Systemic pro-inflammatory response following bronchoscopic lung volume reduction using endobronchial valves

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Our study showed an elevation in systemic pro-inflammatory cytokine levels following EBV treatment, which was not associated with adverse clinical outcomes. It would be interesting to further explore whether this is attributed to a foreign body response. https://bit.ly/4gRrYK4

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Abstract

Rationale Bronchoscopic lung volume reduction treatment using endobronchial valves (EBV) is an effective treatment for severe COPD patients by improving lung function and quality of life. However, little is known about its effects on systemic inflammation. Therefore, the aim of our study was to investigate whether EBV treatment impacts the inflammatory cytokine profile.

Methods This study was a predefined sub-study of the SoLVE trial (NCT03474471) that investigated the combination of EBV treatment with pulmonary rehabilitation (PR). The sub-study included the collection of blood samples with assessment of 10 inflammatory markers prior to EBV treatment and 6 months after EBV or EBV+PR treatment.

Results In 66 patients, 6 months after treatment a pro-inflammatory cytokine profile was observed, with an increase in all pro-inflammatory markers and a decrease in the anti-inflammatory cytokine interleukin-10. The changes in plasma cytokine profile were not associated with changes in clinical outcomes such as lung function or exercise capacity.

Discussion In conclusion, our study demonstrated an elevation in systemic pro-inflammatory cytokine levels following successful EBV treatment, which was not associated with adverse clinical outcomes. It would be interesting to further explore whether this increase is attributed to a foreign body response or if other factors contribute to this phenomenon.

Introduction

Bronchoscopic lung volume reduction using endobronchial valves (EBV) has been shown to provide clinical benefits for patients with emphysema including improvements in lung function, exercise capacity, dyspnoea severity and quality of life [1]. Recently, there has been increased attention on the potential extrapulmonary effects of this treatment. For example, we previously demonstrated that EBV treatment also has a positive effect on cardiac function and furthermore an increase in adipose tissue and fat mass were found after treatment [2–4]. Another important extrapulmonary manifestation of COPD is the presence of enhanced systemic inflammation [5]. The implantation of EBVs in the lungs may trigger a foreign body response, inducing local inflammation. This may ultimately result in spill-over of pro-inflammatory cytokines into the circulation, contributing to systemic inflammation. To our knowledge, it has not been

investigated whether EBV treatment affects systemic inflammation. Therefore, the aim of our study was to investigate whether EBV treatment changes the systemic inflammatory cytokine profile.

Methods

Study design and population

This study was a predefined sub-study of the SoLVE trial (NCT03474471) conducted at two clinical sites: the University Medical Center Groningen and CIRO Horn (both in The Netherlands). The SoLVE trial was a randomised controlled trial involving 97 COPD patients who underwent EBV treatment and two-thirds of the patients also a pulmonary rehabilitation programme (PR). Patients were included if they had a diagnosis of COPD, severe static hyperinflation (residual volume (RV) >175% predicted) and were deemed eligible for EBV treatment. The comprehensive list of inclusion and exclusion criteria and details regarding the EBV treatment and PR programme can be found in VAN DER MOLEN *et al.* [6]. Blood samples were collected prior to EBV treatment and 6 months after EBV or EBV+PR treatment. Only patients from whom blood samples were available at both time points were included in this sub-study. Ethical approval for the SoLVE trial was obtained from both local ethics committees (METc 2018/241), and all patients provided written informed consent.

Measurements

Blood samples from the participants were collected in a fasted state. In the event of an infection or COPD exacerbation, the study visit was postponed by at least 6 weeks. Plasma-EDTA samples were obtained from blood and stored at −80°C until further usage. Next, a panel of 10 inflammatory markers was measured in the plasma samples. The following markers were measured using the microfluidic ELLA next generation multi-array technology (Bio-Techne, Minneapolis, MN, USA): interferon gamma (IFN-γ), interleukin-6 (IL-6), interleukin-8 (CXCL8), tumour necrosis factor-α (TNF-α), chemokine ligand 18 (CCL-18), surfactant protein D (SP-D), IL-10, soluble receptor for advanced glycation endproducts (sRAGE) and high-sensitivity C-reactive protein (hsCRP). Additionally, fibrinogen levels were measured using the fibrinogen functional turbidimetric assay [7].

Both at baseline and during the 6-month follow-up visit, patients performed spirometry, body plethysmography and a 6-minute walk distance test, all conducted in adherence to current guidelines [8–10]. Additionally, patients completed the St. George's Respiratory Questionnaire to assess quality of life [11].

Statistical analyses

Changes in clinical outcomes or plasma cytokine levels between baseline and 6-month follow-up were assessed using either a paired sample t-test for normally distributed data or a Wilcoxon signed rank test for non-normally distributed data. To examine the association between changes in plasma cytokine levels and clinical outcomes, Spearman's rho correlation coefficient was calculated. Additionally, Spearman's rho was utilised to explore the association between baseline plasma cytokine levels and changes in clinical outcomes. All statistical analyses were performed using IBM SPSS statistics version 28 (IBM, Armonk, NY, USA). Statistical significance was defined as a p-value below 0.05.

Results

Study population

Of the 97 patients enrolled in the SoLVE study, 74 attended the study sites for the 6-month follow-up visit [6] among whom a total of 66 had plasma cytokine levels available at baseline as well as at the 6-month follow-up and were included in the analyses (see flowchart in supplementary figure S1). Patient characteristics are shown in table 1. Patients experienced significant improvements in all clinical outcomes at 6 months of follow-up (table 1).

A more pro-inflammatory plasma cytokine profile 6 months after EBV

Changes in the plasma cytokine profile are shown in table 2 and figure 1. After EBV treatment, on average all pro-inflammatory plasma markers significantly ($p<0.05$) increased, apart from IL-10, which significantly decreased ($p=0.023$).

Associations between changes in plasma cytokine levels and changes in clinical outcomes

The associations between changes in plasma cytokine levels and changes in clinical outcomes are shown in supplementary table S1. Overall, the increase in plasma cytokine levels was not associated with an improvement or deterioration in clinical outcomes. Only the increase in SP-D was significantly associated with an increase in forced expiratory volume in 1 s (rho: 0.273, $p=0.028$) and an increase in CCL-18 was significantly associated with an increase in RV (rho: 0.321, $p=0.010$). No other significant associations were observed.

TABLE 1 Patient characteristics at baseline and changes in clinical outcomes at 6-month follow-up (n=66)

	Baseline	Change at 6-month follow-up	p-value
Sex, female	43 (65)	NA	NA
Age years	63.2±6.7	NA	NA
FEV_1 L	0.77±0.23	0.15±0.16	<0.001
RV L	4.86±1.0	−0.68±0.73	<0.001
6MWD m	326.7±87.7	41.8±58.4	<0.001
SGRQ total score	55.9±14.6	−11.6±14.9	<0.001

Data are shown as n (%) or mean±SD. The difference between baseline and 6 months of follow-up were tested with a paired sample t-test or Wilcoxon signed-rank test. NA: not applicable; FEV_1: forced expiratory volume in 1 s; RV: residual volume; 6MWD: 6-minute walk distance; SGRQ: St George's Respiratory Questionnaire.

Association between baseline plasma cytokine levels and change in clinical outcomes

No significant associations were found between the baseline plasma cytokine levels and a change in clinical outcomes, as indicated in supplementary table S2.

Discussion

To our knowledge, this is the first study that investigated changes in the circulating cytokine profile after EBV treatment in COPD patients. In order to get a comprehensive overview of the levels of systemic cytokines 10 different circulating cytokines were assessed. The cytokines were chosen to provide a broad overview of the inflammatory status as well as having shown previous associations with COPD. hsCRP and fibrinogen are widely assessed acute-phase systemic inflammation markers. IL-6, CXCL8 and TNF-α are well-known pro-inflammatory cytokines that are released in response to infections as well as tissue damage and are increased in COPD, while IFN-γ is related to viral infections. IL-10 is an anti-inflammatory cytokine that is often lower in COPD patients. CCL-18 is a TH-2-associated cytokine and sRAGE is an anti-inflammatory decoy receptor; the levels of both have previously been shown to be associated with lung function and emphysema severity. In the current study we observed a consistent pro-inflammatory effect following EBV treatment, which was accompanied by significant beneficial outcomes and not associated with any worse clinical outcomes.

Interestingly, a pro-inflammatory response was found 6 months after treatment which was consistent across all inflammatory markers. Only a few other studies have investigated changes in systemic inflammation following lung volume reduction treatments, but they reported contradictory results. One such study involving 29 patients undergoing lung volume reduction surgery (LVRS) demonstrated significant reductions in the pro-inflammatory cytokines IL-6 and CXCL8 [12]. However, it is important to note that baseline and follow-up cytokine levels were substantially higher in that population compared to ours. Additionally, it is unclear whether these measurements were performed in serum or plasma. Another study

TABLE 2 Plasma cytokine levels before and 6 month after EBV treatment (n=66)

	Baseline	6-month follow-up	p-value
IL-6 $pg{\cdot}mL^{-1}$	1.46 (0.80–2.40)	3.1 (2.05–5.41)	<0.001
CXCL8 $pg{\cdot}mL^{-1}$	5.71 (4.01–7.39)	6.51 (5.18–8.27)	0.007
IL-10 $pg{\cdot}mL^{-1}$	2.22 (1.54–3.71)	1.75 (1.41–2.74)	0.023
TNF-α $pg{\cdot}mL^{-1}$	7.01 (5.50–8.69)	8.77 (7.10–10.85)	<0.001
IFN-γ $pg{\cdot}mL^{-1}$	0.14 (0.05–0.71)	0.68 (0.43–1.06)	<0.001
CCL-18 $pg{\cdot}mL^{-1}$	40 924 (31 860–54 958)	48 427 (36 235–63 957)	<0.001
SP-D $pg{\cdot}mL^{-1}$	8510 (5043–12 395)	11 818 (6730–16 247)	<0.001
sRAGE $pg{\cdot}mL^{-1}$	461 (307–647)	689 (484–874)	<0.001
Fibrinogen $g{\cdot}L^{-1}$	2.4 (2.18–2.70)	2.6 (2.4–2.9)	0.003
hsCRP $mg{\cdot}L^{-1}$	1.65 (0.9–3.6)	3.2 (1.7–6.5)	<0.001

Data are shown as median (interquartile range). Differences between baseline and 6-month follow-up were tested with a Wilcoxon signed rank test. EBV: endobronchial valve; IL-6: interleukin-6; CXCL8: interleukin-8; IL-10: interleukin-10; TNF-α: tumour necrosis factor-α; IFN-γ: interferon-γ; CCL-18: chemokine ligand 18; SP-D: surfactant protein D; sRAGE: soluble receptor for advanced glycation end products; hsCRP: high-sensitivity C-reactive protein.

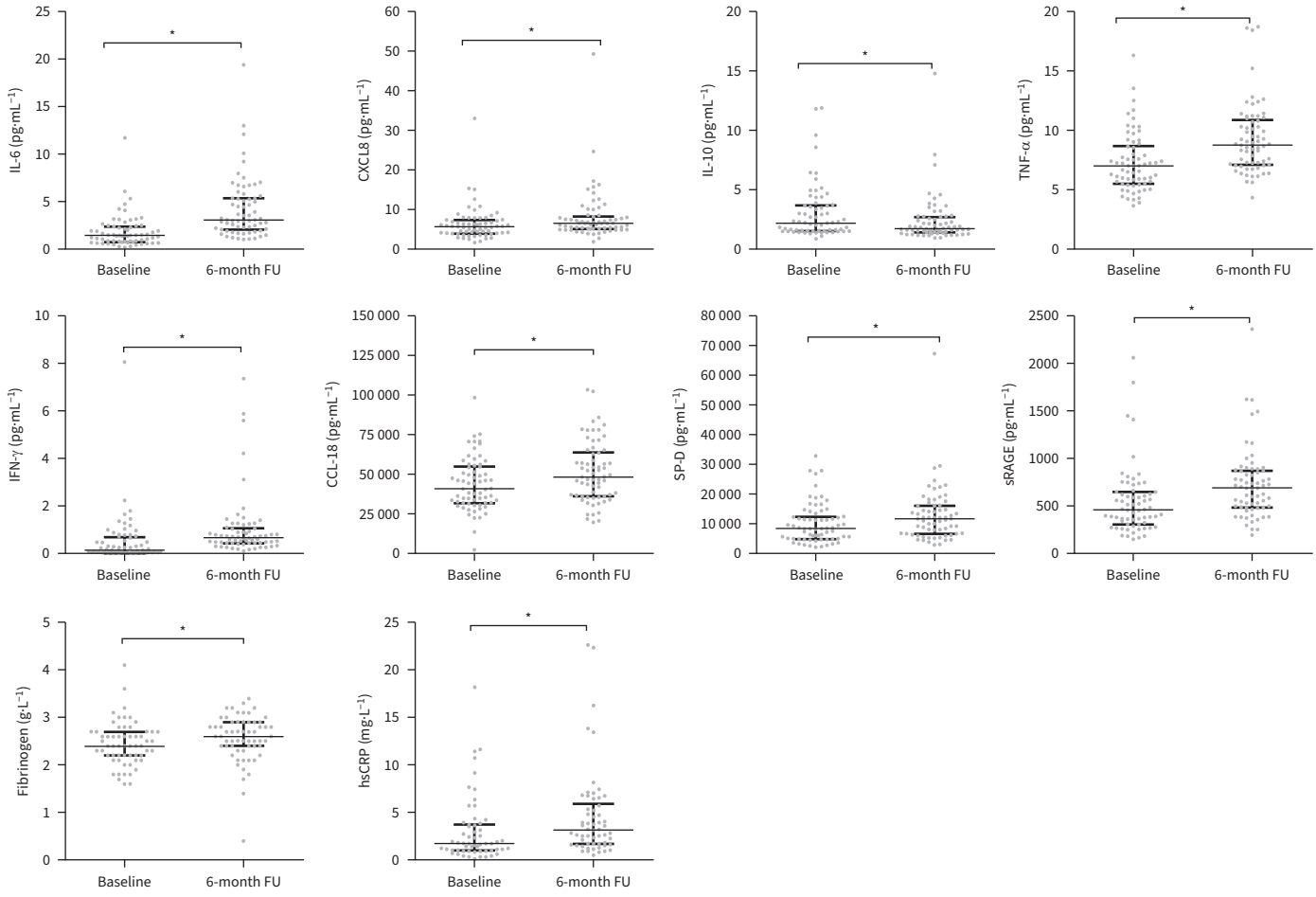

FIGURE 1 Plasma cytokine levels at baseline and 6-month follow-up (FU). Whiskers indicate the median and interquartile ranges. Differences between baseline and 6-month follow-up were tested with a Wilcoxon signed rank test. *: p<0.05. IL-6: interleukin-6; CXCL8: interleukin-8; IL-10: interleukin-10; TNF-α: tumour necrosis factor-α; IFN-γ: interferon gamma; CCL-18: chemokine ligand 18; SP-D: surfactant protein D; sRAGE: soluble receptor for advanced glycation endproducts; hsCRP: high-sensitivity C-reactive protein.

involving 14 patients showed no changes in systemic CRP levels following LVRS treatment [13]. Additionally, changes in inflammation were examined after bronchoscopic thermal vapour ablation treatment [14]. This treatment induces a localised inflammatory response with the intention of promoting healing through fibrosis and scarring, ultimately leading to lung volume reduction. No significant changes in CRP levels were found 3 and 6 months after treatment [14].

The difference between EBV treatment and both LVRS and the thermal vapour treatment is that with the EBV treatment biomedical materials (in this case silicone and nitinol) are placed in the airways, likely triggering a chronic foreign body response [15]. It is plausible that this foreign body response is responsible for the observed increase in systemic inflammatory cytokines. To our knowledge, little is known of the foreign body response in terms of systemic inflammation associated with medical implantable devices in the airways, although evidence exists from stent placement in the cardiology field [16]. It has been shown that lung implantable devices induce the formation of granulation tissue, which is also the most frequent reason for a revision bronchoscopy after EBV treatment [15, 17]. Unfortunately, blood was only collected at baseline and after 6 months and no information is available on the presence of granulation tissue. Tuleta *et al*. [18] observed higher CRP levels at time of valve removal due to frequent COPD exacerbation episodes or insufficient benefits, but unfortunately CRP levels were not measured at baseline in their study, and there was no investigation into whether the elevated CRP levels were associated with a foreign body response.

Despite the observation that the systemic levels of pro-inflammatory cytokines are increased after EBV treatment, it did not result in adverse clinical outcomes. The pro-inflammatory response was not associated

with a decrease in lung function, exercise capacity, dyspnoea severity or quality of life. Moreover, although the cytokine levels increased, the clinical relevance of the increase remains questionable. For example, the mean CRP level post-treatment was 3.2 $mg \cdot L^{-1}$ which still falls within the normal range.

Contrary to expectations, several studies have reported an increase in adipose tissue and fat mass as measured on computed tomography scan following EBV treatment [3, 4]. This finding might contribute to the observed increase in systemic pro-inflammatory cytokines post EBV treatment, as an increase in visceral fat has been associated with elevated inflammation in COPD [19]. Similarly, after LVRS an increase in fat mass as assessed by DEXA scan was found [20]. However, one study observed an increase in fat mass after LVRS but also found a decrease in pro-inflammatory cytokines IL-6 and CXCL8 [12]. Therefore, for future studies it would be interesting to investigate whether changes in fat tissue are associated with alterations in systemic inflammation.

In the current study, blood samples were only collected at two time points, thereby we were unable to identify any acute systemic effects of EBV or identify how the cytokine levels may have changed over time. Furthermore, besides blood collection, no additional data were gathered before or after a revision bronchoscopy, which could have provided more insight into the assumed foreign body response. Additionally, due to the primary aim of the SoLVE study, patients either underwent PR before or after EBV treatment or EBV alone. In the patients who were randomised to the EBV+PR group the blood samples after treatment were collected slightly later compared to the other groups. However, no differences in outcomes between groups were found (data not shown). Future studies should include a longer and more extensive follow-up after EBV treatment in order to fully unravel the effects of EBV treatment on systemic inflammation.

In summary, our study demonstrated an elevation in systemic pro-inflammatory cytokine levels following EBV treatment, which was not associated with adverse clinical outcomes. In fact, patients had in general a good outcome after treatment. It would be interesting to explore in future research whether this increase is attributed to a foreign body response or if other factors contribute to this phenomenon.

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Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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References

1 Hartman JE, Vanfleteren LEGW, van Rikxoort EM, *et al.* Endobronchial valves for severe emphysema. *Eur Respir Rev* 2019; 28: 180121.
2 Van Der Molen MC, Hartman, JE, Vanfleteren LEGW, *et al.* Reduction of lung hyperinflation improves cardiac preload, contractility, and output in emphysema: a prospective cardiac magnetic resonance study in patients who received endobronchial valves. *Am J Respir Crit Care Med* 2022; 206: 704–711.
3 Wienker J, Darwiche K, Rüsche N, *et al.* Body composition impacts outcome of bronchoscopic lung volume reduction in patients with severe emphysema: a fully automated CT-based analysis. *Sci Rep* 2024; 14: 8718.
4 Sanders KJC, Klooster K, Vanfleteren LEGW, *et al.* CT-derived muscle remodelling after bronchoscopic lung volume reduction in advanced emphysema. *Thorax* 2019; 74: 206–207.
5 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2024 report. https://goldcopd.org/2024-gold-report/
6 van der Molen, MC, Posthuma R, Vaes AW, *et al.* Impact and timing of pulmonary rehabilitation in patients undergoing bronchoscopic lung volume reduction with endobronchial valves: a multicentre randomized controlled trial in patients with severe emphysema. *Respirology* 2024; 29: 694–703.
7 Stief TW. The fibrinogen functional turbidimetric assay. *Clin Appl Thromb* 2008; 14: 84–96.
8 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
9 Wanger J, Clausen JL, Coates A, *et al.* Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; 26: 511–522.
10 Crapo RO, Casaburi R, Coates AL, *et al.* ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.
11 Jones PW, Quirk FH, Baveystock CM. The St George's respiratory questionnaire. *Respir Med* 1991; 85: Suppl. B, 25–31.
12 Mineo D, Ambrogi V, Cufari ME, *et al.* Variations of inflammatory mediators and α1-antitrypsin levels after lung volume reduction surgery for emphysema. *Am J Respir Crit Care Med* 2010; 181: 806–814
13 Clarenbach CF, Sievi NA, Brock M, *et al.* Lung volume reduction surgery and improvement of endothelial function and blood pressure in patients with chronic obstructive pulmonary disease a randomized controlled trial. *Am J Respir Crit Care Med* 2015; 192: 307–314.
14 Gompelmann D, Eberhardt R, Ernst A, *et al.* The localized inflammatory response to bronchoscopic thermal vapor ablation. *Respiration* 2013; 86: 324–331.
15 Roodenburg SA, Pouwels SD, Slebos DJ. Airway granulation response to lung-implantable medical devices: a concise overview. *Eur Respir Rev* 2021; 30: 210066.
16 Gori T. Vascular wall reactions to coronary stents: clinical implications for stent failure. *Life (Basel)* 2021; 11: 63.
17 Roodenburg SA, Klooster K, Hartman JE, *et al.* Revision bronchoscopy after endobronchial valve treatment for emphysema: indications, findings and outcomes. *Int J COPD* 2021; 16: 1127–1136.
18 Tuleta I, Pizarro C, Molitor E, *et al.* Recurrent chronic obstructive pulmonary disease exacerbations after endobronchial valve implantation are associated with the presence of *Pseudomonas aeruginosa*. *Respiration* 2016; 91: 510–516.
19 van den Borst B, Gosker HR, Koster A., *et al.* The influence of abdominal visceral fat on inflammatory pathways and mortality risk in obstructive lung disease. *Am J Clin Nutr* 2012; 96: 516–526.
20 Mineo D, Ambrogi V, Lauriola V, *et al.* Recovery of body composition improves long-term outcomes after lung volume reduction surgery for emphysema. *Eur Respir J* 2010; 36: 408–416.