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Efficacy of Inhaled Steroids in Undiagnosed Subjects at High Risk for COPD*

Results of the Detection, Intervention, and Monitoring of COPD and Asthma Program

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Background and aim: COPD leads to a progressive decline of pulmonary function. Family physicians treat a substantial number of patients with COPD and are encouraged to start treatment at as early a stage as is possible. This study analyzed the effectiveness of early inhaled corticosteroid treatment on the decline of pulmonary function in COPD patients.

Patients and setting: Subjects with a rapid decline in lung function (ie, FEV₁ decline, > 80 mL/yr) who had never before received a diagnosis of asthma or COPD.

Methods: Two-year, randomized, controlled, double-blind clinical trial of fluticasone propionate (250 µg bid; 24 patients) or placebo (25 patients), followed by a 7-month open-label study in which all subjects received fluticasone propionate. The primary outcome was the post-bronchodilator therapy FEV₁, and secondary outcomes were respiratory symptoms, exacerbations, health state, quality of life, and health-care utilization.

Results: After 31 months, there were no statistical differences in post-bronchodilator therapy FEV₁ between the intervention group and the control group. No statistical differences were observed for symptoms, exacerbations, or quality of life, although tendencies were consistently in favor of treatment. There was no significant impact on the direct or indirect costs.

Conclusions: There are no indications that early treatment with inhaled corticosteroids modifies a rapid decline in lung function or respiratory symptoms and quality of life.

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Key words: COPD; early treatment; inhaled corticosteroid; lung function decline

Abbreviations: BHR = bronchial hyperresponsiveness; CRQ = chronic respiratory questionnaire; DIMCA = Detection, Intervention, and Monitoring of COPD and Asthma; FP = family physician; MCID = minimal clinically important difference; QALY = quality-adjusted life year

COPD is becoming one of the leading causes of disability and death, and presents an increasing burden of illness to society. In the past, considerable underdiagnosis and undertreatment of chronic airway disease have been reported. At the same time, several studies have reported promising results with inhaled corticosteroid treatment. In asthma patients, inhaled steroids are effective as first-line therapy. In COPD patients, the beneficial effects of inhaled steroids remain controversial. The annual rate of lung function decline is greater in patients with COPD and asthma than in healthy subjects. In patients with COPD, inhaled steroid treatment results in the improvement of lung func-
tion during the first 6 months\textsuperscript{14–16} and some deceleration of lung function decline.\textsuperscript{17} Improvement of health status\textsuperscript{1,4,18} and reduction of exacerbations\textsuperscript{14,19} also have been reported. These observations have resulted in recommendations to start treatment as early as possible.\textsuperscript{6} For asthma patients, this is included in international guidelines,\textsuperscript{20} but for COPD patients the beneficial effects of early treatment have not yet been demonstrated. From our observation of patients in the practice of family medicine, we hypothesized that the maximum effect of inhaled steroid treatment on lung function decline could be expected if treatment was instituted at the earliest stage of disease, before patients received diagnoses in regular patient care.\textsuperscript{7} This resulted in the establishment of the Dutch Detection, Intervention, and Monitoring of COPD and Asthma (DIMCA) in family practice project in 1991.\textsuperscript{4,21} The identification of early stages of COPD was later supported by the Global Initiative for Chronic Obstructive Lung Disease classification with the stages 0 (at risk) and I (mild disease).\textsuperscript{9,10} In the current study, we assessed the effects of early inhaled steroid treatment in subjects in whom COPD had not been diagnosed who, prior to intervention, showed a rapid decline of lung function. Subjects receiving early inhaled steroid treatment were compared with subjects in whom this treatment had been postponed for 2 years.

**Materials and Methods**

**Design**

Selection for the trial followed a screening and monitoring approach of subjects who had never before received a diagnosis and/or had been treated for asthma or COPD.\textsuperscript{3} All subjects aged 21 to 70 years fulfilling this criterion who were listed in 1 of the 10 family practices involved in the study were invited to the initial screening program (Fig 1). All subjects completed a respiratory symptoms questionnaire, and underwent spirometry and histamine provocation testing. All subjects who reported at least one respiratory symptom and showed airflow obstruction and/or bronchial hyperresponsiveness (BHR) were invited to the second study phase, which consisted of 6 to 24 months of monitoring comprising four to eight lung function measurements. All subjects with an annual pre-bronchodilator therapy FEV\textsubscript{1} decline of ≥ 80 mL were considered to be at risk for developing COPD and were invited into the current study (Fig 1).

To study the effects of early inhaled steroid intervention, a 2-year, randomized, double-blind, placebo-controlled trial was initiated (also referred to as early inhaled steroid treatment), followed by an open-label extension period of 7 months (also referred to as postponed inhaled steroid treatment). The allocation of subjects to the intervention and control groups followed a block randomization within each family practice. Study medication (fluticasone propionate, 250 µg bid administered by metered-dose inhaler, and matching placebo) was prepared by the manufacturer (GlaxoSmithKline; Research Triangle Park, NC). Fluticasone and placebo were packed in identical canisters.

The patients’ family physician (FP) handed out a new set of study medication every 3 months. To record drug compliance, the old canisters were taken in and weighed. Subjects also recorded their medication use in a trial diary. Individual compliance rates were determined by expressing the number of puffs consumed (ie, the dosages provided minus dosages returned) as a percentage of the amount prescribed during the study.\textsuperscript{22} When noncompliance was observed during trial visits, subjects were reminded of the need to adhere to prescribed medication and were instructed in proper use. Subjects were permitted to use short-acting bronchodilator agents as rescue medication. In case of an exacerbation, a 10-day course of therapy with oral prednisolone was advised.

Post-bronchodilator therapy FEV\textsubscript{1} decline served as the primary outcome. During the monitoring phase, 4 following the trial, the observed mean annual FEV\textsubscript{1} decline for the subjects who were eligible for study participation was > 200 mL/yr. Halving this rate to 100 mL/yr was considered a relevant treatment effect. A per-protocol participation of 56 subjects (28 per group) was required to detect this difference (assumptions: 1 − β = 0.80; α = 0.05; SD = 132 mL). Secondary outcomes were respiratory symptoms, exacerbations, health state, quality of life, and healthcare utilization. The medical ethics review board of the University Medical Centre Nijmegen approved the study. Subjects gave their written informed consent.

**Measurements**

**Lung Function, Reversibility, and BHR:** Lung function measurements were performed in a lung function laboratory (Microspiro HI-298 spirometer; Chest Corporation; Tokyo, Japan)\textsuperscript{24} following American Thoracic Society standards.\textsuperscript{23} Measurements were scheduled at baseline and repeated every 6 months. The European Community for Coal and Steel predicted values were required to detect this difference (assumptions: 1 − β = 0.80; ν = 0.05; SD = 132 mL). Secondary outcomes were respiratory symptoms, exacerbations, health state, quality of life, and healthcare utilization. The medical ethics review board of the University Medical Centre Nijmegen approved the study. Subjects gave their written informed consent.

**Quality of Life and Health State:** Disease-specific quality of life was measured at baseline and every 6 months using the interviewer-administered version of the chronic respiratory questionnaire (CRQ).\textsuperscript{29} A within-subject improvement of 0.5 U at the end of the 2-year observation period was considered to be a minimal clinically important difference (MCID).\textsuperscript{30} Preference-based utilities were measured every 6 months by standard gamble procedure using the Maastricht utility measurement questionnaire.\textsuperscript{27} Quality-adjusted life years (QALYs) were determined by calculating the area under the utility-time curve for each subject. One additional QALY is interpreted as one additional year in perfect health for one subject.

**Health-Care Resource Use and Productivity Losses**

Consultations and prescriptions for respiratory medication were recorded by the patients’ FPs and were verified by the
investigators through medical record audit and a standardized interview that was conducted every 3 months with study subjects. Medication cost included pharmacy cost and the value added tax. Subjects recorded their use of over-the-counter medications and the number of days they had been unable to perform paid or unpaid work in the diary. Indirect costs were assessed using the Human Capital Approach. Dutch guilders were converted to Euros (€). One day of lost work was valued as 8 h times €8.18 per hour. For conversion to US dollars, Euros should be multiplied by a factor 0.912, based on the 2000 Purchasing Power Parities, as issued by the Organization for Economic Cooperation and Development.

**Statistical Analysis**

Subjects who participated in the 2-year early intervention trial and in the 7-month open-label extension with fluticasone treatment, and who had used at least 70% of their trial medication...
were included in a per-protocol analysis. Treatment groups were compared on baseline characteristics using appropriate univariate statistical tests. Because of the observed initial increase of the post-bronchodilator therapy FEV₁, a linear regression model with one breaking point showed the best fit for the course of this parameter over time. This so-called *piecwise* model was used to analyze both early and postponed treatment effects. For early treatment, the model discriminated between the initiation of treatment (ie, 0 to 3 months) and ongoing treatment (ie, 4 to 24 months), and for postponed treatment it discriminated between the initiation of treatment (ie, 24 to 26 months) and ongoing treatment (ie, 27 to 31 months). The mean change in post-bronchodilator therapy FEV₁ over time was estimated by a mixed linear effect model for repeated measurements,¹¹ which included baseline FEV₁, age, gender, height, and smoking history as covariates. The paired t test was used to compare the change per period. Differences in symptom-free weeks and CRQ scores were tested using t test statistics. The course of the CRQ total and domain scores was analyzed using a mixed-effects model. Poisson analysis was used to analyze the number of exacerbations.

Utilities were converted to QALYs by calculating the area under the curve for the periods from 0 to 24 months and from 24 to 31 months. The mean differences in QALYs were tested using the t test, and longitudinal analysis (a mixed-effects model with correction for baseline values) was used to estimate utility over time. A statistical software package (SAS, version 6.12; SAS Institute; Cary, NC) was used for all analyses.

## RESULTS

During the DIMCA monitoring phase, 85 subjects with a rapid decline in lung function were identified (Fig 1). Forty-one subjects were randomized to receive early fluticasone treatment, and 44 subjects were randomized to receive placebo treatment. Of these subjects, 57 (67%) participated in the open-label, postponed fluticasone study. The per protocol analysis included all 49 subjects who finished both the early treatment trial and the open-label extension analysis included all 49 subjects who finished both the early treatment trial and the open-label extension. The early treatment group included more ever-smokers with a history of more pack-years of smoking.

### Clinical Effects

**Lung Function:** There were no statistically significant differences in the course of the post-bronchodilator therapy FEV₁ over time between the treatment groups (Fig 2). The estimated mean changes of the post-bronchodilator therapy FEV₁ during the subsequent study phases are shown in Table 2. For other pulmonary function measures (ie, mean maximal expiratory flow and inspiratory vital capacity), similar patterns were found (data not shown). An explorative subgroup analysis on smoking behavior, allergy, and BHR, in addition to the rapid FEV₁ decline, did not modify the effect of those using fluticasone relative to those using placebo (data not shown).

**Respiratory Symptoms and Exacerbations:** During the monitoring phase preceding the trial, eight exacerbations were recorded in the group that was later allocated to receive fluticasone treatment, and three exacerbations occurred in the group that was later allocated to receive placebo treatment. During the

| Table 1—Baseline Characteristics of Study Subjects by Treatment Group* |
|-------------------------------------------------|-----------------|-----------------|
| Treatment Groups                              | Fluticasone Propionate | Placebo |
| Characteristics                               | (n = 24)         | (n = 25)       |
| Age, yr                                       | 51.8 (10.3)      | 47.9 (10.0)    |
| Female gender, %                              | 58.3             | 40.0           |
| Height, cm                                    | 168 (10)         | 172 (9)        |
| Smoking history at entry                      | 75.0             | 48.0           |
| % ever                                        | 9 (0.5–24)       | 0 (0–8)        |
| Pack-years†                                   | 54.5             | 45.8           |
| Allergy, %                                    | 37.5             | 52.0           |
| No bronchial symptoms reported, %             |                  |                |
| Pre-bronchodilator therapy FEV₁               |                  |                |
| L                                            | 2.62 (0.75)      | 3.02 (0.66)    |
| % predicted                                   | 88.3 (14.5)      | 91.2 (14.4)    |
| Post-bronchodilator therapy FEV₁              |                  |                |
| L                                            | 2.73 (0.75)      | 3.10 (0.72)    |
| % predicted                                   | 91.9 (12.0)      | 94.0 (14.8)    |
| Post-bronchodilator therapy FEV₁/IVC          |                  |                |
| Reversibility of FEV₁, % predicted            | 2.93             | 1.62           |
| PC₂₀ histamine, mg/mL‡                        | 3.20             | 3.62           |
| BHR, %                                       | 66.7             | 52.0           |
| CRQ score§                                    | 5.9 (0.86)       | 6.1 (0.79)     |
| Dyspnea domain                                | 6.2 (1.2)        | 6.5 (1.2)      |
| Emotions domain                               | 5.6 (0.9)        | 5.7 (0.9)      |
| Fatigue domain                                | 5.5 (1.1)        | 5.7 (1.1)      |
| Mastery domain                                | 6.3 (0.8)        | 6.6 (0.6)      |
| Utility¶                                      |                  |                |
| Reference health state                        | 0.55 (0.16)      | 0.61 (0.21)    |
| Own health state                              | 0.79 (0.17)      | 0.85 (0.13)    |

*Values given as mean (SD), unless otherwise indicated.  
PC₂₀ = concentration of histamine provoking a fall in FEV₁ of ≥ 20%.  
†Values given as median (interquartile range).  
‡Values given as geometric mean.  
§Range, 1 to 7.  
¶Range, 0 to 1.
early treatment trial, three exacerbations were recorded in the fluticasone group vs seven exacerbations in the placebo group. During the open-label extension period, one additional exacerbation was recorded in the group that continued to receive fluticasone, and three exacerbations in the postponed fluticasone treatment group. Poisson analysis did not show a difference in exacerbations between the groups for the subsequent periods ($p = 0.18$). Of the 25 exacerbations reported, 17 (68%) were first exacerbations.

During early treatment, the number of symptom-free weeks did not differ between the early treatment and postponed treatment groups (61.5% vs 71.5%, respectively; $p = 0.34$). During postponed treatment, these percentages were somewhat different (early treatment group, 56.5% symptom-free weeks; postponed treatment group, 76.5% symptom-free weeks; $p = 0.06$).

**Quality of Life and Health State:** Baseline CRQ scores indicated a mild impairment in quality of life (Table 1). During early treatment, there was no difference between the treatment groups in either the CRQ total score or the domain score (Fig 3). The

<table>
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<tr>
<th>Table 2—Corrected Mean Change of the Annual Post-Bronchodilator Therapy FEV$_1$ Decline as Estimated by the (Piecewise) Regression Models*</th>
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</thead>
<tbody>
<tr>
<td>Intervention</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Early fluticasone treatment FEV$_1$, decline, mL/yr</td>
</tr>
<tr>
<td>Continued early fluticasone treatment FEV$_1$, decline, mL/yr</td>
</tr>
<tr>
<td>Placebo treatment FEV$_1$, decline, mL/yr</td>
</tr>
</tbody>
</table>

*Values given as mean (SE).
proportion of subjects with an MCID on the CRQ was 21% in the early treatment group vs 24% in the placebo group (p = 0.79). The dyspnea score (25% vs 12%, respectively), the fatigue score (21% vs 16%, respectively), and the mastery domain scores (17% vs 8%, respectively) were consistently higher in the fluticasone treatment group than in the placebo treatment group (not statistically significant). For the CRQ emotions domain, the proportion of subjects was higher in the placebo group than in the fluticasone treatment group (25% vs 32%, respectively; not statistically significant). After postponed treatment, the proportions of subjects with an MCID in quality of life were 14% for the postponed treatment group and 33% for the early treatment group (p = 0.12).

There were no significant differences in baseline utilities between the subjects' own health state and the hypothetical health state (Table 1). During both the early and postponed treatment, a large proportion (ie, 36 to 45%) of the health state descriptions collected did not indicate any impairment of generic quality of life. The course of the mean utility of the subject's health status is shown in Figure 4. Early treatment resulted in a mean difference of 0.0244 in
favor of fluticasone ($p = 0.72$; Table 3). Expressed in QALYs, health state was indicative of the effect of treatment. For early treatment, 1.22 QALYs were gained per year per 100 treated subjects (95% confidence interval, $-5.5$ to $7.9$). Postponed treatment resulted in a mean difference of 0.0038 in favor of fluticasone treatment ($p = 0.87$; Table 3). Expressed in QALY gains, this amounts to 0.76 QALYs per year per 100 treated subjects (95% confidence interval, $-7.0$ to $8.6$). In the early treatment period, the estimated mean difference in utility was 0.0099 per year ($p = 0.75$). Assuming that this effect persists in subsequent years, 0.99 QALYs would be gained by early fluticasone intervention per 100 treated subjects per year.

**Health-Care Resource Use:** During early treatment, the mean annual cost of experimental medication was €310 per subject (Table 4). The costs of nonexperimental respiratory medication in the fluticasone group and the placebo group were €10.99 and €17.39, respectively ($p = 0.34$). The average number of prescriptions written per year for respiratory medication was lower in the fluticasone treatment group (0.70 prescriptions per subject) compared to that in the placebo group (1.19 prescriptions per subject). The total mean health-care cost was similar in both groups ($p = 0.87$). There were no referrals to chest physicians or respiratory disease-related hospital admissions. The cost of fluticasone treatment constituted the major part of the direct health-care cost. The average number of days that a subject had been unable to perform his or her normal activities due to respiratory symptoms was 3.1 days in the fluticasone group and 2.5 days in the placebo group. The associated mean indirect cost was €203.05 and €164.52, respectively ($p = 0.65$). During postponed fluticasone treatment, the cost of nonexperimental respiratory medication remained higher (€8.03 vs €15.80, respectively; $p = 0.15$). The use of nonexperimental respiratory medication during the trial (placebo treatment) appeared to be highly correlated with the extent of use during the extension period (postponed fluticasone treatment; $r = 0.90$). During postponed fluticasone treatment, the average number of prescriptions per year decreased, mainly in the early fluticasone treatment group. The average cost of health-care resource use remained constant ($p = 0.93$), and there were no referrals or hospital admissions. Loss of productivity changed over time. In the early fluticasone treatment group, the number of days lost showed a threefold increase ($p = 0.05$), whereas in the postponed treatment group the increase was twofold ($p = 0.14$). The associated indirect costs were €589 and €334, respectively. There was no significant difference in indirect costs between the groups ($p = 0.27$).

**Table 3—The (Piecewise) Calculated Gain in Health State**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early Treatment</th>
<th>Postponed Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 25)</td>
<td>Fluticasone (n = 24)</td>
</tr>
<tr>
<td>QALY gains</td>
<td>0.0890</td>
<td>0.1134$^*$</td>
</tr>
</tbody>
</table>

$^*$p = 0.72.
$^+$p = 0.57.

**Discussion**

In the DIMCA program, subjects in whom COPD formerly had been undiagnosed but had objective signs of COPD had their condition detected and treated in a family practice. Although chronic airway obstruction can be identified in such an early stage, a final diagnosis, differentiating between asthma and COPD, often is not yet possible. As subjects with airway obstruction who show a rapid decline in lung function bear an increased risk for the development of COPD, this study focused on this particular group. Following active detection, subjects were treated at an earlier stage than would have been possible in a regular general practice setting. In the current study, the effect of treatment was measured by the change in the course of post-bronchodilator therapy FEV$_1$. In conformance with our initial hypothesis, lung function follow-up values were analyzed in a model that allows for differentiation between the initial improvement of lung function and the long-term mediatisation of the course of lung function decline, in subjects receiving both early and postponed treatment. However, there was no initial improvement among the fluticasone-treated subjects in the group of rapid decliners. Also, the hypothesis that a delay in treatment would cause irreversible damage could not be confirmed. The decline in lung function in the early intervention group did not differ from that after postponed intervention. A post hoc power analysis based on the actual number of trial participants (49 participants, instead of the assumed 56 participants) revealed that with the per-protocol participation of 49 subjects a treatment difference of 105 mL/yr (80% power; $\alpha = 0.05$; SD, 132 mL/yr) could have been detected.

Several early studies$^5,6$ showing promising results with inhaled steroid treatment expected maximum benefit (ie, the prevention of the irreversible loss of lung function) if treatment was instituted as early as possible in the development of the disease. In a metaanalysis,$^32$ it was observed that patients with
clearly defined moderate-to-severe COPD had a slowdown in the course of lung function decline during 2 years of treatment with a relatively high dosage of inhaled corticosteroids. A number of large randomized clinical trials evaluating the efficacy of inhaled steroids have demonstrated initial improvement in lung function. However, these studies confirmed the findings of our study that inhaled steroid treatment does not substantially modify the course of pulmonary function.

Although randomized at the start, the treatment groups did not have a similar baseline health profile. Subjects who were later allocated to early fluticasone treatment had a slightly lower lung function and showed less reversibility. Although not statistically significant, they were found to be older, shorter, more often allergic, less often without symptoms, and more (often) to be smokers. This might indicate that the early treatment group had a somewhat worse prognosis at baseline. This is also illustrated by the change in lung function (Table 1). Rapid decline in lung function may be considered a strong indicator of COPD, however, its (short-term) value in evaluating treatment can be debated. Judged by the percentage change in the two groups, however, the actual gains in health in the two groups were quite comparable.

At the time of planning this study (1992), change in lung function was the predominant concept of the outcome of COPD, and for that reason it was chosen as the primary outcome measure. Nowadays, it is recognized that a rapid decline is not the only clinical characteristic of early stage COPD.

The rationale for the early treatment of COPD is its progressive nature and poor response to therapy once the disease is fully developed. But its early diagnosis is problematic, as the initial minimal symptoms and pulmonary function impairment are difficult to distinguish from self-limiting respiratory illness or asthma. For that reason, participants were included in this study after an observed decline in FEV1 of 80 mL/yr over 2 years, which is an observation period during which other studies had been able to find clinically relevant developments in pulmonary function. Irreversible loss of pulmonary function is characteristic of COPD, although (partial) irreversibility is also seen in asthma. Some patients in this study had BHR and were allergic, which are features of asthma. However, BHR is also often present in COPD patients.

Today, the emphasis is less on pulmonary function development as the outcome of the treatment of COPD, but is more on symptoms, exacerbations, health effects, and cost. However, in an exploratory analysis these secondary effect measures did not show a relevant effect of early fluticasone treatment. There was no significant increase in QALYs, nor were there any differences in exacerbation rate, health-related quality of life, or respiratory symptoms. Considering the economic consequences,
there was no difference in total mean health-care cost or indirect cost. Incremental costs were predominantly due to the use of experimental medications. As subjects for this study were recruited in the very early stage of their disease (before they had received a diagnosis from a regular care physician), room for improvement is likely to be small in any disease-related outcome measure. However, several tendencies on fluticasone treatment effects were identified. Preceding intervention, more exacerbations were recorded in the group that was later allocated to fluticasone treatment. During fluticasone treatment, improvement was found in the fluticasone group, suggesting a protective effect of therapy with inhaled steroids on the exacerbation rate. Furthermore, subjects in the postponed treatment group reported more symptom-free weeks after the initiation of fluticasone treatment. At baseline, subjects rated their health as relatively good. In both groups, there was a slight improvement in health status, implying an in-care effect. Early treatment did not show significant improvement in the subjects’ health state, but the results were suggestive for some health benefit. Furthermore, it was remarkable that the difference in the use of nonexperimental respiratory medication was mainly due to bronchodilator use. In the placebo group, medication use remained constant throughout the open-label extension period. This may reflect a person’s adaptation to medication use. Between groups, the main difference in health-care utilization had to be attributed to days lost from work, either paid or unpaid. After 2 years, the average number of days lost from work increased in both groups, but mostly in the group with early treatment. As these data do not allow for a more advanced analysis, it remains unclear whether subjects’ health became worse despite treatment or whether group prognoses were different at the start.

The DIMCA project is unique in that it has set out to study subjects who were in the state of developing COPD before signs and symptoms had brought them to seek regular medical care. In this phase, no effect from inhaled steroid treatment on lung function could be found. This implies that for this group the delay in initiating treatment did not result in the irreversible loss of lung function. On secondary outcomes, the results of both early and postponed treatment were suggestive of subtle health gains in respiratory symptoms, exacerbation rate, and health state. FPs therefore should continue to focus on the early detection and treatment of those visiting them who have respiratory signs and symptoms. But the study did not present evidence of the benefits of screening in order to begin treatment in the preclinical phase of the disease.

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