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Synbiotic Bactecal® reduces airway obstruction, sputum eosinophils and IL-4 but increases sputum IL-8 in patients with uncontrolled asthma

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ABSTRACT

Rationale: Asthma disease is linked to a dysbiosis. Synbiotics are a combination of probiotics and prebiotics which are well tolerated and safe. Although they have been shown to have beneficial effects on asthma using in vivo models, the literature focusing on their effects on human asthma is still limited.
Methods: We performed a double-blind randomized placebo-controlled trial to assess the impact of a synbiotic Bactecal® on asthma control, quality of life, lung function, blood and airway inflammation in 50 patients with uncontrolled asthma 1–3-6 months after the synbiotic intake.
Results: Compared to placebo, the synbiotic significantly improved FEV_1/FVC and significantly reduced eosinophilic airway inflammation and sputum IL-4 level while increasing sputum IL-8 level.
Conclusions: The synbiotic Bactecal® had a positive impact on patients with uncontrolled asthma. It improved airway obstruction while decreasing airway type-2 inflammation.
Trial registration: The study has been registered at ClinicalTrials.gov under the identifier NCT03341403 (name of registry: Effect of a Synbiotic "Probiotical®/Bactecal® " in Asthma). Date of registration: 08/11/2017.
URL: https://clinicaltrials.gov/study/NCT03341403?term=NCT03341403&rank=1#study-overview.

1. Introduction

Asthma is a common chronic airway inflammatory disease often, but not always, featuring a type 2 immune profile [1]. From previous studies, it is established that exposure to bacterial antigens stimulates the formation of regulatory dendritic cells with inhibition of type-2 inflammation [2]. Asthma is associated with intestinal dysbiosis due to a lack of bacteria species diversity in the gut microbiome [3] thereby impacting the immune system response in the body including the lungs. There is indeed a well-known crosstalk between gut and lungs referred as the "gut-lung axis" [4,5]. In this context, modulating the gut microbiome could constitute a strategy when dealing with asthma.

Synbiotics (association of probiotics and prebiotics) can modulate the intestinal microbiota homeostasis and appeared to be very well tolerated and safe [6]. Synbiotics have been shown to have anti-inflammatory properties as well as immunomodulatory activities [7].

In vitro experiments evaluated the impact of probiotics on peripheral blood mononuclear cells (PBMCs) from allergic asthmatic patients and indicated a lower pro-inflammatory cytokine production such as interleukin (IL)-13 and IL-17 coupled with an increase of IL-10 release [8]. In

Abbreviations: ACQ, asthma control questionnaire; *B.*, *Bifidobacterium*; CRP, C reactive protein; FeNO, fractional exhaled nitric oxide value; Ig, Immunoglobulin; IFN-γ, Interferon-gamma; IL, interleukin; *L.*, *Lactobacillus*; TNF-alpha, tumor necrosis factor.

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OVA-sensitized mouse models of asthma, some probiotic species such as *Lactobacillus (L.) bulgaricus* [9], *L. casei* [10], *Bifidobacterium (B.) infantis* [11] or *Clostridium butyricum* [12] were able to downregulate the Th2 and Th17 axis and decrease Immunoglobulin (Ig)-E levels while increasing Treg and Th1 responses. The same results were found in other publications using similar asthma models and L. *salivarius* [13] or *B. breve* [14] as probiotics, in addition to a reduced allergen-induced airway hyperresponsiveness.

In asthmatic patients, probiotics improved peak expiratory flow after 4 weeks of intervention and reduced the systemic Th2 cytokines production from blood [15]. In a clinical trial assessing L. *gasseri* A5 in asthmatic children, the authors also observed an increase in lung function parameters (FEV_1, FVC, FEV_1/FVC) as well as a reduction in bronchial hyperresponsiveness [16]. Moreover, a recent study highlighted that the use of probiotics in asthmatic children reduced the exacerbation rate in this population [17].

However, clinical studies analyzing the effects of probiotics and/or synbiotics in asthmatic patients appeared to be limited and controversial results are found in the literature which might been explained by strain-dependent effects, different sub-species, treatment duration and probiotics dosage.

The goal of this study was to assess the impact of Bactecal®, a synbiotic containing five strains of probiotics (*L. rhamnosus, L. acidophilus, B. lactis, B. infantis* and *Streptococcus thermophilus*) and a prebiotic (fructo-oligosaccharides), on asthma control, quality of life, lung function, as well as systemic and airway inflammation in adult patients suffering from uncontrolled asthma despite maintenance treatment with inhaled corticosteroids.

2. Materials and method

2.1. Patients (flow chart in Fig. 1)

The randomized double blind placebo control study was performed at the CHU of Liege between November 2017 and September 2020. Inclusion criteria included age between 18 and 75 years old, a diagnosis of asthma defined by the Global Initiative for Asthma [18], an asthma control questionnaire (ACQ) score > 1.5, a treatment based on beclomethasone equivalent dose >200 µg per day and a treatment stable for at least 3 months. Patients were excluded in case of treatment change, exacerbation (deterioration in asthma requiring oral corticosteroids), or infection during the completion of the study. In total, 55 patients were enrolled by the pulmonologists, and the patients were assigned by biomedical researchers to the groups in a blinded way. Atopy was evaluated with skin prick-test or specific Immunoglobulin E (IgE) antibody radioallergosorbent tests (RAST) levels for common aeroallergens.

This study was approved by the Ethics committee of CHU Liege (2017/248) and all subjects gave written informed consent for participation. The study has been registered at ClinicalTrials.gov under the identifier NCT03341403.

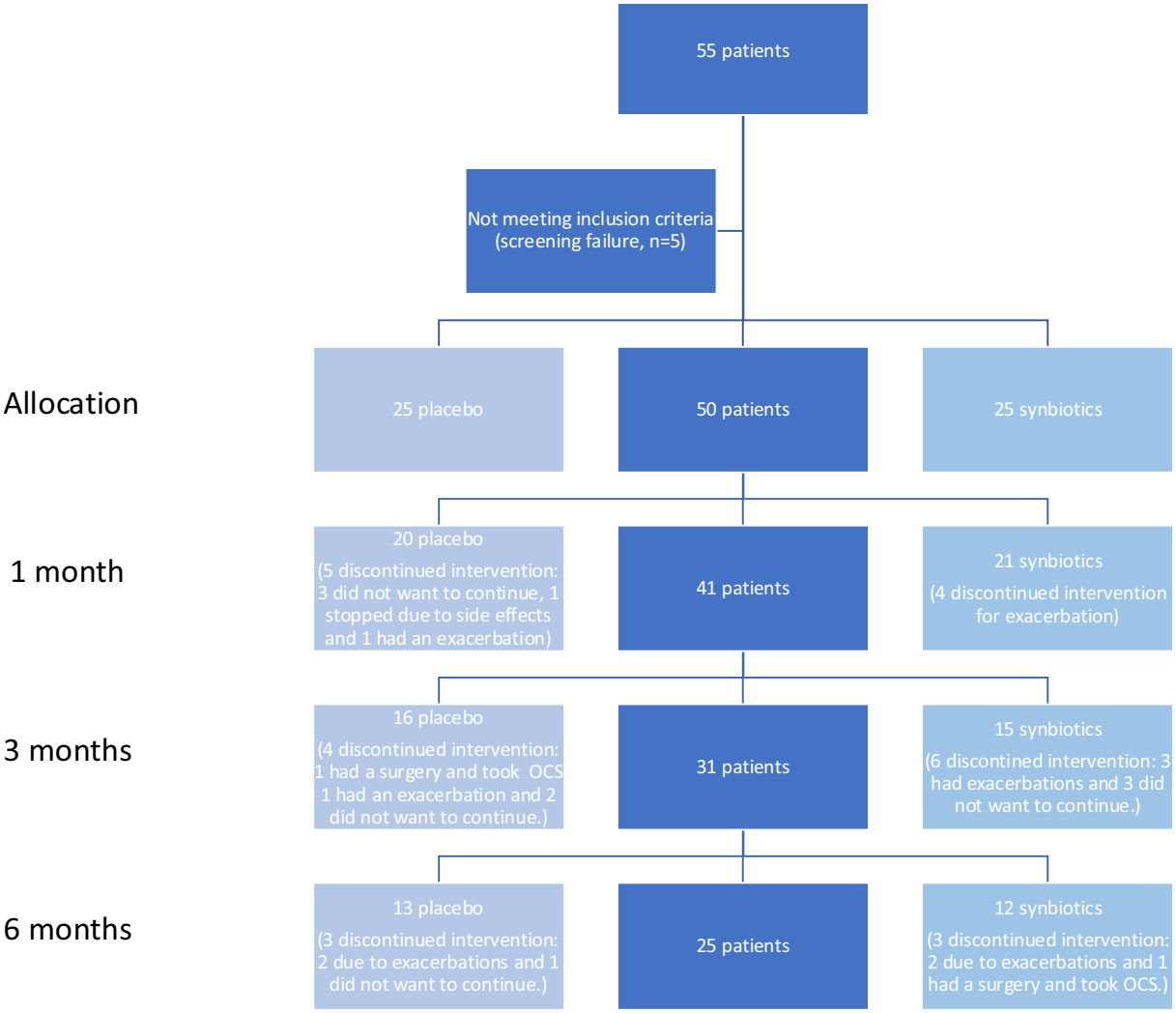

Fig. 1. Flow Chart.

2.2. Study design (Fig. 2)

Patients were randomized with a 1:1 allocation using block randomization with a random block size of four by means of a computer random number generator provided by an online open-source software [23]. To guarantee the masking, two external persons were designated for the code key. The persons who knew the randomization sequence did not participate in the clinical trial in any way, neither in the enrollment of the patients, nor in the assignment of the patients to the interventions nor in the data analysis, nor in the writing of the manuscript.

The patients allocated to treatment group received 3 pills a day of the dietary supplement Synbiotic "Bactecal®" (capsules prepared and coded by Astel Medica, Belgium/Luxembourg) or of a placebo for 3 months. The composition was based on 5 probiotic strains with 18 billion CFU/dose (*L. rhamnosus, L. acidophilus, B. lactis, B infantis* and *Streptococcus thermophilus*) associated with 20 mg of prebiotic fructo-oligosaccharides and 1.2 mg of ascorbic acid. Bactecal® was previously named Probiotical® and it was renamed at the end of 2021. The composition of Bactecal® and Probiotical® are identical. The placebo was the same capsule as the treatment capsule but without probiotics and prebiotic. The compliance was assessed by checking the number of remaining pills at each visit and was considered as adequate if the patients took 80% or more of dietary supplement.

Patients were evaluated before and 1 and 3 months after treatment initiation. A follow-up visit at 6 months after treatment initiation, i.e. 3 months after stopping the treatment was also planned. At each visit, the lung function, the fractional exhaled nitric oxide value (FeNO), the inflammatory blood and sputum inflammatory profiles and the quality of life and asthma control by questionnaires: asthma control test (ACT), asthma control questionnaire (ACQ), asthma quality of life questionnaire (AQLQ) were monitored.

The pre-specified primary outcome was a clinically significant ACQ improvement in the probiotic group which corresponds to a decrease of 0.5, considered as clinically relevant.

The secondary outcomes included an improvement of the asthma control assessed by ACT and of the asthma quality of life assessed by AQLQ. In addition, T2 biomarkers including FeNO, blood and sputum eosinophil count and total serum IgE were also assessed together with classical systemic inflammatory markers including C reactive protein (CRP) and fibrinogen.

Finally, cytokines in the blood and sputum supernatant were analyzed as exploratory outcomes.

2.3. Respiratory function

FeNO was measured using NiOX (Aerocrine, Solna, Sweden) at a flow rate of 50 mL/s in the morning. Spirometry was performed (forced expiratory volume in 1 s [FEV_1] and forced vital capacity [FVC] maneuver) before and after bronchodilation according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) standard criteria [19]. Patients had a washout period of 12 h of inhaled corticosteroids (ICS) and long-acting beta agonists (LABA) treatment before performing the tests. Bronchodilation test was performed by inhalation of 400 µg salbutamol as previously reported [20].

2.4. Blood samples

Blood samples of patients were analyzed by the routine laboratory of the CHU of Liege for leucocyte count, CRP, IgE and fibrinogen levels.

2.5. Sputum induction and processing

The sputum was induced before and 3 months after treatment initiation and processed as previously described [21,22]. Cell viability was determined by trypan blue exclusion, and the differential cell count was performed by counting 500 non-squamous cells on cytospins stained with May-Grünwald-Giemsa stain.

2.6. Blood and sputum cytokines measurement

IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-25, IL-33, and tumor necrosis factor (TNF)-alpha were measured in the serum by ELISA multiplex (Biotechne, Minneapolis, USA) according to the manufacturer's instructions. Detection limits were respectively 7.1, 1.0, 3.7, 6.5, 1.1, 1.3, 32.2, 14.8, 4.2 and 9.7 pg/ml. Interferon-gamma (IFN-γ) was measured by human IFN-gamma Quantikine HS ELISA kit (Biotechne, Minneapolis, USA) and the detection limit was 0.3 pg/ml.

In the sputum, IgE levels were measured with Human IgE ELISA kit from Abcam (Amsterdam, Netherlands). The detection limit was 0.03 ng/ml. IL-1b, IL-4, IL-5, IL-6, IL-8, IL-10, TNF-alpha and IFN-γ were measured using an ELISA multiplex high sensibility (Biotechne, Minneapolis, USA) according to the manufacturer's instructions. Detection limits were 0.1, 1.1, 0.3, 0.2, 0.2, 0.9 and 2.2 pg/ml respectively. Spiking experiments of cytokines in sputum supernatants showed that recovery was between 80% and 120% for all the analytes except IL-6 and IFN-γ which were then not considered for further analysis.

2.7. Statistical analysis

Q-Q plots and Shapiro-Wilk normality tests were applied before the main analysis to investigate the normality of the distribution of the quantitative variables. The quantitative variables with a normal distribution were summarized using mean and standard error (SE); while medians and interquartile ranges (P25 - P75) were used for quantitative variables with skewed distributions. Qualitative variables were summarized using counts and percentages.

The sample size was determined based on the primary outcome and was specified in the protocol submitted to the Ethics committee before any patient recruitment. When considering a mean ACQ value of 2.79 ± 0.88 in uncontrolled asthmatics recovered from our data base, a total of 98 patients was needed (49 per group, source: see [23]) to find a 0.5 decrease in ACQ with a significance level (alpha) of 5% and a power (1-beta) of 80%. However, due to time and financial issues, we had to stop recruiting after 3 years. Therefore, the data were reported as results from an exploratory study.

General linear mixed models (GLMM) were applied to analyze the differences in the change of primary and secondary outcomes from baseline, between treatment and placebo, with patients as a random variable while groups and visits were considered as fixed variables. No specific imputation or data correction was applied for missing values.

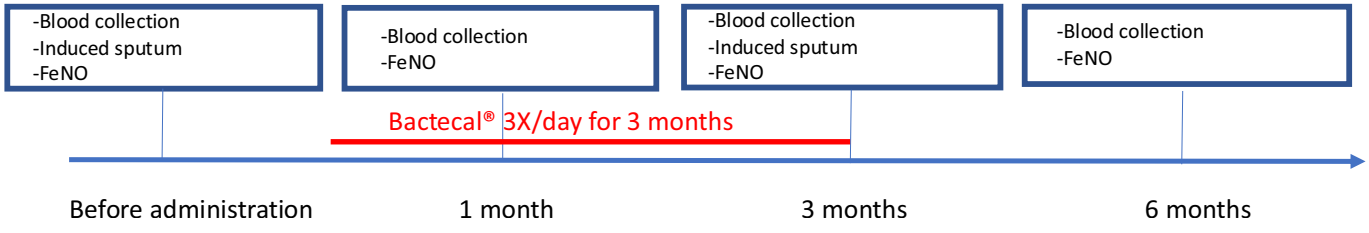

Fig. 2. Protocol and follow-up.

The GLMM included all available data from each participant and provided valid estimates under the missing at random (MAR) assumption. This approach allowed subjects with incomplete follow-up to remain in the analysis, reducing data loss and potential bias compared with complete case methods. We acknowledge that if the MAR assumption does not hold meaning the probability of missingness depends on unobserved outcomes, our estimates may be biased. However, since the proportion of missing data was low and the mixed-model framework efficiently uses all observed information, no additional methods such as multiple imputation or sensitivity analyses were applied. R Studio 4.2.1 was used for statistical analysis and graphic generation.

As for exploratory outcomes, the statistical analysis was performed at a later stage and the data were not included in the linear mixed model due to the limited number of repeated measures per subject and the high proportion of missing data. Because of the skewed distribution of the exploratory outcomes (cytokines), the changes expressed as delta from baseline between baseline and 1–3 and 6 months were compared between the two groups by using Mann-Whitney tests, while the differences within a group over time were compared with a Wilcoxon matched-pairs tests. No specific imputation or data correction was applied for missing values. Only the paired results were reported for sputum mediator levels. GraphPad Prism 9 (GraphPad Software San Diego, CA, USA) was used for these analyses.

Differences were considered statistically significant when a two-sided p-value was <0.05.

3. Theory

The goal of this study was to determine if the addition of a synbiotic to the maintenance treatment was beneficial by improving patient outcomes in uncontrolled asthmatics despite using maintenance ICS/LABA.

4. Results

The flow chart is presented in Fig. 1. Among the 55 recruited patients, 50 fitted with the inclusion criteria. Their baseline characteristics before treatment initiation are detailed in Table 1.

Patients in the two treatment groups were not comparable for all baseline parameters. Indeed, the patients treated with synbiotic appeared younger and had a lower BMI than the placebo group. In addition, the ACQ score was higher while the AQLQ score was lower in the synbiotic group compared to the placebo group. Finally, the sputum eosinophil count was lower, and the blood neutrophil proportion was higher in the synbiotic group compared to placebo group.

Globally, patients did not present any side effects, some patients experimented some light troubles within a few days after taking the drug. Seven had bowel discomfort, five patients reported episodes of diarrhea, two reported an increase of stool volume, two had constipation episodes and 1 reported vomiting. The compliance was similar in both groups.

The results were displayed for the primary and secondary outcomes first, followed by the exploratory outcomes.

4.1. Effect on asthma control and quality of life

Results from the linear mixed model are detailed in the online supplementary material.

Inter-group comparison: Regarding asthma control the ACQ and ACT scores followed the same evolution over time in both groups witnessing improved asthma control but with no significant difference between the two interventional groups. Likewise, AQLQ evolved similarly in both groups indicating improvement in quality of life without significance difference between the two groups.

Intra-group comparison: A significant difference was observed between baseline and 1 month in the synbiotic group ($p = 0.04$) while a trend was observed for a lower ACQ value in the placebo group compared to baseline ($p = 0.055$). Compared to baseline, both groups exhibited a significant lower ACQ value after 3 months ($p < 0.05$ for both, Table E1 and Fig. E1). However, the effect size at one and 3 months compared to baseline did not reach 0.5 in any of the two groups as stated in the description of the primary outcome.

When we looked at the ACT score, there was a significant effect over time in the synbiotic group: at 1 month compared to baseline, at 3 months compared to baseline and at 6 months compared to baseline (Table E2 and Fig. E2). More specifically, an increase of 3 points, the minimally important difference to assess a clinical change over time, was observed after 1 month ((11 (10–14) vs 15 (10–16), $p < 0.01$)). However, a significant improvement of the ACT score was also noticed in the placebo group when comparing baseline and 3 months ($p < 0.05$).

For AQLQ, the difference in the value at 1 and 6 months compared to baseline was significant in the synbiotic group (Table E3 and Fig. E3). An increase of 0.5 point, which is clinically relevant, was observed after 1 month as well ((3.53 (3.13–3.80) vs 4.07 (3.2–4.7), p < 0.05)) in the

Table 1
Baseline demographic, clinical and inflammatory characteristics: $N = 50$.

	Placebo	Synbiotic	P value
N. (%)	25 (50%)	25 (50%)	>0.999
Women, N (%)	18 (72%)	18 (72%)	>0.999
Age (year)	56 ± 2	47 ± 2	0.022
Asthma Onset (year)	27 (4–57)	28 (11–43)	0.617
BMI (kg/m^2)	29 ± 1	26 ± 1	0.013
Atopy (Yes) (%)	15 (60%)	18 (72%)	0.463
Smoking status (%)			
NS/CS/ES	11 (44%)/3 (12%)/ 11 (44%)	12 (48%)/7 (28%)/ 6 (24%)	0.211
Pack/Year	7 (0–40)	0 (0−20)	0.345
Pre-BD FEV_1 (% pred)	74 ± 3	73 ± 3	0.87
Post-BD FEV_1 (% pred)	82 ± 3	76 ± 3	0.303
Post-BD FVC (% pred)	88 ± 3	82 ± 3	0.271
Post-BD FEV_1/FVC (%)	76 ± 1	75 ± 2	0.745
PC20M (mg/mL)	1 (0−12)	4 (1−22)	0.517
ACT score	15 (10–16)	11 (10–14)	0.108
ACQ score	2.1 (1.9–2.9)	2.9 (2.3–3.1)	0.028
AQLQ score	4.1 ± 0.1	3.5 ± 0.1	0.012
Exacerbations in previous year			
($N = 24$ vs 24)	14 (56%) - 6 (24%)	10 (40%)- 7 (28%)	0.380
0–1	2 (8%)- 2 (8%)	6 (24%)- 1 (4%)	
2–3			
FeNO (ppb)	25 (15–37)	17 (7–30)	0.218
Sputum eosinophils (%)	3.6 (0.7–10.8)	1.2 (0.1–3.3)	0.074
Sputum neutrophils (%)	62 ± 3	63 ± 4	0.861
Total serum IgE (kU/L)	199 (63–592)	233 (101–456)	0.999
Blood leukocytes (x 10^3/ µL)	7 (7–8)	8 (7–9)	0.069
Fibrinogen (g/l)	3.7 ± 0.1	3.5 ± 0.1	0.359
CRP (mg/l)	3.7 (1.5–8.1)	2.1 (1.3–5.1)	0.205
Blood eosinophils (/µL)	116 (67–299)	119 (98–287)	0.386
Blood neutrophils (/µL)	4011 (3245–5086)	4800 (4210–6300)	0.068
ICS dose (beclomethasone equivalent)	2000 (1600–2000)	1600 (1000−2000)	0.077
LABA, N (%)	24 (96%)	25 (100%)	0.312
LTRA, N (%)	10 (40%)	10 (40%)	>0.999
SABA, N (%)	14 (56%)	15 (60%)	0.775
SAMA, N (%)	10 (40%)	10 (40%)	0.999
LAMA, N (%)	2 (8%)	3 (12%)	0.637
Biotherapies:			
Anti-IgE	5 (20%)	7 (28%)	0.742
Anti-IL5	5 (20%)	0 (0%)	0.050

Results are presented as median (interquartile range) or mean ± standard error; BMI: body mass index; NS: non-Smoker; CS: current smoker; ES: ex- smoker; FEV_1: forced expiration volume in 1 s; BD: bronchodilation; coefficient; FVC: forced vital capacity; ACT: asthma control test; ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; FeNO: fractional exhaled nitric oxide; CRP: C reactive protein; ICS: inhaled corticosteroids; LABA: long acting beta 2 agonist; LTRA: leukotriene receptor antagonist; SABA: short acting beta agonist; SAMA: short acting muscarinic antagonist; LAMA: long acting muscarinic antagonist; IgE: immunoglobulin E; IL-5: interleukin-5.

synbiotic group only.

4.2. Effect on lung function

Inter-group comparison: No modification was observed for FEV_1 pre bronchodilation expressed as predicted % (Table E4 and Fig. E4). We noted a significant impact of the synbiotic compared to placebo on FEV_1/FVC % pre bronchodilation and a trend for an impact on FEV_1 post bronchodilation expressed as predicted % (see global p value for the linear mixed model, Fig. 3A and Table E5 and Fig. E5). Indeed, groups showed an opposite change in these 2 parameters, from baseline to 3 months. FEV_1/FVC % and post bronchodilation FEV1% predicted increased in the synbiotic group but decreased in the placebo group.

Intra-group comparison: In the placebo group, there was a significant decrease of FEV_1/FVC pre bronchodilation between baseline and 3 months. Also, within the synbiotic group, there was a significant increase of FEV_1 post bronchodilation between 1 month and 3 months and a significant decrease between one month and 6 months (Table E6 and Fig. E6). In addition, we observed a significant increase of FEV_1/FVC post bronchodilation between one month and 3 months for the synbiotic group (Table E7 and Fig. E7).

4.3. Effect on systemic inflammation and blood cell count

Inter-group comparison: There was no significant difference between synbiotic group and placebo regarding any of the blood cells and immune-inflammatory proteins.

Intra-group comparison: When removing the patients treated with anti-IgE (n = 12) to avoid measuring IgE molecules that are part of omalizumab-IgE complexes, a significant decrease of IgE levels was found between baseline and 6 months in the synbiotic group (Table E8 and Fig. E8). Similarly, there was a significant decrease of fibrinogen level between baseline and 1 month, 3 months and 6 months in the synbiotic group (Table E9 and Fig. E9). No such differences were found in the placebo group. No difference was observed on CRP blood levels nor on the blood eosinophil and neutrophil counts within each of the two groups (Table E10–12 and Fig. E10–12).

4.4. Effect on airway inflammation

Inter-group comparison: There was no statistically significant difference for the change in FeNO between the two groups.

Intra-group comparison: FeNO values presented the same pattern in both groups and decreased over time although the difference between 3 and 6 months appeared to be statistically significant only in the synbiotic group (p = 0.022, Table E13 and Fig. E13). The values at baseline in the placebo group was 25.0 (14.7–36.7) vs 23.0 (15.5–32.5) at 1 month, 19.0 (13.0–39.0) at 3 months and 16.5 (12.5–21.0) at 6 months and in the synbiotic group, the FeNO values was 17.0 (7.0–30.0) at baseline, 19.5 (10.0–36.0) at 1 month, 19.0 (14.0–27.0) at 3 months and 13.0 (7.5–16.25) at 6 months.

Inter-group comparison: The sputum neutrophil percentage was not impacted by the addition of the synbiotic (Table E14 and Fig. E14). However, both groups showed a different pattern of change for sputum eosinophils. While the percentage of sputum eosinophils increased from baseline to 3 months in the placebo group, it decreased in the synbiotic

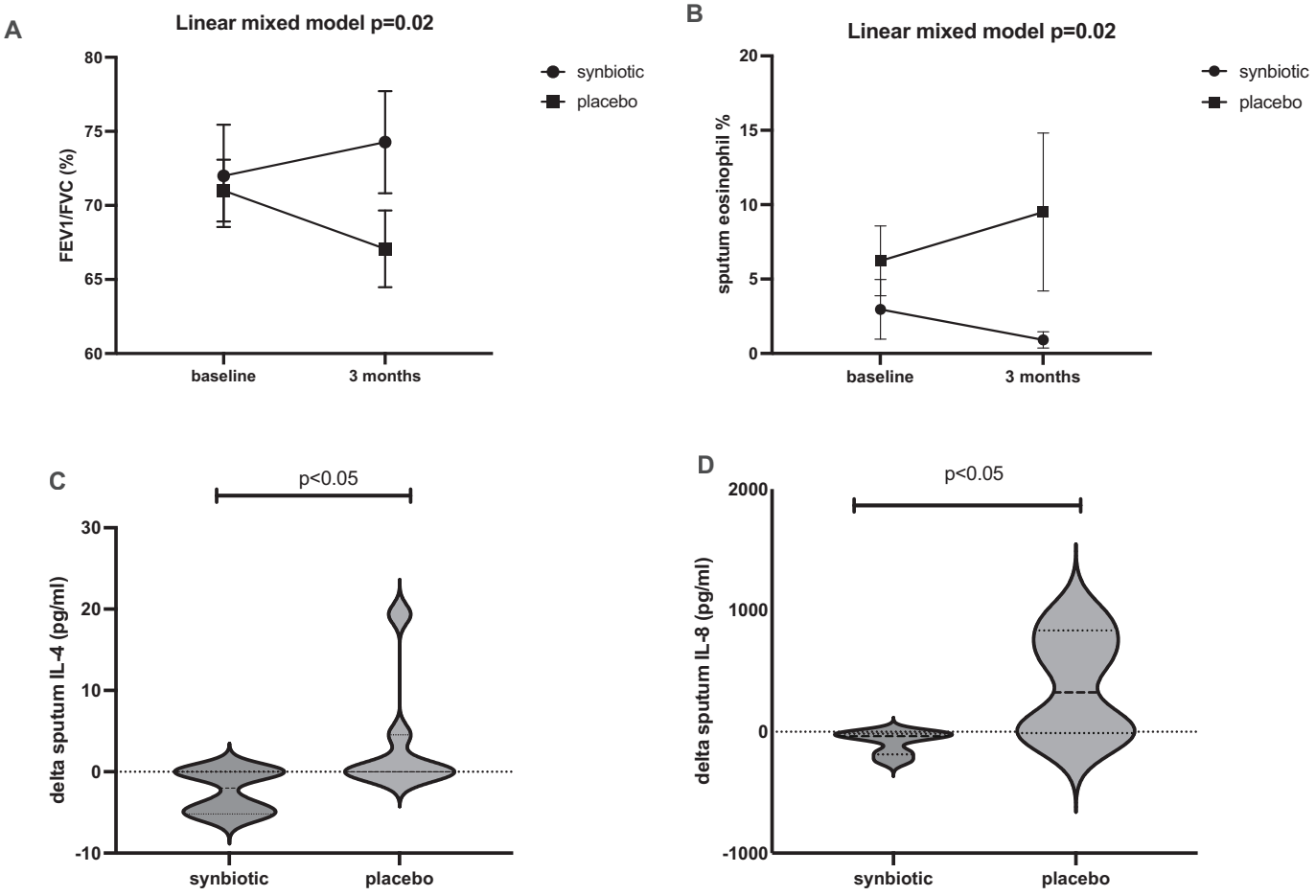

Fig. 3. Parameters significantly impacted by the synbiotic. A: FEV_1/FVC evolution in placebo and synbiotic groups; B: sputum eosinophils evolution in placebo and synbiotic groups. C: sputum IL-4 level evolution in placebo and synbiotic groups. D: sputum IL-8 level evolution in placebo and synbiotic groups.

Table 2
Blood Cytokines.

Mediator	baseline	1 month	3 months	6 months
IL-8 (pg/ml)				
Synbiotic	12.8 (8.2–19.5) ($n = 20$)	9.7 (6.7–14.0) ($n = 17$)	19.3 (11.6–61.6) (n = 13)	11.2 (9.3–11.6) (n = 10)
Change (%)		−19.7 (−50.7- +47.9) ($n = 15$)	+80.0 (+3.4 − +364.9)*($n = 12$)	+15.4 (−36.2 − +33.5) ($n = 10$)
Placebo	15.3 (9.6–23.6) ($n = 18$)	11.8 (9.4–18.8) ($n = 14$)	15.5 (12.2–31.5) (n = 12)	9.8 (7.1–18.2) ($n = 9$)
Change (%)		−2.1 (−25.0 − +24.5) ($n = 13$)	+28.4 (−15.7 − +51.4) ($n = 11$)	−12.0 (−69.2 − +18.8) ($n = 8$)
IL-13 (pg/ml)				
Synbiotic	72.5 (0.0–91.3) (n = 18)	73.0 (58.5–97.6) ($n = 16$)	61.6 (0.0–82.8) (n = 12)	71.9 (0.0–90.6) (n = 11)
Change (%)		−0.2 (−28.7 − +25.8) (n = 14)	−6.7 (−100.0–0.0) (n = 10)	0.0 (−100.0 − +29.5) ($n = 7$)
placebo	80.4 (68.8–105.2) (n = 18)	88.4 (34.7–118.9) (n = 13)	89.2 (17.8–105.3) (n = 12)	80.9 (70.2–97.6) (n = 9)
Change (%)		+3.4 (−1.6 − +9.3) (n = 11)	−3.1 (−32.4 − +38.5) (n = 11)	+2.3 (−20.3 − +12.2) (n = 8)
IFN-γ (pg/ml)				
Synbiotic	0.6 (0.4–0.7) (n = 9)	0.4 (0.4–0.5) (n = 9)	0.5 (0.5–2.0) (n = 9)	0.5 (0.3–0.7) ($n = 6$)
Change (%)		−14.8 (−44.5–1.2)* (n = 8)	+5.3 (−33.2 − +153.7) (n = 8)	−15.9 (−66.4 − +42.9) ($n = 5$)
placebo	0.4 (0.4–1.9) (n = 9)	0.5 (0.2–0.6) (n = 9)	0.4 (0.4–0.5) (n = 9)	0.4 (0.3–0.4) ($n = 6$)
Change (%)		−10.0 (−82.5 − +25.9) (n = 9)	+1.7 (−87.5 − +11.4) (n = 8)	−13.5 (−67.9–1.2) (n = 6)

Results are expressed as median (25%–75%).
* $p < 0.05$ versus 0; Median of the change from baseline were compared with 0 with a Wilcoxon signed rank test. Changes from baseline expressed in % in the two groups were compared with a Man-Whitney tests.

Table 3
Sputum Cytokines.

Mediator	baseline	3 months
IL-1b (pg/ml)		
Synbiotic	3.6 (2.1–40.4) ($n = 7$)	8.1 (1.9–22.3) (n = 7)
Change (pg/ml)		−0.4 (−15.6 − +0.4)
Placebo	14.9 (5.2–53.6) (n = 7)	14.5 (4.4–18.4) (n = 7)
Change (pg/ml)		−0.8 (−45.3 − +5.8)
IL-4 (pg/ml)		
Synbiotic	2.6 (0.0–6.2) (n = 6)	0.0 (0.0–1.2) (n = 6)
Change (pg/ml)		−2.0 (−5.2 − +0.0)$
Placebo	0.0 (0.0–0.0) (n = 7)	0.0 (0.0–4.5) (n = 7)
Change (pg/ml)		0.0 (0.0 − +4.5)
IL-5 (pg/ml)		
Synbiotic	0.3 (0.0–0.5) (n = 7)	0.0 (0.0–0.4) (n = 7)
Change (pg/ml)		0.0 (−0.4 − +0.1)
Placebo	0.6 (0.0–1.4) (n = 6)	0.5 (0.3–0.9) (n = 6)
Change (pg/ml)		−0.2 (−0.4 − +0.2)
IL-8 (pg/ml)		
Synbiotic	64.9 (52.0–118.0) (n = 6)	179.0 (70.7–263.6)* (n = 6)
Change (pg/ml		+36.2 (+16.1 − +187.1)$
Placebo	465.3 (115.2–994.4) (n = 4)	154.0 (89.1–182.7) ($n = 4$)
Change (pg/ml)		−324.1 (−834.8 − +10.0)
TNF-α (pg/ml)		
Synbiotic	2.2 (1.6–2.8) (n = 7)	1.8 (1.3–3.6) (n = 7)
Change (pg/ml)		−0.6 (−1.3 − +0.8)
Placebo	4.4 (3.0–5.8) (n = 7)	3.0 (2.4–3.8) (n = 7)
Change (pg/ml)		−0.8 (−2.0 − +0.2)
IgE (pg/ml)		
Synbiotic	285.2 (249.2–373.7) (n = 7)	243.7 (222.8–283.4)* (n = 7)
Change (pg/ml)		−34.4 (−219.4 − +12.37)
Placebo	319.2 (268.3–883.5) (n = 5)	289.6 (229.1–923.2) (n = 5)
Change (pg/ml)		−76.2 (−135.3 − +159.0)

Results are expressed as median (25%–75%). Data compared with a Wilcoxon matched pairs signed rank test. *: $p < 0.05$ versus baseline. Changes from baseline were expressed in absolute values and not in percentage of decrease from baseline due to the presence of too many 0 values. They were compared between groups with a Man-Whitney tests, $: $p < 0.05$ versus placebo.

group (p value =0.018 for the linear mixed model, Fig. 3B).

Intra-group comparison: Furthermore, a significant difference was also noted for the sputum eosinophils% between baseline and 3 months within the synbiotic group ((1.2 (0.1–3.3) at baseline vs 0.1 (0–1.25) at 3 months, $p = 0.027$, Table E15 and Fig. E15)).

4.5. Exploratory outcomes: Effect on serum and sputum cytokines

Only IL-8, IL-13 and IFN-gamma gave measurable results in the serum (Table 2).

Inter-group comparison: There was no significant changes between the two groups for any of these 3 cytokines.

Intra-group comparison: There was an increase in IL-8 at 3 months compared with baseline in the synbiotic group (change of +80% (+3.4 − +364.9), $p = 0.03$) but not in the placebo group. By contrast, IFN-γ level dropped significantly between baseline and 1 month in the synbiotic group but not in the placebo group.

Results for sputum cytokines are given in Table 3. Sputum IL-10 was under the detection limit for most of the samples.

Inter-group comparison: The difference between baseline and 3 months for sputum IL-4 was significantly different between groups with a decrease in IL-4 observed in the synbiotic group contrasting with no evolution in the placebo group ((−2.0 (−5.2–0.0) pg/ml vs 0.0 (0.0–4.5) pg/ml, $p = 0.03$, Fig. 3C)). In contrast, patients receiving the synbiotic displayed an increase of sputum IL-8 level while there was a reduction in the placebo group ((+36.2 (+16.1 − +187.1) pg/ml vs −324.1 (−834.8 − +10.0) pg/ml, $p = 0.04$, Fig. 3D)).

Intra-group comparison: There was a significant increase of sputum IL-8 ((from 64.9 (52.0–118.0) pg/ml at baseline to 179.0 (70.7–263.6) pg/ml at 3 months, p = 0.03)) and a significant decrease of sputum IgE levels (when the patients treated with Omalizumab were removed) between baseline and 3 months within the synbiotic group while the other inflammatory cytokines did not show modifications over time in any of the two groups (patients treated with anti-IL5 therapy were removed to assess the sputum IL-5 level).

5. Discussion

Our study showed that, compared to placebo, the synbiotic Bactecal® had no significant effect on asthma control in patients with moderate to severe uncontrolled asthma. However, we found significant effect of the synbiotic compared to placebo on FEV_1/FVC, sputum eosinophils and sputum IL-4 and IL-8 levels. The impact of the synbiotic on lung function and airway inflammatory cells were explored using linear mixed models while results regarding sputum mediators were based on non-parametric tests and should be interpreted as exploratory.

The lack of significant effect of synbiotics on asthma control and quality of life is likely to be related to the strong effect seen in the placebo group on these PROMS. This makes difficult for the synbiotic to further improve the asthma control above what has already been achieved with the placebo although intra-group comparisons showed that the magnitude of change in ACT and AQLQ were more pronounced in the synbiotic group. The primary outcome was not achieved but the limited data number may have underpowered the analysis.

The lung function parameters pre-bronchodilation FEV_1/FVC % and post bronchodilation % predicted FEV_1 also slightly improved within the synbiotic group whereas they declined in the placebo group. An improvement in FEV_1 and FEV_1/FVC was already reported after 10 weeks in another study in asthmatic children [16]. In the current study the slight improvement in spirometric parameters was already seen after 1 month, reached its maximum at 3 months but disappeared 3 months after stopping the synbiotic thereby indicating the lack of long-lasting effect.

In our study, the airway eosinophil percentage was also decreased with the synbiotics compared to placebo corroborating previous in vivo results obtained in animal model [24]. Knowing the importance of eosinophilic inflammation in asthma exacerbation [25], the effect found on sputum eosinophil may explain observations in children where *Ligilactobacillus salivarius* LS01 and *B. breve* B632 reduced exacerbation rate [17]. Indeed, strategies based on a decrease of sputum eosinophil counts were found to lead to reduced asthma exacerbations [26]. Our study was not long enough to demonstrate the effect of the synbiotic on exacerbation rate. In contrast, Satia et al did not observe a change of sputum eosinophil percentage after *Limosilactobacillus reuteri* DSM-17938 [27] but this study investigated a limited number of mild allergic steroid naïve asthmatic patients with a different probiotic strain.

Interestingly, we found a reduction of IL-4 in the sputum supernatant in patients receiving the synbiotic compared to patients receiving the placebo. This reduction in IL-4 level may play a role in curbing the T2 inflammation within the airways and in particular sputum eosinophils. To the best of our knowledge, this is one of the first time that it is demonstrated that a synbiotic may reduce the T2 inflammation within the airways as previous studies concentrated on blood analysis.

Although no significant inter group comparisons could be demonstrated, it is worth mentioning that patients who received synbiotics displayed a progressive reduction in blood and sputum IgE as well as in FeNO. Indeed, we observed a reduction compared to baseline of blood IgE level in the synbiotic group, which lasted over time as it became significant after 6 months (3 months after stopping the synbiotic intake). IgE represents a marker of allergic asthma and a decrease of IgE blood levels was already shown after the intake of probiotics such as L. *paracasei* and *L.fermentum* in asthmatic children [28]. However, the impact of synbiotics on sputum IgE is novel and it extends the effect of synbiotics at the airway compartment. In the literature, several mice asthma models based on different probiotic strains also showed a reduced systemic IgE level and airway Th2 inflammation markers including IL-4, which is responsible for the production of IgE by the B cells [29–31]. In our study the airway inflammatory marker FeNO was significantly reduced after the use of the symbiotic in line with a previous study [32]. All these observations point to a reduction in T2 inflammation in patients receiving synbiotics and fit with what was reported in a meta-analysis on the effects in the blood of asthmatic children [33] as well as with in a recent clinical trial conducted in adults [34].

Although not characterizing T2 inflammation, the fibrinogen level decreased at each time point compared to baseline with an effect that lasted over 6 months. This is in keeping with the fact that *Lactobacilli* were shown to reduced blood fibrinogen levels in a rat model [35].

IL-8 increased in the serum and sputum IL-8 in the synbiotic group. The explanation for this observation is unclear but could result from an activation of the airway epithelium, a strain specific effect or can arise from assay variability on a limited sample size.

In our study, sputum IL-4 decrease after synbiotic treatment. This might explain the contemporaneous rise in IL-8 as, in several in vitro models involving different cell lines, IL-4 was able to down-regulate IL-8 production [36–38]. The decrease in sputum IL-4 might also be linked to the reduction of sputum eosinophils due to the decrease production of eotaxin mediated by IL-4 [39]. Taken together, the variations in IL-8 and IL-4 observed after synbiotic treatment remain of uncertain biological significance and should be considered exploratory and hypothesis-generating.

The limitations of this study included small sample size, single center, lack of microbiome data, and limited follow-up. The relatively low number of patients recruited was due to financial difficulties making it not possible to extent the recruitment to a suitable number of patients as planned in the statistical analysis. In addition, the matching of the cohort was not optimal, and imbalances were present between cohorts for BMI and ICS use which could have potentially impacted the results. Indeed, a higher BMI in the placebo group could have limited the pulmonary function and asthma control improvement and could have impaired a reduction in the level of systemic inflammation. A BMI of 29, although below the obesity threshold, corresponds to the overweight category. Finally, the ICS dose tended to be slightly higher in the placebo

group although there are clearly belonging to the high dose ICS category in both groups as defined by GINA [18]. Furthermore, while there was a difference in ACQ between the two groups at baseline, it worth to highlight that both groups displayed uncontrolled asthma, thereby leaving room for improvement with additional therapy. No adjusted analyses for these baseline imbalances were performed due to sample size constraints, and the reported effects should therefore be interpreted as unadjusted estimates. Another limitation of this study is that the multiple endpoints analyze was performed without multiplicity correction and therefore the results, particularly the exploratory biomarkers, should be interpreted with caution.

Despite these limitations, our study showed a significant effect of the synbiotics on several parameters that characterize T2 inflammation in patients remaining uncontrolled despite ICS/LABA. The adjunct of synbiotics to ICS/LABA could therefore become in the future an interesting therapeutic avenue in patients remaining uncontrolled despite standard mainstay treatment. It might be especially true in patients where T2 biomarkers are not markedly elevated where we know that room for improvement with increasing the dose of ICS is useless [40], however, these implications remain speculative until confirmed by larger, adequately powered multicenter trials assessing clinical outcomes such as exacerbation rate.

6. Conclusions

Three-month supplementation with the synbiotic Bactecal® significantly decreased airway obstruction, reduced sputum eosinophils and IL-4 levels while increasing sputum IL-8, suggesting attenuation of airway type-2 inflammation in uncontrolled asthma thereby opening the way for adjunct nutritional treatment in that group of patients. Larger multicenter trials are warranted to confirm these findings.

Authors contribution

CM participated in the study design, recruited the patients, performed the clinical tests, the lab experiments and data analysis and wrote the manuscript; **SG** and **LM** participated in the recruitment of patients and performed the clinical tests and participated in the manuscript writing. **HN**, **A-FD** and **CP** performed the statistical analysis. **NN** participated in the study design and conception. **CM**, **SG, LM, CK, NB, RB, SG, VP, FG** and **CZ** participated in the sputum induction and processing and patient data collection. **FS** and **RL** designed the study and interpreted the data. All authors participated in the manuscript reviewing and gave final approval of the manuscript and ensured that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Generative AI-based tools

The graphical abstract has been made using Gemini.

CRediT authorship contribution statement

C. Moermans: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **S. Graff:** Writing – review & editing, Methodology, Investigation, Data curation. **L. Medard:** Writing – review & editing, Methodology, Investigation, Data curation. **H. Nekoee:** Writing – review & editing, Validation, Formal analysis. **A.-F. Donneau:** Writing – review & editing, Visualization, Supervision, Formal analysis. **M.S. Njock:** Writing – review & editing, Methodology, Investigation, Formal analysis. **C. Kempeneers:** Writing – review & editing, Methodology, Investigation, Formal analysis. **N. Bricmont:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **R. Bonhiver:** Writing – review & editing, Methodology, Investigation, Data curation. **S. Gerday:** Writing – review & editing, Methodology, Investigation, Data curation. **N. Nasir:** Resources, Conceptualization. **C. Poulet:** Writing – review & editing, Methodology, Formal analysis. **V. Paulus:** Writing – review & editing, Investigation, Data curation. **F. Guissard:** Writing – review & editing, Methodology, Investigation, Data curation. **C. Sanchez:** Writing – review & editing, Methodology, Investigation. **F. Schleich:** Writing – review & editing, Supervision, Resources, Investigation, Funding acquisition, Conceptualization. **R. Louis:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **CM, SG, LM, HN, A-FD, MSN, NB, RB, SG, CP, MH, VP** and **FG** have no conflicts to declare. **NN** is an employee of the company Astel Medica working as Scientific Manager but had no role in the data collection, data analysis, and reporting of this study. Also, **NN** is a member of the Board of Directors of Pharmacobiotics Research Institute (PRI) which operates as an independent, NON-PROFIT organization adhering to a transparent governance structure, required by French law. **CK** declared support for attending meetings and/or travel by GSK. **RL** and **FS** had educational and research grants from GSK, AstraZeneca and Chiesi. Also, **RL** and **FS** received consulting fees from GSK and AstraZeneca (national and international advisory boards). **RL** and **FS** received lecture fees from GSK, AstraZeneca and Chiesi.

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Appendix A. Supplementary data: Results of the linear mixed models for all parameters.

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Data availability

Data will be made available on request.

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