

Varenicline in smokers with severe or very severe COPD after 24 weeks of treatment. A descriptive analysis: VALUE study

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Abstract

A large number of COPD patients are smokers. The particular characteristics of this group as well as their need to quit usually require psychological counselling and pharmacological treatment to achieve abstinence and, often, intensively. The main objective of the study was to evaluate the effectiveness of varenicline after 24 weeks of treatment, with continuous abstinence between weeks 9 and 24, in patients with severe or very severe COPD. This study was a post-authorization, open label, observational study of prospective follow-up. Patients included were smokers with severe or very severe COPD criteria who were treated with

varenicline for 24 weeks, *i.e.* with a 12-week extension over the usual treatment. The outcomes in the population of subjects completing 24 weeks of follow-up were at week 24: continuous abstinence 36.8%, 7 days point prevalence abstinence 65.7%, and continuous smoking 31.5%. The outcomes in the intention-to-treat population included at baseline were: continuous abstinence 17.7% of patients, 7 days point prevalence abstinence 31.6%, continuous smoking 15.1% and not valid/unknown 51.8%. The mean CAT score at week 24 was 15 and reduction from the baseline was 3.77 (paired *t*-test, *p*<0.01). The most common adverse events reported were nausea, vivid dreams, stomach ache, insomnia, headache and vomiting. Patients included in VALUE were active smokers despite all of them had a severe COPD which suggests a very high degree of dependence. Although the study do not allow to infer the results to the global population of smokers with severe COPD, the outcomes have shown that, at 24 weeks follow up 36.8% of the patients were successful in quitting but from 79 patients enrolled initially only 17.7% quit.

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Introduction

Smoking cessation is the only measure that has been shown to be effective in stopping the progressive impairment of pulmonary function in COPD [1,2]. Despite this, a significant percentage of these patients continue smoking [3]. A recent meta-analysis reports that the most effective treatment to help COPD smokers quit is a combination of medication and intensive psychological counselling [4]. Nicotine Replacement Therapy (NRT), bupropion and varenicline have been shown to be effective and safe in helping patients with COPD quit [4].

Two studies have analysed the efficacy and safety of varenicline in smoking cessation in patients with COPD [5,6]. Patients with moderate/mild COPD participated in the first study which evaluated the efficacy of varenicline 2 mg/day for 12 weeks *vs* placebo, with a follow-up of 56 weeks. The data on abstinence after 12 weeks for varenicline *vs* placebo were 42.3% *vs* 8.8%; *p*<0.0001; OR=8.40; 95% CI, 4.99; 14.14. The differences persisted at one-year follow up: 18.6% *vs* 5.6%; *p*<0.0001; OR=4.04; 95% CI; 2.13; 7.67. The study also showed there were no differences between the two groups in terms of side effects [5]. The second is a study on 472 smokers with severe or very severe COPD. The rates at 24 weeks of continuous abstinence for each type of

treatment were: 38.2% for nicotine replacement therapy, 60% for bupropion and 61% for varenicline. The overall rate was 48.5%. Varenicline was more effective than nicotine patches, 61% *vs* 44.1% [OR: 1.98 (95% CI 1.25-3.12); $p=0.003$]. Another important finding of the study was that the patients treated with varenicline for 24 weeks had higher abstinence rates than those treated for 12 weeks: 59.7% *vs* 66.7% (OR: 0.74; 95% CI: 0.32-1.7) [6]. The clinical trial performed in smokers with COPD included patients with mild-moderate COPD that received intensive cognitive behavioural therapy. However, it is also relevant to observe efficacy and safety in the actual clinical practice of smokers with severe or very severe COPD.

Varenicline is generally administered for 12 weeks, although it is important to consider that two studies have shown that treatment prolongation to 24 weeks is safe and can increase success rate [7,8]. The number needed to treat with varenicline to obtain a favourable outcome, based on weighted average rates, is 11 (95% IC: 9-13) [9]. In this study, we report the outcomes obtained for VALUE, a descriptive study with no comparative arm, in patients with severe or very severe COPD treated with varenicline for 24 weeks.

Material and Methods

Study design

VALUE was a post-authorisation, observational, prospective follow-up study (PAS-PF) involving 11 smoking cessation units. The VALUE study was performed in Spain during the years 2014 and 2015.

The patients included in VALUE were smokers with severe or very severe COPD (stages III or IV according to GOLD 2009 or stages C or D according to GOLD 2011). The investigators decided which patients were eligible for the protocol and their inclusion in the study. The inclusion and exclusion criteria of the participants are shown in Table 1. Brief psychological counselling was planned for each visit and 24 weeks of treatment with varenicline. Psychological counselling focused on educational advice to quit was provided by the investigators. The primary objective of the study was to evaluate the effectiveness of varenicline after 24 weeks of treatment, with continuous abstinence between weeks 9th and 24th confirmed by measurement of CO in expired air, in smokers diagnosed with severe or very severe COPD.

Table 1. Inclusion and exclusion criteria of the participants.

Inclusion criteria

- Female or male smokers over 40 years of age
- Diagnosis of severe or very severe COPD according to the GOLD guide
- Motivation to stop smoking*
- Patients smoking ≥ 5 cigarettes/day
- Signing the informed consent

Exclusion criteria

- Presence of psychiatric diseases
- Presence of contraindications to the drug
- Treatment with systemic corticosteroids or hospitalizations for acute worsening of COPD during the 4 weeks prior to inclusion in the study
- Absence of stability in health condition
- Alcohol or drug abuse (except for nicotine) in the week prior to inclusion in the study
- Inability to meet the study conditions

* Motivation to quit was appraised by responding yes or not.

Procedures and interventions

The patients were treated with varenicline 0.5 mg/day for the first three days, 0.5 mg/12 hours for the next four days and from day 8 with 1 mg/12 hours to complete, if possible, 24 weeks of treatment.

The schedule of visits for each participant were as follows: at baseline, at 2, 4, 8, 12, 16, 20, 24 weeks and additionally at 9 and 12 months. Also, there were two telephone calls at 8th and 20th weeks. At each visit, data were collected on abstinence from smoking, treatment compliance and side effects of the medication. In addition, data were recorded on CO levels in exhaled air, exacerbation of symptoms and hospital admissions in the past year, concomitant treatments and other conditions. CAT questionnaire score was performed at baseline and visits 7 and 9. CAT is a patient-completed questionnaire assessing globally the impact of COPD (cough, sputum, dyspnea, chest tightness) on health status. Score ranges from 0-40 and higher scores denote a more severe impact of COPD on a patient's life. Three visits included assessment using spirometry (at baseline, at 6 and 12 months).

7 days point prevalence abstinence was defined as not smoking in the past week, while continuous abstinence was defined as not smoking from at least the ninth week to the time of follow-up. Participants were considered abstinent who self-reported tobacco abstinence throughout the period in conjunction with no exhaled carbon monoxide concentration greater than 10 ppm. Measurement of CO in expired air was performed at visits 1, 2, 4, 5, 7, and 9. The planned duration of the follow-up of the participants was one year.

Ethics

The study was performed according to the principles of the Declaration of Helsinki (last revision Washington 2002), it was classified by the Spanish Agency for Medicines and Medical Devices and approved by an independent ethics committee. The investigators ensured the anonymity of the participating subjects. Therefore, the participants could not be identified in the clinical research form or in any other document and identification was always performed using a code. The investigators kept the records of the participating subjects specifying the codes, names and addresses. All documents were kept under strict confidentiality conditions by the investigators.

Results

Characteristics of the patients

The number of subjects completing the baseline visit was 79, of whom 39 completed at least 24 weeks of follow-up. The characteristics of these 79 patients are shown in Table 2, while the reasons for not continuing or not starting the study are classified in the Supplementary Table 1. One patient did not suffer severe or very severe COPD according to the GOLD guidelines, so he was excluded from the study despite completing over 7 visits.

Results abstinence from smoking

The outcomes in the intention-to-treat population included at baseline are given in Table 3 and were for 9-24 weeks continuous abstinence, point prevalence abstinence and continuous smoking 17.7%, 31.6% and 15.1% respectively. 51.8 of patients were reported as not valid/unknown (patients excluded for some criterion despite completing the baseline visit, patients not starting treatment or patients for

which no data are available). The outcomes in the population of subjects completing 24 weeks of follow-up were at week 24: 9-24 weeks continuous abstinence 36.8%, 7 days point prevalence abstinence 65.7%, and continuous smoking 31.5% (Table 4).

Adverse events

After two weeks of treatment with varenicline, 57.8% of the participants reported some type of adverse event. This percentage decreased progressively and at Visit 7, after 24 weeks of treatment, was 7.8%. The most common adverse events were nausea (36.8% after 2 weeks of treatment), vivid dreams (26.3% after 2 weeks), stomach ache (15.7% after 4 weeks), insomnia (13.1% after 2 weeks), headache (10.5% after 2 weeks) and vomiting (5.2% after 2 weeks).

A progressive reduction in the incidence of adverse events was seen over time, with the maximum occurring at the start of treatment. In patients discontinuing the study before performing the control at week 24

Table 2. Characteristics of the patients completing the study. The number of patients performing controls until week 24 was 39, but one of whom was excluded as they were not suffering from severe COPD.

	Patients recorded at the baseline
Male/female gender in %	75.9 /24.1 (n=79)
Mean age ± SD (n)	60.6 ± 8 (n=79)
Cigarette smokers %	94.9 (n=75)
Cigar smokers %	5.1 (n=4)
Mean ± SD number of cigarettes consumed/day	24.1 ± 5 (n=73)
Mean ± SD FTND- score	6.1 ± 2 (n=75)
Mean n of previous attempts to stop smoking	1.98 (n=75)

Table 3. Intention-to-treat outcomes at week 24.

Intention-to-treat outcomes at week 24 (n=79)	n	% TOTAL
Continuous abstinence	14	17.7%
7 days point prevalence abstinence	25	31.6%
Continuous smoking	12	15.1%
Not valid/unknown*	41	51.8%

*Patients excluded for some criterion despite completing the baseline visit, patients not starting treatment or patients for which no data are available.

Table 4. Outcomes in the population performing controls at least until week 24.

Outcomes in the population performing controls until week 24 n=38	Weeks 9-12 n=38	Weeks 9-24 n=38	Weeks 9-52 (n=38)
Continuous abstinence	57.8% (n=22)	36.8% (n=14)	26.3% (n=10)
7 days point prevalence abstinence	73.6% (n=28)	65.7% (n=25)	42.1% (n=16)
Continuous smoking	21.0% (n=8)	31.5% (n=12)	39.4% (n=15)
Not-valid/unknown	5.2% (n=2)	2.6% (n=1)	18.4% (n=7)

Table 5. CAT questionnaire results at baseline and at week 24. The mean score at week 24 was 15.1 ±5.7 points. The reduction in relation to the baseline data was about 4 points, and this reduction was statistically significant (paired T test, p<0.01).

	N	Mean	Standard deviation	Median
Baseline CAT questionnaire score	31	18.94	7.61	20.00
CAT questionnaire score at week 24	31	15.16	5.79	16.00
Raw data difference	31	3.77	-	4.00
Difference in %	31	19.9	-	20

two deaths were reported, one due to neoplasm of the pancreas and the other due to an episode of acute worsening of COPD. Two participants discontinued the study due to adverse events probably related to treatment, both related with digestive intolerance. The main adverse neuropsychiatric events observed were mild sleep disturbances. Anxiety was recorded in one participant, and a feeling of apathy in another. No cases of suicidal ideation or adverse cardiovascular events were reported.

CAT questionnaire and acute worsening of COPD

In patients who underwent controls until week 24, the mean CAT score at this week was 15 points. The reduction from the baseline data was 3.77 points, and this reduction was statistically significant (Table 5). In the subgroup that stopped smoking a higher percentage reduction was seen from the baseline score as compared to the subgroup that continued smoking (-22.2% versus -19.3%), although the difference was not significant. At one-year visit mean CAT score was 16.4±5.9. The reduction from the baseline data was about 3 points, and this reduction was statistically significant.

The average number of acute exacerbations of COPD at week 12 was 0.49 episodes/patient and a mean of 0.07 episodes/patient required hospital admission. At week 24 these rates were 0.84 and 0.15 and at the visit one-year after starting the study they were 1.57 and 0.29, respectively. No statistically significant differences were seen in the number of episodes with or without hospital admission and smoking cessation (p=0.15).

Discussion

We performed an open-label, follow-up study where a group of smokers with severe or very severe COPD have been treated with varenicline at standard doses for a period of 24 weeks in association with brief counselling along with 8 face-to-face visits and 2 phone calls. The results by intention to treat were: 9-24 weeks continuous abstinence 17.7%, 7 days point prevalence abstinence 31.6%, continuous smoking 15.1% and not valid/unknown 51.8%. In patients who performed at least 24 weeks of follow up the outcome shown that 9-24 weeks continuous abstinence was 36.8% and 7 days point prevalence abstinence 65.7%. No serious cardiovascular or neuropsychiatric adverse events occurred and we detected a significant improvement in the quality of life measured by CAT in the group of subjects who stopped smoking.

Studies on smoking cessation with varenicline in patients with COPD are rare. There are not many studies. As shown above, Tashkin *et al.* published a continuous abstinence rate in mild/moderate COPD at Weeks 9-12 of 42.3% (*versus* 8.8% with placebo) and at Weeks 9-52 of 18.6% (*versus* 5.6% with placebo) [5]. Jiménez Ruiz *et al.* published a percentage of continuous abstinence at Weeks 9-24 of 58.3% in severe or very severe COPD. [6] In our study the results for 9-24 weeks continuous abstinence could be rated as intermediate between the two. It must be noted that psychological counselling in the studies by Tashkin *et al.* and Jiménez-Ruiz *et al.* were intensive, while in our study the patients received brief counselling. The need for intense psychological counselling in smokers with COPD in order to increase smoking cessation rates has been highlighted in a recent meta-analysis [4]. Probably, this could be a reason for the low abstinence rates found in this study. All subjects included in the study had severe or very severe COPD and, in spite of that, they continue smoking. They would have needed a most intensive psychological intervention.

It must be noted that most subjects in the study had concomitant diseases and all of them had severe COPD. Despite this context, most adverse events were rated as mild and they only led to treatment discontinuation in two cases. The neuropsychiatric type adverse events reported were not particularly significant, and those of a cardiovascular nature were not either. As in the studies previously published [10-12] the adverse events recorded showed a high incidence of nausea at the start of treatment (36.8% in the first two weeks), although the incidence of adverse events decreased progressively over time and at the last visit only 7.8% notified some. Most participants registered at the baseline visit had concomitant diseases and two of them died during the study, one due to a malignant neoplasm of the pancreas and the other due to an episode of acute worsening of COPD. Neither of the two events was attributed to the treatment.

The CAT questionnaire is a tool developed by Jones in 2009 to measure quality of life in subjects with COPD [13]. It has been suggested that a variation of 2 units can show a clinically significant change in the patient's health condition [14]. In the study the patients completed the CAT three times: at the baseline visit, after 24 weeks and one year after the start. A reduction of almost four points was seen at Week 24 and of three points at one year. Both differences were statistically significant in relation to the score at the baseline visit. It shows that smoking cessation clearly contributes to improving quality of life in patients with severe or very severe COPD.

The study has two major limitations, the lack of a control group and the percentage of patients not completing or not starting the visits. However, it must be considered that VALUE is a post-authorisation, prospective study, so it was designed without a control arm. Post-authorisation studies with prospective follow-up (PAS-PF) are an essential part of the development and follow-up of drugs. This is because, unlike the controlled clinical trials that investigate a population selected according to very strict inclusion and exclusion criteria, a PAS-PF study observes patients under real conditions and in uncontrolled settings that are receiving a standard treatment in accordance with the investigator's criterion. The second limitation relates to the high percentage of patients initially included who did not take part in the follow up until Week 24 and many of them did not even take part in the first follow up visit. Initially 79 patients were enrolled but only 38 finished the study. However, it is important to consider that, in this type of therapy, drop-outs are relatively frequent, amounting to 30-40% of the subjects discontinuing treatment with varenicline in the reference clinical studies, 35-45% with bupropion and 40-45% with placebo [11]. Moreover, it is important to consider that this group of patients is a hardcore group of smokers. In spite of receiving a specific smoking cessation treatment free of charge in a context where these types of treatments are unfunded, most of them did not attend even the first visit of follow up.

In summary, it must be noted that an open-label, follow-up study on the treatment of smoking with varenicline has been performed for six months in a group of patients where little information is available. Patients included in VALUE were active smokers despite all of them had a severe COPD and half of them ischaemic heart disease, which suggests a very high degree of dependence. In this regard it is important to highlight the number of patients who did not initiate or were missed from the study. Considering these facts, interventions aimed at improving compliance should be a priority and in a recent systematic revision promising interventions are reported in this aspect [15].

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