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COPD: Journal of Chronic Obstructive Pulmonary Disease

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/icop20

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To cite this article: Naomi Nanke Kappe, Noga Alagem, Naveh Tov & Jan Stolk (2023) Governmental Non-Pharmaceutical Interventions during the COVID-19 Pandemic and the COPD Exacerbation and Respiratory Infection Rate in Patients with Alpha-1 Antitrypsin Deficiency, COPD: Journal of Chronic Obstructive Pulmonary Disease, 20:1, 292-297, DOI: 10.1080/15412555.2023.2249108

To link to this article: https://doi.org/10.1080/15412555.2023.2249108

Published online: 04 Sep 2023.

COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2023, VOL. 20, NO. 1, 292–297
https://doi.org/10.1080/15412555.2023.2249108

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Governmental Non-Pharmaceutical Interventions during the COVID-19 Pandemic and the COPD Exacerbation and Respiratory Infection Rate in Patients with Alpha-1 Antitrypsin Deficiency

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ABSTRACT

During the COVID-19 pandemic the number of hospital admissions due to chronic obstructive pulmonary disease (COPD) exacerbations was significantly reduced. The reason for this decline is not fully understood. Governmental non-pharmaceutical interventions (NPI's), an increase in community treated exacerbations, or healthcare avoidance by patients, are potential reasons. For the current study, the impact of Dutch governmental NPI's on the COPD exacerbations and respiratory infections rate in patients with severe alpha-1 antitrypsin deficiency (AATD) was analyzed. The patients participated in the NCT04204252 study, a randomized controlled trial evaluating the efficacy and safety of inhaled alpha-1 antitrypsin. Data collected in the time-period from March 2020 until February 2022 was analyzed. In this period the Dutch government imposed variable NPI's to contain the spread of SARS-CoV-2. Patients were required to document their daily symptoms in an electronic diary. The strictness of the governmental NPI's was measured by the COVID-19 Stringency Index. 19 patients participated in this study during the analysis period. A total of 40 respiratory infections and COPD exacerbations occurred. The Spearman's correlation coefficient of the monthly average COVID-19 Stringency Index and respiratory infections and COPD exacerbations rate was −0.316 ($p=0.132$). When months known for a low respiratory infection rate were excluded, the correlation coefficient was −0.625 ($p=0.010$). This study showed a significant negative correlation between the COPD exacerbations and respiratory infection rate and the COVID-19 Stringency Index in patients with AATD related COPD in the autumn-winter months.

ARTICLE HISTORY
Received 13 June 2023
Accepted 5 August 2023

KEYWORDS
COPD exacerbations; covid-19; respiratory infections; alpha-1 antitrypsin deficiency; public health control measures

Introduction

During the peak of the COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the number of hospital admissions due to chronic obstructive pulmonary disease (COPD) exacerbations was significantly reduced [1–3]. The reason for this decline is not fully understood. It could be due to an actual reduction of COPD exacerbations which may be attributed to different non-pharmaceutical interventions (NPI's) imposed by local governments and the consequential possible reduction of the transmission of viral respiratory infections [2]. Other potential reasons for this reduction of hospital admissions could be an increase in community treated exacerbations or healthcare avoidance by patients [4, 5]. It is difficult to determine the real reason for this decline, as most studies relied on data from hospital admissions and lack data on patient behavior [6]. The studies that analyzed more detailed information about patient behavior and community treated exacerbations show conflicting results: some show a decline in COPD exacerbations when comparing 2020 to the preceding years, while others show a similar exacerbation rate or even an increased exacerbation rate [4, 5, 7–9]. The question remains whether social distancing and other preventive measures like wearing face masks lower the COPD exacerbation rate. This is an important issue, because of the implications for the future care of patients with COPD.

For the current study, the impact of Dutch governmental NPI's to retain the spread of SARS-CoV-2 on COPD exacerbations and respiratory infections in patients with severe alpha-1 antitrypsin deficiency (AATD) participating in the NCT04204252 study, a randomized controlled trial evaluating the efficacy and safety of inhaled alpha-1 antitrypsin (AAT), was analyzed. AATD is a hereditary condition caused by a mutation in the SERPINA1 gene which increases the risk of developing emphysema [10]. The recruitment of patients for NCT04204252 started in the Netherlands just prior to the first lockdown in March 2020. As part of the study, patients made regular visits to the clinic, received telephone calls and importantly, were required to document their daily symptoms in an electronic diary. The results of

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this study exclude any healthcare avoidance in the study population and give an accurate account of the number of community treated exacerbations.

It was hypothesized that there would be a negative correlation between the COPD exacerbations and respiratory infection rate and the strictness of the governmental NPI's, as measured by the COVID-19 Stringency Index [11, 12].

Material and methods

Patients and study design

The patients in this study participated in the NCT04204252 study in the Netherlands. This is a phase III multi-center, placebo controlled, double blind study evaluating the efficacy and safety of AAT inhalation of 80 mg per day in adult patients with hereditary AATD. The patients were randomized 1:1 to inhale either 80 mg/day alpha-1 antitrypsin or placebo. The patients had a moderate airflow obstruction (forced expiratory volume in 1 s between 50% and 80% of predicted) and were non-frequent exacerbators (for eligibility, it was required that patients have fewer than 2 moderate exacerbations and no severe exacerbations during the year before baseline). Included patients were either homozygous for the Z mutant allele, homozygous for a rare severe deficiency allele, or were carriers of one Z mutant allele and one rare severe deficiency allele, respectively Z/Z, Rare/Rare or Z/Rare [13].

The study treatment period was 104 weeks and the follow-up period was 26 weeks. All patients in this study concluded their treatment period. For all patients the majority of the treatment period was during the time frame starting from March 2020 until February 2022. In this time frame the Dutch government imposed multiple and variable NPI's to contain the spread of the SARS-CoV-2 virus. Only data collected in this time-period was analyzed.

This study was conducted in compliance with the current Helsinki Declaration, International Conference on Harmonization Good Clinical Practice (ICH GCP) Guidelines for GCP and the Code of Federal Regulations (CFR) 21 CFR. The study was approved by the local Medical Ethics Committee (METC). Written informed consent was obtained from all the subjects involved in the study.

Monitoring

During the course of the study there were 14 visits to the clinical site and 7 telephone calls. In addition, the patients were required to fill out a daily e-diary during the study treatment period. The e-diary collected information among other parameters: change in breathlessness, sputum volume, sputum color, cough frequency, use of antibiotics or steroids and medical visits.

To determine if an adverse event like a respiratory infection or COPD exacerbation had occurred, the e-diary data was used as a guide for confirmatory adjudication together with each patient.

COPD exacerbation definition

An exacerbation was defined as an acute worsening of one or more cardinal COPD symptoms (namely, dyspnea, sputum volume and sputum color) for at least 2 consecutive days that resulted in additional therapy. An exacerbation was considered mild if an increase in inhaled long-acting beta 2 adrenergic agonist or inhaled corticosteroids was required, moderate if it was treated by antibiotics and/or systemic corticosteroids and severe if it lead to hospitalization.

SARS-CoV-2

For the study, patients were not obliged to test for SARS-CoV-2 when experiencing possible COVID-19 symptoms. Patients did however perform a test when experiencing these symptoms (either a polymerase chain reaction (PCR) test or a rapid antigen test), as it was advised by the Dutch government. There were no extra non-pharmaceutical interventions imposed by the study staff or study sponsor.

The COVID-19 Stringency Index

The COVID-19 Stringency Index was used as a measure of the strictness of the governmental NPI's. The Stringency Index, developed by the Blavatnik School of Government at the Oxford university and some partner institutions, is a composite measure based on the following nine response indicators: school closures, workplace closures, travel bans, cancelation of public events, restrictions on public gatherings, closures of public transport, stay-at-home requirements, public information campaigns, restrictions on internal movements, and international travel control. The index is calculated for each day as the mean score of the nine metrics, which all take a value between 0 and 100. A higher score expresses a stricter response [11, 12]. For this study an average of the Stringency Index was calculated for each month starting from March 2020 until February 2022. Before and after this time frame there were no or very limited social restrictions imposed by the Dutch Government.

Statistical analysis

A Spearman correlation analysis was performed to study the association between the average monthly COVID-19 Stringency Index and the sum of all the respiratory infections and COPD exacerbations rate. This analysis was done for the months where the rate of viral respiratory infections is expected to be high to analyze the effect of seasonal influences. A separate analysis was performed which included the spring-summer months (May, June, July, August), because viral infections may also occur during summer depending on the weather conditions [9, 14, 15]. The association was analyzed with both the SARS-CoV-2 infections included and excluded from the above mentioned rate.

Due to the low number of participants and therefore a low incidence of respiratory infections and COPD exacerbations, the sum of the respiratory infections and COPD

exacerbations were used in the analyses. A p-value below 0.05 was considered to be statistically significant. Statistical analyses were performed and graphs were made using IBM SPSS, version 25.

The investigators and patients were blinded to treatment allocation and for the purpose of data analysis, it was assumed that the study treatment did not modify the risk of acquiring respiratory infections or exacerbations of COPD.

Correction for difference in number of participants during the study

When the first lockdown was instated by the Dutch government 9 patients were included in the study. When the governmental measures became less strict the inclusion of patients was restarted. To account for the variation in total participants during the time frame of the study the rate of the total respiratory infections plus COPD exacerbations and total participants was used for the statistical analysis.

Results

Nineteen patients in total participated in this study during the analysis period. All were enrolled at the Leiden University Medical Center. At the start of the COVID-19 pandemic 9 patients were randomized. In the second half of 2020 an additional 10 patients were randomized. Demographic and baseline characteristics are shown in Table 1.

Table 1. Demographic and baseline characteristics.

Age years	
Mean ± SD	53.4 ± 8.7
Median [IQR]	56.0 [46-61]
Sex	
Men	12 (63.2)
Women	7 (36.8)
Genotype	
ZZ	17 (89.5)
Z/Rare	1 (5.26)
Rare/Rare	1 (5.26)
BMI kg·cm^{-2}	
Mean ± SD	21.7 ± 2.3
Median [IQR]	24.1 [22.8-27.0]
FEV_1 L	
Mean ± SD	2.36 ± 0.59
Median [IQR]	2.36 [1.84-2.91]
FEV_1 % predicted	
Mean ± SD	64.4 ± 9.0
Median [IQR]	64.5 [53.9-72.4]
D_{LCO} % predicted	
Mean ± SD	57.8 ± 7.3
Median [IQR]	61 [52-64]
Concomitant medication	
LAMA	17 (89.5)
LABA	16 (84.2)
ICS	14 (73.7)
Antibiotic prophylaxis	2 (10.5)
Oxygen users at study entry	2 (10.5)

Data are presented as n (%) if not otherwise indicated. IQR: interquartile range; ZZ: homozygous Z AAT allele; Z/Rare: heterozygous Z AAT allele and heterozygous rare AAT allele; Rare/Rare: homozygous rare allele; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; LAMA: long-acting muscarinic antagonist; LABA: long-acting β2 agonist; ICS: inhaled corticosteroid. D_{LCO} corrected for hemoglobin and normalized to healthy subjects.

Respiratory infections and COPD exacerbations

A total of 40 respiratory infections and COPD exacerbations (27 non-SARS-CoV-2 related respiratory infections, 6 SARS-CoV-2 related respiratory infections and 7 moderate COPD exacerbations) occurred during the study period. Table 2 shows the average COVID-19 Stringency Index, the sum of respiratory infections and COPD exacerbations (SARS-CoV-2 infections included and excluded), and the respiratory infections and COPD exacerbations rate, for each month separately.

The Spearman's correlation coefficient of the monthly average COVID-19 Stringency index and the respiratory infections and COPD exacerbations rate in months with an expected high respiratory infection rate, was −0.625 ($p = 0.010$, Figure 1). When the spring-summer months were included the Spearman's correlation coefficient was −0.316 ($p = 0.132$, Figure 2).

When the SARS-CoV-2 infections were excluded from the analyses the Spearman's correlation coefficients were −0.512 ($p = 0.042$, Figure 1) and −0.330 ($p = 0.115$, Figure 2).

SARS-CoV-2 infections

During the previously mentioned time-period, 6 out of 19 patients got infected with SARS-CoV-2, this was either confirmed by a PCR test or a rapid antigen test. In two patients this led to a hospital admission, none were admitted to the intensive care unit.

Study compliance

All visits to the clinical sites were conducted and all telephone calls were performed. During the 104 weeks treatment period 92.1% of the e-diary reports were filled out. The average treatment adherence was 93.7%. All patients completed the study and there was no loss to follow-up.

Discussion

This prospective study with daily data on the presence of a COPD exacerbation or respiratory infections in patients with alpha-1 antitrypsin deficiency during the COVID-19 pandemic contributes to the notion that the governmental NPI's imposed during the pandemic may reduce the COPD exacerbation and respiratory infection rate. The mandatory e-diary reports in our study dismiss the potential effect of healthcare avoidance and give detailed information on the number of community treated exacerbations.

The current study collected unique information on the presence of exacerbations and respiratory infections in patients with COPD during the 2 years of governmental restrictions. This made it possible to study the effect of the different levels of policy strictness in two autumn-winter seasons. During the autumn-winter seasons the stringency index significantly correlated with the sum of respiratory infections and exacerbation rate. When the stringency index was reduced by the Dutch government in view of the

Table 2. Stringency index average and sum of respiratory infections and exacerbations per month.

Month and Year	Stringency Index average	Participants	RI and exacerbations (incl. SARS-CoV-2)	RI and exacerbations (excl. SARS-CoV-2)	Rate RI and exacerbations[a] (incl. SARS-CoV-2)	Rate of RI and exacerbations[a] (excl. SARS-CoV-2)
March 2020	45.9	9	0	0	0	0
April 2020	78.7	9	0	0	0	0
May 2020	73.7	9	0	0	0	0
June 2020	61.0	9	1	1	11,1	11.1
July 2020	45.4	11	0	0	0	0
August 2020	47.9	12	0	0	0	0
September 2020	50.8	14	1	1	7.1	7.1
October 2020	62.0	15	1	1	6.7	6.7
November 2020	62.6	17	2	2	11.7	11.7
December 2020	68.4	18	2	0	11.7	0
January 2021	79.6	19	1	1	5.3	5.3
February 2021	79.9	19	0	0	0	0
March 2021	75.0	19	1	0	5.3	0
April 2021	73.9	19	3	3	15.8	15.8
May 2021	67.7	19	1	1	5.3	5.3
June 2021	59.0	19	1	1	5.3	5.3
July 2021	36.7	19	1	1	5.3	5.3
August 2021	41.7	19	1	1	5.3	5.3
September 2021	41.7	19	7	7	36.8	36.8
October 2021	37.0	19	3	3	15.8	15.8
November 2021	42.9	19	3	3	15.8	15.8
December 2021	57.8	19	5	5	26.3	26.3
January 2022	58.2	19	3	0	15.8	0
February 2022	39.9	19	3	1	15.8	5.3

[a]Rate of RI and exacerbations: (total respiratory infections and exacerbations/total participants) x 100. RI: respiratory infections; incl.: including; excl.: excluding.

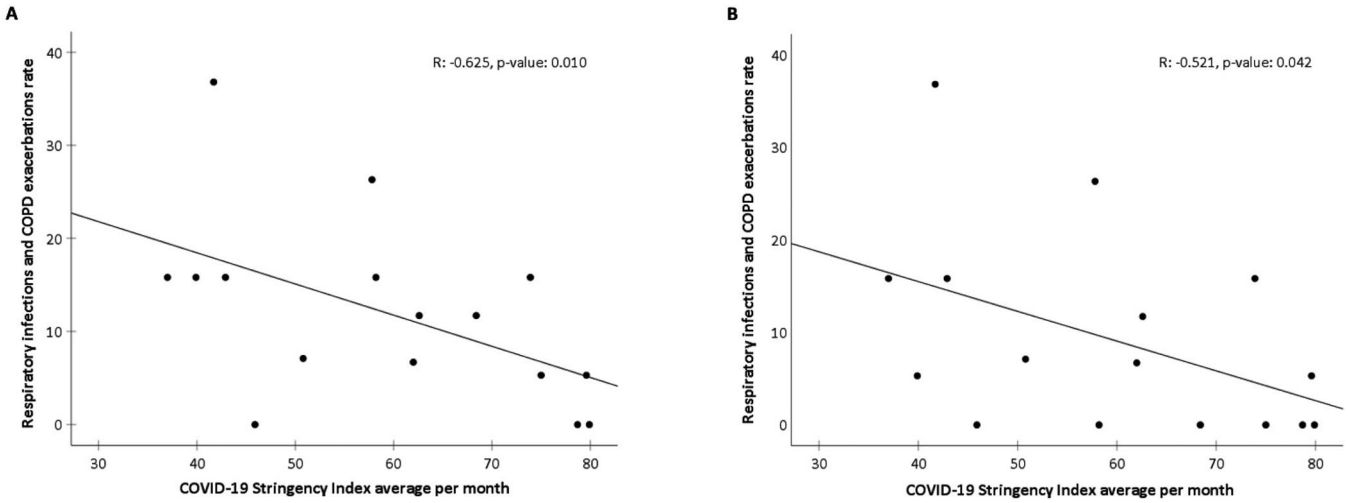

Figure 1. Scatter plot of the respiratory infections and COPD exacerbations rate[a] by the COVID-19 Stringency Index average per month in the autumn-winter months (A) SARS-CoV-2 infections included (B) SARS-CoV-2 infections excluded. All data points of graph a and B are shown in Table 2. [a]Respiratory infections and COPD exacerbations rate: (total respiratory infections and exacerbations/total participants) x 100.

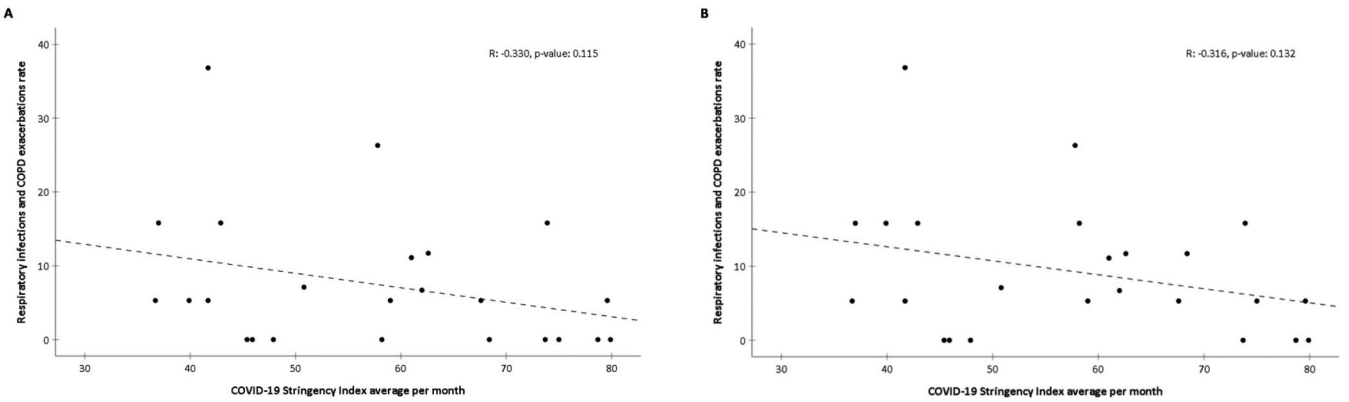

Figure 2. Scatter plot of the respiratory infections and COPD exacerbations rate[a] by the COVID-19 Stringency Index average per month including the spring-summer months (A) SARS-CoV-2 infections included (B) SARS-CoV-2 infections excluded. All data points of graph a and B are shown in Table 2. [a]Respiratory infections and COPD exacerbations rate: (total respiratory infections and exacerbations/total participants) x 100.

approaching spring-summer period with an expected low incidence of viral infections the significance disappeared. This data supports the previously published articles that have advised to implement certain measures in the treatment guidelines during the influenza season, in order to prevent exacerbations in patients with COPD [3, 16, 17]. A large online survey conducted among patients with varying airway diseases, including COPD, showed that these patients are also willing to continue with some of the measures, especially during the influenza season [16].

A few other studies have studied community treated COPD exacerbations during the COVID-19 pandemic, these studies all compared the exacerbation rate of 2020 and/or 2021 to the preceding year(s) [4, 5, 7–9]. Three studies showed a reduction of COPD exacerbations. One COPD cohort study that already started before the pandemic performed follow-ups over the phone in 2020 [7]. The two other studies used primary medical care records or medical prescription data [8, 9]. In contrast, one study which closely observed patients with COPD admitted in a rehabilitation center, showed a similar exacerbation rate during the winter of 2020-2021 when compared to the same period in the preceding years [5]. Another study, which used primary care prescription records and contacted patients by telephone, even showed an increase in exacerbations [4]. All but one of the previously mentioned studies have less accurate data on the health status of the included individuals than in the current study. However, the only study in which patients were closely observed, they were not living in their home environment and they had more severe COPD, which might explain why this study could not show a significant reduction in the number of COPD exacerbations [5].

The main limitations to this study are the limited sample size and the low number of COPD exacerbations recorded. The results of the study should therefore be interpreted with some caution, and firm conclusions cannot be drawn. However, the study design makes the data highly reliable and thus adding to the previously published literature. The potential effect of AAT inhalation on the COPD exacerbations observed in the study period could also be a possible limitation. The existing data on the effect of augmentation therapy on the incidence of exacerbations is limited [18]. The only randomized controlled trial on AAT inhalation, in which 168 patients were included, did not show a difference in the COPD exacerbations incidence between the treatment and placebo group, therefore for this study it was assumed that AAT inhalation did not modify the risk of acquiring COPD exacerbations [19]. Another limitation is the possible effect of selection bias. Patients with high risk variants of AATD related COPD become more risk averse after receiving the diagnosis than patients with non-AATD COPD or patients with lower risk variants of AATD related COPD [20]. The patients in this study could have been extra careful and highly motivated to respect the governmental NPI's in order to reduce chance to become infected with SARS-CoV-2. If this was the case however, the results of this study could be a good representation of the potential effect of the measures imposed by the government. One more limitation is the possible underdiagnosis of SARS-CoV-2 infections. Patients were not obliged to test when experiencing COVID-19 like symptoms, however patients did test for SARS-CoV-2, as it was advised by the Dutch government. Participating in a clinical trial could be a potential limitation on the real-world applicability of the data, the patients were however not restricted by any extra non-pharmaceutical interventions by the investigators.

Conclusion

This study showed a significant negative correlation between the COPD exacerbations and respiratory infection rate and the COVID-19 Stringency Index in patients with alpha-1 antitrypsin deficiency related COPD in the autumn-winter months. Certain non-pharmaceutical interventions could potentially be beneficial for all types of patients with COPD to prevent exacerbations. Further research is needed to determine which measures are most effective, when these measures should be taken, and what the characteristics are of the patients who still had exacerbations.

Acknowledgements

We would like to thank Prof. Dr. Goemans (Leiden University Medical Center, the Netherlands) for assisting us with the statistical analysis. Dr. Kappe conceived the idea of this manuscript, analyzed the data and wrote the manuscript. Dr. Tov, Dr. Alagem and Dr. Stolk designed the NCT04204252 study. Dr. Stolk and Dr. Alagem reviewed and revised the manuscript.

Disclosure statement

Kamada provided salary to Dr. Kappe as study physician for study NCT04204252. Dr. Stolk reports personal fees for consultancy from Kamada Ltd, during the conduct of the study. Dr. Alagem and Dr. Tov are employed by Kamada, Ltd.

Kamada Ltd. sponsored the study and delivered all data.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, Dr. Kappe. The data are not publicly available due to privacy and ethical restrictions.

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