International Immunopharmacology 162 (2025) 115185

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Short-term therapeutic effectiveness of tezepelumab in patients with severe asthma: A real-world study

Corrado Pelaia [a,*], Marta Greco [b], Enrico Iaccino [c], Claudia Crimi [d], Marcello Biafora [b], Francesco Dragone [b], Alessandro Vatrella [e], Girolamo Pelaia [b]

[a] Department of Medical and Surgical Sciences, University "Magna Graecia" of Catanzaro, Catanzaro, Italy
[b] Department of Health Sciences, University "Magna Graecia" of Catanzaro, Catanzaro, Italy
[c] Department of Experimental and Clinical Medicine, University "Magna Graecia" of Catanzaro, Catanzaro, Italy
[d] Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
[e] Department of Medicine, Surgery and Dentistry, University of Salerno, Salerno, Italy

ARTICLE INFO

Editor: Dr. Lifei Hou

Keywords:
Real-world
TSLP
T2-high severe asthma
T2-low severe asthma
Tezepelumab

ABSTRACT

Background: Tezepelumab is a fully human monoclonal antibody which specifically binds to thymic stromal lymphopoietin (TSLP), thus effectively inhibiting its pleiotropic pathogenic actions. Tezepelumab has been licensed for add-on biologic therapy of severe asthma, regardless of biomarker levels or phenotype expression.
Objective: The aim of this real-life, retrospective, single-centre investigation has been to evaluate the therapeutic efficacy of tezepelumab in different phenotypes of severe asthma.
Methods: At baseline and after 4 weeks of add-on therapy with tezepelumab, several clinical, functional and biologic parameters were assessed in 30 patients with either T2-high or T2-low severe asthma, who had been or not previously treated with other biologics.
Results: After 4 weeks of treatment, tezepelumab induced significant improvements in symptom control (ACT score), asthma-related quality of life (AQLQ score), oral corticosteroid intake, and lung function (FEV_1, $FEF_{25–75}$, R_{tot}). Tezepelumab also significantly decreased the levels of fractional exhaled nitric oxide (FeNO) and blood basophil count. Moreover, tezepelumab significantly lowered the serum concentrations of interleukin-2 (IL-2) and vascular endothelial growth factor (VEGF). The above clinical, functional, and biologic effects of tezepelumab were observed in both T2-high and T2-low severe asthmatic patients, as well as in subjects with or without previous therapeutic experiences based on the use of other biologics.
Conclusions: The results of this real-world study suggest that tezepelumab can be used, in both T2-high and T2-low severe asthmatic patients, as a valuable add-on biologic drug characterized by a very fast onset of action.

1. Introduction

Severe asthma is characterized by uncontrolled respiratory symptoms, recurrent exacerbations, poor quality of life and impaired lung function, which occur despite an optimized treatment including high dosages of inhaled corticosteroids (ICS), bronchodilators, and often also oral corticosteroids (OCS) [1,2]. The hallmark of this complex disease is airflow limitation, associated with different phenotypes such as type 2 (T2-high) and T2-low inflammatory patterns [3]. T2-high severe asthma is frequently refractory to corticosteroids, but can be successfully treated with add-on biologic therapies comprising monoclonal antibodies targeting immunoglobulin E (IgE) (omalizumab), interleukin (IL)-5 (mepolizumab and reslizumab), IL-5 receptor (benralizumab), or IL-4/13 receptors (dupilumab), respectively [4]. For each patient, the choice of the best one among the above drugs is mainly driven by the individual levels of T2 biomarkers including serum IgE, blood eosinophils and fractional concentration of exhaled nitric oxide (FeNO) [5]. More recently, for the add-on treatment of severe asthma another biologic named tezepelumab has been licensed, which can be prescribed regardless of T2 biomarker levels [6,7].

Tezepelumab is a fully human IgG2λ monoclonal antibody which specifically binds to thymic stromal lymphopoietin (TSLP), thus impeding its interaction with the TSLP receptor complex [6,8]. TSLP directly stimulates group 2 innate lymphoid cells (ILC2) to produce IL-5

* Corresponding author.
E-mail address: pelaia.corrado@unicz.it (C. Pelaia).

https://doi.org/10.1016/j.intimp.2025.115185
Received 4 January 2025; Received in revised form 3 June 2025; Accepted 2 July 2025
Available online 7 July 2025

and IL-13, promotes dendritic cell-mediated differentiation of Th2 lymphocytes, favours the polarization of M2 macrophage lineage, inhibits eosinophil apoptosis, and activates mast cells and basophils [9–16]. Therefore, after being released from airway epithelial cells injured by several noxious environmental agents (allergens, respiratory viruses, bacteria, airborne pollutants, cigarette smoking), TSLP plays a pivotal pathogenic role in the induction, persistence and amplification of T2-high asthma [17–19]. Moreover, by eliciting a process of dendritic cell-mediated lymphocyte polarization towards the Th17 immunophenotype, TSLP is also involved in the pathophysiology of neutrophilic airway inflammation associated with T2-low asthma [20].

The therapeutic efficacy of tezepelumab in patients with severe asthma has been proven by several randomized controlled trials (RCTs). In particular, the phase 2 PATHWAY study showed that in subjects with either high or low blood eosinophil counts, tezepelumab significantly decreased the annualized rate of asthma exacerbations and also increased pre-bronchodilator forced expiratory volume in one second (FEV_1) [21,22]. In addition, tezepelumab lowered the levels of T2 biomarkers [21]. All these findings were further corroborated by the subsequent phase 3 RCT NAVIGATOR [22,23], which led to the approval of tezepelumab by regulatory agencies. Furthermore, the long-term, phase 3 extension trial DESTINATION again showed that tezepelumab was able to significantly reduce the annualized rate of asthma exacerbations regardless of the baseline levels of T2 biomarkers [24]. Hence, tezepelumab can be used in severe asthmatic patients characterized by either the T2-high or T2-low phenotypic trait [25,26]. However, because of the very recent introduction of tezepelumab in clinical practice, only a few real-world studies have been published to date [27–32].

Thus, the main aim of our present real-life, observational, single-centre investigation has been to evaluate in patients with either T2-high or T2-low severe asthma the short-term effects of tezepelumab on several clinical, functional and biologic parameters. In regard to the latter, we also decided to assess the early impact of tezepelumab on blood levels of interleukin-2 (IL-2) and vascular cell endothelial growth factor (VEGF), which are important mediators of Th2 lymphocyte differentiation and airway remodeling, respectively [33,34].

2. Patients and methods

2.1. Study design and endpoints

In the present single-centre, observational study, between January 2024 and August 2024 we enrolled 30 consecutive outpatients with either T2-high or T2-low severe asthma, who were under add-on biologic treatment with tezepelumab. All participants were referred to the Pulmonology Unit of "Magna Graecia" University Hospital located in Catanzaro, Italy. They complained of persistent asthma symptoms and needed high dosages of ICS/long-acting β2-adrenergic agonist (LABA) combinations associated with a long-acting muscarinic antagonist (LAMA), and also received a nearly continuous OCS therapy. All recruited patients met the criteria for severe uncontrolled asthma indicated by the international guidelines issued by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) [1,2]. Every enrolled patient completed an informed consent form. The inclusion criteria were the same as those required for tezepelumab prescriptions in Italy: i) age $\geq$ 12 years; ii) $\geq$2 exacerbations during the prior year treated with systemic steroids or that required hospitalization, despite maximal inhaled therapy (GINA step 4–5 treatment); or iii) in addition to inhaled treatment, use of a continuative OCS therapy to treat asthma for at least six months (age $\geq$ 18 years) or one month (age 12–17 years), depending on age [35]. Tezepelumab was injected subcutaneously at a dose of 210 mg once every four weeks. This observational study met the standards of Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki, and was authorized by the Ethics Committee of Calabria Region, Italy (Catanzaro, Italy; authorization n. 9, 11th January 2024).

2.2. Data collection and evaluation

Clinical, functional, and biological data were collected at baseline and after 4 weeks of add-on anti-TSLP treatment with tezepelumab. We evaluated the ACT score [36], the score of the asthma quality of life questionnaire (AQLQ) [37], the daily OCS dosage (prednisone, mg/day), lung function, blood eosinophil and basophil counts, FeNO, as well as the serum levels of IL-2 and VEGF.

Lung function measurements included pre-bronchodilator FEV_1, forced vital capacity (FVC), forced expiratory flow between 25 and 75 % of FVC ($FEF_{25–75}$), and total airway resistance (R_{tot}). Spirometry and body plethysmography were carried out using the MasterScreen pulmonary function testing system and MasterScreen Body (Jaeger-Viasys; CareFusion, Höchberg, Germany), according to ATS/ERS recommendations [38]. A Vivatmo Pro FeNO instrument (Bosch, Waiblingen, Germany) was used to monitor FeNO levels on the basis of ATS/ERS criteria [39,40]. Venous blood was drawn after a 12-h fast, and serum was immediately stored at −80 °C. Serum levels of IL-2 and VEGF were simultaneously determined by the "Evidence Investigator" biochip analyzer (Randox Labs, United Kingdom), through the chemiluminescent immunoassay "Cytokine & Growth Factors Array (CTK)" kit (Randox Labs, United Kingdom) [41].

Any of the following criteria were used to identify the eventual presence of an underlying T2 inflammation (T2-high) [27]: i) at least two assessments of FeNO levels, measuring 25 ppb or higher values; ii) at least two measurements of blood eosinophils, with resulting counts of 150 cells/μL or higher; iii) clinically significant allergies with associated sensitization.

After receiving tezepelumab, patients were observed for two hours, in order to detect potential adverse effects. Furthermore, after every tezepelumab administration the possible development of adverse effects was investigated during weekly telephone calls.

2.3. Statistical analysis

Mean ± standard deviation (SD) was used to represent normally distributed data, whereas median values with interquartile range (IQR) were applied to report skewed data distributions. Based on data normality, parametric or non-parametric tests were chosen. Data normality was assessed by performing the Anderson-Darling and Kolmogorov-Smirnov tests. When applicable, the Mann-Whitney *U* test and the student *t*-test were carried out to compare variables. Fisher's exact test was performed to compare categorical variables. The overall study population was stratified according to T2 biomarker levels (T2 high/T2 low) and previous use of biological therapies ("naïve"/switch).

In addition, we performed a multivariate logistic regression analysis to determine the adjusted odds ratio (OR) of baseline variables predicting the likelihood of a 100 mL or higher rise in FEV_1 [42]. A *p*-value lower than 0.05 (two-tailed) was considered to be statistically significant. Statistical analyses and figures were realized using Prism Version 10.3.0 software (GraphPad Software Inc., San Diego, California, USA).

3. Results

3.1. Patient features

Among the 30 patients included in this real-life study, 20 (66.67 %) were female. Their mean age was 58.17 ± 17.05 years, and their mean duration of asthma was 20.63 ± 13.95 years. The average pre-bronchodilator FEV_1 was 58.07 ± 14.25 % of the predicted (pred.) value, and the mean body mass index (BMI) was 27.43 ± 5.49 kg/m^2. Twenty (66.67 %) of the included patients were naïve with respect to previous biological therapies for severe asthma, and 15 (50 %) were characterized by a T2-high endotype. Among the latter, 10 subjects previously treated with other monoclonal antibodies were switched to add-on biologic therapy with tezepelumab; the washout period

Table 1
Baseline patient characteristics, stratified according to asthma endotype (T2-high/T2-low) or previous biological therapies (naïve/switch).

Characteristic	Overall $N = 30$	T2-high $N = 15$	T2-low N = 15	p	Naïve $N = 20$	Switch $N = 10$	p
Female gender, N (%)	20 (66.67)	11 (73.33)	9 (60.00)	0.6999	11 (55.00)	9 (90.00)	0.1008
Age, mean values (SD), years	58.17 (17.05)	57.53 (15.33)	58.80 (19.14)	0.5875	60.45 (17.10)	53.60 (16.87)	0.3876
Duration of asthma, mean values (SD), years	20.63 (13.95)	21.40 (14.69)	19.87 (13.65)	0.9427	16.30 (12.02)	29.30 (14.04)	0.0713
BMI, mean values (SD), kg/m^2	27.43 (5.49)	28.23 (5.98)	26.63 (5.05)	0.6529	27.76 (6.10)	26.77 (4.24)	0.7990
R_{tot}, mean values (SD), % predicted	195.4 (97.40)	193.0 (79.41)	197.9 (115.5)	0.7748	195.3 (108.4)	195.7 (76.05)	0.9983
FEV_1, mean values (SD), % predicted	58.07 (14.25)	53.13 (12.85)	63.00 (14.26)	0.1813	59.10 (12.36)	56.00 (18.01)	0.2365
$FEF_{25–75\%}$, median values (IQR), % predicted	42.00 (30.50–53.00)	32.00 (27.00–48.00)	49.00 (33.00–72.00)	0.3752	45.00 (32.00–53.00)	32.50 (26.50–54.75)	0.5860
Smoking habit, N (%)	15 (50.00)	8 (53.33)	7 (46.67)	> 0.9999	12 (60.00)	3 (30.00)	0.2451
CRSwNP, N (%)	2 (6.67)	1 (6.67)	1 (6.67)	> 0.9999	1 (5.00)	1 (10.00)	> 0.9999
Anxiety, N (%)	12 (40.00)	4 (26.67)	8 (53.33)	0.2635	6 (30.00)	6 (60.00)	0.1391
Gastro-esophageal reflux disease, N (%)	13 (43.33)	5 (33.33)	8 (53.33)	0.4621	8 (40.00)	5 (50.00)	0.7055
Bronchiectasis, N (%)	14 (46.67)	6 (40.00)	8 (53.33)	0.7152	11 (55.00)	3 (30.00)	0.2602
Atopy, N (%)	11 (36.67)	11 (36.67)	0 (0.00)	< 0.0001	4 (20.00)	7 (70.00)	0.0147

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; R_{tot}, total airway resistance; FEV_1, forced expiratory volume in one second; $FEF_{25–75\%}$, forced expiratory flow between 25 and 75 % of forced vital capacity; CRSwNP, chronic rhinosinusitis with nasal polyps.

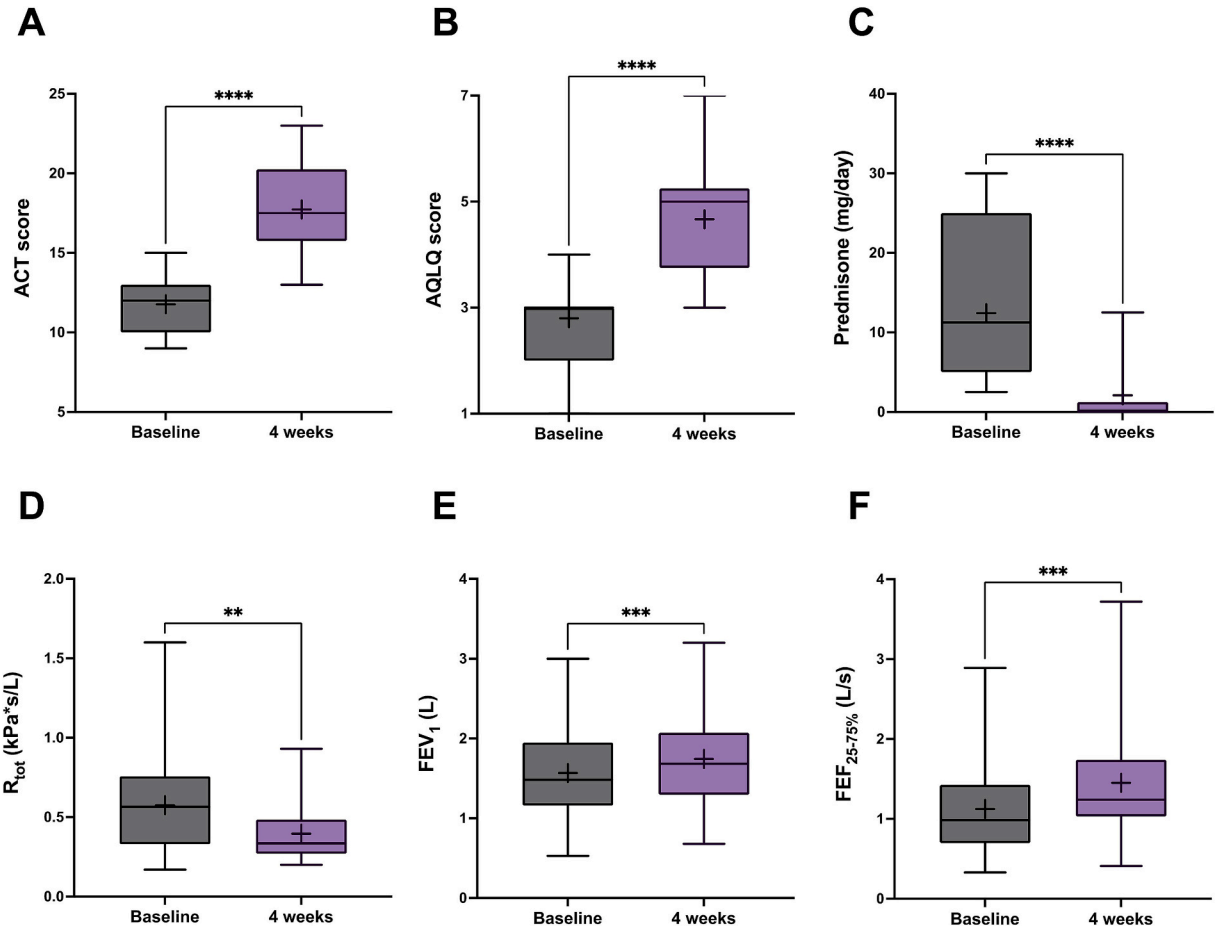

Fig. 1. Efficacy of tezepelumab in the overall population with regard to ACT score (A), AQLQ score (B), prednisone intake (C), R_{tot} (D), FEV_1 (E), and $FEF_{25–75}$ (F). The '+' symbol is plotted at the mean. The line in the middle of the box indicates the median value; the box extends from the 25th to 75th percentile. Whiskers express the highest and the lowest values. Abbreviations: $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$.

interposed between the interruption of a previous treatment with another biologic and the beginning of tezepelumab therapy lasted at least 6 months. The baseline features of our patients, also characterized on the basis of T2-high/T2-low endotype and naïve/switch status, are summarized in Table 1.

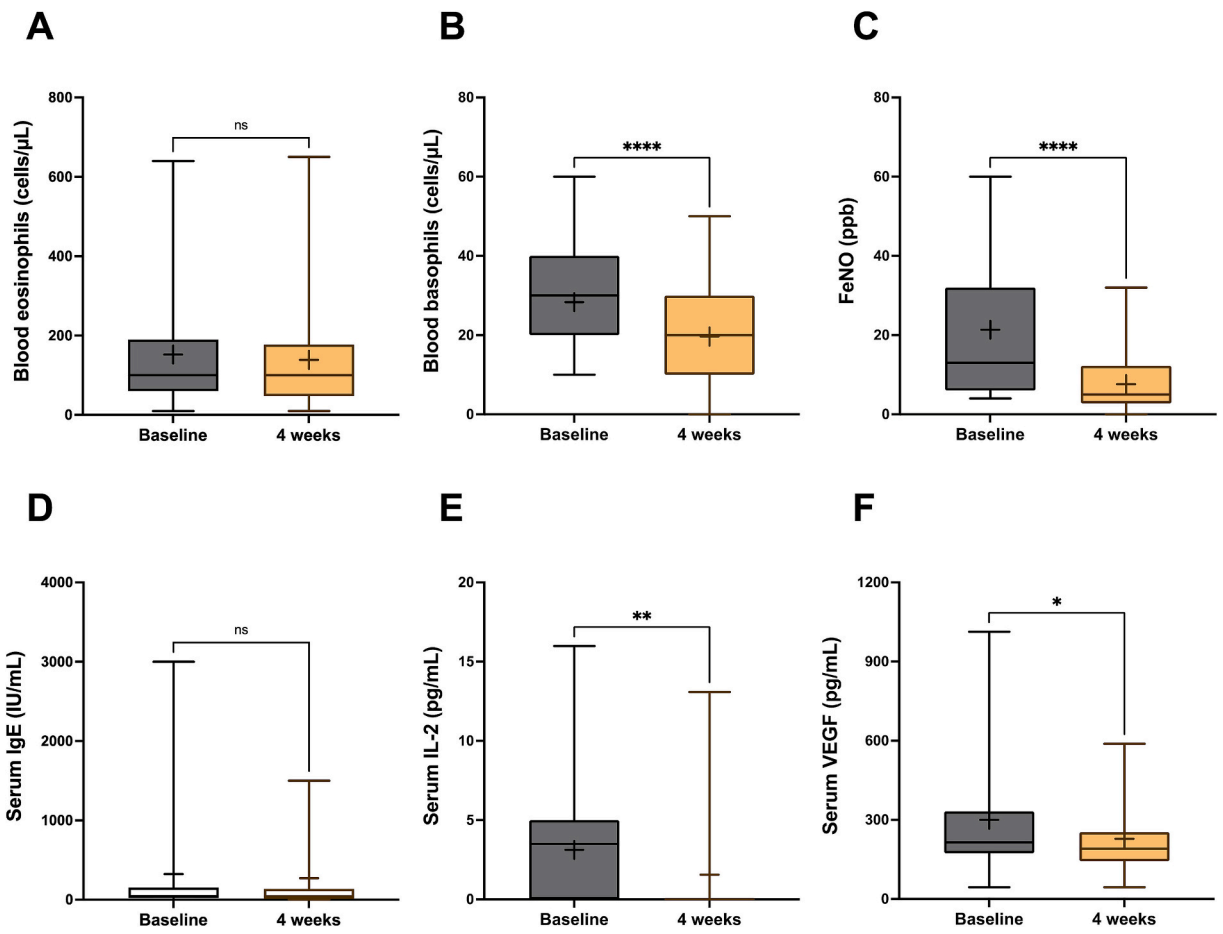

Fig. 2. Efficacy of tezepelumab in the overall population with regard to blood eosinophils (A), blood basophils (B), FeNO (C), serum IgE (D), serum IL-2 (E), and serum VEGF (F). The '+' symbol is plotted at the mean. The line in the middle of the box indicates the median value; the box extends from the 25th to 75th percentile. Whiskers express the highest and the lowest values. Abbreviations: *$p < 0.05$; **$p < 0.01$; ****$p < 0.0001$; ns, not significant.

3.2. Efficacy of tezepelumab in the overall population

After 4 weeks of add-on therapy with tezepelumab, ACT score significantly increased from a baseline value of 11.77 ± 1.83 to 17.73 ± 2.92 ($p < 0.0001$) (Fig. 1-A). During the same period, AQLQ score significantly enhanced from a baseline value of 2.80 ± 0.76 to 4.67 ± 1.21 ($p < 0.0001$) (Fig. 1-B). Such relevant improvements of both asthma control and quality of life allowed to quickly and progressively lower OCS intake; within 4 weeks, the median prednisone consumption fell from a baseline daily dosage of 11.25 (5.00–25.00) mg/day to 0.00 (0.00–1.25) mg/day ($p < 0.0001$) (Fig. 1-C).

The above clinical effects of tezepelumab were paralleled by marked improvements of lung function. Indeed, after 4 weeks of add-on biological treatment with tezepelumab we detected a significant reduction of R_{tot} from baseline 0.58 ± 0.29 kPa*s/L to 0.39 ± 0.17 kPa*s/L ($p < 0.01$) (Fig. 1-D). During the same period, pre-bronchodilator FEV_1 increased from a baseline value of 1.56 ± 0.57 L to 1.74 ± 0.60 L ($p < 0.001$) (Fig. 1-E). Moreover, $FEF_{25–75}$ incremented from the baseline measure of 0.98 L/s (0.69–1.42) to 1.24 L/s (1.03–1.74) ($p < 0.001$) (Fig. 1-F).

After starting anti-TSLP therapy, blood eosinophil levels underwent a not significant decrease from the baseline count of 152.3 ± 138.3 cells/μL to 138.7 ± 135.1 cells/μL at 4 weeks ($p = 0.167$) (Fig. 2-A), and blood basophil number significantly decreased from 28.33 ± 13.15 cells/μL (baseline) to 19.67 ± 10.33 cells/μL ($p < 0.0001$) in the same period (Fig. 2-B). Moreover, FeNO levels dropped from baseline 21.37 ± 17.15 ppb to 7.60 ± 7.77 ppb ($p < 0.0001$) (Fig. 2-C) after 4 weeks of treatment with tezepelumab, whereas we detected a very slight and not significant difference in total serum IgE, whose levels changed from baseline 43.15 IU/mL (20.75–152.5) to 40.65 IU/mL (10.00–138.5) ($p = 0.472$) at 4 weeks (Fig. 2-D). In comparison to baseline, after 4 weeks of anti-TSLP biologic therapy the serum levels of IL-2 and VEGF significantly decreased from 3.50 pg/mL (0.00–5.00) to 0.00 pg/mL (0.00–0.00) ($p < 0.01$) (Fig. 2-E), and from 214.5 pg/mL (173.7–332.1) to 191.0 pg/mL (143.3–253.5) ($p < 0.05$) (Fig. 2-F), respectively.

Multivariate logistic regression analysis showed that baseline blood basophils (OR = 1.13; $p < 0.05$) and BMI (OR = 0.76; $p < 0.05$) were independent predictors of a 100 mL or higher rise in FEV_1 after 4 weeks of add-on biological therapy with tezepelumab (Fig. 3).

3.3. Comparative evaluation in relation to asthma endotype (T2-high/T2-low)

By evaluating the effects of 4-week treatment with tezepelumab on clinical and functional parameters with respect to baseline, we did not find any relevant difference between T2-high and T2-low patients with regard to ACT score increases (Fig. 4-A), AQLQ score changes (Fig. 4-B), daily OCS intake (Fig. 4-C), R_{tot} decrements (Fig. 4-D), FEV_1 increases (Fig. 4-E), and $FEF_{25–75}$ increments (Fig. 4-F), respectively.

3.4. Comparative evaluation in regard to previous biological therapies (naïve/switch)

We did not detect any significant difference between naïve and switch patients when comparing the impact of 4-week tezepelumab therapy on clinical and functional outcomes, with regard to ACT score

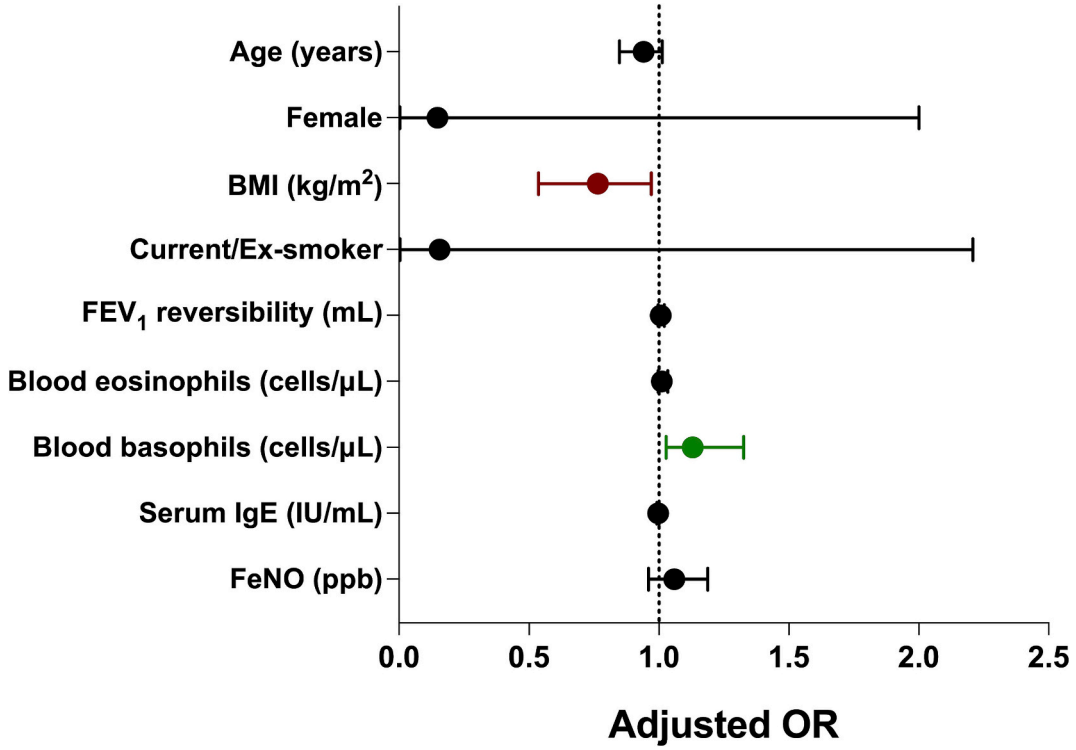

Fig. 3. Forest plot of adjusted odds ratios (OR) for variables associated with 100 mL or higher FEV_1 increase after 4 weeks of add-on biological therapy with tezepelumab. Predictors that favor FEV_1 increase are highlighted in green, whereas those with a negative impact are shown in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

increases (Fig. 5-A), AQLQ score changes (Fig. 5-B), daily OCS intake (Fig. 5-C), R_{tot} decrements (Fig. 5-D), FEV_1 increments (Fig. 5-E), and $FEF_{25–75}$ changes (Fig. 5-F), respectively.

3.5. Safety profile of tezepelumab

Add-on biologic therapy with tezepelumab was well tolerated, and no serious side effects or adverse reactions were experienced by our patients throughout this real-world observational investigation.

4. Discussion

Overall, the results of our single-centre observational study, performed within a real-life context in patients with severe asthma, strongly suggest that tezepelumab quickly induced remarkable therapeutic outcomes. Indeed, after four weeks of add-on biologic treatment with this monoclonal antibody, we showed relevant positive changes in several clinical, functional and biologic parameters, the latter also including significant reductions of serum levels of IL-2 and VEGF. Such beneficial effects were detected in patients with either T2-low or T2-high severe asthma, the latter including subjects who had been or not previously treated with other biologics.

In comparison to baseline, all participants enjoyed a fast and noticeable amelioration of their asthmatic symptoms, as documented by the significant ACT score increase reported 4 weeks after the first injection of tezepelumab. This finding is consistent with recent real-world data, which were however collected across longer time-lapses [27–32]. With respect to the asthma control questionnaire (ACQ) usually utilized in RCTs, ACT questionnaire is often preferred in real-life because of its simplicity and easiness to be filled in [43]. The quick increase in ACT score was paralleled by a significant increment of the AQLQ score, promptly induced by tezepelumab. This result is quite interesting, because it reflects the ability of tezepelumab to rapidly improve a relevant issue within the context of a patient-centered approach. Indeed, AQLQ is currently considered to be an appropriate and feasible tool for the assessment of asthma-specific quality of life including dyspnea, wheezing, chest tightness, sleep disorders, depression, and anxiety [44]. Such a quick and effective clinical improvement made it possible to rapidly and progressively taper the daily OCS intake. This real-life finding is highly relevant, because the phase 3 RCT SOURCE was not previously able to show a significant OCS-sparing action of tezepelumab, although a trend towards a decrease in OCS consumption was detected in patients with relatively high blood eosinophil counts [45]. The decrement of OCS use is a very important goal for patients with severe asthma who are often OCS-dependent and potentially exposed to the adverse events induced by OCS, including osteoporosis, diabetes, hypertension, cataract and glaucoma [46,47].

In relation to lung function, tezepelumab quickly bettered airflow limitation at level of both large and small airways, as shown by the significant changes in pre-bronchodilator FEV_1 and $FEF_{25–75}$. Such functional benefits regarded indifferently T2-high and T2-low severe asthmatics, as well as naïve and switch patients. The multivariate logistic regression analysis of our results also showed that higher baseline blood basophil counts, as well as lower baseline BMI values, were independent predictors of an at least 100 mL FEV_1 increase after 4 weeks of treatment with tezepelumab. The therapeutic effectiveness of tezepelumab in inducing relevant FEV_1 increments has been clearly shown in patients with T2-high severe eosinophilic asthma. In particular, recent meta-analyses of several RCTs have demonstrated in such subjects that tezepelumab is capable of eliciting significant FEV_1 improvements, thus resulting to be even more efficacious of the powerful anti-eosinophilic monoclonal antibodies mepolizumab and benralizumab [48,49]. The positive impact on lung function of tezepelumab is likely mediated by its ability to drastically attenuate airway eosinophilic infiltration in patients with moderate-to-severe uncontrolled asthma, as shown by the phase 2 RCT CASCADE [50]. In fact, it is well known that both the number and the activation state of eosinophils present in peripheral blood, bronchoalveolar lavage (BAL) and bronchial biopsies of

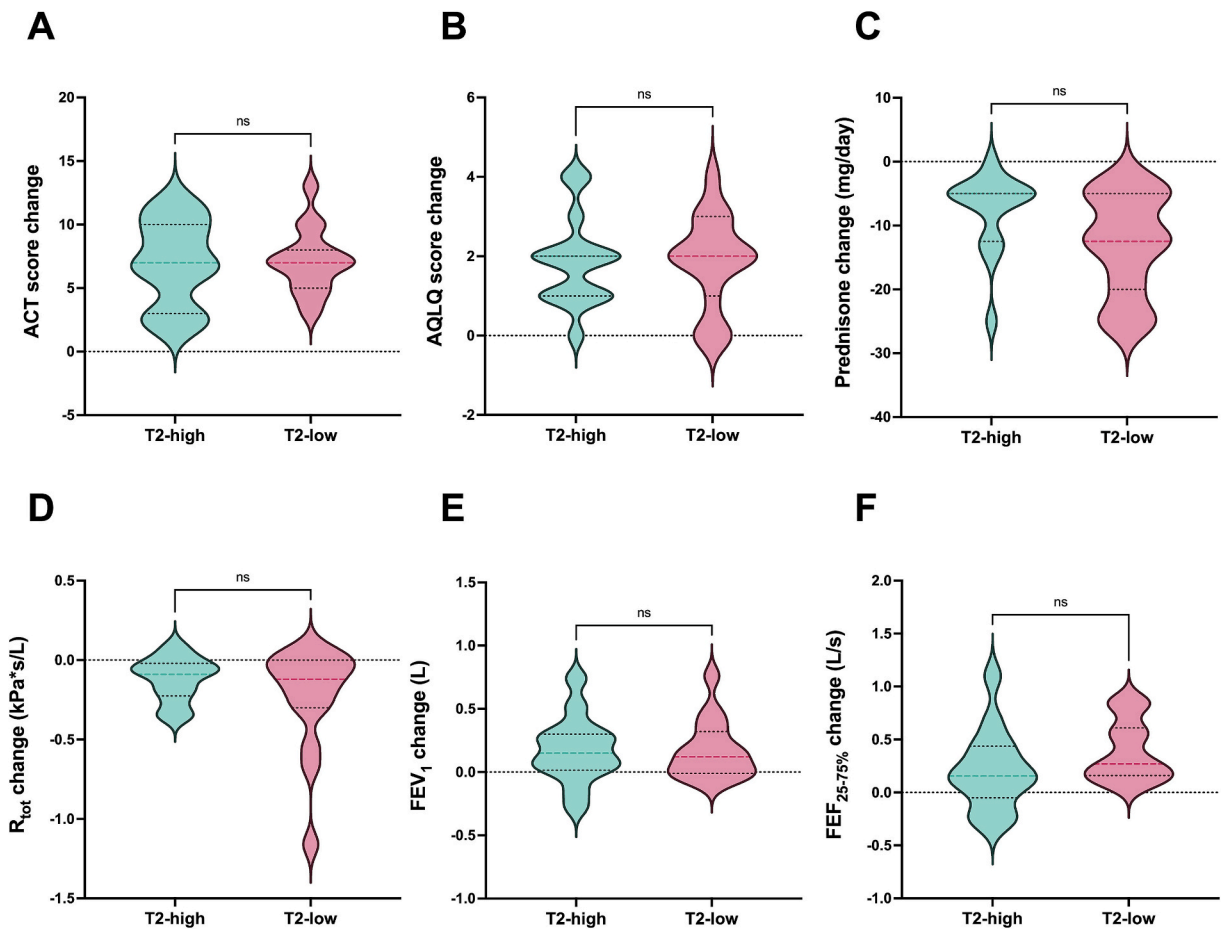

Fig. 4. Efficacy of tezepelumab in relation to T2-high or T2-low endotype, regarding ACT score change (A), AQLQ score change (B), prednisone intake change (C), R_{tot} change (D), FEV_1 change (E), and FEF_{25-75} change (F). The dashed line in the middle of the violin plot indicates the median value; the dotted lines are plotted at 25th and 75th percentile. Abbreviations: ns, not significant.

asthmatic patients are correlated with the severity of asthma and the impairment of pulmonary function [51]. Moreover, we also detected important FEV_1 increases in patients with severe T2-low asthma. In our T2-high and T2-low severe asthmatic patients, the relevant improvement of airflow limitation induced by tezepelumab was also documented by its very positive effects on airway resistance, which significantly decreased when compared to baseline. This therapeutic efficacy of tezepelumab is related to its upstream site of action, responsible for suppression of the wide biological activities exerted by TSLP on several groups of innate lymphoid cells, as well as on T lymphocytes, dendritic cells, mast cells, basophils, eosinophils and neutrophils [52]. Thus, it is very likely that the powerful anti-inflammatory action of tezepelumab translates into a relevant improvement of airway obstruction. Differently from the results of the CASCADE trial [50,53], we detected a rapid beneficial effect of tezepelumab also on small airways, as suggested by the significant FEV_{25-75} increase.

Among several factors potentially contributing to the early clinical and functional effects of tezepelumab, observed in our real-life study, a very important mechanistic issue could regard the positive impact of this biologic on mucus plugging. In asthmatic patients CT scanning has recently shown that mucus plugging is associated with ventilation defects, detected by hyperpolarized helium-3 magnetic resonance imaging [54]. Therefore, by rapidly and markedly reducing the size of occlusive mucus plugs, tezepelumab is able to significantly improve airflow limitation in moderate-to-severe asthma [55]. Such a powerful therapeutic action is likely dependent on tezepelumab-mediated upstream suppression of several proinflammatory pathways leading to mucus overproduction.

In addition to the above mentioned, fast-onset clinical and functional changes, in our real-life investigation we also observed some important biologic effects induced by tezepelumab. In particular, in our patients with T2-high severe asthma tezepelumab elicited a rapid and effective drop of FeNO levels, thus confirming the results of the PATHWAY trial [21]. Moreover, after 4 weeks of add-on treatment tezepelumab did not significantly affect serum IgE concentrations and blood eosinophil numbers, whereas this biologic therapy caused a significant decrease in blood basophil counts. The latter biologic effect of tezepelumab is due to inhibition of TSLP-induced basophilopoiesis [56]. Indeed, basophils express TSLP receptors, and TSLP promotes the formation of eosinophil/basophil colony forming units [56,57].

Furthermore, we found that tezepelumab quickly decreased the serum levels of IL-2 in both T2-high and T2-low severe asthmatic patients. This effect can contribute to elucidate the mechanism of action of tezepelumab with regard to its capability of inhibiting T cell differentiation and activation. In fact, IL-2 participates in the pathobiology of T2-high asthma by stimulating the activation of Th2 lymphocytes and the production of type 2 cytokines such as IL-4, IL-13, and IL-5, which are known to trigger IgE synthesis, bronchial hyperresponsiveness, mucus hypersecretion and airway eosinophilia [58]. IL-2 is also involved in the pathogenesis of T2-low asthma by boosting the differentiation of the Th1 cellular immunophenotype [59]. The pivotal pathogenic role of IL-2 in asthma is further corroborated by the detection in asthmatic patients of high levels of this cytokine, which correlate with disease activity and severity [58]. In addition to being implicated in the development and amplification of airway inflammation in asthma, IL-2 can also contribute to airway remodeling by up-regulating the

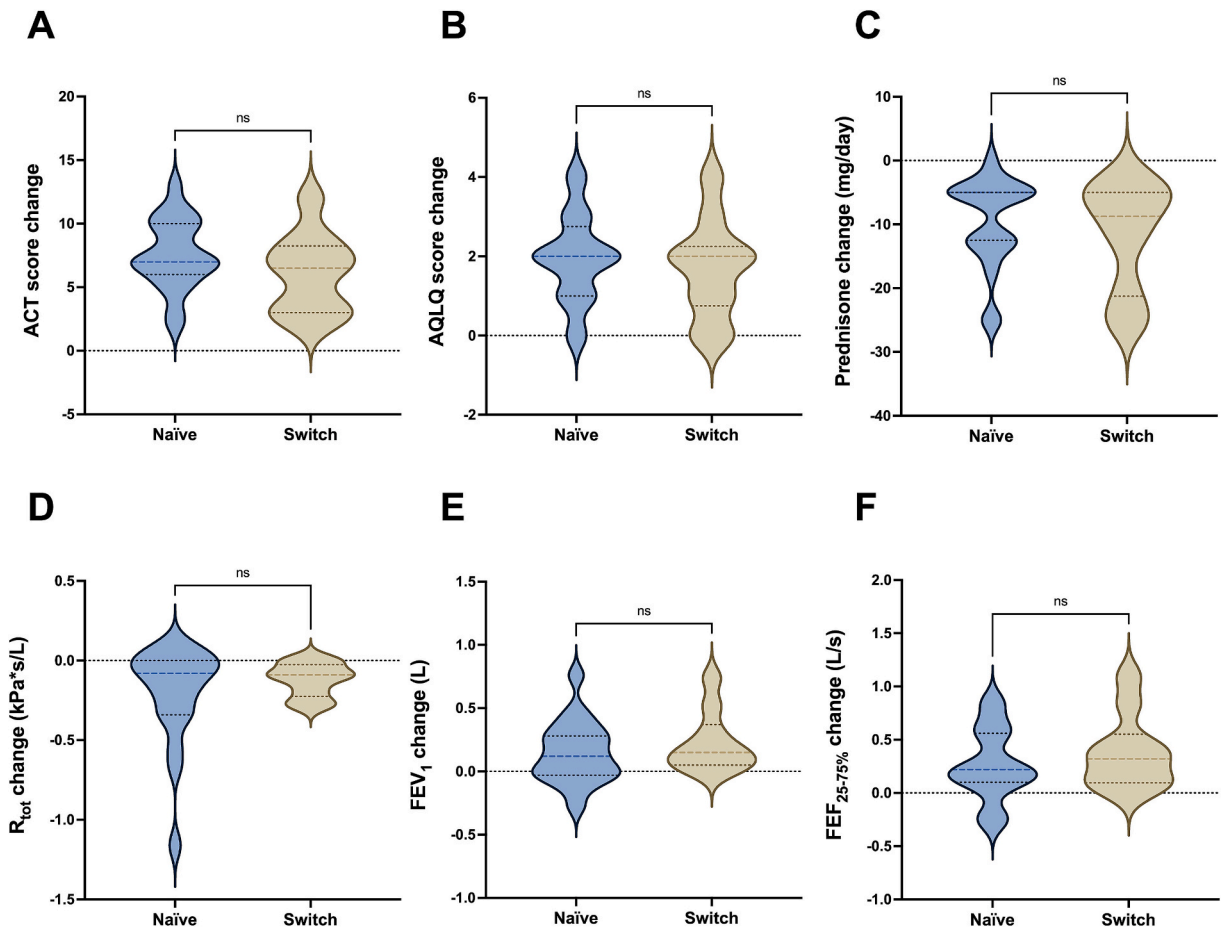

Fig. 5. Efficacy of tezepelumab in relation to naïve or switch status, regarding ACT score change (A), AQLQ score change (B), prednisone intake change (C), R_{tot} change (D), FEV_1 change (E), and $FEF_{25–75}$ change (F). The dashed line in the middle of the violin plot indicates the median value; the dotted lines are plotted at 25th and 75th percentile. Abbreviations: ns, not significant.

expression of type-1 collagen [58]. Lastly, in the present real-life retrospective study we also show that tezepelumab promptly and significantly lowered the serum levels of the powerful angiogenic factor VEGF in both T2-high and T2-low severe asthmatic patients. If such a very interesting effect of tezepelumab will be confirmed during longer periods of time, another piece of evidence could be added to the potential anti-remodeling action of this monoclonal antibody in severe asthma. Indeed, it has been recently shown that TSLP is able to induce the release of VEGF from human macrophages activated by both T2-high (IL-4, IL-13) and T2-low (lipopolysaccharide) immunological stimuli [34].

Taken together, the most relevant findings of this real-life research regard the very rapid onset of the pharmacologic effects of tezepelumab, detected after only 4 weeks of treatment in both T2-high and T2-low severe asthmatic patients, as well as in subjects with or without previous therapeutic experiences based on the use of other biologics. It is thus likely that the early beneficial response experienced by our patients towards tezepelumab is due to the blockade of TSLP-dependent upstream activation of pathogenic mechanisms leading to either eosinophilic, neutrophilic, or mixed airway inflammation. As a consequence, remarkable clinical, functional and biologic results were observed during our real-life, short-term utilization of tezepelumab.

The detection of similar positive effects of tezepelumab in both T2-high and T2-low severe asthmatic patients confirms in a real-world setting the therapeutic usefulness of this monoclonal antibody regardless of biomarker status. Moreover, the relevant inhibitory impact on the pathogenic mechanisms underlying severe asthma implies a potential role of tezepelumab in deep remission, which preludes to clinical remission when biologic treatment is initiated quite early, before the occurrence of long-term and irreversible airway damage [60]. Attainment of remission can in turn be coupled with the concept of disease-modifying target therapy, possibly leading to a halt of asthma deterioration and progressive lung function decline [61,62]. In this regard, our present real-life results suggest that tezepelumab can promptly pave the way for the achievement of key components of asthma remission such as decrease of OCS use, better symptom control and improvement of lung function. Of course, these preliminary findings must be integrated by a longer lasting assessment of tezepelumab effects on asthma exacerbations.

In conclusion, the main strength of this real-world retrospective research is expressed by the demonstration of the valuable celerity of the therapeutic effects induced by tezepelumab in a wide range of severe asthmatic phenotypes/endotypes. This important outcome was associated with a very good safety and tolerability profile of tezepelumab. On the other hand, we think that the most critical limitations of our work are quite common to other single-centre real-life studies, and include the relatively low number of recruited patients, the retrospective design, and the lack of both randomization and placebo control. A further limitation of the current real-world clinical investigation regards the lack of assessment in our patients of tezepelumab effects on common comorbidities eventually associated with severe asthma, including nasal polyps, obesity, and sleep apnea syndrome (SAS). Such therapeutic evaluations acquire relevant importance in light of the recent demonstration of tezepelumab efficacy in the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) [63]. Indeed, the accomplishment of clinical remission of severe asthma can be facilitated by the concomitant

treatment of comorbid nasal polyposis with the same biologic drug [64,65].

Authorship contribution

All authors contributed to data analysis, drafting, or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

CRediT authorship contribution statement

Corrado Pelaia: Visualization, Software, Data curation, Writing – original draft, Resources, Investigation, Conceptualization, Writing – review & editing, Supervision, Formal analysis, Validation, Methodology. **Marta Greco:** Validation, Methodology, Conceptualization, Formal analysis, Software, Investigation, Supervision. **Enrico Iaccino:** Investigation, Methodology, Supervision, Conceptualization, Software, Data curation. **Claudia Crimi:** Supervision, Data curation, Formal analysis, Writing – review & editing. **Marcello Biafora:** Validation, Investigation, Methodology, Data curation, Software. **Francesco Dragone:** Validation, Methodology, Data curation, Software, Investigation. **Alessandro Vatrella:** Writing – review & editing, Supervision, Conceptualization, Validation, Visualization, Formal analysis. **Girolamo Pelaia:** Writing – review & editing, Methodology, Conceptualization, Investigation, Writing – original draft, Visualization, Validation, Supervision, Resources.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: C. Pelaia has received lecture fees and advisory board fees from AstraZeneca, GlaxoSmithKline, and Sanofi-Regeneron. C. Crimi has received honoraria for lectures from AstraZeneca, GlaxoSmithKline, Novartis, Resmed, Sanofi-Regeneron. A. Vatrella has received honoraria for speaking, advisory committees, or research grants from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Guidotti, Lusofarmaco, Menarini, Novartis, Sanofi-Regeneron. G. Pelaia has received lecture fees and advisory board fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Guidotti, Insmed, Lusofarmaco, Menarini, Neopharmed Gentili, Novartis, Sanofi-Regeneron, Zambon. The authors have no other relevant affiliations or financial involvements with any organization or entity with a financial interest in, or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Data availability

Data will be made available on request.

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