IMPACT OF A PHARMACEUTICAL INTERVENTION TO IMPROVE ADHERENCE OF INHALED MEDICATION IN ASTHMA AND COPD PATIENTS: STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Introduction: Despite progress in pharmacological and non-pharmacological treatment in recent years, the burden of disease among asthma and COPD patients is high and patients may be frequently hospitalized due to exacerbations. Reasons for uncontrolled disease are manifold, but are frequently associated with poor inhalation technique and non-adherence to the prescribed treatment plan which may cause substantial mortality, morbidity, and cost to the healthcare system. In this respect, the study of causes for non-adherence and the development of measures to increase respectively maintain treatment adherence, particularly in chronic diseases, is of major clinical importance.

Therefore, the primary aim of this study is to measure medication adherence in patients with chronic obstructive lung diseases such as asthma and COPD, and to investigate the impact of a reminder on disease outcomes and quality of life.

Methods and analysis: In this ongoing prospective single-blind randomized controlled study, the adherence to inhaled medication is analyzed over a six-months period in in- and outpatients with asthma or COPD, who have experienced at least one exacerbation during the last year. Adherence is measured using electronic data capture devices which save date and time of each inhalative device actuation and transfer these data daily via wireless-connection to a web-based database. Patients are randomly assigned to an intervention, respectively control group. Patients assigned to the intervention group will receive audio reminder and support calls in case medication is not been taken as prescribed or if rescue medication is used more frequently than prespecified in the study protocol. During the study, participants are assessed every two months.

Ethics and dissemination: The study has been approved by the Ethics Committee of Nordwest- and Zentralschweiz (registry number: EK- 269/13). The results of this study will be disseminated via scientific seminar and conference presentations and in academic peer-reviewed journals.

Trial registration: ClinicalTrials.gov: NCT02386722.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Adherence estimation using state of the art method
- The primary outcome is of clinical relevance
- Primarily real-life study setting
- A limitation of this study is that we have a potential selection bias
- Single-centre and not multi-centre study

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are both prevalent lung diseases that require daily and often lifelong-use of inhaled medication[1]. According to the World Health Organisation (WHO) COPD currently represents the fourth leading cause of death worldwide and is predicted to become the third leading cause of death by 2030[2]. The prevalence of COPD is increasing due to continuing exposure to COPD risk factors (i.e. tobacco smoke or air pollution) and the continuously aging world's population[3]. The prevalence of asthma is increasing as well[4]. In Swiss adults, prevalence of asthma and COPD was found to be around 7% and 7-9%, respectively[5, 6].

TREATMENT AND DISEASES CONTROL

Despite progress in pharmacological and non-pharmacological treatment in recent years, the burden of disease among asthma and COPD patients is high and patients may be frequently hospitalised due to exacerbation. Based on data from the Swiss COPD cohort, the exacerbation rate is 23% per year[7]. Acute exacerbations are a risk factor for disease progression, and are associated with higher mortality[8]. A survey published by Leuppi et al. showed that the level of asthma control in Switzerland is very low with 15% of all the investigated patients[9]. This has also been confirmed by a cross-sectional survey of Miedinger et al. that found controlled asthma in 27% of all patients according to the international GINA guidelines[10]. A good adherence to therapy can increase the likelihood of achieving better asthma control[11].

Reasons for lack of diseases control in asthma and COPD are manifold, but are frequently associated with poor inhalation technique and non-adherence to prescribed treatment plan, which may influence diseases' mortality and morbidity as well as the costs to the health care system[12].

MEDICATION ADHERENCE

According to WHO, adherence is defined as "the extent to which a person's behaviour (including medication-taking) corresponds with agreed recommendations from a health care provider"[13]. Adherence represents the basic condition for the effectiveness of drug therapy and for complete disease control. Non-adherence not only leads to suboptimal treatment of individual patients. It also causes disease prolongation and increases hospital readmissions what in turn leads to an increase of the health care system costs[14].

Based on a systematic review of medication adherence literature, Vrijens et al. proposed a new taxonomy for describing and defining adherence to medication[15]. The Ascertaining Barriers to Compliance (ABC) taxonomy considers a sequence of events that have to occur for a patient to achieve an optimal benefit from his or her prescribed treatment regimen and to minimize the risk of harm. This process is divided into 3 essential components, which are

initiation, *implementation* and *persistence*. The process starts with the *initiation*, characterised by the intake of the first dose of a prescribed medication by the patients. It continues with the *implementation* of the dosing regimen, which is defined as the extent to which a patient's actual dosing corresponds to the prescribed medication, from initiation until the last dose is taken. This represents a longitudinal description of patient behaviour over time. The last step of the process is the *persistence*, which is the time duration from initiation, until eventual treatment discontinuation. After discontinuation, a period of nonpersistence may follow until the end of the prescribed period.

According to the above defined processes, non-adherence to medications can occur in the following situations: late or non-initiation of the prescribed treatment, suboptimal implementation of the dosing regimen or early discontinuation of the treatment. The subdivision into individual processes helps to focus research questions and to find measures and corresponding data to answer them.

On average, adherence to long-term therapy is estimated to be around 50% as shown in a systematic review summarising the results of randomised controlled trials (RCTs) of interventions to help patients follow prescriptions for medications for medical problems[16]. In general, adherence to medication can be measured using direct or indirect methods. Direct methods include direct observation of drug intake or measurement of drug concentration respectively biologic markers in blood, urine, or other body fluids. Indirect methods include assessment of a patient's clinical response, pills count, rates of refilling prescriptions, patient's self-report, and as most recommended method the electronic monitoring[17, 18]. Currently, no method is considered to represent the gold standard for measuring adherence to medications[19, 20]. Nevertheless, the method of choice that has emerged recently is the use of electronic monitoring[21].

A review by Makela et al.[22] analysed studies about asthma and COPD adherence between 2000 and 2012. The three leading methods were self-reported measures (37.8%), prescription refill adherence (32.8%) and electronic monitoring (19.1%)[22].

Self-reporting by patients was shown to be the most cost-effective in clinical and research settings[22]. However-being a subjective method-it also bears the highest risk of overestimating adherence compared to electronic measurements[23].

Observational retrospective studies based on dispensing data from pharmacy record database analyzed the refill adherence for different inhaled medication in asthma and COPD patients[24-26]. The importance of refill adherence is limited, since this measurement cannot assess the timing of the ingested or inhaled doses, which depends on the duration of drug action, and this has an important impact on the efficacy of treatment[27].

To investigate the variability in timing and taking adherence, measurements of dose and timing are necessary, which can be done with electronic medication monitors. Electronic monitoring provides precise data on the timing and pattern of inhaler actuation as well as detect multiple successive actuations (dumping)[28]. Electronic monitoring methods are non-invasive and represent one of the best ways to detect adherence patterns when using additional tools attached on the inhaler devices[29]. One of the electronic monitoring systems on the market are SmartInhaler™ devices (Adherium Ltd., Auckland, New Zealand), which have been validated for the assessment of adherence to inhaled medication on a daily basis[30]. The SmartInhaler™ devices are able to track time and date of each actuation of the inhaler device (incorporated switch activates by depression or rotation of the device) and

transmit the data via a wireless connection to a secure web database[30]. This method of electronic monitoring has been used in several studies measuring adherence to inhaled medication[31, 32]. One study conducted with asthma patients using inhalative corticosteroids showed that the integrated audio-visual reminder function of these devices significantly improved adherence to inhaled medication[33]. For orally administered drugs or inhaled medications available as powder capsules, a new technology is used, which is called Polymedication Electronic Monitoring System (POEMS). This technology is composed of printed electronics, self-adhesive polymer film carrying loops of conductive wires that can be affixed to multidose punch card (Pharmis GmbH, Beinwil am See, Switzerland) with 28 cavities. Every time a powder capsule is taken out of the blister, a loop is broken leading to changes in electrical resistance that can be measured and recorded with date and time[34]. The reports generated by Smartinhalers and POEMS allow to detect whether the patients have taken the medication at the right time and dose.

Interventions to improve medication adherence

Maintenance of a sufficient adherence to the prescribed medication is of major importance for achieving a therapeutic success, particularly in chronic diseases. Haynes et al.[35] have reviewed randomized controlled intervention trials to improve the adherence to pharmacological regimens in patients with chronic diseases, including asthmatic patients. Both, adherence and clinical outcomes were measured in these studies. The authors found that less than 50% of the interventions achieved a significant improvement of adherence while only 30% demonstrated an improvement in clinical outcome. The best success was attained with interventions combining several intervention strategies (information, reminders, self-monitoring, reinforcement, counselling, telephone follow-up, supportive care, etc.). Interventions to improve medication adherence have had mixed results and successful interventions had been shown as usually complex[35].

Study objective

The objective of this study is to investigate the adherence to inhaled medication in asthma and COPD patients with an innovative methodology using specific electronic devices, which are able to provide data about the timing of inhaler action. Moreover, we want to assess the effect of an acoustic reminder and a close supervision by a pharmacist on the adherence, course of diseases and quality of life.

METHODS AND ANALYSIS

Participants and Recruitment

In- and outpatients with a diagnosis of asthma bronchiale or COPD from several hospitals in the Basel region illustrated on table 1 and patients treated by pulmonologists in private practice are screened for eligibility. In addition, advertisement is made using posters, flyers, as well as on ad-screens (Cantonal Hospital Baselland Liestal and Bruderholz) including the most important information about the study. Advertisement is also placed in local newspapers.

Table 1 Recruitment locations and related recruitment types

Hospital	Location	Type of recruitment
Cantonal Hospital Baselland	Liestal, Switzerland	- Screening of hospitalized

		patients - Screening of emergency department - Screening of DRG-lists
Cantonal Hospital Baselland	Bruderholz, Switzerland	- Screening of DRG-lists - Collaboration with pulmonology department
Claraspital	Basel, Switzerland	- Collaboration with pulmonology department
Clinic Barmelweid	Barmelweid, Switzerland	- Collaboration with pulmonology department
Gesundheitszentrum Fricktal AG	Rheinfelden, Switzerland	- Collaboration with pulmonology department

DRG, Diagnosis Related Groups.

In- and exclusion criteria initially are checked via telephone or during hospitalizations or practice visits. Eligible patients are invited for an initial training course. Before the study start, the investigator provides written and verbal information on content and duration of the study. In case of willingness to participate, patients have to sign an informed consent.

Patient inclusion criteria

- males and females aged ≥18 years with
- asthma- and/or COPD diagnoses and
- prescribed daily inhaled medication with
- at least one exacerbation in the previous twelve months

Patient exclusion criteria

- patients with malignancies and/or other severe diseases or
- insufficient German language
- pregnant or lactating women

Enrolment started on January 2014 and will end as soon as at least 154 individuals are included in the study.

Study Design and Procedures

In this prospective single-blinded randomized controlled trial (RCT) (see figure 1 for study flow chart) 169 participants are followed up for six months. Prior to study start, patients have to be in a stable phase of their obstructive lung disease, which is defined as an exacerbation-free period of at least one month prior to commencement of the study and no current hospitalization for any other medical condition. Study participants will continue to be cared by their usual treating physician(s). They decide on all prescriptions and treatments.

All participants take part in a training course before the baseline visit. The goal of the training course is to provide refresher training on inhalation techniques in order to ensure that all participants are at the same level of disease knowledge and use their medication correctly. The training begins with a brief introduction about asthma and COPD. Then, the most frequently used devices are presented and briefly demonstrated. Correct technique depends on inhaler type, and it is important that patients use their own inhaler correctly. In addition, common mistakes and problems associated with the use of the devices are explained. The

correct use of the individual devices is demonstrated by a short film (produces by the "Deutsche Atemwegsliga" Bad Lippspringe, Germany)[36] which presents the most important steps to follow in order to achieve an effective inhalation. Notably, it has been shown that the manufacturer's instruction sheet is not effective enough to achieve correct techniques[37-39]. In contrast verbal and visual instructions seem to have a higher success rate in improving the application of inhalation devices[40]. At the end of the training, participants are given the opportunity to ask questions concerning the devices.

Visits take place at baseline (T0), after two (T1), four (T2) and six months (T3). Each visit includes a spirometry (EasyOne Pro, ndd Medizintechnik AG, Zurich, Switzerland), measurement of diffusion capacity (EasyOne Pro, ndd Medizintechnik AG, Zurich, Switzerland), exhaled nitric oxide (NIOX MINO®, Aerocrine AB, Sweden) and carbon monoxide (piCO⁺ Smokerlyzer, Bedfont Scientific Ltd., Kent, UK) measurements. To detect false device applications, each patient is asked to demonstrate the inhalation technique with all prescribed devices to the investigator using a placebo device (to avoid overdosing). Moreover, participants have to fill out the COPD Assessment Test (CAT)[41], the Asthma Control Test (ACT)[42], the St. George's Respiratory Questionnaire (SGRQ) and the Short Form (SF)-36[43, 44] to assess quality of life at baseline, after two, four and six months. To assess patients' beliefs about the necessity of the prescribed medication and their concern about the potential adverse consequences of taking it, the Beliefs about medicines Questionnaire (BMQ) is used at baseline[45, 46]. During these visits we also obtain information about exacerbation since the previous visit.

Randomization

After having given written informed consent eligible subjects are randomly assigned either to the intervention or to the control group. The intervention group is provided with an acoustic reminder for inhalation and receives support calls when the medication is not taken as prescribed while the control group receive no further support regarding the adherence. A randomization list with study group allocation is generated using R (RStudio®, Boston, USA). Randomization procedure is provided in block size of two. Therefore, examinations between study groups are sequent. This reduces the risk of a season effect between study groups. The patients are not aware of which group they have been randomized to (single-blinded).

Clinical Interventions

Patients assigned to the intervention group receive an audio-reminder, generated by a smartphone. For patients with Smartinhaler, the inhalation times are entered on the Smartinhalerlive.com website by the investigator. These are generated by an app on the smartphone. For patients with POEMS, the inhalation times are entered also by the investigator directly as an alarm clock on the smartphone. Patients were allowed to choose the inhalation times themselves, depending on their personal habits and daily routine, and it was possible to define a time for the working days and a time for the weekend. In both cases, the generated reminders have to be stopped by the patient and will have no link to the inhalation actuation. Moreover, these patients receive support calls when the use of rescue medication doubles or if the inhaled medication is not inhaled as prescribed for more than two consecutive days. They also receive a feedback on their adherence at each visit, especially for the results of the POEMS.

Patients assigned to the control group have no reminder and will receive no further support regarding the adherence of their inhaled medication.

Calculation of Sample Size

"Time to next exacerbation" is subject to the power calculation. A previous study has shown that 30% of COPD patients are readmitted again within six months because of an exacerbation[47]. We expect that 12% of the patients in the intervention group will have an exacerbation. This corresponds to a hazard ratio (intervention/control) of 0.36. Assuming a sample size of 70 subjects for each study group, there is a power of 80% to detect a HR of 0.36 based on a one-tailed test. The calculation is based on the assumptions mentioned above and on a one-tailed significance level of 5%. Additional 14 subjects (7 for each study group) have been added to account for dropouts. Therefore, 154 subjects will be investigated in this study.

Measurement of Objective Adherence

Adherence is measured in both groups using Smartinhalers and POEMS as outlined above. Daily measurements are started after the baseline visit (T0) and are continued until the end of the study (visit T3).

Recorded data are uploaded daily at 00:00 to a web-based database via a wireless connection. Participants are asked to take their medication at the first visit in order to ensure the correct handling and usage of the Smartinhaler. Once the devices are installed on the inhalers, patients can use their medication as usual.

Currently, no monitoring devices exist that were specifically developed for monitoring the adherence of the newly introduced inhalation-device Ellipta®. To assess adherence in patients undergoing treatment with Ellipta® a Smartinhaler with a placebo-device is handed out and patients are instructed to trigger a puff of the placebo every time when they inhale their active treatment. This procedure allows an indirect recording of date and time actuation of the Ellipta® inhaler.

For inhalation with powder capsules (Breezhaler and HandiHaler), POEMS are used. The capsules are pre-filled for the following 2 weeks with a patient's individualized prescription plan (mostly one time daily inhalation of capsule contents). The multidose punch cards are filled manually by a pharmacist. The participants with Breezhaler and HandiHaler will receive one multidose punch card for every 2 weeks. Every time the patients break a loop for taking the capsules, date and time are recorded on a microchip, which can be read when the patients bring back the empty punch card.

Data collection and outcome measures

The primary outcome of this study is "time to next asthma or COPD exacerbation", defined as acute-onset worsening of the patient's condition beyond day-to-day variations requiring interaction with a health care provider[48], which may occur during the index exacerbation or follow-up. Data collections about this outcome are assessed after two, four and six months (number of exacerbations since last visit with exact period of exacerbation and number of exacerbation with hospitalization). If patients are not able to give information about the time of exacerbation, treating physician is contacted.

Sociodemographic variables such as gender, civil status, age, education level and employment status are obtained by a generic questionnaire at the baseline visit. Furthermore, body mass index (BMI), smoking status, as well as pack years (py) are assessed during this visit. In addition, disease-related questions such as allergies,

comorbidities, current medication and number of exacerbations in the previous twelve months are recorded including hospitalizations and emergency department attendance.

This project focuses on the implementation of a prescribed dosing regimen. Objective adherence will be analyzed according to the following widely used definitions[49]:

- Taking adherence: (Number of puffs inhaled during 24h/number of puffs prescribed during 24h) x 100.
- Timing adherence: (Number of correct dosing intervals during 24 hours/number of dosing intervals during 24 hours) x100; correct dosing intervals are prescribed intervals ±25%:
    - For once daily dosing: 24h±25%=18-30h
    - For twice daily dosing: 12h±25%= 9-15h
    - For three daily dosing: 8h±25%= 6-10h
- Gaps: (Number of days without inhalation during the whole study period/number of days in same time period) x 100.
- Maximal gap length: Number of consecutive days of the longest period of time without inhalation.

Different lung function tests are performed at baseline, after two, four and six months to assess changes in lung function (FEV_1, FVC, FEV_1/FVC), diffusion capacity, NO-measurements and CO-measurements.

To evaluate the inhalation technique, participants demonstrate at baseline and at every follow up visit how they actually use their device at home. For this purpose, placebo devices are used to prevent overdosing. Correctness of inhaler use is assessed using pre-defined checklists for each inhaler type based on user guidelines and instruction package inserts from the manufacturers[50-55]. Correct inhaler usage is defined as correct performance of every step on the checklist. Incorrect inhaler usage is defined as one or more steps done incorrectly. A total score is calculated (incorrect application =0, correct application =1) and applied to every step. Possible errors are corrected by verbal instruction and visual demonstration. For ethical reasons the correction was performed in both groups. Patients demonstrate their inhalation technique until it is performed correctly.

To assess patients' beliefs about the need of the prescribed medication and their concerns about the potential adverse consequences of taking it, the BMQ is used at baseline.

Changes in quality of life are assessed at baseline, after two, four, six months using different disease-specific questionnaires: SGRQ, CAT and ACT. To assess general quality of life, SF-36-questionnaire is used.

STATISTICAL ANALYSIS

Statistical analyses, including descriptive statistic and survival analyses, are done using the software R (RStudio®, Boston, USA) and SPSS (IBM Corporation, Armonk, USA). Statistical significance is set at the 5% level. Time to next exacerbation is compared using the Kaplan-Meier method and Cox proportional hazard model. Results will be reported as HR (hazard ratio) with corresponding 95% confidence interval (CI) and p-value. A hazard ratio smaller than one is expected. This means that the intervention group will have a smaller risk for exacerbations. Associations between time to between exacerbation and independent predictors will be analyzed (taking adherence, timing adherence and gaps without

inhalation). Comparisons of secondary parameters are done using t-tests or chi-square-tests (or their nonparametric equivalents if continuous data are not normally distributed).

Handling of missing data and drop outs

Patients will be rated as drop out when they will be excluded from the study at their request or if they will be no longer able to participate in the study until the final visit at six months. Patients, who will not be able to undergo all clinical examination during the follow-up visits, will remain in the study. Multiple imputation methods will be used to impute missing data with less than 25% missing values, which is typically more efficient than complete cases analysis when covariates have missing values[56].

Ethics and dissemination

This study is conducted according to the Helsinki Declaration and according to the good clinical practice guidelines. The study participation of the patients is voluntary and can be revoked at any time without specification of reasons and will have no disadvantages for their future medical care. The study was approved by the Ethics Committee of Nordwest- and Zentralschweiz (registry number: EK- 269/13) and was registered in the https://clincialtrials.gov/trials database (NCT02386722).The results of this study will be disseminated via seminar and conference presentations and in academic peer reviewed journals.

Data security/disclosure of original documents

All patients' data are collected and stored under confidentiality rules. All study related data and documents are stored on a protected server of the Cantonal Hospital Baselland. Data access is limited to members of the Medical research group at the Cantonal Hospital Liestal. After the end of the study, all documents and informed consent are retained in the archive of the University Department of Internal Medicine at the Cantonal Hospital Liestal for 10 years according to the applicable Swiss regulatory requirements.

Expected results and significance of the research project

To date, only few studies have investigated medication adherence in patients with chronic obstructive lung diseases. These studies were retrospectively analysed and limited to refill adherence, comprising several important limitations, such as not assessing the relationship between the duration of drug action and the timing of the ingested doses, which has an important impact on the efficacy of treatment[57]. Other disadvantages of this measurement are missing data, if refill medication is obtained outside of the investigated system and incomplete records if the medication plan is verbally modified by the prescriber without informing the dispensing pharmacy. Moreover, assumptions have to be made on medication-taking behaviour corresponding to prescription refilling and the medications that are taken according to prescription[58].

We expect that a regular adherence reminder and a close supervision by a health care professional will have a beneficial effect on the adherence to inhaled medication in patients with asthma or COPD, resulting in an increased time to next exacerbation. Moreover, we expect that an improved adherence will increase the quality of life in these patients.

With the prospective study design and the use of state-of-the-art devices for measuring adherence, we expect scientifically relevant and clinically meaningful results that will have a

substantial and positive impact on the provision of health care in chronically ill patients with asthma or COPD.

CONTRIBUTORS

CG TD and JDL are chief investigators of the project. CG, TD, SD, IA, KH and JDL made contributions to the protocol in their specific areas of expertise. CG prepared the first draft of this manuscript and all authors revised the paper critically for important intellectual content and gave approval for the final version.

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COMPETING INTERESTS

None declared.

ETHICS APPROVAL

Ethics Committee of Nordwest- and Zentralschweiz (EK- 269/13).

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