The effects of nebulized ketamine and intravenous magnesium sulfate on corticosteroid resistant asthma exacerbation; a randomized clinical trial

Kimia Farshadfar1, Maryam Sohooli2, Ramin Shekouhi2, Ali Taherinya3, Mostafa Qorbani4 and Mehdi Rezaei-kojani3*

Abstract

Background and aims: Asthma exacerbation is defined as an acute attack of shortness of breath with more than 25% decrease in morning peak flow compared to the baseline on 2 consecutive days, which requires immediate standard therapy. The majority of asthmatic patients are considered to be steroid-sensitive; however, corticosteroid-resistant asthma is a subset of asthma with poor response to corticosteroids and is responsible for frequent hospital admissions. In this study we aimed to compare the effects of two enhancing strategies, the nebulized ketamine and IV magnesium sulfate, in treatment of severe steroid resistant asthma.

Materials and methods: This double-blind randomized clinical trial was conducted on patients who presented to a referral clinic in Alborz, Iran. Using random allocation, patients were divided into two groups. The first group was treated with nebulized ketamine and the second group was treated with intravenous magnesium sulfate. Peak expiratory flow rates were assessed before the intervention, 30 and 60 min after the intervention and compared with the aid of SPSS software.

Results: The Peak expiratory flow rates before the intervention, 30 min and 60 min after the intervention was statistically significantly different in both ketamine and magnesium sulfate groups. Peak expiratory flow rates change between 0 and 60 min were 29.4 and 15.2% in the ketamine and magnesium sulfate group respectively. Although the ketamine group showed much higher increase in mean PEFR compared to the MgSO4 groups, there was no statistically significant difference across both groups.

Conclusion: Our study concluded that combined with standard therapy, both ketamine and IV magnesium sulfate are effective agents in the improvement of PEFR in patients with acute severe asthma that failed to respond to traditional therapies. However, there were no statistically significant difference between the two groups.

Keywords: Asthma, Ketamine, Peak expiratory flow rate, Magnesium sulfate

Introduction

Asthma is a heterogenous chronic respiratory disease usually characterized as reversible airflow obstruction that presents with symptoms including shortness of breath, wheezing and cough caused by airway hyper-responsiveness to stimuli [1]. The pathophysiology of
asthma involves an antigen-mediated inflammatory cascade causing immediate airway smooth muscle con-
traction, mucosal injury and edema, and ventilation perfusion mismatch [2]. Acute asthma exacerbation is
account for most emergency department admissions and requires special attention [3]. Moreover, it is considered
as one of the major causes of morbidity and mortality among asthmatic patients which is associated with life-
threatening complications and variability in response to different therapies [4, 5]. Asthma exacerbation is defined
as an acute attack of shortness of breath with more than 25% decrease in morning peak flow compared to the
baseline on 2 consecutive days, which requires immediate standard therapy [6]. The initial asthmatic attack ther-
apy comprises of oxygen supplementation, inhaled beta-2 agonists, and oral or parenteral corticosteroids. Fortu-
nately, the prevalence of asthma exacerbation is declining as a result of well-developed preventive measures by
national asthma guidelines [1].

The majority of asthmatic patients are considered to be steroid-sensitive, which is defined as achievable disease
control with the aid of glucocorticoids and β2-adrenergic agonists. However, corticosteroid-resistant asthma is a
subset of asthma with poor response to corticosteroids and is responsible for frequent hospital admissions in
approximately 5–10% of asthmatic patients [7]. The exact pathophysiology of steroid-resistant (SR) asthma is not
well understood. However, increased production of the IL-17A in pulmonary secretions seem to be associated
with both severe and SR asthma. IL-17A, produced primarily by a distinct CD4+ TH cell subtype (TH17), is a
proinflammatory cytokine that has been correlated with airway hyperresponsiveness and poor response to gluco-
corticoids [8–10].

For steroid-resistant asthma, second-line pharmacological therapies are currently being tested. They consist of
steroid-sparing medications including magnesium sulfate, parenteral beta-2 agonist, intravenous (IV) ami-
nophylline, or ketamine. However, there is no consensus regarding their therapeutic benefits and superiority. Ket-
amine for instance, is a sedative/analgesic agent mainly used for procedural anesthesia. However, its putative
beneficial effects in bronchospasm management of SR asthma are less clear. Limited studies have shown prom-
ising results regarding its effects on bronchodilation and treatment of recurrent SR asthma due to its symp-
pathomimetic properties, particularly in children [11]. Intravenous magnesium sulfate has emerged as another
bronchodilator agent which reduce the rate of hospital admission amongst asthmatic patients. Its main mecha-
nism of action modulating pulmonary bronchodilation is secondary to transient calcium channel blockage lead-
ing to smooth muscle relaxation and bronchodilation [12, 13]. However, the role of IV Mgso4 for refractory SR
asthma remains relatively unexplored. In this study we aimed to compare the effects of two enhancing strate-
gies, the nebulized ketamine and IV magnesium sulfate (Mgso4), in treatment of severe steroid resistant asthma.

Materials and methods

Study design

This randomized double blind clinical trial was con-
donducted on patients who referred to emergency depart-
ment of Shahid Rajaee Educational and Medical Center,
Alborz, Iran from 2019 to 2020 with the chief complaint
of severe asthma exacerbation*. Also, all patients who
were aged between 18 and 65 years and patients who
showed resistance to corticosteroids as a treatment for
asthma exacerbation, were included in this study. Fur-
thermore, patients who had the history of ketamine and
sulfonamide sensitivity reaction in addition to the
patients who did not consent were excluded from the
study. The sample size was calculated to be 35, in which

\[
Z = \frac{Z_{α/2} + Z_{β}}{\sqrt{2}} \times \frac{(\bar{X} - \mu)}{S}
\]

\[n = \left[\left(\frac{Z_{α/2} + Z_{β}}{\sqrt{2}}\right) \times (2(\text{SE})^2)\right]/(\mu_1 - \mu_2)^2\]

*Severe asthma defined as failure to improve symp-
toms, blood oxygen saturation and persistent respiratory
distress (peak expiratory flow < 50%) following first-line
regimen administration. As we mentioned before, the
first-line treatment options include IV hydration, oral/IV
corticosteroids, nebulized beta-2 adrenergic (i.e., salbuta-
om) and muscarinic anticholinergics.

Randomization and intervention

Patients were chosen to be in the ketamine and magne-
sium sulfate groups based on a 1:1 allocation using block
randomization method and GraphPad Software. Both
groups received primary treatments at first and patients
in the ketamine group received nebulized ketamine (0.1–
0.3 ml/kg); for patients in the magnesium sulfate group
2 g of MgSO4 was infused intravenously over a period of
20 min. Patients of both groups were assessed for PEFR
30 min and 60 min after the intervention by a peak flow
meter (SIBEL, Spain) after a deep inhalation with the
same measurement technique.

Statistical analysis

Data were entered to version 25 of SPSS software for
final analysis. Quantitative variables were reported as
mean ± SD and qualitative variables were reported as
numerical (percentage) data. The Anderson-Darling test
was used for assessing the normality of data. Considering
the normality of data based on the Anderson-Darling

\[Z = \frac{\bar{X} - \mu}{\sigma} + \frac{1}{2} \ln \left(1 + \frac{\sigma^2}{\bar{X}^2}\right)\]

\[Z = \frac{\bar{X} - \mu}{\sigma} + \frac{1}{2} \ln \left(1 + \frac{\sigma^2}{\bar{X}^2}\right)\]

\[Z = \frac{\bar{X} - \mu}{\sigma} + \frac{1}{2} \ln \left(1 + \frac{\sigma^2}{\bar{X}^2}\right)\]

\[Z = \frac{\bar{X} - \mu}{\sigma} + \frac{1}{2} \ln \left(1 + \frac{\sigma^2}{\bar{X}^2}\right)\]

\[Z = \frac{\bar{X} - \mu}{\sigma} + \frac{1}{2} \ln \left(1 + \frac{\sigma^2}{\bar{X}^2}\right)\]
test, two-way repeated measures ANOVA was used for analyzing PEFR changes between two groups. Furthermore, independent t-test was used for measuring the differences of PEFR between two study groups.

**Results**
Seventy patients were enrolled in this study with mean age of 40.9 ± 10.6. There were 36 (51.43%) male subjects and 34 (48.60%) females, which were divided into two groups of ketamine and MgSO₄. There were not any significant differences between groups in terms of gender distribution (P value = 0.8). The mean of age in ketamine and MgSO₄ groups was 39.4 ± 9.7 and 41.9 ± 11.5 respectively. Also, there were not any significant differences in the context of age between two groups (P value = 0.4).

In the ketamine group, the rate of hospitalization was 46% (n = 13). According to Table 1, the mean of PEFR before the intervention was 360.71 ± 83.31. The mean of PEFR 30 and 60 min after ketamine administration increased to 376.0 ± 81.28, and 390.12 ± 79.44, respectively. As seen on Table 2, the mean PEFR after 60 min of drug administration had 29.42% increased. The observed finding in ketamine group in both males and females were statistically significant (P-value < 0.001) (Fig. 1).

In the MgSO₄ group, the rate of hospitalization was estimated to decreased to 54% (n = 15). Accordingly, both groups showed significant reduction in hospital admission. However, there were no statistically significant difference between two groups (ketamine and MgSO₄) in terms of rate of hospitalization (P-value = 0.5). In the MgSO₄ group, the mean value of PEFR in patients before the intervention was 332.85 ± 74.72. Moreover, the values of PEFR 30 min and 60 min after MgSO₄ administration were 345.57 ± 71.80 and 356.28 ± 71.98, respectively (Table 1). Accordingly, the mean PEFR had increased 15.28% compared to baseline in the MgSO₄ group (Fig. 1). These findings were also statistically significant (P-value < 0.001). Although the ketamine group showed much higher increase in mean PEFR compared to the MgSO₄ groups, there was no statistically significant difference across both groups (P value = 0.1) (Fig. 2).

**Discussion**
In the current study, the effects of ketamine and magnesium sulfate in the cases of steroid-resistant (SR) asthma were evaluated. This study reveals that nebulized ketamine can significantly improve PEFR in steroid resistant asthma exacerbation. Also, intravenous magnesium sulfate (MgSO₄) showed promising results in treatment of severe SR asthma. However, the PEFR improvements were not significant between the two groups. To the best of our knowledge, this is the first study which compares the effects of nebulized ketamine and magnesium sulfate in the SR severe asthma exacerbation.

As we mentioned before, asthma is a heterogenous disease with various phenotypes caused by airway hyperresponsiveness resulting in inflammation, and expiratory airflow limitation that clinically presents with wheezing,

| Table 1 | PEFR values in the study groups |
|---|---|---|
| PEFR | Value (mean ± SD) | P value* |
| Ketamine group (n = 35) | MgSO₄ group (n = 35) |
| Before the intervention | 360.71 ± 83.31 | 332.85 ± 74.72 | 0.46 |
| 30 min after the intervention | 376.0 ± 81.28 | 345.57 ± 71.80 | 0.32 |
| Mean Difference | 15.29 | 12.71 | P-value < 0.001 |
| 60 min after the intervention | 390.14 ± 79.44 | 356.28 ± 71.98 | 0.15 |
| Mean Difference | 14.15 | 10.71 | P-value < 0.001 |

*Independent t-test

| Table 2 | PEFR changes in both groups |
|---|---|---|
| PEFR | Changes (%) | P value* |
| Ketamine group (n = 35) | MgSO₄ group (n = 35) |
| Between baseline and 30 min | 23.42% | 12.71% | 0.1 |
| Between baseline and 60 min | 29.42% | 15.28% | P-value < 0.001 |

*Repeated measures ANOVA
cough, and dyspnea [1]. According to its inflammatory pattern, asthma has been classified into two groups of “T helper 2 (Th2)/ type 2 asthma” and “non-Th2/ type 2 asthma” [15]. The first group is consisted of exercised-induced, early-onset allergic, and late-onset eosinophilic asthma. Unlike early-onset allergic asthma which is considered steroid-responsive, the late-onset eosinophilic subtype is often resistant to corticosteroid. The main pathophysiology behind this steroid-resistance phenotype involves persistent sputum eosinophilia despite long-term use of corticosteroids [9]. The latter group, non-Th2/type 2 asthma, which includes obesity-related and neutrophilic asthma usually manifest with steroid-resistant airway inflammation. Airway neutrophilia and
increased levels of cytokines release (particularly IL-17) have been suggested to be the cause of steroid-resistance [16, 17].

SR asthma has been reported to contribute to persistent airway inflammation, especially if left untreated [18]. Prolonged inflammation may lead to airway remodeling and permanent biomechanical alterations in airways [19]. Previous studies proven the fact that an imbalance between metalloproteinases and metalloproteinase inhibitors plays an important role in airway remodeling. These modifications include increased airway basement membrane thickening, angiogenesis, and smooth muscle mass [20, 21].

Generally, the first-line treatment of steroid-sensitive asthma is consisted of avoidance of allergen exposure, frequent use of bronchodilators, and glucocorticoids. However, SR phenotype of asthma should be suspected after lack of response following a 2-week course of oral/inhaled glucocorticoids administration. Thus, alternative treatment options are introduced when SR asthma is suspected in order to prevent the patients from on-going disease activity, and steroid adverse effects with lack of symptom relief.

Ketamine is a rapid-acting phencyclidine derivative with analgesic, sedative, and anti-emetic properties [22]. It can cause airway bronchodilation by interfering with various receptors and can interfere with inflammatory cascades which may result in bronchospasm modification [23]. We concluded that combined with standard therapy, ketamine is effective in the improvement of PEFR in patients with acute severe asthma that failed to respond to traditional therapies. Also, our study demonstrated that ketamine administration is generally effective in relieving bronchospasm and increasing blood oxygen saturation in SR asthmatic patients. Our study concluded that the mean PEFR raised significantly (p-value < 0.001) after 30, and 60 min of ketamine administration. Additionally, administration of the nebulized form of ketamine has no influence on central respiratory response compared to the intravenous form of ketamine. Thus, using the nebulized ketamine seems to be the safer treatment option, since it lacks the respiratory depression side effect of IV ketamine.

Accordingly, Betts et al. in 1971 demonstrated the effect of ketamine on asthmatic patient for the first time [24]. In the study of Petrillo et al., loading dose of 1 mg/kg ketamine followed by 0.75 mg/hour infusion showed significant relief in asthma symptoms [25]. Furthermore, in the study conducted by Esmailian et al., ketamine administration with the dosage of 0.4–0.5 mg/kg intravenously followed by infusion of the same dosage 30 min later, can rapidly increase the mean PEFR in patients with mild to moderate asthma [26].

Magnesium sulfate on the other hand, is a cellular hemostatic agent involved in histamine, and acetylcholine release leading to bronchodilation. It can also cause bronchial smooth muscle relaxation by interfering with calcium influx [27]. The current study demonstrated that IV MgSO4 probably provides desirable results in severe SR acute asthma in adult patients treated with conventional bronchodilators. In addition, we concluded that 2 g IV MgSO4 administration through 30 to 60 min, reduces hospital stay and improves PEFR significantly. Rowe et al., observed the similar results regarding the effects of IV MgSO4 as an adjuvant therapy [28]. Previous guidelines introduced IV MgSO4 as a safe and effective alternative treatment option for adult patients with acute severe SR asthma, who have not had sufficient response to first-line therapies [29]. However, the role of nebulized MgSO4 in treatment of severe SR asthma is not yet established. There have been few studies demonstrating the effects of nebulized MgSO4 in improvement of pulmonary function and decreasing the admission rate in asthmatic patient [30, 31]. Generally, use of nebulized MgSO4 is not fully recommended for treatment of severe SR asthma exacerbation in adults [29].

The last-line pharmacologic treatment for SR asthma includes cyclosporine, dapsone, gold salts, intravenous immunoglobulin (IVIG), and hydroxychloroquine. However, the majority of these medications are associated with significant risk of side effects and there are limited studies confirming their safety and efficacy. For instance, Alexander et al. [32] concluded that cyclosporine is associated with higher rate of morning PEFR and FEV1 with a 50% decreased chance of hospital admission in 33 patients with severe asthma. Methotrexate, an immunosuppressive agent with various anti-inflammatory properties, has been also studied for asthma management. However, most studies failed to show long-term remission and asthma control. Also, other pharmacological therapies such as IVIG have shown short-time pulmonary function improvement with lack of long-term beneficial effects. However, due to its high cost and adverse effects IVIG treatment is not generally recommended for severe asthma [33].

Overall, our study suggests that combined with standard therapy both ketamine and IV MgSO4 are highly effective in treatment of severe steroid-resistant asthma exacerbation in adults. Additionally, nebulized form of ketamine showed more desirable effects on improvement of respiratory function and decreasing hospital stay compared to IV MgSO4. However, these differences were not statistically significant.

A potential limitation of this study is the lack of interfering factors such as duration of asthma, number of previous attacks, severity of previous attacks and
comorbidities in the study. It would be useful for future studies to consider these factors. Methodological limitations were small sample size, and short follow-up time. Also, another limitation of this study might be the fact that magnesium sulfate was administered as a standard dose of 2 g intravenously compared to ketamine, which was administered through a dose-dependent fashion with a nebulizer. However, it must be taken into consideration that the role of inhaled magnesium sulfate in management of severe steroid-resistant asthma is not generally recommended, which was the main reason for the use of IV MgSO4.

Conclusion
Our study concluded that combined with standard therapy, both ketamine and IV magnesium sulfate are effective agents in the improvement of PEFR in patients with acute severe asthma that failed to respond to traditional therapies. Also, our study demonstrated that both therapies are generally effective in relieving bronchospasm and increasing blood oxygen saturation in severe steroid-resistant asthmatic patients. Additionally, nebulized form of ketamine showed more desirable effects on improvement of respiratory function and decreasing hospital stay compared to IV MgSO4. However, there were no statistically significant difference between the two groups.

Abbreviations
MgSO4: Magnesium sulfate; PEFR: Peak expiratory flow rate; SD: Standard deviation; IV: Intravenous; IVG: Intravenous immunoglobulin; SR: Steroid resistanto.

Acknowledgments
Not applicable.

Authors’ contributions
Mehdi Rezaei-kojani contributed Study Design. Kimia Farshadfar contributed Data Collection and Interpretation. Ramin Shekouhi, and Maryam Schooli contributed Manuscript Preparation and Literature Search. Ali Taherinya, and Mostafa Qorbani contributed Statistical Analysis and Data Interpretation. The author(s) read and approved the final manuscript.

Funding
This study did not receive any specific funding.

Availability of data and materials
SPSS data of the participants can be requested from the authors. Please write to the corresponding author if you are interested in such data.

Declarations
Ethics approval and consent to participate
This study was conducted after obtaining permission from Medical Ethics Committee of Alborz University of Medical Sciences with the registration number of IR.ABZUMS.REC.1399.080. In addition, this study was registered in the Iranian Center for Clinical Trials (IRCT) with the registration number of IRCT20200914048715N1. Written informed consent was obtained from the patients regarding the participation of this study. A copy of the written consent is available for review by the editor-in-chief of this journal.

Consent for publication
Written informed consent was obtained from the patients regarding the publication of this study.

Competing interests
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Author details
1 Alborz University of Medical Sciences, Karaj, Iran. 2 Colorectal Research Center, Department of Surgery, Shiraz University of Medical Sciences, Shiraz, Iran. 3 Department of Emergency Medicine, Shahid Rajaei Educational and Medical Center, Alborz University of Medical Sciences, Taleghani Boulevard, Taleghani Square, P.O. Box 31497-79453, Karaj, Iran. 4 Department of Epidemiology and Vital Statistics, Alborz University of Medical Sciences, Karaj, Iran.

Received: 26 September 2021   Accepted: 14 November 2021
Published online: 30 November 2021

References
1. Maioli M, et al. The global burden of asthma: executive summary of the GINA dissemination committee report. Allergy. 2004;59(5):469–78.
2. Belvisi MG. Overview of the innervation of the lung. Curr Opin Pharmacol. 2002;2(3):211–5.
3. Corlateanu A, et al. Asthma and stroke: a narrative review. Asthma Research and Practice. 2021;7(1):1–17.
4. Kang H-R, et al. Risk factors of asthma exacerbation based on asthma severity: a nationwide population-based observational study in South Korea. BMJ Open. 2018;8(3):e020825.
5. Covantev S, et al. Spontaneous Pneumomediastinum—a rare asthma complication. Folia Med. 2019;61(3):472–7.
6. Dougherty R, Fahy. JV. Acute exacerbations of asthma: epidemiology, biology and the exacerbation prone phenotype. Clin Exp Allergy. 2009;39(2):193–202.
7. Kim RC, et al. Role for NLRP3 inflammasome—mediated, IL-1β–dependent responses in severe, steroid-resistant asthma. Am J Respir Crit Care Med. 2017;196(3):283–97.
8. Barczyk A, Pierzchala W, Sozanska E. Interleukin‑17 in sputum correlates with airway hyperresponsiveness to methacholine. Respir Med. 2003;97(6):726–33.
9. Chambers, E.S., et al., Distinct endotypes of steroid-resistant asthma characterized by IL-17Ahigh and IFN-γ-high immunophenotypes: Potential benefits of calcitriol. Journal of Allergy and Clinical Immunology. 2015;136(3): p. 628–637. e4.
10. McKinley L, et al. TH17 cells mediate steroid-resistant airway inflammation and airway hyperresponsiveness in mice. J Immunol. 2008;181(6):4089–97.
11. Tiwari A, Gugliani V, Jat KR. Ketamine versus aminophylline for acute asthma in children: a randomized, controlled trial. Annals of thoracic medicine. 2016;11(4):283.
12. Del Castillo J, Engbaek L. The nature of the neuromuscular block produced by magnesium. J Physiol. 1954;124(2):370–84.
13. Gougouliatis K, et al. Magnesium as a relaxing factor of airway smooth muscles. Journal of aerosol medicine. 2001;14(3):301–7.
14. Julious SA. Sample sizes for clinical trials with normal data. Stat Med. 2004;23(12):1921–86.
15. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med. 2012;18(5):716–25.
16. Wils-Karp, M. Neutrophil ghosts worsen asthma. Science immunology, 2018. 3(26): p. eaao4747.
17. Krishnamoorthy, N., et al., Neutrophil cytoplasts induce TH17 differentiation and skew inflammation toward neutrophilia in severe asthma. Science immunology, 2018. 3(26): p. eaa04747.
18. Wenzel SE. Asthma: defining of the persistent adult phenotypes. Lancet. 2006;368(9537):804–13.
19. Bergeron C, Boulet L-P. Structural changes in airway diseases: characteristics, mechanisms, consequences, and pharmacologic modulation. Chest. 2006;129(4):1068–87.
20. Matsumoto H, et al. Relationship of airway wall thickening to an imbalance between matrix metalloproteinase-9 and its inhibitor in asthma. Thorax. 2005;60(4):277–81.
21. Slade DJ, Kraft M. Airway remodeling from bench to bedside: current perspectives. Clin Chest Med. 2006;27(1):71–85.
22. Zanos P, et al. Ketamine and ketamine metabolite pharmacology: insights into therapeutic mechanisms. Pharmacol Rev. 2018;70(3):621–60.
23. Goyal, S. and A. Agrawal, Ketamine in status asthmaticus: a review. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine, 2013. 17(3): p. 154.
24. BETTS EK, PARKIN CE. Use of ketamine in an asthmatic child: a case report. Anesth Analg. 1971;50(3):420–1.
25. Petrillo T, et al. Emergency department use of ketamine in pediatric status asthmaticus. J Asthma. 2001;38(8):657–64.
26. Esmailian, M., M.K. Esfahani, and F. Heydari, The effect of low-dose ketamine in treating acute asthma attack; a randomized clinical trial. Emergency. 2018; 6(1).
27. Song W-J, Chang Y-S. Magnesium sulfate for acute asthma in adults: a systematic literature review. Asia Pacific Allergy. 2012;2(1):76–85.
28. Rowe BH, et al. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. Cochrane Database Syst Rev. 2000;
29. Network BTSSIG. British guideline on the management of asthma. Thorax. 2014;69(Suppl 1):1–192.
30. Gallegos-Solórzano M, Pérez-Padilla R, Hernández-Zenteno RJ. Usefulness of inhaled magnesium sulfate in the coadjuvant management of severe asthma crisis in an emergency department. Pulm Pharmacol Ther. 2010;23(5):432–7.
31. Blitz M, et al. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database Syst Rev. 2005;3.
32. Alexander AG, Kay A, Barnes N. Trial of cyclosporin in corticosteroid-dependent chronic severe asthma. Lancet. 1992;339(8789):324–8.
33. Mazer BD, Gelfand EW. An open-label study of high-dose intravenous immunoglobulin in severe childhood asthma. J Allergy Clin Immunol. 1991,87(5):976–83.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.