



Oral CorticoSteroid sparing with biologics in severe asthma: A remark of the Severe Asthma Network in Italy (SANI)

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ABSTRACT

According to the data derived from several national and international registries, including SANI (Severe Asthma Network Italy), and considering the strong impact that frequent or regular use of oral corticosteroid has on quality of life (QoL) of severe asthmatics, as well as on the costs for managing corticosteroid-related diseases, oral corticosteroid sparing up to withdrawal should be considered a primary outcome in the management of severe asthma. New biologics have clearly demonstrated that this effect is possible, with concomitant reduction in the rate of exacerbations and in symptom control. Then, there is no reason for using so frequently oral corticosteroid before having explored all alternatives currently available for a large part of severe asthmatics.

Keywords: Severe asthma, Biologics, Oral corticosteroids, Real-life, Registr

MAIN TEXT

Oral CorticoSteroids (OCSs) have been used for a long time in treating asthma patients. Over the last three decades up to now, it was reported to

use them in a short-term schedule, having efficacy in asthma patients after an Emergency Department visit¹ and for treating acute severe exacerbations.² For a long time, OCSs have been considered the

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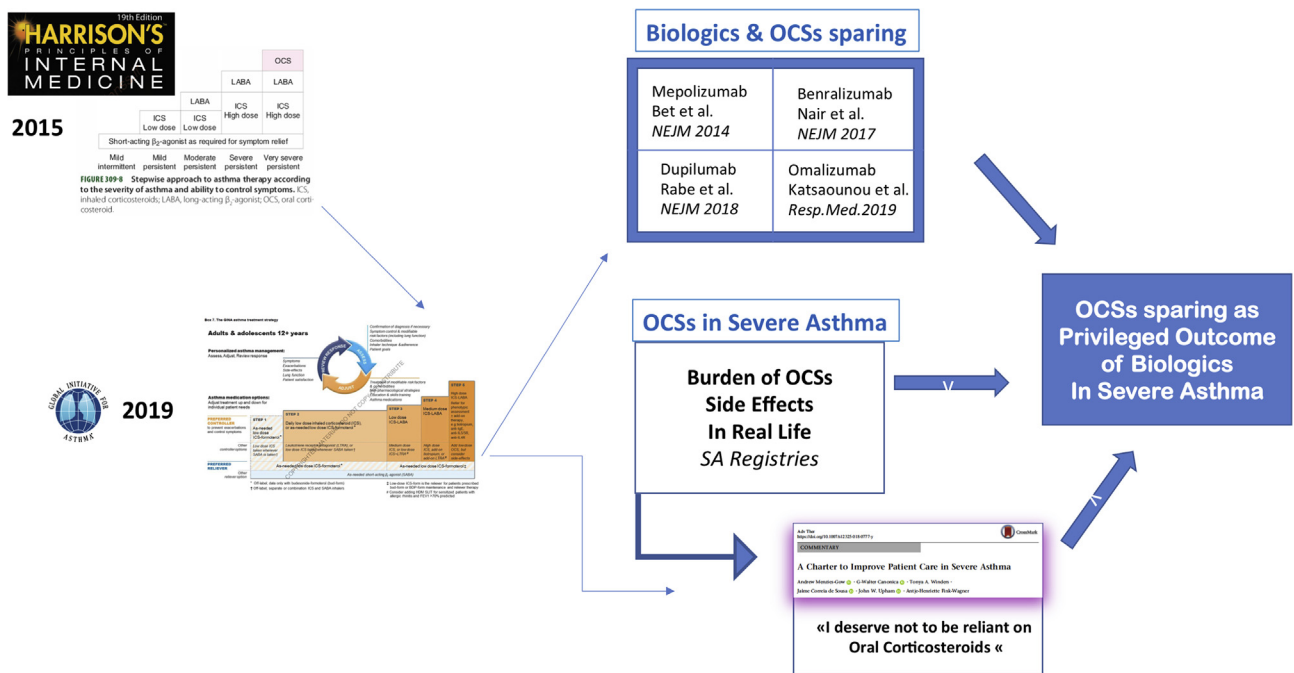
most effective treatment also in severe patients as reported in the *Harrison's Principles of Internal Medicine* (2015)³. The GINA asthma guidelines (Global INitiative for Asthma)⁴ (Fig. 1) also recommended them, ever since the first version of the document, as drugs to be used in more severe patients or in patients not well controlled with other treatments.

GINA also considered the first biologic treatment (omalizumab) for severe asthma (SA) since its approval by US Food & Drug Administration (FDA) (2003) and European Medicines Agency (EMA) (2005). This was just the beginning of a new scenario, but we had to wait for a decade or so, due to the fact that other monoclonal antibodies with different targets became recently available. The new biologic drugs significantly modified the scenario of SA treatment.⁵⁻⁷ For example, the main primary outcome of phase III clinical trials, starting from the Innovate study,⁸ became the number of exacerbations per year, whereas previously the outcomes were mainly related to the spirometric values. The definition(s) of exacerbation have

been more properly stated⁹ and adopted in the international severe asthma documents.^{2,4,10-12}

Interestingly, the availability of the new biological "bullets"⁵ prompted new discoveries and understandings about asthma mechanisms and mode of actions of the biologic drugs.¹³⁻¹⁵ Biologics demonstrated to be effective on several clinical and functional outcomes.¹⁶⁻¹⁹ These molecules have been also evaluated as OCS sparing agents,²⁰⁻²³ and all of them substantiated their impacting role in OCS tapering or withdrawal (Fig. 1). Herein, we do not want to perform any comparison of the different biologics as OCS sparing agents, due to the different selection criteria of the enrolled patients: in fact, the bias of patient's selection makes it incorrect to compare the effects of the different agents. Nonetheless, all the biologic drugs provided a remarkable and clinically significant decrease of OCS use in SA patients.

The objective of this paper is to analyze the reasons and the data substantiating the OCS sparing effect of the biologic agents approved for



OCSs, oral corticosteroids

Fig. 1 OCS Sparing or withdrawal as priority outcome in SA treatment. The figure focuses on the key points described in the paper: since the 2015 textbook, reporting OCSs as a key treatment for SA, through GINA 2019, the current evidences of OCSs sparing with biologics, the burden of OCSs in SA, and finally the SA Patient's Charter

SA treatment as a privileged/priority effect in the entire context of SA.

Overuse of OCSs: data from national and international registries

Real World (RW) evidences, as recently proposed by a manifesto,²⁴ are obtaining an increasing interest. In the last decades, most of the RW data have been collected in a retrospective manner, whose validity is methodologically questionable, whereas the prospective RW data are considered more reliable. One of the recognized systems to collect RW data is to establish disease registries. As far as SA registries are concerned, very well done and fruitful examples are available, such as the Severe Asthma Research Program (SARP) in the United States,²⁵ or some registries in European countries such as France,^{26,27} United Kingdom,²⁸ or Italy,²⁹ or registries at continental level (SHARP, Severe Heterogeneous Asthma Research collaboration, Patient-centred)³⁰ or international level (ISAR, International Severe Asthma Registry).^{31,32} A high number of valid information came from these registries,³³ thus revealing very interesting and sometimes unexpected facts.

Severe Asthma Network Italy (SANI) related findings

In our own experience,²⁹ we faced two realities: a) an impacting prevalence of bronchiectasis has been found, prompting a change in SA diagnosis; b) a relevant number of subjects with chronic rhinosinusitis with nasal polyposis (CRSwNP) was observed, accounting for more than 40% of our SA patients. In SA registries, a surprising outcome is the remarkable overuse of OCSs. According to our data, 64% of SA Italian patients are treated with OCSs, with a mean daily dosage exceeding 10 mg. The available literature papers³⁴ on OCS daily dosages and side effects suggest not to exceed 2.5 mg/day, which is a very low dosage not adopted in real daily practice. The most recent version of the GINA guidelines⁴ clearly recommend the use of OCSs as the last option in Step 5 of asthma treatment, suggesting to consider and monitor the potential side effects of these drugs. This

message is probably insufficient to prompt the clinicians to limit OCS use. In fact, the burden of OCS side effects, although well known, is not always adequately evaluated and monitored.³⁵ All together, these real-life data are strongly leading to a focus on the impact of OCS side effects in SA patients and the strategies to reduce them.³⁶ Actually, the costs of OCS side effects have been already highlighted and analyzed by some authors, such as Barry.³⁷ On the basis of these data, we decided to make a pharmacoeconomic analysis of OCS side effects on a yearly basis, relative to the SA Italian population treated with OCSs. The impressive cost observed in the analysis frankly prompts a more careful evaluation of OCS use.³⁸ In addition to these data, the "impact" of OCS treatment on the quality of life (QoL) of these patients, not yet evaluated, should also be added. An even more impacting but still neglected outcome of OCS overuse in SA is the increase in mortality.³⁹ This fearful observation has been further substantiated by a detailed study,⁴⁰ which demonstrated not only an increased mortality in SA patients during OCS treatment with respect to those not treated with OCSs, but also a dose-dependent effect on the survival of SA patients.

Nowadays, more and more attention in clinical practice has to be paid to phenotyping SA patients through biomarkers and/or clinical features such as comorbidities.^{7,33,41} In this context, a significantly higher use of OCSs has been surprisingly observed in SA patients with CRSwNP enrolled in the SANI registry. The presence of nasal polyposis accounted for a significant higher OCS use (double days/year on OCSs) with respect to SA patients without nasal polyposis.⁴² Once again, we need to highlight how a detailed evaluation/analysis of the real-life data coming from registries can provide challenging information, leading to a change in the treatment algorithms in clinical practice. [Table 1](#) summarizes the already published data derived from the SANI registry, focusing the attention on the use of OCSs in severe asthmatics, and evidence from the literature on the OCS sparing effect of the main biologics used for treating severe asthma.

Real-world data from SANI registry on the use of oral corticosteroids (OCS)

Article	Main results
Heffler E et al. - JACI in Pract 2019 ²⁹	<p>n = 437; mean age: 54.1 years; mean age of asthma onset: 32.4 years 57.2% females; 70.7% atopics; Comorbidities: - Allergic rhinitis: 44.6% - CRSwNP: 42.6% - Bronchiectasis: 16% - Atopic dermatitis: 9.6% OCS long-term users: 64.1% Mean OCS dose: 10.7 mg Prednisone equivalents</p>
Canonica GW et al. - WAO J 2019 ³⁸	<p>Pharmacoeconomic model to assess OCS-related adverse events cost in severe asthmatics: - 92.7 milion Euro estimated for the entire severe asthmatic Italian population; - 41.5 milion Euro estimated incremental expenditure compared to non-asthmatics - 26.3 milion Euro estimated incremental expenditure compared to moderate-asthmatics</p>
Canonica GW et al. - Respir Med 2020 ⁴²	<p>n = 695 mean age: 54.9 years mean age of asthma onset: 33.7 years 60.6% females; 75.9% atopics; Prevalence of CRSwNP: 40.6%; patients with CRSwNP had: - higher annual exacerbation rate (3.69 vs 2.46) - higher prevalence of bronchiectasis (20.9 vs 11.9) - higher FENO (54.4 vs 34.6) - lower serum IgE (379.4 vs 533.3) - higher frequency of long-term OCS use (60.6% vs 37.3%) - higher number of days/year in OCS treatment (161.4 vs 78.9)</p>

Literature evidence showing OCS sparing effect of the main biologics used for severe asthma

Article	Main results
Braunstahl GJ et al. Allergy Asthma Clin Immunol 2013 ⁴⁷	<p>Biological agent: Omalizumab.</p> <p>Data from "eXpeRience", a multinational, observational registry. n = 694</p> <p>28.6% of patients were taking OCS at baseline.; after 12 months: 16.1% (43.7% reduction) and after 24 months: 14.2% (50.3% reduction).</p> <p>Mean daily OCS dose at baseline: 15.5 mg Prednisolone equivalents; after 12 months: 7.7 mg (50.3% reduction) and after 24 months: 5.8 mg (62.6% reduction).</p>
Bel EH et al. N Engl J Med 2014 ²¹	<p>Biological agent: Mepolizumab</p> <p>Data from "SIRIUS" clinical trial. n = 135</p> <p>23% treated patients vs 11% of placebo-treated patients achieved a 90-100% reduction in OCS dose at 20-24 weeks of treatment.</p> <p>Reduction of 70-90% OCS dose in 17% treated vs. 8% placebo patients.</p>
Nair P et al. N Engl J Med 2017 ²²	<p>Biological agent: Benralizumab</p> <p>Data from "ZONDA" clinical trial. n = 220</p> <p>Reduction in median final oral glucocorticoid doses from baseline by 75% in treated in treated patients vs 25% in the placebo group.</p>
Rabe KF et al. N Engl J Med 2018 ²³	<p>Biological agent: Dupilumab</p> <p>Data from "LIBERTY ASTHMA VENTURE" clinical trial. n = 210</p> <p>Reduction in OCS dose of 70.1% in treated patients vs 41.9% in the placebo group.</p> <p>80% versus 50% of the patients had a dose reduction of at least 50%. 69% versus 33% had a dose reduction to less than 5 mg per day. 48% versus 25% completely discontinued OCS use.</p>

Table 1. Published data derived from the SANI registry, focusing the attention on the use of OCSs in severe asthmatics, and evidence from the literature on the OCS sparing effect of the main biologics used for treating severe asthma

CONCLUSIONS

Even if the exacerbation rate of asthma represents the most clinically relevant outcome, this parameter is usually evaluated on an annual basis both in clinical trials and in clinical practice, thus requiring a long period to establish the efficacy/effectiveness of the administered treatments. OCS sparing might impact the life of SA patients even more than the reduction of the exacerbation rate. For this reason, OCS tapering can/should be evaluated more rapidly, providing a substantial outcome of the biological treatment used.

The decrease of exacerbation rate and OCS tapering should run parallel for confirming a real effect of the treatment; in this way, these two outcomes should be always monitored together in the single patient treated with a biological drug.

A pediatric study⁴³ showed that OCS sparing was associated with an improved QoL. The improvement of both QoL and other outcomes, such as FEV1 (forced expiratory volume in the 1st second), during OCS tapering have also been evaluated, but data are not consistent for all the agents.

A recent study by Tran et al shown a promising slight trend in the reduction of OCS use in the last few years in France, Germany, Italy, and the United Kingdom,⁴⁴ but still not enough to say that OCS overuse is a thing of past.

FINAL DECLARATION

Finally, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) procedure,⁴⁵ used for evaluating clinical evidences and making recommendations, includes the item "patients' value and preference" in the decision process. This should be properly considered in the present context, too. In fact, SA patients already expressed their worrisome concern about OCS overuse in "*The Charter to improve Patient Care in Severe Asthma*",⁴⁶ where principle 5 clearly declares: "I DESERVE NOT TO BE RELIANT ON ORAL CORTICOSTEROIDS" (Fig. 1).

Abbreviations

CRSwNP: chronic rhinosinusitis with nasal polyposis; EMA: European Medicines Agency; FDA: Food & Drug

Administration; FEV1: forced expiratory volume in the 1st second; GINA: Global Initiative for Asthma; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ISAR: International Severe Asthma Registry; OCSs: Oral CorticoSteroids; RW: Real World; SA: severe asthma; SANI: Severe Asthma Network in Italy; SARP: Severe Asthma Research Program; SHARP: Severe Heterogeneous Asthma Research collaboration, Patient-centred

Ethics approval and consent to participate

Not applicable (this is a review article).

Consent for publication

All the authors confirm that they consent the publication of this article.

Availability of data and materials

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Authors' contributions

All authors conceived the study, participated in the interpretation of the findings, drafted and reviewed the manuscript and revised it critically before submission.

Declaration of competing interest

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REFERENCES

1. Chapman KR, Verbeek PR, White JG, Rebeck AS. Effect of a short course of prednisone in the prevention of early relapse after the emergency room treatment of acute asthma. *N Engl J Med*. 1991 Mar 21;324(12):788-794.
2. Reddel Helen K, Robin Taylor D, Bateman Eric D, et al. An official American thoracic society/European respiratory society statement: asthma control and exacerbations. Standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009;180:59-99.
3. Harrison S, et al. *Principles of Internal Medicine*. nineteenth ed. New York: McGraw-Hill Education; 2015.
4. Global INitiative for Asthma. *Global Strategy for Asthma Management and Prevention*; 2019. Available from: www.ginasthma.org.
5. Tarantini F, Baiardini I, Passalacqua G, Braido F, Canonica GW. Asthma treatment: 'magic bullets which seek their own targets. *Allergy*. 2007 Jun;62(6):605-610.
6. Busse WW. Biological treatments for severe asthma: a major advance in asthma care. *Allergol Int*. 2019 Apr;68(2):158-166.
7. Papadopoulos NG, Barnes P, Canonica GW, et al. The evolving algorithm of biological selection in severe asthma. *Allergy*. 2020;75(7):1555-1563.
8. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): innovate. *Allergy*. 2005 Mar;60(3):309-316.
9. Virchow JC, Backer V, de Blay F, et al. Defining moderate asthma exacerbations in clinical trials based on ATS/ERS joint statement. *Respir Med*. 2015 May;109(5):547-556.
10. Bousquet J, Mantzouranis E, Cruz AA, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol*. 2010 Nov;126(5):926-938.
11. Chung KF, Wenzel SE, Brozek JL, et al. ERS/ATS2014. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014 Feb;43(2):343-373.
12. Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European respiratory society/American thoracic society guideline. *Eur Respir J*. 2020 Jan 2;55(1):1900588.
13. Chanez P, Contin-Bordes C, Garcia G, et al. Omalizumab-induced decrease of FcεRI expression in patients with severe allergic asthma. *Respir Med*. 2010 Nov;104(11):1608-1617.
14. Diamant Z, Vijverberg S, Alving K, et al. Toward clinically applicable biomarkers for asthma: an EAACI position paper. *Allergy*. 2019 Oct;74(10):1835-1851.
15. Riccio AM, Mauri P, De Ferrari L, et al. PROXIMA sub-study centers. Plasma Galectin-3 and urine proteomics predict FEV1 improvement in omalizumab-treated patients with severe allergic asthma: results from the PROXIMA sub-study. *World Allergy Organ J*. 2020 Jan 24;13(1):100095.
16. Ortega HG, Liu MC, Pavord ID, et al. MENSA Investigators.-Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014 Sep 25;371(13):1198-1207.
17. Bleecker ER, FitzGerald JM, Chanez P, et al. SIROCCO study investigators. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β(2)-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016 Oct 29;388(10056):2115-2127.
18. FitzGerald JM, Bleecker ER, Nair P, et al. CALIMA study investigators. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016 Oct 29;388(10056):2128-2141.
19. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018 Jun 28;378(26):2486-2496.
20. Katsaounou P, Buhl R, Brusselle G, et al. Omalizumab as alternative to chronic use of oral corticosteroids in severe asthma. *Respir Med*. 2019 Apr;150:51-62.
21. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014 Sep 25;371(13):1189-1197.
22. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017 Jun 22;376(25):2448-2458.

23. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018 Jun 28;378(26):2475-2485.
24. Roche N, Anzueto A, Bosnic Anticevich S, et al. The importance of real-life research in respiratory medicine: manifesto of the respiratory effectiveness group: endorsed by the international primary care respiratory group and the world Allergy organization. Respiratory effectiveness group collaborators. *Eur Respir J*. 2019 Sep 19;54(3), 1901511.
25. Szeffler SJ, Chinchilli VM, Israel E, et al. National heart, lung and blood institute asthma clinical research network. Key observations from the NHLBI asthma clinical research network. *Thorax*. 2012 May;67(5):450-455.
26. Bourdin A, Fabry-Vendrand C, Ostinelli J, et al. The burden of severe asthma in France: a case-control study using a medical claims database. *J Allergy Clin Immunol Pract*. 2019 May - Jun;7(5):1477-1487.
27. Nordon C, Grimaldi-Bensouda L, Pribil C, et al, COBRA Study Group. Clinical and economic burden of severe asthma: a French cohort study. *Respir Med*. 2018 Nov;144:42-49.
28. Heaney LG, Djukanovic R, Woodcock A, et al. Research in progress: medical research council United Kingdom refractory asthma stratification programme (RASP-UK). *Thorax*. 2016 Feb;71(2):187-189.
29. Heffler E, Blasi F, Latorre M, et al. The severe asthma network in Italy: findings and perspectives. *J Allergy Clin Immunol Pract*. 2019;7(5):1462-1468.
30. Djukanovic R, Adcock IM, Anderson G, et al, SHARP Clinical Research Collaboration; Members of the CRC-SHARP. The severe heterogeneous asthma research collaboration, patient-centred (SHARP) ERS clinical research collaboration: a new dawn in asthma research. *Eur Respir J*. 2018 Nov 29;52(5): 1801671.
31. ISAR Study Group. International severe asthma registry: mission statement. pii: S0012-3692 *Chest*. 2019 Dec 12;(19), 34287-4.
32. Bulathsinghala L, Eleangovan N, Heaney LG, et al. Development of the international severe asthma registry (ISAR): a modified delphi study. *J Allergy Clin Immunol Pract*. 2019 Feb;7(2):578-588.e2.
33. Wang E, Wechsler ME, Tran TN, et al. Characterization of severe asthma worldwide: data from the international severe AsthmaRegistry. pii: S0012-3692 *Chest*. 2019 Nov 27;(19), 34295-3.
34. Voorham J, Xu X, Price DB, et al. Healthcare resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. *Allergy*. 2019 Feb;74(2): 273-283.
35. Heffler E, Bagnasco D, Canonica GW. Strategies to reduce corticosteroid-related adverse events in asthma. *Curr Opin Allergy Clin Immunol*. 2019 Feb;19(1):61-67.
36. Bleecker ER, Menzies-Gow AN, Price DB, et al. Systematic literature review of systemic corticosteroid use for asthma management. *Am J Respir Crit Care Med*. 2020 Feb 1;201(3): 276-293.
37. Barry LE, Sweeney J, O'Neill C, Price D, Heaney LG. The cost of systemic corticosteroid-induced morbidity in severe asthma: a health economic analysis. *Respir Res*. 2017 Jun 26;18(1):129.
38. Canonica GW, Colombo GL, Bruno GM, et al. Shadow cost of oral corticosteroids-related adverse events: a pharmaco-economic evaluation applied to real-life data from the Severe Asthma Network in Italy (SANI) registry. *World Allergy Organ J*. 2019 Jan 26;12(1):100007.
39. Bourdin A, Molinari N, Vachier I, Pahus L, Suehs C, Chanez P. Mortality: a neglected outcome in OCS-treated severe asthma. *Eur Respir J*. 2017 Nov 30;50(5):1701486.
40. LeeH RyuJ, NamE ChungSJ, Yeo Y, et al. Increased mortality in patients with corticosteroid-dependent asthma: a nationwide population-based study. *Eur Respir J*. 2019;54:1900804.
41. Heffler E, Paoletti G, Giorgis V, et al. Real-life studies of biologics used in asthma patients: key differences and similarities to trials. *Expert Rev Clin Immunol*. 2019 Sep;15(9): 951-958.
42. Canonica GW, Malvezzi L, Blasi F, et al. Chronic rhinosinusitis with nasal polyps impact in severe asthma patients: evidences from the Severe Asthma Network Italy (SANI) registry. *Respir Med*. 2020;166:105947.
43. Brodli M, McKean MC, Moss S, Spencer DA. The oral corticosteroid-sparing effect of omalizumab in children with severe asthma. *Arch Dis Child*. 2012 Jul;97(7):604-609.
44. Tran TN, King E, Sarkar R, et al. Oral corticosteroid prescription patterns for asthma in France, Germany, Italy and the UK. *Eur Respir J*. 2020;55(6):1902363.
45. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. GRADE Working Group. *BMJ*. 2008 Apr 26;336(7650):924-926.
46. Menzies-Gow A, Canonica GW, Windes TA, de Sousa JC, Upham JW, Fink-Wagner AH. A charter to improve patient care in severe asthma. *Adv Ther*. 2018;35(10):1485-1496.
47. Braunstahl GJ, Chlumský J, Peachey G, Chen CW. Reduction in oral corticosteroid use in patients receiving omalizumab for allergic asthma in the real-world setting. *Allergy Asthma Clin Immunol*. 2013 Dec 4;9(1):47.