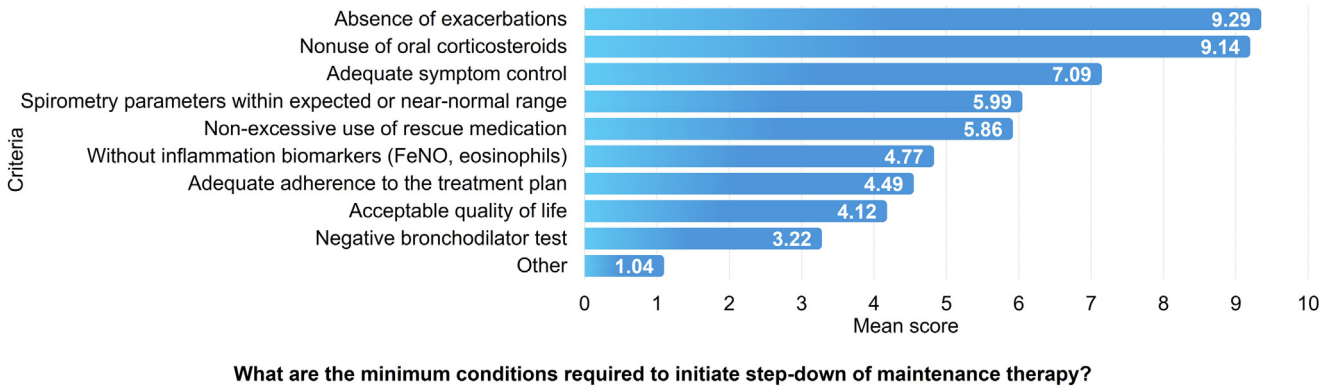

Fig. 2. Ranking of minimum conditions required to initiate step-down of maintenance therapy ($n = 61$). Mean score: the response options are ranked according to the priority level assigned by participants in this survey. Each option received a score inversely proportional to its position in each participant's individual ranking (in this case, the top-ranked option received 10 points, the second 9, and so on until the last option, which received 1 point). The average score for each option was then calculated across all participants, resulting in a mean value that reflects the overall agreement on the priority of each option. "Absence of exacerbations" refers to a situation of asthma control sustained for at least 12 months, while "no oral corticosteroids requirement" refers to the absence of necessity of rescue courses using these therapies.

the top conditions, it remains an indispensable prerequisite before considering therapy tapering.

During discussions, participants highlighted lung function and FeNO as key factors in treatment adjustment monitoring, given that these parameters can be particularly sensitive in detecting a potential rebound in airway obstruction and underlying inflammation.

Patient perspectives also emerged as an important consideration throughout experts' discussion, especially in cases where symptoms persist despite good overall control, underscoring the value of assessing quality of life and patients' feelings, as well as to consider their thoughts in a shared decision-making process when thinking in initiating a step-down of maintenance therapy.

Minimum duration of sustained control

Experts also debated the minimum duration of sustained control with a biological therapy before starting maintenance therapy step-down. While in televoting 47.2% found a period of at least six months of sustained control enough before starting step-down, 41.2% considered one year of sustained control preferable and 11.6% indicated that three months of control could be acceptable in selected cases (Fig. 3).

Besides, during the corresponding debate, participants mentioned that the best moment to start step-down of maintenance therapy depends on factors such as local healthcare logistics, including visit frequency and follow-up capabilities of the clinicians. In routine clinical practice, the available number of follow-up visits is often limited, normally one appointment every six months. This healthcare reality influences therapeutic adjustment strategies, requiring caution when considering the timing and conditions for step-down.

Environmental factors were also cited as relevant, particularly the potential risks of tapering therapy during seasons with allergy or infection peaks, like spring and autumn, where an elevated risk of decompensation exists.

Sequence of tapering of maintenance therapy

To establish a logical sequence for a stepwise tapering of asthma maintenance therapies (excluding reliever medication), experts were asked, through televoting, to rank the priority of withdrawal/reduction of LTRA, LABA, LAMA and the different dosages of ICS (high, medium, low). The agreed sequence was to start with the withdrawal of LTRA, followed by either tapering high-dose ICS to medium doses or withdrawing LAMA. Both strategies ranked similar and were considered equally plausible to be conducted, one before the other, at the discretion of the physician. Next, further reduction of ICS from medium to low doses was proposed, finally followed by discontinuation of LABA (Table 1). Experts agreed that reducing ICS should be a key therapeutic objective. The stepwise approach to ICS reduction was particularly emphasized, highlighting the need to avoid abrupt changes, starting with the reduction of high-dose ICS.

Table 1
Sequence of tapering maintenance therapy ($n = 61$).

Treatment option	Mean score[a]
LTRA	5.45
LAMA	4.79
High-dose ICS	4.49
Medium-dose ICS	2.71
LABA	2.47
Low-dose ICS	1.05

[a] The response options are ranked according to the level of priority assigned by participants in this survey. Each option is awarded a score inversely proportional to its position in each individual ranking (in this case, the first-ranked option receives 6 points, the second 5, and so on until the last, which receives 1 point). The average score for each option is then calculated based on all participants' responses, providing a mean value that reflects the overall agreement on the priority of each item.
ICS: inhaled corticosteroids, LABA: long-acting β_2 agonist, LAMA: long-acting muscarinic antagonist, LTRA: leukotriene receptor antagonist.

In line with these results, participants discussed that the most appropriate approach for step-down of maintenance therapy is the inverse path followed during the treatment escalation strategies proposed by asthma guidelines. They also mentioned combination inhalers as an element that could complicate the step-down process, particularly single inhaler triple therapy formats that limit the ability to withdraw individual components.

There was an agreement that LABA should generally be among the last medications to be reduced or withdrawn, given their role in symptom control. In patients with well-controlled symptoms but persistently elevated FeNO levels, some experts recommended considering bronchodilator adjustment before reducing ICS to avoid inflammatory rebound. It was also noted that the response to biologic therapy, particularly when rapid and pronounced, may influence the timing and extent of asthma maintenance treatment reduction. This is especially relevant in the context of biologics like benralizumab, which has a rapid onset of action.

Based on expert opinion, a stepwise algorithm to guide the step-down of asthma maintenance therapy in patients with SA with sustained disease control with biologic therapy in clinical routine practice was developed (Fig. 4). The algorithm considers the prioritization of treatment components and the minimum condition to initiate tapering.

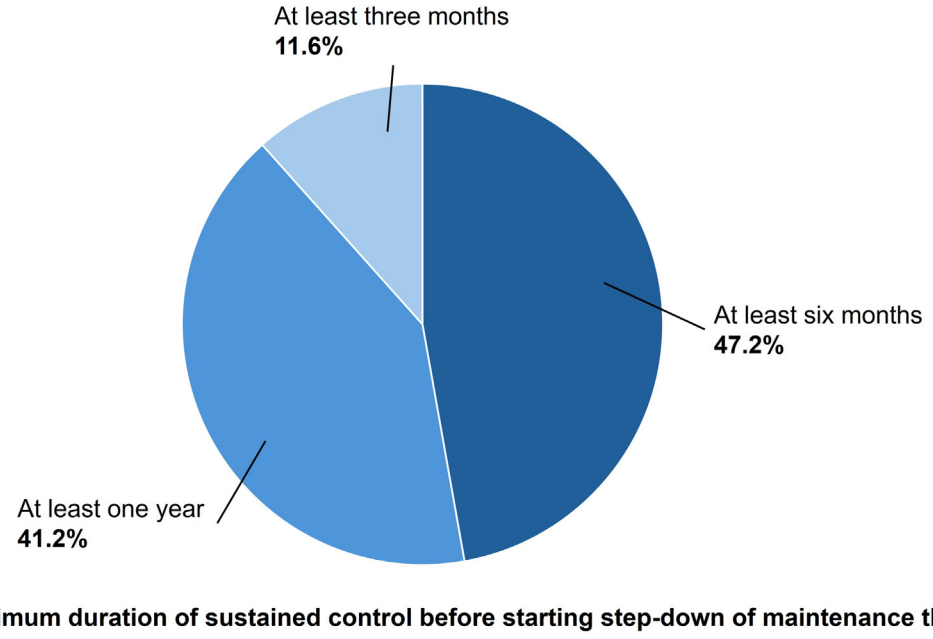

Fig. 3. Minimum duration of sustained control before starting step-down of maintenance therapy (percentage of participants) ($n = 61$).

Step-down of maintenance therapy should only be considered in patients with sustained asthma control, absence of exacerbations and OCS use, and adequate symptom control maintained for at least 6 or 12 months. During step-down, reassessment of control every 3–6 months is recommended to ensure ongoing stability and to guide further treatment adjustments. Importantly, if one criterion or more defining a sustained control are not met, no step-down in maintenance treatment should be initiated. In addition, if following a maintenance therapy step-down results in the loss of one parameter or more for sustained control (e.g., an exacerbation occurs), the situation must be properly managed and the previous guideline within the proposed algorithm should be resumed, re-evaluating the patients after 6 months.

The proposed algorithm starts with the withdrawal of LTRA, followed by either discontinuation of LAMA or the reduction of high-dose ICS to medium doses, depending on the patient's clinical profile and through an individualized decision-making process. LAMA withdrawal is recommended when symptoms and lung function remain stable without airflow limitation ($FEV_1 \geq 80\%$ predicted) and no residual bronchial hyperresponsiveness is present. In contrast, tapering of high-dose ICS may be preferred when eosinophilic inflammation is well controlled (e.g., blood eosinophils < 150 cells/μL, FeNO < 25 ppb, and no exacerbations for 6 or 12 months), especially in patients with SA ≥ 60 years. The two approaches, LAMA withdrawal and tapering of high-dose ICS, may be valid in many patients, but they should not occur simultaneously.

Subsequent steps include the reduction of medium-dose ICS to low-dose ICS, and finally, the withdrawal of LABA, while maintaining low-dose ICS. The complete withdrawal of ICS is not recommended by the experts, as these play a crucial role in maintaining long-term control of airway inflammation.

Discussion

Significant advances in the management of SA and control of the symptoms and disease have been achieved with biologic therapies.[41] Guidance on adjusting maintenance treatment after achieving control with biologics remains scarce, despite the known risks of prolonged high-dose ICS and systemic corticosteroid,[14–18] and the shared priority of reducing pharmacological burden.[26] This manuscript: (1) identifies the current evidence gap in relation to the maintenance therapy step-down in biologic-treated patients; (2) integrates expert opinion to fill this gap; and (3) proposes a structured, evidence-informed algorithm applicable to clinical practice.

The concept of maintenance therapy step-down in SA has gained increasing attention in recent years, particularly in the context of biologic therapy. Current guidelines (GINA 2025, GEMA 5.5) clearly state that therapy should be tailored to the minimum effective dose.[2,3] However, as shown in this manuscript, they offer only general principles and limited operational detail on how to implement step-down strategies in patients controlled with biologic agents. Expert opinions aligned with the ICS maintaining strategy included both in GINA 2025 and GEMA 5.5,[2,3] while may be different with the GINA 2025 proposal of an on-demand use of ICS/LABA.[3] Therefore, the insights gathered here also complement these data and provide practical conditions for considering step-down.

Experts noted that step-down is already practiced in specialized units, usually based on clinical judgement, aligning with real-world data showing reduced ICS and other controllers after biologic initiation. Trials like SHAMAL and ANDHI-In Practice, and retrospective studies, have shown that patients can safely benefit from maintenance medication tapering.[30,31] In this context, expert insights confirm that tapering should be considered not only a possibility but a clinical goal, particularly in patients in whom a significant response is observed, or those who have experienced sustained benefits from biologic therapy.

Absence of exacerbations and OCS, symptom control and stable lung function were identified as the top four key criteria to initiate tapering, consistent with clinical trial criteria and recent definitions of remission.[7,27,39,40]

Timing to initiate step-down remains a critical issue. The time considered by the experts to be observed before reducing therapy aligns with recent expert recommendations that suggest reassessing disease control every 3–6 months before each step-down step.[7,39] Notably, some experts even believed that step-down of maintenance therapy could begin after only 3 months of control in selected patients, particularly in individuals showing a rapid and robust response to biologics. On the one hand, clinical trial protocols, such as those used in the SHAMAL and ANDHI-In Practice

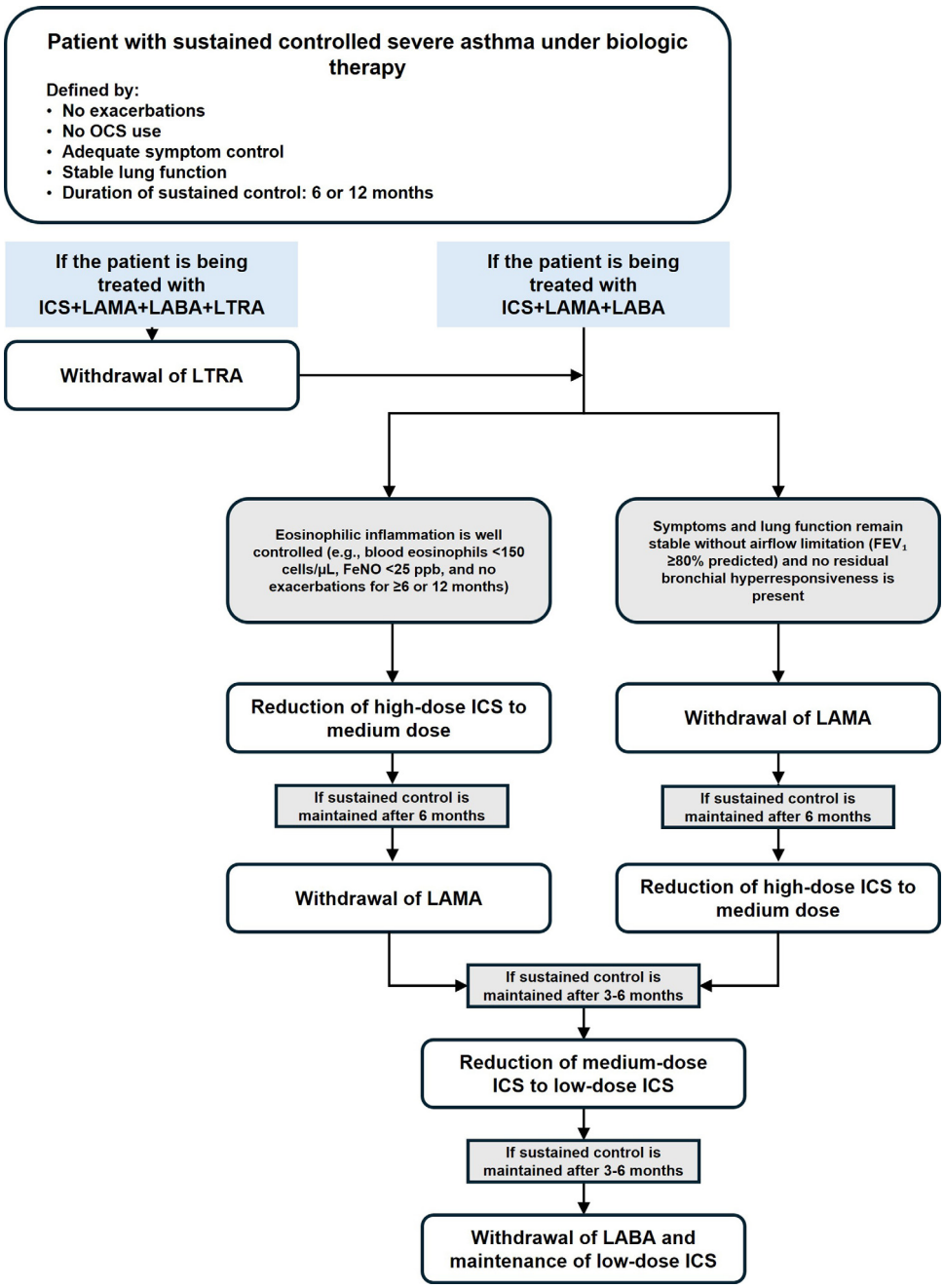

Fig. 4. Maintenance therapy step-down algorithm in patients with SA with sustained disease control with biologic therapy. FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; LAMA: long-acting muscarinic antagonists; LTRA: leukotriene receptor antagonists; OCS: oral corticosteroids. "Stable lung function" refers to a situation with no airway limitation ($FEV_1 \geq 80\%$ predicted) and no residual bronchial hyperresponsiveness, or when the lung function could be defined as stable on the basis of the historical/better result of the patient, time-sustained. When considering ICS dose reduction versus LAMA withdrawal, an individualized decision should be taken, and in those patients in whom both approaches may be equally valid these two step-down strategies should not be practiced simultaneously. If the step-down treatment plan fails at any stage, a maintenance therapy step-up should be considered returning to, at least, the previous therapeutic action taken before the asthma control was lost or, e.g., before an exacerbation occurred.

studies in which controlled maintenance dose reduction appeared safe when performed gradually and under biomarker monitoring, support this more proactive approach. These trials initiated maintenance therapy tapering after 4–6 months of control.[30,31] On the other hand, observational studies suggested that abrupt ICS withdrawal can increase the risk of exacerbation,[42,43] therefore emphasizing the proposed 6- or 12-month stability period before any reduction to mitigate this risk.

However, the timing of step-down should also consider real-world healthcare limitations, such as limited frequency of follow-up visits and seasonal factors. These considerations underline the importance of tailoring the step-down process not only to the patient's clinical status but also to logistical and environmental factors.

Experts outlined a structured tapering sequence for SA patients controlled on biologics, ultimately avoiding complete withdrawal of low-dose ICS. These preferences are strongly aligned with both recent expert recommendations and real-world data,[30,31] while the safety of implementing this step-down strategy nonetheless remains to be assessed, so further specific studies should be performed in this respect. The complete withdrawal of low-dose ICS therapies is a feasible practice that should also be analyzed.

This work has some limitations inherent to expert opinion-based manuscripts. The experts' agreements are subjective and may be influenced by local practice patterns or healthcare system characteristics. In addition, although 87 clinicians participated in the scientific meetings, not all contributed quantitatively via the televoting system, which may slightly limit the representativeness of some results. Nevertheless, these views were often expressed verbally and are captured qualitatively in this document. One of the main strengths is the integration of evidence from both RCTs and real-world studies with systematically collected expert insights. This approach provides a balanced understanding of theoretical and practical aspects of asthma maintenance therapy step-down in SA. The use of structured meetings across multiple Spanish regions also offers a representative perspective of current clinical reasoning and practice variability.

Conclusion

Step-down of maintenance therapy in patients with SA well controlled on biologics is emerging as a therapeutic goal. While current guidelines support using the lowest effective dose, lack of clear protocols for maintenance therapy tapering exists. Expert perspectives, together with clinical trial and real-world evidence, support a gradual, individualized approach guided by objective markers and close monitoring. To our knowledge, this work presents the first nationwide expert opinion in Spain proposing a structured algorithm for step-down of maintenance therapy in SA patients controlled with biologics.

Disclosure of the use of generative AI and AI-assisted technologies in the process of writing

During the elaboration of this manuscript, the authors used ChatGPT to improve legibility and language. After using this tool, the authors reviewed and edited the content when needed, assuming all the responsibilities regarding the manuscript's contents.

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Authors' contributions

All authors contributed equally to the manuscript.

Conflicts of interest

Vicente Plaza declares that he has received honoraria for speaking at sponsored meetings from AstraZeneca, Boehringer-Ingelheim, Chiesi, Gebro, GSK, Luminova-Medwell, and Sanofi; assistance to meeting travel from AstraZeneca and Chiesi; and act as a consultant for AstraZeneca, Chiesi, GSK and Menarini.

Gregorio Soto Campos declares that he has received honoraria for participating as a speaker at meetings sponsored by AstraZeneca, Sanofi, Menarini, and GSK and as a consultant for AstraZeneca, Sanofi, GSK, Chiesi, and Gebro in the last three years. He has received financial support for attending conferences from Sanofi and AstraZeneca.

Juan Carlos Miralles López declares that he has received consultancy fees from AstraZeneca, and speaker fees from GSK, AstraZeneca, Sanofi, Chiesi, Menarini, and Gebro.

Alicia Padilla Galo declares that she has received grants, personal fees and non-financial support from AstraZeneca, Menarini and Sanofi; personal fees and non-financial support from Chiesi; and personal fees from ALK, FAES Farma, GSK, and Bial.

Eva Martínez Moragón declares that she has received consulting fees from Sanofi, Regeneron, AstraZeneca, and GSK; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sanofi, Regeneron, AstraZeneca, GSK, Gebro, and Menarini; payment for expert testimony from AstraZeneca and GSK; support for attending meetings and/or travel from Menarini, AstraZeneca, Chiesi, and GSK; and participation on a Data Safety Monitoring Board or Advisory Board from Sanofi and Regeneron.

Fernando Rodríguez declares that he has received honoraria for participating as a speaker at meetings sponsored by AstraZeneca, Sanofi, and GSK.

Mar Mosteiro Añón, declares that she has received honoraria for participating as a speaker at meetings sponsored by AstraZeneca, Sanofi, Menarini, Gebro, FAES, and GSK; and as a consultant for AstraZeneca, Sanofi, and GSK in the last three years. She has received financial support for attending conferences from Sanofi and AstraZeneca.

Pilar Ausín declares that she has received honoraria for participating as a speaker at meetings sponsored by AstraZeneca, Sanofi, and GSK and as a consultant for AstraZeneca and Sanofi.

Pilar Cebollero declares that she has received honoraria for participating as a speaker at meetings sponsored by AstraZeneca, Sanofi, and GSK in the last three years.

Santiago Quirce declares that he has received honoraria for participating as a speaker and advisor in meetings sponsored by Allergy Therapeutics, AstraZeneca, Chiesi, GSK, Gebro, Novartis, Regeneron, and Sanofi.

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Annex 1. List of participants in the collaborative working group (Working group on adjusting maintenance medication in severe asthma with biologics)

Name	Affiliation
Dr. Beatriz Abascal	Hospital Universitario (H. U.) Marqués de Valdecilla, Santander, Spain
Dr. Manuel Alcántara Villar	H. U. de Jaén, Spain
Dr. Darío Antolín	H. U. Ramón y Cajal, Madrid, Spain
Dr. Rubén Andújar	Hospital Clínico Virgen de Arrixaca, Murcia, Spain
Dr. Ebymar Arismendi	Hospital Clínic, Barcelona, Spain
Dr. María Basagaña	Hospital Germans Trias i Pujol, Barcelona, Spain
Dr. Gonzalo Bernaola	Hospital de Galdakao-Usansolo, Galdakao, Spain
Dr. Nagore Blanco	H. U. Lucus Augusti (HULA), Lugo, Spain
Dr. Irina Bobolea	Hospital Clínic, Barcelona, Spain
Dr. Remedios Cárdenas Contreras	H. U. Virgen del Rocío, Sevilla, Spain

Name	Affiliation
Dr. Francisco Campano	H. U. de Navarra, Pamplona, Spain
Dr. José Ángel Carretero	Hospital Royo Villanova, Zaragoza, Spain
Dr. Francisco Casas Maldonado	H. U. San Cecilio, Granada, Spain
Dr. Carolina Cisneros	H. U. de La Princesa, Madrid, Spain
Dr. Eusebi Chiner	Hospital Sant Joan d'Alacant, Alicante, Spain
Dr. Dolores Corbacho	Hospital Ribera Povisa, Vigo, Spain
Dr. Daniel del Castillo Otero	H. U. Puerto Real, Cádiz, Spain
Dr. Alfredo de Diego	Hospital La Fe, Valencia, Spain
Dr. Julio Delgado	H. U. Virgen Macarena, Sevilla, Spain
Dr. Ignacio Dávila	H. U. de Salamanca, Spain
Dr. Rocío Díaz Campos	H. U. 12 de Octubre, Madrid, Spain
Dr. Miguel Díaz Palacios	H. U. Politécnica La Fe, Valencia, Spain
Dr. David Elqutob	Hospital La Plana, Castellón, Spain
Dr. Marta Entrenas Castillo	Hospital Quirónsalud Córdoba, Spain
Dr. Luis Manuel Entrenas Costa	Hospital Quirónsalud Córdoba, Spain
Dr. Eduardo Fernández Ibáñez	H. U. de Araba (HUA), Vitoria-Gasteiz, Spain
Dr. Juan Fernández Madera	H. U. Central de Asturias (HUCA), Oviedo, Spain
Dr. Marta Frías	H. U. de Araba (HUA), Vitoria-Gasteiz, Spain
Dr. Sara Garrido	H. U. de Navarra, Pamplona, Spain
Dr. Antonio Manuel García Dumpiérrez	H. U. Doctor Negrín, Gran Canaria, Spain
Dr. Fernando García	H. U. de Basurto, Bilbao, Spain
Dr. Raquel García	Hospital San Pedro, Logroño, Spain
Dr. Ismael García Moguel	H. U. 12 de Octubre, Madrid, Spain
Dr. Rocío García García	H. U. 12 de Octubre, Madrid, Spain
Dr. Juan José Garrido	H. U. de Mérida, Spain
Dr Ana Gómez-Bastero	H. U. Virgen Macarena, Sevilla, Spain
Dr. David González de Olano	H. U. Ramón y Cajal, Madrid, Spain
Dr. Justo Grau	Hospital General de Elche, Alicante, Spain
Dr. Tamara Gutiérrez	H. U. de Navarra, Pamplona, Spain
Dr. Alicia Habernau	H. U. de Badajoz, Spain
Dr. Sonia Herrero	H. U. de Navarra, Pamplona, Spain
Dr. Sara Hermoso	H. U. de Navarra, Pamplona, Spain
Dr. Tamara Hermida	H. U. Central de Asturias (HUCA), Oviedo, Spain
Dr. Hemily Izaguirre Flores	H. U. de Canarias, Santa Cruz de Tenerife, Spain
Dr. José Luis Izquierdo Alonso	H. U. de Guadalajara, Spain
Dr. Ana Lapuente	Hospital General de Granollers, Barcelona, Spain
Dr. Inmaculada Lluch	Hospital La Ribera, Valencia, Spain
Dr. Olga Luengo	Hospital Vall d'Hebron, Barcelona, Spain
Dr. Nuria Marina	H. U. Cruces, Barakaldo, Spain
Dr. Javier Montoro	Hospital Arnau Vilanova, Lleida, Spain
Dr. Concepción Morales	H. U. Virgen de las Nieves, Granada, Spain
Dr. Mariana Muñoz	Hospital Bellvitge, Barcelona, Spain
Dr. Xavier Muñoz	Hospital Vall d'Hebron, Barcelona, Spain
Dr. Antonio Parra Arrondo	Complejo Hospitalario Universitario A Coruña (CHUAC), A Coruña, Spain
Dr. Celia María Pinedo Sierra	Hospital Clínico San Carlos, Madrid, Spain
Dr. Francisco Pérez Grimaldi	H. U. de Jerez de la Frontera, Cádiz, Spain
Dr. Gerardo Pérez Chica	H. U. de Jaén, Spain
Dr. Dolores Quiñones Estevez	H. U. Central de Asturias (HUCA), Oviedo, Spain
Dr. David Ramos	Hospital Santa Creu i Sant Pau, Barcelona, Spain
Dr. Manuel Rial Prado	Complejo Hospitalario Universitario de Ferrol (CHUF), Ferrol, Spain
Dr. David Romero	H. U. La Paz, Madrid, Spain
Dr. Ana Rosado	H. U. de Alcorcón, Spain
Dr. Berta Ruiz	H. U. Reina Sofía, Córdoba, Spain
Dr. Gladis Sabater	Hospital Dr. Josep Trueta, Gerona, Spain
Dr. Fernando Sánchez-Toril	Hospital Arnau Vilanova, Lleida, Spain
Dr. Silvia Sánchez Cuéllar	H. U. Ramón y Cajal, Madrid, Spain
Dr. Agustín Sojo	Hospital San Pedro de Alcántara, Cáceres, Spain
Dr. Lorena Soto	Hospital Santa Creu i Sant Pau, Barcelona, Spain
Dr. Nuria Toledo	Hospital Son Espases, Islas Baleares, Spain
Dr. Andrea Trisán	H. U. Puerta de Hierro, Madrid, Spain
Dr. Olga Uriel	H. U. de Araba (HUA), Vitoria-Gasteiz, Spain
Dr. Tamara Gutiérrez	H. U. de Navarra, Pamplona, Spain
Dr. José María Vega Chicote	Hospital Regional Universitario de Málaga, Spain
Dr. José Luis Velasco Garrido	H. U. Virgen de la Victoria, Málaga, Spain
Dr. Mónica Venturini	Hospital San Pedro, Logroño, Spain
Dr. Carmen Vidal Pan	Hospital de Conxo, Santiago de Compostela, Spain
Dr. Elisabet Vera	H. U. Miguel Servet, Zaragoza, Spain

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