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ORIGINAL RESEARCH

Oscillococcinum® for upper respiratory tract infections and exacerbations in COPD: an observational, prospective study (OXITUNIS)

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Abstract

Background: Upper respiratory tract infections (URTIs) are a major cause of exacerbations in patients with chronic obstructive pulmonary disease (COPD). We assessed the effectiveness of Oscillococcinum® in the protection from URTIs in patients with COPD who had been vaccinated against influenza infection over the 2018–2019 winter season.

Methods: Patients (*n*=106; mean ± standard deviation age: 66.0 ± 10.3 years; 89.6% men) were randomized into two groups: group V received influenza vaccination only and group OV received influenza vaccination plus Oscillococcinum® (one oral dose per week from inclusion in the study until the end of follow-up, with a maximum of 6 months follow-up over the winter season). The primary endpoint was the incidence rate of URTIs (number of URTIs/1000 patient-treatment exposure days) during follow-up compared between the two groups.

Results: There was no significant difference in any of the demographic characteristics, baseline COPD, or clinical data between the two treatment groups (OV and V). The URTI incidence rate was significantly higher in group V than in group OV (2.9 *versus* 1.2 episodes/1000 treatment days, difference OV–V = –1.7; p=0.0312). There was a significant delay in occurrence of an URTI episode in the OV group versus the V group (mean ± standard error: 48.7 ± 3.0 *versus* 67.0 ± 2.8 days, respectively; p=0.0158). Limitations to this study include its small population size and the self-recording by patients of the number and duration of URTIs and exacerbations.

Conclusion: Oscillococcinum may decrease the incidence rate and delay the appearance of URTIs in patients with COPD.

Keywords: chronic obstructive pulmonary disease, chronic respiratory illness, exacerbations, homeopathy, influenza vaccination, Oscillococcinum, upper respiratory tract infection.

Citation

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Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory illness defined by permanent and progressive obstruction of the airways. The disease is a major cause of morbidity and mortality worldwide, ranking as the fourth leading cause of death in the world in 2010[1] and projected to be the third leading cause of death by 2020.[2] In 2017, there were estimated to be 3.2 million deaths worldwide from COPD, an increase of 17.5% over the previous decade,[3] and 4.5 million annual COPD-related deaths are predicted by 2030.[4]

In contrast to industrialized Western countries where the incidence of COPD appears to be decreasing,[5] the prevalence and burden of COPD are increasing in developing countries such as those in the Asia-Pacific region,[6] the Middle East and North Africa.[7] This is due principally to the high prevalence of tobacco smoking, poor indoor and outdoor air quality, and biomass heating in these regions. In Tunisia, the prevalence of COPD has been estimated to range from 3.7% to 7.0% and is higher in men than in women.[7,8] Smoking is the major risk factor for COPD,[5,9] especially in patients hospitalized for exacerbations.[10]

Symptoms of COPD include dyspnoea, chronic cough and chronic sputum production. Acute exacerbations of COPD, where respiratory symptoms worsen beyond normal day-to-day variations and are serious enough to lead to a change

in management, are frequently observed, particularly in patients with moderate-to-severe COPD and in those with the exacerbator phenotype. These exacerbations severely affect quality of life (QoL) and are associated with a decline in lung function, increased risk of cardiovascular events, elevated healthcare costs, and increased morbidity and mortality.[11–13]

The main causes of exacerbations are viral or bacterial upper respiratory tract infections (URTIs).[11,13–17] In a study by Papi et al., bacteria, viruses or both were detected in 78% of 64 patients with exacerbations requiring hospital admission.[16] In this population, patients with infectious exacerbations had a longer hospital stay and greater impairment of lung function than those with non-infectious exacerbations.[16] Exacerbations severe enough to require hospital admission have been identified as a significant predictive factor for mortality.[11,13] One of the main goals of COPD therapy is therefore to prevent the frequency and decrease the severity of exacerbations.[16,17]

A number of studies, including randomized controlled trials, have reported the long-term positive benefits of seasonal influenza vaccination in patients with COPD, including a decrease in number of exacerbations, reduced hospital admissions and hospital visits, and decreased mortality.[18–20] International guidelines recommend that all patients with COPD are vaccinated against influenza virus.[4,21–23]

Most of the trials implemented to find new complementary and alternative therapeutic approaches that could prevent the development of comorbidities and exacerbations in these patients report inconclusive results. An inadequate vitamin D status is associated with a susceptibility to URTIs in patients with COPD. However, vitamin D supplementation trials for the prevention of acute respiratory tract infections report conflicting results.[24,25] Helium should be theoretically useful in several obstructive conditions of the airways but there is not enough evidence to support its use to treat exacerbations of COPD.[26] The prevention of exacerbations has become a major outcome for the evaluation of therapeutic agents for COPD. Clinical trials are therefore needed to evaluate the efficacy of strategies for avoiding exacerbations and complications in patients with COPD.

A recent retrospective observational study conducted in Spain demonstrated that patients with COPD treated with Oscillococcinum (a patented homeopathic medicine (Boiron SA, Messimy, France), authorized since 1944 and sold in over 80 countries around the world) had an important reduction in mean number and duration of URTIs and COPD exacerbations compared with untreated patients.[12] Oscillococcinum is traditionally used in the relief of flu-like symptoms such as fever, headache, chills and body aches. Several studies have shown the efficacy of this medication in the treatment of influenza-like illness and URTIs.[27–29] Two studies have also reported the preventive effects of Oscillococcinum against URTIs.[30,31]

Preventing URTIs would be helpful in avoiding exacerbations and complications in patients with COPD. Influenza vaccination, recommended in this population, does not protect from all URTI viruses, hence the interest in evaluating the benefit of Oscillococcinum in reducing the incidence of URTIs.

Oscillococcinum has been commercially available in Tunisia since 1990 and has been used in daily clinical practice in the Pneumology Department of the Charles Nicolle Hospital in Tunis for several years in conjunction with the influenza vaccine. The current observational study (OXITUNIS, trial registry reference TN2017-NAT-IND-6) was conducted in this department to assess its use in protecting patients with COPD who had been vaccinated against influenza infection from URTIs over the 2018–2019 winter season.

Methods

Study design

This prospective, randomized, single-centre study, funded by Laboratoires Boiron, was conducted in the Pneumology Department of Charles Nicolle Hospital, Tunis, Tunisia, between 1 October 2018 and 31 March 2019. The first patient was recruited on 27 October 2018 and the recruitment period lasted 49 days. The study duration was 161 days, with the last patient visit on 5 April 2019. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki, European Good Clinical Practice and Tunisian regulations. The study was approved by the National Ethics Committee CPP Nord Tunis (2/8/17) and the Ministry of Health in Tunis (17/10/18).

Study population

The study population consisted of patients with a diagnosis of COPD (post-bronchodilator spirometry – forced expiratory volume in one second [FEV_1]/forced vital capacity <0.7) who had been vaccinated against influenza for the 2018–2019 winter season (October 2018–March 2019). Inclusion criteria were age >40 years, patients wishing to protect themselves against URTIs over the 2018–2019 winter season, patients wishing to protect themselves against influenza for the 2018–2019 winter season and follow-up possible over the whole study period. Exclusion criteria were an unstable clinical state or comorbidity, a contraindication to influenza vaccination, participation in another study, a major linguistic problem or the inability to understand the study protocol. All patients gave their written informed consent before taking part in the study.

Patients were randomized into two groups: group V received influenza vaccination only and group OV received Oscillococcinum plus influenza vaccination. Random allocation to one of the two groups was performed at a 1: 1 ratio using a random block permutation method. The blocks were blocks of four patients. Randomization was recommended by the local ethics committee and was performed using SAS 9.4 software.

According to data in the literature, the risk of observing at least one episode of an URTI during the winter period lies between 86% and 90%.[32] Assuming a lower bound rate of 85%

of vaccinated patients experiencing an URTI during the study and supposing a 50% reduction in the risk of URTIs in group OV compared with group V (decrease by half), with an alpha risk of 5% and 80% power of demonstrating significant superiority of Oscillococcinum plus influenza vaccination compared with vaccination alone, it was necessary to include 88 patients in total (44 per group). To account for a possible loss of 20% of patients during the study, 106 patients (53 per group) were included.

Study treatment

After recruitment into the study, the treating clinician ensured that each patient, if not previously vaccinated against influenza, was vaccinated during or within a few days of the first consultation. The vaccine used was either Influvac (Abbott Laboratories) or Vaxigrip (Sanofi Pasteur).

Patients in the OV group also received Oscillococcinum (Laboratoires Boiron, France), a diluted and dynamized extract of Muscovy duck liver and heart (*Anas barbariae* hepatis et cordis extractum; one oral dose per week from inclusion in the study until the end of the follow-up, with a maximum of 6 months of follow-up over the winter season).

Oscillococcinum is made by the 'Korsakovian' or single-flask method, wherein the extractum is shaken in a flask and then poured out. A water/alcohol mixture is added to dilute the liquid that remains on the walls of the flask (approximately 1%). This new dilution is succussed and poured out. The process is conducted serially a total of 200 times, to give a '200K' dilution or 'potency'.

Oscillococcinum was administered according to the recommended dosage schedule of one oral dose per week, from inclusion in the study until the end of follow-up, with a maximum of 6 months of follow-up over the winter season.

All other treatments for COPD were administered according to clinical criteria and in line with normal clinical practice.[32]

Data collection

After inclusion in the study, patients were followed up over the winter period (October 2018–March 2019) during consultations with their clinician. Data were collected from the patients during five follow-up visits over 6 months (one per month) or during unscheduled consultations for aggravated symptoms. The following data were collected at inclusion: age, sex, weight, height, smoking status, duration of COPD diagnosis, FEV_1, comorbidities, management of COPD, and exacerbations. Patients were also called by telephone once a month by a nurse or hospital technician; during this call, they completed a questionnaire about their compliance with Oscillococcinum and tolerance of treatment. The maximum duration of follow-up was 6 months.

Primary endpoint

The primary endpoint was the incidence rate of URTIs (number of URTIs/1000 patient-treatment exposure days) in the two groups during the follow-up period. This rate is calculated as the number of episodes of URTIs per 1000 days of follow-up/treatment exposure. The rates were then compared between the OV and V groups. The following symptoms were considered indicative of an URTI: fever, shivering, runny or blocked nose, sneezing, muscular aches/pain, sore throat, watery eyes, headaches, nausea/vomiting, diarrhoea, fatigue and loss of appetite.

Secondary endpoints

Secondary endpoints included duration of URTI symptoms, time to appearance of URTI symptoms in relation to the start of treatment, number, duration and intensity of exacerbations, QoL of patients with COPD evaluated using the CAT (COPD Assessment Test) questionnaire,[33] the Global Initiative for Obstructive Lung Disease (GOLD) score,[4,34] modified Medical Research Council (mMRC) dyspnoea score,[35] the consumption of drugs for URTIs and exacerbations (antibiotics, analgesics, bronchodilators, corticosteroids), consultations and hospital admissions, tolerance of treatment (adverse events (AEs)), compliance, satisfaction with treatment, and efficacy as perceived by the patient.

Adherence and tolerance

Patients were asked about adherence to Oscillococcinum at each visit. Adherence was classified as high if ≥90% of doses were taken, medium if 75–89% of doses were taken, and low if <75% of doses were taken.

The number, nature, duration and severity (mild, moderate, severe) of AEs in the two treatment groups were recorded and their relationship to the study medication determined. Admission to hospital for a severe exacerbation of COPD or any other cause was recorded as a severe AE.

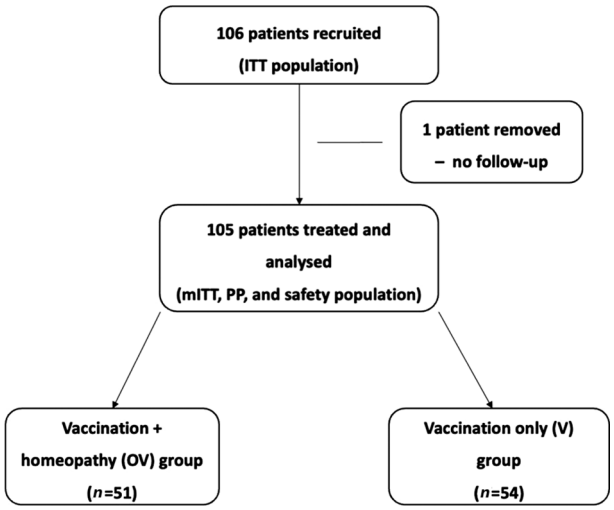
Statistical analysis

Quantitative variables are shown as means with standard deviation (SD) or median and range (minimum–maximum). Qualitative variables are described as number and percent.

The demographic characteristics at inclusion were analysed in the intent to treat (ITT) population. The primary endpoint was analysed in the modified ITT (mITT) population, which included all patients who were randomized and attended at least one follow-up visit. The secondary endpoints were evaluated in the ITT population (Figure 1).

Qualitative variables were compared using Fisher's test and quantitative values were compared using the Wilcoxon–Mann–Whitney test. The log-rank test was used to assess the difference in time to occurrence of URTIs. The difference in incidence rates between groups was estimated using the method described by Sahai and Khurshid[36] and the results are provided with 95% confidence intervals (CI) and *p* values for nullity tests.

Figure 1. Flowchart of the patients included and analysed in the study.



ITT, intent to treat; mITT, modified intent to treat; PP, per protocol population.

A *p* value of <0.05 was considered to indicate statistical significance. Statistical analyses were conducted by Delta Consultants (CRO, Eybens, France) using SAS 9.4 software (Cary, NC, USA).

Ethics approval and consent to participate

The study was performed in compliance with the ethical principles laid down in the Declaration of Helsinki and according to Good Clinical Practice. The study protocol was registered as TN2017-NAT-IND-6 and reviewed by the Ministry of Health of the Tunisian Republic. It was approved by the Ethics Committee (CPP Nord) on 2 August 2017 and by the INPDP on 31 October 2018. The study was classified by the Ethics Committee as a post-authorization, non-interventional study.

Results

Study population

In total, 106 patients were enrolled (ITT population). One patient was eliminated from the primary analysis as he had major deviations from the study protocol. Thus, 105 patients were included in the primary analysis and made up the mITT population (Figure 1).

The demographic characteristics of the ITT population at inclusion are summarized in Table 1. There was no significant difference in any of the characteristics between the two treatment groups (OV and V). The number of comorbidities, including asthma, cardiovascular disease, gastroduodenal ulcers, osteoporosis, diabetes, anxiety/depression, or other, did not differ significantly between the two groups, with the most common being cardiovascular disease (41.5%). In terms of influenza vaccination, more than half (57.5%) of the patients were vaccinated after the inclusion visit, 13.2% were vaccinated during the inclusion visit and 29.2% were already vaccinated before their enrolment in the study.

The mean ± SD interval between the start of treatment and end of study was 130.0 ± 16.3 days. This was similar in the two treatment groups (V: 129.1 ± 17.8 *versus* OV: 131.0 ± 14.7 days).

Baseline COPD and clinical data

COPD data for the two groups were compared at inclusion (Table 2). Mean ± SD time since COPD diagnosis did not differ significantly between the two groups. Patients in the OV group had more COPD exacerbations and hospital admissions for exacerbations in the 12 months prior to the study, although the difference was not statistically significant. The number of URTIs in the year before the study did not differ significantly between the two groups. There was no significant difference in the severity of bronchial obstruction in the two groups according to the GOLD classification (Table 2).

At inclusion, all patients were receiving treatment for COPD (salbutamol). The other drug treatments received were long-acting bronchodilators (formoterol (34.0%), theophylline (30.2%) or indacaterol (19.8%)) in combination with inhaled corticosteroids (beclomethasone (41.5%) or budesonide (24.5%)). Another type of therapy (long-term oxygen therapy ± non-invasive ventilation, respiratory physiotherapy, other) was used by 12.3% of patients (Table 2).

Primary endpoint: number of URTIs

The primary endpoint was evaluated in the mITT population (V: 54 patients, OV: 51 patients; *n*=105).

The majority of patients (*n*=82; 78.1%) had no URTI episodes during follow-up (OV: 88.2% *versus* V: 68.5%) (Figure 2); 14 patients in the V group and 6 in the OV group had a single URTI episode and 3 *versus* 2 patients, respectively, had 2 episodes (Table 3). The incidence rate of URTIs was significantly higher (2.9 *versus* 1.2 /1000 days, difference = –0.1671%, *p*=0.0312) in the V group than in the OV group (Table 3).

The mean duration of confirmed URTI episodes was shorter in the OV group than in the V group (difference OV–V = –1.18, 95% CI –3.27 to 0.92) but the difference was not statistically significant (*p*=0.2602) (Table 4).

Secondary endpoints

The secondary endpoints were evaluated in the ITT population (*n*=106).

Number and duration of URTI symptoms

The most common symptom of URTIs in both groups was a blocked/runny nose, which was present in 10 patients in the V group (10/54, 18.5%) and 4 patients in the OV group

Table 1. Sociodemographic and clinical characteristics of the patients at inclusion (ITT population).

Characteristic	Group V (*n*=54)	Group OV (*n*=52)	ITT population (*n*=106)
Age (years)			
Mean ± SD	66.0 ± 8.9	66.0 ± 11.6	66.0 ± 10.3
Median (min–max)	65.5 (50.0–83.0)	66.0 (40.0–90.0)	65.5 (40.0–90.0)
Male (%)	92.6	86.5	89.6
BMI (kg/m^2)			
Mean ± SD	24.5 ± 5.6	23.4 ± 5.6	23.9 ± 5.6
Median (min–max)	24.9 (14.7–41.5)	22.4 (15.2–46.6)	23.4 (14.7–46.6)
Current smoker, yes (%)	44.4	46.2	45.3
Previous smoker, yes (%)	51.9	50.0	50.9
Mean ± SD duration of smoking (years)[a]	42.5 ± 11.1	44.2 ± 12.8	43.4 ± 11.9
Mean ± SD number of cigarettes/day[a]	25.6 ± 10.6	26.1 ± 11.4	25.8 ± 10.9
Mean ± SD number of pack years[a]	53.5 ± 22.5	58.7 ± 33.1	56.0 ± 28.1
At least one comorbidity, yes (%)[b]	63.0	63.5	63.2
Influenza vaccination (%)			
Influvac	38.9	54.9	46.7
Vaxigrip	61.1	45.1	53.3

No significant difference was observed between the groups for any parameter (qualitative variables were compared using Fisher's test and quantitative values were compared using the Wilcoxon–Mann–Whitney test).
[a]Amongst current and previous smokers. [b]Asthma, cardiovascular disease, gastroduodenal ulcer, osteoporosis, diabetes, anxiety/depression and others.
BMI, body mass index; ITT, intent to treat; OV, patients treated with influenza vaccination and homeopathic medication; SD, standard deviation; V, patients treated with influenza vaccination only.

Table 2. Clinical data at inclusion for COPD patients treated with influenza vaccine only (V) or with Oscillococcinum + influenza vaccine (OV).

Baseline clinical characteristics	Group V (*n*=54)	Group OV (*n*=52)	ITT population (*n*=106)
Time since COPD diagnosis (years)			
Mean ± SD	5.1 ± 5.7	4.5 ± 4.6	4.8 ± 5.2
Median (min–max)	4.0 (0–23.0)	3.0 (0–18.0)	3.0 (0–23.0)
FEV_1 post bronchodilation (% predicted)			
Mean ± SD	43.9 ± 16.4	42.0 ± 14.6	42.9 ± 15.5
Median (min–max)	44.0 (18.0–82.0)	42.0 (11.0–81.0)	42.0 (11.0–82.0)
FVC (%)			
Mean ± SD	55.6 ± 10.0	54.9 ± 8.4	55.2 ± 9.2
Median (min–max)	56.0 (28.5–70.0)	54.0 (33.0–69.0)	55.8 (28.5–70.0)
GOLD classification (%)			
Stage I	3.8	1.9	2.9
Stage II	30.2	30.8	30.5
Stage III	43.4	44.2	43.8
Stage IV	22.6	23.1	22.9
Consumption of drugs for COPD, yes (%)[a]	100	100	100
At least one other therapy for COPD (long-term oxygen therapy, non-invasive ventilation) yes (%)[b]	11.1	13.5	12.3

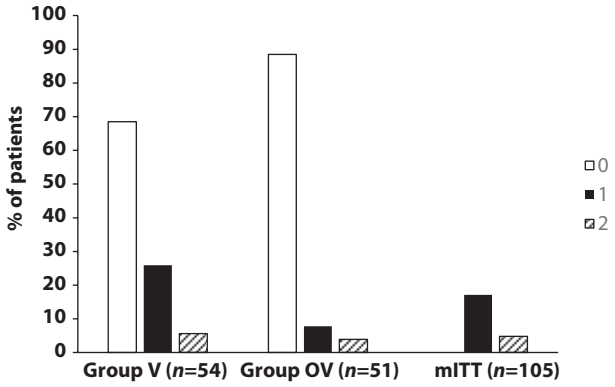
(Continued)

Table 2. ***(Continued)***

Baseline clinical characteristics	Group V (*n*=54)	Group OV (*n*=52)	ITT population (*n*=106)
At least one exacerbation in the previous year, yes, *n* (%)	28 (51.9)	32 (61.5)	60 (56.6)
Exacerbations in previous year, *n* (%)			
0	26 (48.1)	20 (38.5)	46 (43.4)
1	15 (27.8)	16 (30.8)	31 (29.2)
2	11 (20.4)	12 (23.1)	23 (21.7)
≥3	2 (3.8)	4 (7.7)	6 (5.7)
Hospital admissions for exacerbations in previous year, *n* (%)			
0			
1	44 (81.5)	35 (67.3)	79 (74.5)
≥2	9 (16.7)	10 (19.2)	19 (17.9)
	1 (1.9)	7 (13.4)	8 (7.5)
URTIs in previous year, *n* (%)			
0	39 (72.2)	39 (75.0)	78 (73.6)
1	15 (27.8)	11 (21.2)	26 (24.5)
2	0	2 (3.8)	2 (1.9)

No significant difference was observed between the groups for any parameter (qualitative variables were compared using Fisher's test and quantitative values were compared using the Wilcoxon–Mann–Whitney test).
[a]Corticosteroids (oral, inhaled, parenteral), bronchodilators (short-acting, long-acting); [b]Non-invasive ventilation (± oxygen therapy), respiratory physiotherapy, other.
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ITT, intent to treat; OV, patients treated with influenza vaccination and homeopathic medication; SD, standard deviation; URTI, upper respiratory tract infection; V, patients treated with influenza vaccination only.

Figure 2. Primary endpoint, comparison of the number of upper respiratory tract infections in the two treatment groups during follow-up.



mITT, modified intent to treat; OV, patients treated with influenza vaccination and homeopathic medication; V, patients treated with influenza vaccination only.

(4/52, 7.7%), followed by a high temperature (V: 5/54, 9.3% *versus* OV: 2/52, 3.8%). There was no significant difference between the two groups in terms of URTI symptoms.

The median (Q1; Q3) number of different URTI symptoms per patient was 2 (0; 3) (range 0–5), without any significant difference between the groups (p=0.8273). The episodes of URTI corresponded to rhinitis/cold in 17 cases (60.7% of episodes) and rhinopharyngitis/sore throat in 11 cases (39.3% of episodes). These results were identical for the mITT population.

Incidence rate, duration and intensity of exacerbations

Thirty-eight (35.8%) patients had at least one COPD exacerbation and 10 (9.4%) patients had two exacerbations. In total, there were 48 episodes of exacerbation, 24 per group, without any significant difference between the two groups.

The incidence rate of COPD exacerbations did not differ between the groups. The mean duration of COPD exacerbations per episode was slightly longer in OV but this difference was not statistically significant (Table 4).

Three-quarters of exacerbations were classed as moderate and the others were either severe or mild (Table 4). Six patients had at least one severe COPD exacerbation (one patient had two). The incidence rate of severe COPD exacerbations was 0.3/1000 treatment days and 0.7/1000 treatment days in the V and OV groups, respectively; the difference was not statistically significant.

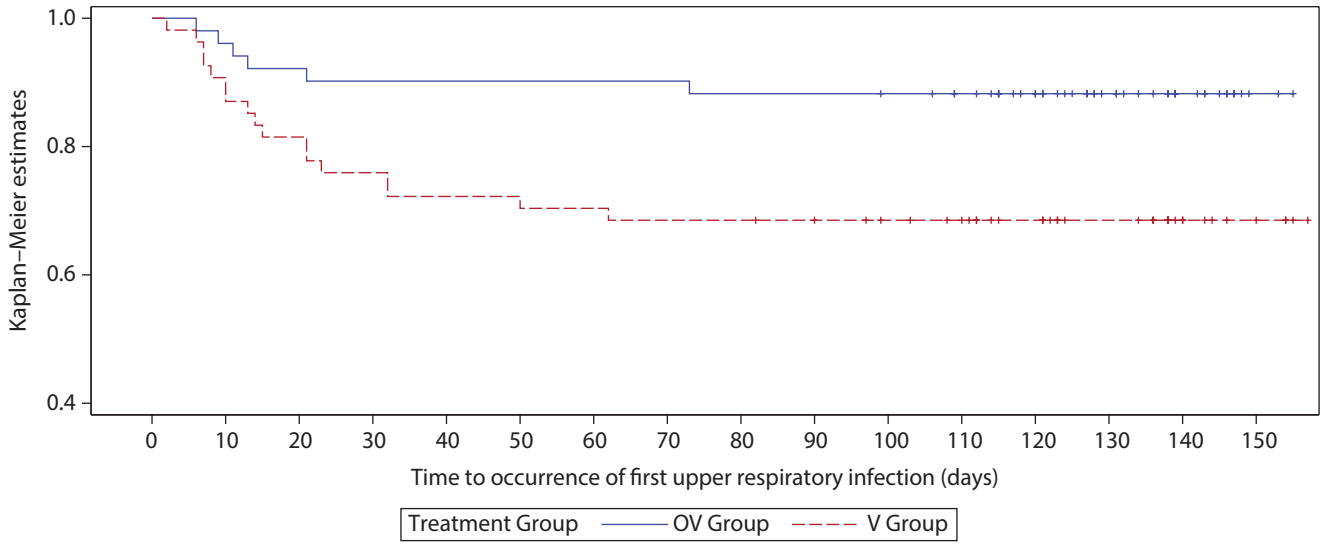
Eleven patients (10.5%) had an exacerbation of their COPD linked to an URTI during follow-up (one exacerbation each). The incidence rate was 0.9/1000 treatment days and 0.8/1000 treatment days in the V and OV groups, respectively (difference OV–V = −0.1, 95% CI −1.1 to 0.8; p=0.8176) (Table 4).

Table 3. Primary endpoint: incidence of URTIs during follow-up (mITT population).

Variable		Group V (*n*=54)	Group OV (*n*=51)	mITT population (*n*=105)
At least one episode of URTI, *n* (%)		17 (31.5)	6 (11.8)	23 (21.7) *p*=0.0184[a]
URTIs/patient, *n* (%)	0	37 (68.5)	45 (88.2)	82 (78.1)
	1	14 (25.9)	4 (7.8)	18 (17.1)
	2	3 (5.6)	2 (3.9)	5 (4.8)
Duration of treatment (days)	Mean ± SD	129.1 ± 17.8	131.0 ± 14.7	130.0 ± 16.3
	Median (min–max)	132.5 (82.0–157.0)	131.0 (99.0–156.0)	131.0 (82.0–157.0)
Incidence rate	No. URTIs/1000 days	2.9	1.2	2.1
	Difference OV–V (95% CI)		–1.7 (–3.2 to –1.5), *p*=0.0312[b]	

[a]Log-rank test; [b]The difference in incidence rates between groups was estimated using the method described by Sahai and Khurshid.[37]
CI, confidence interval; mITT, modified intent to treat; OV, patients treated with influenza vaccination and homeopathic medication; URTI, upper respiratory tract infection; V, patients treated with influenza vaccination only.

Figure 3. Kaplan–Meier estimate of the time to appearance of upper respiratory tract infections in the two treatment groups (intention-to-treat population).



OV, patients treated with influenza vaccination and Oscillococcinum; V, patients treated with influenza vaccination only.

A single patient in group V had a severe COPD exacerbation linked to an URTI. Ten patients (five in each group) had a moderate exacerbation linked to an URTI.

Delay between the start of study treatment and appearance of an URTI

Twenty-three patients (21.7%) had at least one confirmed URTI episode; this did not differ significantly between the groups. Amongst the first 23 URTI episodes, median time (Q1; Q3) to appearance was 14 days (8; 23) in the V group and 12 days (9; 21) in the OV group. Kaplan–Meier estimate of time to appearance of an URTI episode (mean ± standard error) was 67.0 ± 2.8 days in the OV group and 48.7 ± 3.0 days in the V group, highlighting a significant delay in URTI occurrence in the OV group compared with the V group (*p*=0.0158; Table 4, Figure 3).

Overall health of patients with COPD

CAT score

The mean CAT score at inclusion was similar in the two groups. At the last evaluation available, the estimated difference between

Table 4. Secondary endpoints during follow-up of COPD patients treated with influenza vaccine (V) or with influenza vaccine + Oscillococcinum (OV) (ITT population, *n*=106).

	V (*n*=54)	OV (*n*=52)	Total (*n*=106)	*p* value
Delay to the appearance of the first episode of URTI (days)				0.0158[a]
Median (min–max)	14.0 (2.0–62.0)	12.0 (6.0–73.0)	13.0 (2.0–73.0)	
Kaplan–Meier estimate of delay in appearance of URTIs	48.7 ± 3.0	67.0 ± 2.8		
Duration of URTI episodes (days)				0.2602[b]
Mean ± SD	4.6 ± 2.5	3.4 ± 2.2	4.2 ± 2.5	
Median (min–max)	3.0 (2.0–11.0)	3.0 (1.0–7.0)	3.0 (1.0–11.0)	
Exacerbations per patient, *n* (%)				
0	34 (63.0)	34 (65.4)	68 (64.2)	
1	16 (29.6)	12 (23.1)	28 (26.4)	
2	4 (7.4)	6 (11.5)	10 (9.4)	
At least one COPD exacerbation, *n* (%)	20 (37)	18 (34.6)	38 (35.8)	0.8413[c]
Incidence rate of exacerbations (no. per 1000 days)	3.4	3.6	3.5	0.8822[d]
Severity of exacerbations, *n* (%)				0.5044[c]
Mild	2 (8.3)	3 (12.5)	5 (10.4)	
Moderate	20 (83.3)	16 (66.7)	36 (75.0)	
Severe	2 (8.3)	5 (20.8)	7 (14.6)	
Duration of COPD exacerbations per episode (days)				0.2760[b]
Mean ± SD	6.9 ± 3.8	8.6 ± 6.5	7.8 ± 5.3	
Median (min–max)	7.0 (2.0–15.0)	6.0 (1.0–22.0)	6.5 (1.0–22.0)	
At least one exacerbation linked to an URTI, *n* (%)	6 (11.0)	5.0 (9.8)	11.0 (10.5)	
No. exacerbations linked to an URTI/1000 days	0.86	0.75	0.8	0.8176[a]
Consumption of drugs relating to COPD exacerbations, yes, *n* (%)	14 (25.9)	15 (28.8)	29 (27.4)	0.8286[c]
Corticosteroids	0	1 (1.9)	1 (0.9)	0.4906[c]
Antibiotics (URTI)	14 (25.9)	16 (30.8)	30 (28.3)	0.6680[c]
Antibiotics (exacerbation)	12 (22.2)	13 (25.0)	25 (23.6)	0.8206[c]
Bronchodilators (exacerbation)	7.0 (13.0)	2.0 (3.8)	9.0 (8.5)	0.1614[c]
Analgesics				
Incidence rate of consultations				
No. consultations/1000 treatment days	1.0	1.5	1.2	
Difference OV–V (95% CI)		0.5 (−0.7 to 1.7)		0.4145[d]
Incidence rate of hospitalizations				
No. hospitalizations/1000 treatment days	0.3	0.8	0.5	
Difference OV–V (95% CI)		0.5 (−0.3 to 1.2)		0.2337[d]
Evolution of CAT score (QoL)				0.1326[b]
Inclusion, mean ± SD	25.5 ± 6.0	26.2 ± 5.2		
Last visit, mean ± SD	25.0 ± 5.4	24.7 ± 5.4		
Difference OV–V (95% CI)		−0.89 (−2.05 to 0.27)		
Evolution of MRC score (%)				0.0383[c]
Improvement	5.6	19.6		
Stabilized/worsened	94.4	80.4		

[a]Log-rank test; [b]Linear mixed model; [c]Fisher test; [d]The difference in incidence rates between groups was estimated using the method described by Sahai and Khurshid.[37]

CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ITT, intent to treat; MRC, Medical Research Council; OV; patients treated with influenza vaccination and homeopathic medication; QoL, quality of life; SD, standard deviation; URTI, upper respiratory tract infection; V; patients treated with influenza vaccination only.

the OV and V groups was −0.89 (95% CI −2.05 to 0.27; p=0.1326). No difference in QoL was observed between the two groups.

mMRC dyspnoea score

Nearly half of the patients had a mMRC score of stage 3 (45 patients: 42.5%) at inclusion. Stage 2 and stage 4 was observed in 37 (34.9%) and 17 (16.0%) patients, respectively. Only seven patients (6.6%) had a score of stage 1. There was no significant difference in score distribution between the two groups.

At the last evaluable visit, 46 patients had a score of stage 3 (43.8%). A score of stage 2 and stage 4 was observed for 34 (32.4%) and 18 (17.1%) patients, respectively, and 7 patients were stage 1 (6.7%).

Between inclusion and the last evaluation, an improvement in the symptoms score was observed in 13 (12.4%) patients. Significantly more patients in the OV group had an improvement in their symptoms than in the V group (19.6% *versus* 5.6%, respectively; p=0.0383).

Medication, consultations and hospital admissions linked to URTIs and COPD exacerbations

Medications for URTIs

Antibiotics were used to treat URTIs in one patient only (OV group). Analgesic use was not statistically significantly different between the groups.

Medications for COPD exacerbations

The consumption of drugs related to COPD exacerbations (antibiotics, corticosteroids, nebulized bronchodilators) did not differ between the two groups.

Consultations

A total of 16 (15.1%) patients consulted for an URTI episode or aggravation of COPD during the study; 5 (9.3%) patients in the V group and 10 (19.2%) in the OV group consulted once and 1 (1.9%) patient in the V group consulted twice. The incidence rate of consultations was similar in the two groups (OV: 1.5/1000 treatment days *versus* V: 1.0/1000 treatment days, difference OV–V = 0.5, 95% CI −0.7 to 1.7; p=0.4145).

Hospital admissions

Six (5.7%) patients were admitted to hospital for an URTI episode with COPD exacerbation during the study (2 (3.7%) patients in the V group and 4 (7.8%) patients in the OV group). The incidence rate of hospital admissions was similar in the two groups of patients (OV: 0.8/1000 treatment days *versus* V: 0.3/1000 treatment days, difference OV–V = 0.5, 95% CI −0.3 to 1.2; p=0.2337).

Satisfaction and efficacy of study treatment

Satisfaction

At the last evaluation, there was significantly higher satisfaction with treatment in the OV group than in the V group (8.2 ± 1.3 *versus* 6.6 ± 0.9, respectively (scale 0–10); p<0.0001).

Efficacy

The mean efficacy of treatment as perceived by the patients (scale 0–10) was 8.1 ± 1.3 in the OV group *versus* 6.4 ± 1.0 in the V group (p<0.0001).

Compliance and adverse events

The mean delay between inclusion and first dose of Oscillococcinum in OV was 1.7 ± 2.0 days (range 0–8). Adherence to the homeopathic treatment was high, and 46 (88.5%) patients were considered compliant, defined as taking Oscillococcinum three or four times per month (reported in at least two follow-up visits).

Four patients in each group (7.6% overall) had a total of nine AEs (V: five AEs and OV: four AEs). Hospitalization for severe exacerbations or any other cause was considered as a severe AE. All AEs were severe in intensity but none were considered to be related to the study treatment. All but one AE had resolved at the end of the study.

Discussion

The results of this study suggest that the administration of Oscillococcinum to patients with COPD between 1 October 2018 and 31 March 2019 helped to reduce the incidence and delay the appearance of URTIs. At least one URTI episode was observed in 17 patients in the V group compared with only 6 patients in the OV group, the incidence rate of URTIs was significantly greater in the V group than in the OV group (Table 3) and the appearance of URTIs was significantly delayed in the OV group compared with the V group (Table 4). These results support those of a previous study by Conde Diez et al., who reported that the use of Oscillococcinum during the influenza-exposure period decreased the number of URTIs in Spanish patients with COPD.[12] These authors also reported a significant decrease in mean URTI duration per episode in patients treated with Oscillococcinum.[12] Although mean URTI episode duration was slightly shorter in the OV group than in the V group in our study, this difference was not statistically significant (Table 4). Furthermore, like the study of Conde Diez et al.,[12] homeopathic medication use in our study did not appear to affect the mean number or mean duration of COPD exacerbations during the study period.

Beghi and Morselli-Labate conducted a real-life observational study comparing a large number of patients treated with Oscillococcinum (n=248) with untreated patients (n=211), followed for a period of 1–10 years.[30] In their study, treatment with the homeopathic medication resulted in a significant reduction in the mean number of URTI episodes during the observation period compared with the year prior to inclusion (−4.76 ± 1.45 *versus* −3.36 ± 1.30; p=0.001). A sub-analysis of their study population according to concomitant respiratory disease showed that patients with COPD (n=63) treated with the homeopathic medication had a significantly greater decrease in URTI episodes than those who were not treated (−4.16 ± 0.93 *versus* −3.11 ± 0.77, respectively; p=0.033).

The authors concluded that Oscillococcinum may have a positive effect in protecting against URTIs.[30]

In the study of Conde Diez et al., the number of URTIs and frequency of exacerbations was lower in patients with COPD with the exacerbator phenotype (*n*=116) treated with the homeopathic medication.[12] A sub-analysis of our data did not show any significant difference in the number of URTIs or in the frequency of exacerbations in patients with the exacerbator phenotype treated or not with the homeopathic medication (data not shown). However, the number of patients with the exacerbator phenotype in our study was very small (V: 13; OV: 16). Furthermore, Agustí et al. reported considerable variation in the risk of COPD exacerbations between patients and described a number of risk factors for exacerbation, including a history of previous exacerbations, age >65 years, COPD severity, high BODE index (body mass index, airflow obstruction, dyspnoea and exercise), poor health status and presence of comorbidities.[37] Although the multiple genetic factors involved in the development of COPD may influence its clinical management,[38] certain environmental characteristics, such as changes in air temperature and increased air pollution, can be associated with acute exacerbations of COPD.[39] It is therefore extremely difficult to compare populations in different studies.

When measuring the therapeutic effect of an agent, it is also important to assess the impact it has on a patient's symptoms, QoL and lung function, wherever possible. In order to do this, we compared the results of three scores at inclusion and at the end of the study: the CAT questionnaire, which is specially adapted for COPD and well correlated with QoL, the mMRC dyspnoea scale, and the GOLD score. It was not possible to analyse the GOLD score results as only two patients had re-evaluation of their GOLD score during follow-up. GOLD staging has clinical relevance with respect to airflow obstruction and not to integral assessment of health status.[40] For the CAT score (an effective tool to measure health status in patients with COPD[41]), the estimated difference between the OV and V groups at the last evaluation was −0.89 (Table 4). An improvement in mMRC score was observed in 13 patients; significantly more patients in the OV group had an improvement in their health than in the V group.

There were no other significant differences between the V group and the OV group during the study in any other secondary endpoint parameters except for patient satisfaction and perceived efficacy of treatment. At the last evaluation, both patient satisfaction and perceived efficacy of treatment were significantly higher in the OV group than in the V group.

This study of Oscillococcinum was prospective and the study population was randomized into two treatment groups. The two types of preventive management evaluated reflect the practice of the investigating physician. The population size was small (*n*=106) and there were only 29 patients with the exacerbator phenotype, precluding any meaningful analysis in this population. Finally, as in the study of Conde Diez et al.,[12] the number and duration of URTIs and exacerbations were recorded by patients and it was not possible to verify their accuracy. However, even if the analysis relies on a subjective assessment by the patient with great variability in the threshold at which patients perceive a worsening of symptoms, URTIs and exacerbations are the primary concern of the patient and must therefore be fully considered.[39]

Oscillococcinum was well tolerated in the current study, and the low incidence of AEs was similar to that reported by other authors.[12,30]

Conclusion

The use of Oscillococcinum in patients with COPD led to a significant decrease in incidence and a delay in the appearance of URTI symptoms during the influenza-exposure period. The results of this study confirm the impact of this homeopathic medication on URTIs in patients with COPD.

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