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Impact on Patient's Health Status following early identification of a COPD Exacerbation

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ABSTRACT

This study aimed to assess impact on patient health status during AECOPD. COPD patients (421) were enrolled in a multicentre, single-arm study with a 6-month observational follow-up period. Patients received 2 inhalations of Symbicort 200 Turbuhaler twice a day. Patients were assessed before the run-in period, at baseline, 1, 3 and 6 months. Patients were instructed to call upon a change in respiratory symptoms (24 hours +). This defined AECOPD. In addition to the initial call, SGRQ, CCQ, MRC and ADL were completed at 5-7 and 12-14 days. Patients (176) reported at least one AECOPD. Exacerbations were associated with statistically significant mean changes (worsening) in the SGRQ activity and impact domains at onset (12.1, SD 18.1 and 14.0, SD 15.2), during the first (9.8, SD 19.0 and 9.4, SD 16.6) and second weeks (3.1, SD 15.5 and 3.3, SD 14.7). Clinically significant deterioration in SGRQ impact scores was shown in 71% of patients following early identification, 55% and 37% during the first and second week of an AECOPD. Acute exacerbation severely impact on health status. This study provides valuable information on the change in health status during an AECOPD that can be utilized for future trials evaluating therapeutic intervention.

INTRODUCTION

Exacerbations are common for many patients with chronic obstructive pulmonary disease (COPD) and contribute greatly to increase morbidity, frequent emergency department (ED) visits, hospital admissions, and increased health care costs [1-3]. Evidence suggests that patients with recurrent acute exacerbations of COPD (AECOPD) have faster decline in lung function [4;5] possibly due to increased rate of airway inflammation [6]. The impact of AECOPD on patients' health status is far from being negligible [7-9].

Miravitlles et al [7] assessed the long term evolution of COPD patients' health status followed prospectively over a 2-year period. They showed that patients with frequent exacerbations had 2 units per year worsening of the St. George Respiratory Questionnaire (SGRQ) total score, compared to those with infrequent exacerbations. Similarly, hospital admissions resulted in an increased change of almost 2 units per year. In a clinical trial, Spencer et al [9] assessed the rate of recovery following an exacerbation. The greatest improvement in the SGRQ score occurred within the first 4 weeks (mean 8.9 units, 95% CI 6.5 to 11.5). A further improvement of 4.1 units (95% CI 2.2 to 5.9), constituting a clinically important improvement, was noted in patients with no recurrence of exacerbation. There is no data on loss of health during early identification of an AECOPD.

In this study we have prospectively followed a cohort of 421 patients with moderate to severe COPD. These patients had their health status assessed over a 6 month period and following early identification of an AECOPD. The rationale of conducting this trial was

to build the appropriate knowledge to be able to develop future studies evaluating therapeutic interventions for a pragmatic control plan. The primary objective was to assess the impact on patient's health status (SGRQ) following early identification of an AECOPD. The secondary objectives were to assess the impact of an AECOPD on disease control in terms of symptoms, functional and mental state changes as measured by the COPD Control Questionnaire (CCQ), dyspnea (MRC) and activity of daily living. The rate of improvement (return to baseline) in health status, disease control and activity of daily living in patients associated with an AECOPD were measured, and the predictive factors of exacerbation were assessed. The information from this study will increase our understanding of the impact on health status at the onset and during AECOPD. Knowledge of the change in health status of patients with stable, moderate to severe COPD, at the onset and during an AECOPD, could be utilized in designing and evaluating therapeutic intervention(s) aimed at improving the management of AECOPD in future trials.

METHODS

Study patients

Patients were recruited from 59 participating centres across Canada between February 6, 2003 and April 21, 2004, based on the following eligibility criteria: 1) diagnosis of stable COPD; 2) 40 years or older; 3) smoking history of at least 10 pack-years; 4) $FEV_1 \leq 70$ percent of predicted value and FEV1/FVC < 0.70; 5) dyspnea ≥ 2 on the MRC scale; at

least 2 exacerbations requiring medical intervention in the past 3 years; 6) no history of asthma or allergic rhinitis before the age of 40; 7) no regular use of oxygen, beta blockers, oral corticosteroids or the combination of inhaled corticosteroids / long-acting beta 2 agonists; and 8) no unstable or life threatening co-morbid condition. All patients gave informed consent to participate in the study. Additional criteria to be fulfilled at visit 2 were: 1) No AECOPD during the run-in period requiring intervention, unscheduled physician or ED visit, or hospitalization; 2) No course of antibiotic(s) and/or oral corticosteroids; 3) No increase in inhaled steroid and/or parenteral steroid treatment.

Study Design

The study was a multicentre, single-arm prospective cohort with a 2-week run-in period followed by a 6-month observational period, during which patients received 2 inhalations of budesonide/formoterol 200/6 ug (Turbuhaler®) twice a day as maintenance treatment. The run-in period was used to make sure the patients were stable. Patients' assessment included a complete medical history, spirometry, health status, disease control, the modified MRC and activity of daily living (ADL). Health status and disease control were measured prior to the 2-week run-in period, after the run-in period, just before the treatment period (baseline), and at 1, 3 and 6 months. All patients were asked to record daily, in a diary, their symptoms (dyspnea, cough, sputum quantity and color, sleep disturbances), morning peak expiration flow, and use of rescue medication. Patients were reminded at monthly intervals to complete diary records and also had follow-up telephone interviews after they reported acute exacerbations.

Reporting exacerbations and early identification

Patients were asked to report to their investigative site if they had sustained (for more than 24 hours) worsening of at least one of the three cardinal symptoms of AECOPD: dyspnea, sputum volume and purulence. This defined a patient who experienced an AECOPD. The first day of change in symptoms was taken as the day of onset of exacerbation. In addition to the initial patient call, follow-up calls were made at 5-7 days and 12-14 days from the day of onset. Each telephone interview included the completion of the SGRQ (excluding the symptoms domain) and a reminder to the subjects to complete the Exacerbation Notebook (self-administered CCQ, modified MRC and ADL) at home. The research assistant did not provide any intervention but encouraged subjects to follow their usual "care plan" or other channel(s) for intervention. The research assistant was trained with regards to an action plan in the event of an emergency situation related to an AECOPD.

St. George Respiratory Questionnaire

The SGRQ is a 50-item questionnaire with 76 weighted responses. It provides a total score and three domain scores: Symptoms (respiratory symptoms), activity (physical activities that cause or are limited by breathlessness), and impact (social and psychological effects of the disease). The symptoms domain refers to the last year and the activity and impact domains to "these days". The SGRQ is scored from 0 to 100 where 0 indicates the best and 100 the worst health. The SGRQ is a disease-specific questionnaire developed for patients with chronic airway disease. It's validity and

reproducibility have been confirmed [10;11]. As the "symptoms" component of SGRQ cannot be used in frequent administrations (less than one month interval), only the "activity" and "impacts" components were utilized during the Exacerbation Telephone Calls[12] .

COPD Control Questionnaire

The CCQ is a self-administered multidimensional symptom control questionnaire that includes 10 questions in three domains: symptoms, functional state, and mental state. It has been shown to have strong evaluative and discriminative measurement properties [15]. Patients are asked to recall their experiences during the previous 24 hours and to respond to each of the 10 questions using a 7-point scale from 0 = asymptomatic/no limitation to 6 = extremely symptomatic/totally limited.

Activity of Daily Living

The Activity of Daily Living questionnaire used in the study is not standardized and ~~it~~ has not been validated. Subjects were asked "how much did your COPD affect your normal daily activities during the previous 24 hours?" and were required to indicate, by placing a cross (X) on a 10 cm scale (with divisions ranging from 0 to 100%), how their COPD affected their normal daily activities. For example: 1) if activities were not affected at all by the disease (COPD), the X would be placed at the 0% mark; 2) if activities were reduced by half, the X would be placed at the 50% mark; 3) if unable to perform any of their daily activities, the X would be placed at the100% mark.

Medical Research Council (MRC) Dyspnea Scale

The Medical Research Council (MRC) Dyspnea Scale is a commonly used validated, ordinal scale on which the patients rate the type and magnitude of their dyspnea according to five grades of increasing severity [13]. The MRC dyspnea scale was interviewer administered at scheduled Clinic Visits from Visit 2 onwards and with each telephone call related to COPD exacerbations.

EQ-5D

The EQ-5D is a multidimensional measure of health-related quality of life. EQ-5D consists of the EQ-5D descriptive system (a page for obtaining a self reported description of health status) and EQ-5D VAS (a visual analogue scale "thermometer" for eliciting a self-rating of health status)[14]. The EQ-5D was administered at each clinic visit with Visit 1 as a practice session for the completion of the questionnaire. The EQ-5D data at Visit 1 was not entered into the database. Visit 2 responses served as the baseline values. In addition to the completion of the EQ-5D at each scheduled clinic visit, the questionnaire was also completed at the time of each telephone call related to an exacerbation of COPD.

Statistical analysis

Patients who had completed the 2-week run-in period to ensure their disease was stable and received at least one dose of study medication, were considered for the analysis.

Results were expressed as mean, standard deviation, median and interquartile range where appropriate. A p-value of < 0.05 was considered statistically significant.

For subjects experiencing COPD exacerbations, all efficacy variables including the questionnaires SGRQ, CCQ, MRC, EQ-5D, and ADL were presented over the four phases of the first exacerbation. Only data within +/- 1 day deviation were included in the final analysis (i.e., baseline, 0-3 days for the onset, 4-8 days for 5-7 days post exacerbation and 11-15 days for 12-14 days post exacerbation). Baseline health-related quality of life was determined by the most recent SGRQ score taken at least 48 hours prior to early identification of an exacerbation. Changes from baseline were analysed using paired t-tests. Correlations and effect sizes were calculated to compare changes between questionnaires.

Linear extrapolation using the last two data points (5-7 days and 12-14 days) was used to estimate the time that it takes in health status, disease control and activity of daily living to return to baseline after first exacerbation. To assess the predicting factors on exacerbation, an analysis was performed using a logistic regression model of having 1 or more AECOPD versus no AECOPD. Potential predictors included in the logistic analysis were age, sex, education level, smoking history, years since diagnosis, lung function, dyspnea (MRC scale), number of exacerbations in the previous 3 years and number of months since the last event, nebulized bronchodilators, antibiotic and oral corticosteroids required for the last exacerbation, hospitalization in the last year, and taking part ever in pulmonary rehabilitation. Using backward eliminating technique,

statistically significant variables were kept in the model when the p was < 0.10. Age was forced to be included in the final model. SAS® version 8.2 was used for statistical analysis.

RESULTS

Patients

Baseline characteristics of the 421 patients (all patients), patients without exacerbation (245), those with one (135), and with two or more (41) exacerbations are summarized in Table 1. Patient characteristics were similar except among patients who experienced two AECOPD or more. These patients had more AECOPD in the past, increased use of short-acting B_2 agonist and taking part in pulmonary rehabilitation, increased baseline dyspnea and worse health status.

Reported exacerbations

During the 6 month observational period, 176 patients (41.8%) reported a deterioration of at least one cardinal respiratory symptom; 135 patients had a single exacerbation and 41 multiple exacerbations (28 subjects had two exacerbations, 10 subjects had three and 3 subjects had four). At the onset of AECOPD, increased cough and dyspnea worsening were equally reported by patients (69% and 65%). Most patients presented with additional symptoms to change in dyspnea (63%) (i.e., change in sputum color and/or amount, wheezing and/or chest tightness, coughing, colds, and sore throat). Specifically,

61% of patients reporting exacerbations experienced increased amounts of sputum and 41% reported change in sputum color.

Health status

Health status improved after the first month of treatment and remained stable for the duration of the study for patients who had no AECOPD (SGRQ total score mean change of - 6.2 at one month, and - 6.9 at 6 months) and those with only one exacerbation (SGRQ total score mean change of - 4.7 at one month and - 4.2 at 6 months) (Figure 1). Patients with two or more exacerbations did not improve after the first month but their health status remained unchanged during the 6 month study period.

Table 2 shows baseline health status and changes following early identification of an AECOPD. AECOPD are associated with statistically significant mean changes in the SGRQ activity and impact domains at onset, during the first and second weeks. Figure 2 shows the percentage of patients with clinically important SGRQ impact score worsening (increase of 4 or more from baseline). Clinically significant deterioration in SGRQ impact scores was demonstrated in 71% of patients during onset of AECOPD, 55% during the first week, and 37% during the second week.

Other clinical outcomes

Table 3 shows changes in patient responses following early identification of COPD exacerbation. Generally, patients with an AECOPD showed statistically and clinically significant worsening of their disease. This was indicated by patients' responses to the

CCQ, the three domains (symptom, functional and emotional state), the MRC dyspnea, and the ADL questionnaires. The correlations between changes from the SGRQ and the other clinical outcomes were strong between variables (i.e., ≥ .5) and remain stable over time (i.e., no significant changes in correlations from baseline to 14 days after onset) (data not shown). For the change from baseline to onset of exacerbation, the effect sizes were within a moderate and high range (0.6-0.9) for most outcome variables except for activity of daily living (0.3). Impact domain appears to be more responsive to acute exacerbation as it showed a larger change compared to activity domain based on the effect size (data not shown).

Rate of improvement

The estimated time of health status (SGRQ) to return to baseline was 11 days for the Impact domain and 9 days for the Activity domain. Symptoms and functional state as measured by the CCQ returned to baseline at 12 and 13 days while mental state took much longer (39 days). Time for patients to return to their activities of daily living was 18 days.

Predicting factors of exacerbation

The results of the regression model analysis are presented in Table 4. Predictive factors of exacerbation included age, dyspnea (MRC scale) and number of exacerbations in the past year. It also appeared that those who participated in a pulmonary rehabilitation program had higher odds of getting exacerbation compared to those who did not participate.

DISCUSSION

This study revealed a clinically significant deterioration in health status during an AECOPD. This was reflected as a high magnitude on the SGRQ impact domain (increase of 4 or more), which persisted in more than half of patients during the first week and one third of patients during the second week. Based on the linear regression extrapolation, most of the variables of health status, symptoms and functional state returned to baseline after 14 days except for mental state (39 days). AECOPD clearly impacts not only on the functional but also on the emotional state of patients, and markedly restricts activities of daily living.

The study also showed that increased dyspnea and previous exacerbations are predictors of exacerbations. Those who participated in a pulmonary rehabilitation program had higher odds of AECOPD compared to those who did not participate. This is likely to represent a bias from confounding rather than the effect of the exposure to a pulmonary rehabilitation program itself.

The pathophysiology of AECOPD is poorly understood, and it is often difficult to distinguish true exacerbations from normal day-to-day variations of COPD. In 2000, a consensus panel of respiratory physicians from Europe and the USA suggested that an exacerbation of COPD should be defined as “a sustained worsening of the patient’s condition, from stable state and beyond normal day to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying

COPD"[15]. Subsequently, the definition was amended to include exacerbations that did not necessitate a change in treatment [4]. In our study, we used a symptom-based definition to ensure that the main focus would be on patients' perceptions of their symptoms.

It is well known that AECOPD have a considerable impact on patients with respect to disease progression[4;16], morbidity[16], mortality , and health status[7-9;17]. In patients admitted to intensive care units for AECOPD, it was shown that after 6 months only 26 % were alive and able to report a good to excellent health status [3]. In the London East Cohort studies, 35 days after the onset of a AECOPD, PEF and symptoms scores had not returned to baseline levels in 24.8% and 13.9% of patients.[17] In another study by Spencer et al. [9], the rapid improvement observed during the first 4 weeks was followed by a slower recovery of up to 6 months in some patients. This study utilized different methodology than our study which makes comparison difficult. Spencer et al. recruited patients with an acute exacerbation and didn't assess patients while they were stable. However, improvement over the first 4 weeks was greater than over the subsequent 5 months. This seems to be in general agreement with our study results.

Our study is the first to report on health status and worsening symptoms immediately following the identification of an AECOPD. We have learned that from the onset of an AECOPD, and for up to 2 weeks, most patients are disabled to the point of being limited in their activities of daily living and experience noticeably reduced quality of life. These results suggest that timing and choice of treatment of an AECOPD may be based on early symptom changes, loss of disease control (symptom, functional or mental state) and

impact on health status. There was large variability in changes in the SGRQ scores. This is not unexpected based on what clinicians see in their clinical practice. We also presented deterioration with respect to the percentage of patients with clinically important deterioration (SGRQ increase of 4 or more) which may be more meaningful.

The main strengths of this study are that COPD patients were enrolled while their disease was stable, thus ensuring knowledge of their baseline symptoms and health status; that they were followed prospectively; and that patient-centered outcomes were assessed at the onset of an AECOPD and during their short-term recovery. Our cohort is likely to be representative of the COPD population known to be at risk for AECOPD considering the large sampling across the country (59 participating centers) and the participation of primary care as well as hospital-based clinics. The definition of exacerbation used in the study was not too restrictive while at the same time conforming to the consensus definition. While exclusion of a single symptom event could have reduced the false positives arising from natural variability of the disease, it could also have excluded true mild exacerbations. However, study results may apply only to patients who report exacerbations. This may be an important element in health-care definitions of exacerbations that is often overlooked. Some patients may not report frequent day-to-day symptom changes because they become accustomed to them. For example, another study [17] estimated that patients failed to report up to 50% of symptom-based exacerbations.

Preventing AECOPD and improving the prognosis should represent a key treatment goal. Guidelines [18-20] have emphasized the importance of regular therapies such as long-acting

anticholinergics [21], inhaled corticosteroids, [22] and combination therapy [23-26] to prevent an AECOPD. Prevention of these exacerbations may help to slow disease progression and impact on health status. Shortening the duration and severity of an AECOPD should also be considered as important outcome in the management of COPD. Recently, it has been demonstrated that early treatment of an AECOPD can lead to faster recovery from symptoms, improved health status and reduced risk of hospital admission [27]. Other studies [1;28] also suggest that patients who use self-management action plans to promptly treat exacerbations have 40% fewer hospital admissions. Health status has become important in the validation of specific treatments used for AECOPD not solely based on the prevention of the AECOPD, but also on the time to recovery.

In summary, we have demonstrated that health status can be effectively measured during an AECOPD. Acute exacerbations in COPD patients are severely distressing events that impact greatly on health status, loss of symptom control and functional state, and prolonged impact on mental state. This study has, for the first time, been able to lay a theoretical and methodological framework for future trials whereby the effectiveness of therapeutic interventions on health status can be assessed during an AECOPD. Furthermore, the study shows that timing of health status determination post exacerbation is very important, and that if we are to progress in the management of COPD, therapeutic interventions that speed health status recovery will become criteria in the treatment of the disease.

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Table 1. Baseline characteristics of COPD patients for all patients and according to the frequency of exacerbations during 6 months follow up

Characteristic	All patients N= 421	Patients with no exacerbation N=245	Patients with 1 exacerbation N=135	Patients with ≥2 exacerbations N=41
Male, n (%)	239 (57)	142 (58)	79 (59)	18 (44)
Mean age, years (range)	66 (41-88)	67 (41-88)	66 (45-86)	64 (44-80)
FEV_1 pre-BD, % predicted (range)	45 (13-83)	45 (16-83)	45 (14-70)	42 (13-68)
FEV_1 predicted (pre-BD) ≤ 50%, n (%)	275 (65)	158 (64)	87 (64)	30 (73)
FEV_1/FVC pre-BD (range)	0.52 (0.24-0.88)	0.52 (0.24-0.80)	0.51 (0.26-0.71)	0.50 (0.29-0.88)
Current smoker, n (%)	168 (40)	94 (38)	60 (44)	14 (34)
Smoking habits, mean pack-years (range)	46 (10-150)	47 (11-150)	45 (10-117)	41 (12-98)
Years since COPD diagnosis (range)*	8 (0.0-60.0)	8 (0-60.0)	8 (0.1-28.1)	9 (0.2-32.8)
Exacerbations (range) • Past year • Past 3 years	 1.6 (0-12) 4.0 (2-20)	 1.4 (0-12) 3.7 (2-20)	 1.7 (0-6) 4.3 (2-14)	 2.2 (0-6) 5.1 (2-10)
Inhaled medication, n (%)				

• Short-acting B2 agonists (SABA) • Anticholinergics • Combined SABA & anticholinergic • Corticosteroids (ICS) • Long-acting β_2 agonist (LABA) • Combined LABA and ICS	247 (59) 154 (37) 134 (32) 209 (50) 61 (14) 4 (1)	141 (58) 79 (32) 78 (32) 121 (49) 32 (13) 2 (0.8)	80 (59) 55 (41) 44 (33) 67 (50) 22 (16) 2 (1.5)	26 (63) 20 (49) 12 (29) 21 (51) 7(17) 0 (0)
Taking part in a pulmonary rehabilitation program, n (%)	28 (6.7%)	8 (3.3%)	13 (9.6%)	7 (17.1%)
MRC dyspnea (range)	2.9 (2-5)	2.8 (2-5)	2.9 (2-4)	3.2 (2-4)
Health status (SGRQ), (range) Activity score Impact score Total score	 62.9 (0-100) 31.8 (0-83.8) 44.2 (0-89.3)	 62.1 (0-100) 30.9 (0-83.8) 43.1 (8.7-82.7)	 63.1 (0-100) 32.8 (0-83.6) 44.8 (0-89.3)	 67.7 (35.6-92.9) 33.9 (1.6-65.3) 48.4 (22.2-72.2)

*There were 2 subjects with the diagnosis of COPD occurring at visit 1 (year since COPD diagnosis: 0)

All patients were started on combination ICS/LABA as part of standard therapy in the study

Table 2. SGRQ baseline and change during an AECOPD following early identification (report of the first exacerbation)

SGRQ	Baseline†	Change from the most recent SGRQ score (taken at least 48 hours prior to an AECOPD)					
		n	Onset	n	4-8 days	n	11-15 days
Activity	59.3 ± 21.2	93	12.1 ± 18.1*	101	9.8 ± 19.0*	111	3.1 ± 15.5^{+}
Impact	27.2 ± 18.4	93	14.0 ± 15.2*	102	9.4 ± 16.6*	111	3.3 ± 14.7^{+}

Data are presented as mean ± SD, *$p < 0.001$, $^{+}p < 0.05$

† Baseline refers to the most recent SGRQ score taken at least 48 hours prior to an AECOPD (mean time delay between baseline and exacerbation was 33.2 days ± 22.3).

Table 3. Changes during an AECOPD following early identification (report of the first exacerbation) in various patient completed questionnaires

Questionnaire	Baseline	Change from baseline					
		n	Onset	n	4-8 days	n	11-15 days
CCQ							
• Symptoms	2.4±1.2	89	1.0 ± 1.3*	97	0.8 ± 1.4*	101	0.04 ± 1.2
• Functional state	2.1±1.3	90	0.5 ± 1.3*	97	0.6 ± 1.5*	101	0.2 ± 1.2
• Mental state	2.0± 1.8	85	0.8 ± 1.7*	95	0.6 ± 1.6*	98	0.2 ±1.6
• Total score	2.2± 1.2	84	0.8 ± 1.1*	95	0.7 ± 1.2*	98	0.1 ± 1.1
EQ-5D health score	66.6 ± 17.8	91	-12.6 ± 19.0*	96	-9.0 ± 18.2*	101	-1.6 ± 16.2
MRC dyspnea score	3.0 ±0.8	97	0.5 ± 0.8*	104	0.3 ± 0.8*	116	0.0 ± 0.9
ADL score	32.8± 26.9	91	8.7 ± 31.3†	96	10.2 ± 34.2‡	100	3.7 ± 30.1

Data are presented as mean ± SD, * $p<0.001$, † $p=0.01$, ‡$p= 0.004$

Table 4. Predictive factors for AECOPD, having 1 or more AECOPD versus no AECOPD during 6 months follow up

Factor	Adjusted OR	95% CI	P-value
Age[+]	0.98	0.96, 1.00	0.077
Dyspnea*	1.35	1.06, 1.74	0.017
Number of AECOPD[†] in the past 3 years	1.14	1.06, 1.23	0.0008
Pulmonary rehabilitation[§]	0.32	0.15, 0.66	0.0021

OR: odds ratio; CI: confidence interval

[+] Per increased age

* Per increased scale in MRC Dyspnea

[†]Per increased exacerbation

[§]Difference for patients who didn't take part in a rehabilitation program compared to those who took part in a program

Figure legends

Figure 1

Total SGRQ score (mean ± 95%CI) according to patient's exacerbation frequency during the study period: None, 1, 2 or more

Figure 2

Percentage of patients with SGRQ Impact worsening (scores ≥4 from baseline)

Figure 1

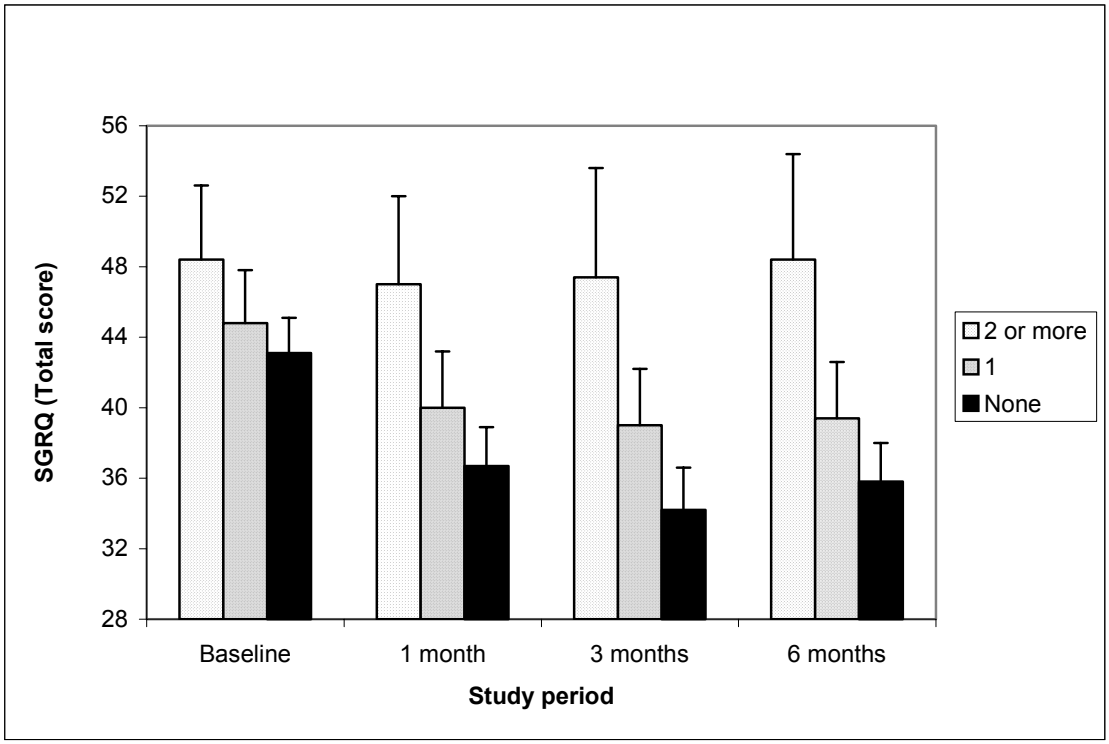
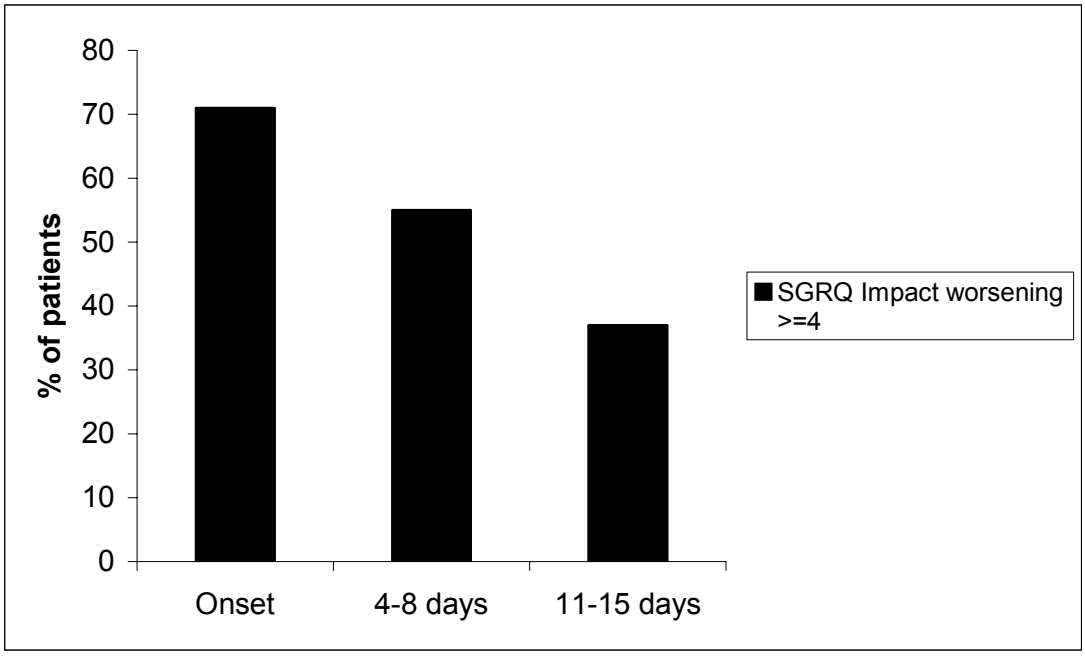

56
52
48
44
40
36
32
28
SGRQ (Total score)
Baseline
1 month
3 months
6 months
Study period
2 or more
1
None

Figure 2


80
70
60
50
40
30
20
10
0
% of patients
Onset
4-8 days
11-15 days
SGRQ Impact worsening >=4

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