Pulmonary Pharmacology & Therapeutics 27 (2014) 129–138

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Review

Randomized controlled trials and real life studies. Approaches and methodologies: a clinical point of view.

S. Saturni [a], F. Bellini [a], F. Braido [b], P. Paggiaro [c], A. Sanduzzi [d], N. Scichilone [e], P.A. Santus [f], L. Morandi [a], A. Papi [a,*]

[a] Respiratory Medicine, Department of Medical Sciences, University of Ferrara, Ferrara, Italy
[b] Allergy and Respiratory Diseases Clinic, DIMI, University of Genoa, IRCS AOU San Martino-IST, Genoa, Italy
[c] Cardio-Thoracic and Vascular Department, University Hospital of Pisa, Italy
[d] Section of Respiratory Diseases, Department of Surgery and Clinical Medicine, University of Naples, Italy
[e] Department of Internal Medicine, Section of Pulmonology (DIBIMIS), University of Palermo, Italy
[f] Dipartimento di Scienze della Salute, Pneumologia Riabilitativa, Fondazione Salvatore Maugeri, Istituto Scientifico di Milano IRCCS, University of Milan, Milan, Italy

ARTICLE INFO

Article history:
Received 3 November 2013
Received in revised form
11 January 2014
Accepted 13 January 2014

Keywords:
Randomized controlled trials
Real life studies
Asthma
COPD

ABSTRACT

Randomized Controlled Trials (RCTs) are the "gold standard" for evaluating treatment outcomes providing information on treatments "efficacy". They are designed to test a therapeutic hypothesis under optimal setting in the absence of confounding factors. For this reason they have high internal validity. The strict and controlled conditions in which they are conducted, leads to low generalizability because they are performed in conditions very different from real life usual care. Conversely, real life studies inform on the "effectiveness" of a treatment, that is, the measure of the extent to which an intervention does what is intended to do in routine circumstances. At variance to RCTs, real life trials have high generalizability, but low internal validity. Recently the number of real life studies has been rapidly growing in different areas of respiratory medicine, particularly in asthma and COPD. The role of such studies is becoming a hot topic in respiratory medicine, attracting research interest and debate.

In the first part of this review we discuss some of the advantages and disadvantages of different types of RCTs and analyze the strengths and weaknesses of real life trials, considering the recent examples of some studies conducted in COPD. We then discuss methodological approaches and options to overcome some of the limitations of real life studies.

Comparing the conclusions of effectiveness and efficacy trials can provide important pieces of information. Indeed, these approaches can result complementary, and they can guide the interpretation of each other results.

1. Introduction

Research evolves by answering new questions, including questions on how research itself should be conducted. Randomized Controlled Trials (RCTs) are well recognized as the "gold standard" for evaluating treatment outcomes [1,2]. They are designed to test a therapeutic hypothesis under optimal conditions in the absence of confounding factors: highly selected patients, optimal management conditions, and ideal settings; thus they provide information on "efficacy" under conditions very different from real life [3,4]. They accomplish this through an experimental design [2,5,6] that, as their name implies, always includes randomization to guarantee that treatment groups are as similar as possible in all attributes that could potentially influence outcomes [2,5]. Thus, RCTs have high internal validity under the ideal conditions in which they are conducted [1,2]. Concerns about the conclusions of RCTs relate mainly to their generalizability to broader patient populations and to less ideal conditions, like routine clinical practice, where even health care costs and availability can be problematic [2]. Indeed, it is argued that, because of statistical need of limiting confounding factors, the highly selected population of RCTs only partially

Abbreviations: RCTs, randomized controlled trials; COPD, chronic obstructive pulmonary disease; CAP, community acquired pneumonia; CF, cystic fibrosis; ITT, intention-to-treat; ICSs, inhaled corticosteroids; BA-pMDIs, breath-actuated pressurized metered dose inhalers; DPIs, dry powder inhalers; pMDIs, pressurized metered dose inhalers; LABA, long acting beta2 agonist; LTRA, leukotriene receptor antagonists; LRTIs, lower respiratory tract infections.

* Corresponding author. Section of Respiratory Medicine, University of Ferrara, Via Savonarola 9, 44121 Ferrara, Italy. Tel.: +39 0532 236908.
E-mail addresses: ppa@unife.it, alberto.papi@unife.it (A. Papi).

1094-5539/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.pupt.2014.01.005

represents the *real-life* population, casting doubts on the external validity of these clinical trials. Assessment of outcomes under these sub-optimal conditions in observational or pragmatic studies informs on the "effectiveness" of a treatment in real life [3,4], that is, the measure of the extent to which an intervention does what is intended to do in routine circumstances.

Observational studies have the power and structure to identify areas in which investigation is needed and to test new hypotheses [7]. Pragmatic trials are designed to evaluate treatment outcomes, but unlike RCTs they adopt usual care settings and procedures in non-selected patients [7], thus mimicking everyday clinical practice, which provides high external validity. Real life studies have limitations, primarily stemming from the lack of randomization and the need to apply the indications only within the local geographic context.

In the first part of this review, we will mainly refer to real life studies conducted in asthma, where they have a long history, as documented by the large number published in the last 10 years. Recently the number of real life studies in pharmacological has been rapidly growing in other areas of respiratory medicine, particularly chronic obstructive pulmonary disease (COPD) (Fig. 1). During the same period the overall number of RCTs in asthma and COPD was several times higher and tended to be constant over time: there were on average more than 400 RCTs every year on asthma (±5%) and more than 200 RCTs/year on COPD (±8%).

The progressive increase of real life studies published in the last years and their recognized scientific value [8,9] underline that their role is becoming constructive in respiratory medicine, attracting research interest and debate [10,11]. The second part of the review will consider some of the advantages and disadvantages, strengths and weaknesses of different types of trials and comment on the complementarity between RCTs and real life studies.

2. Randomised Controlled Trials

2.1. RCTs: definition and features

RCTs are research studies that aim to evaluate treatment efficacy [12].

Evidence-based clinical trials start from the formulation of a research hypothesis [13], which may be an evaluation of "superiority" or "equivalence" [13]. The appropriate primary outcome and corresponding measuring tool are chosen [13] and the number of patients is estimated based on statistical parameters, historical data on the working hypotheses, clinically relevant differences and the inherent variability of the primary outcomes.

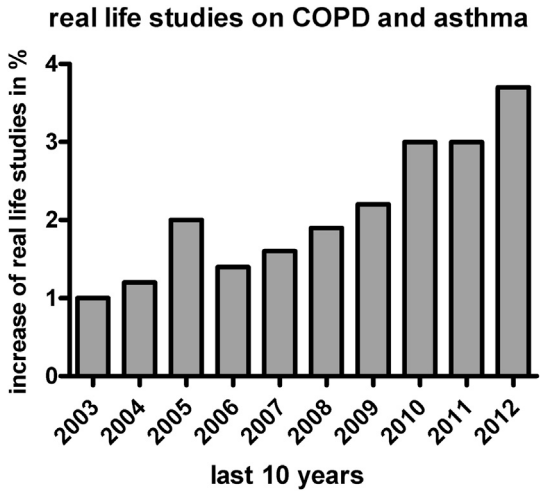

Fig. 1. Real life studies in asthma and/or COPD in the last decade. PubMed search: Percent variations in the last decade of published studies on asthma and/or COPD containing the term "real-life" in the title or abstract.

Random assignment to treatment groups and double blind monitoring minimize bias [13].

The effect of the tested treatment is assessed by comparing it to a control condition, standard treatment or placebo [13]. Different treatment strategies or dosages can also be compared. These criteria maximize internal validity but at the same time, limit generalizability and reduce external validity [14].

2.2. RCTs: advantages

Because of their internal strength, RCTs are universally accepted as the "gold standard" for assessing the effects of therapeutic interventions and of medical devices/equipment under specific controlled conditions [7,15–19].

Historically, the first RCTs available in the respiratory literature addressed community acquired pneumonia (CAP), but they did not follow all of the strict RCT rules. A critical assessment of the early studies revealed design flaws: the diagnosis of pneumonia was not defined in 42.8% of the RCTs, only 33% of the studies were restricted to CAP, and outcomes were not defined in 28.5% of the studies [20]. Moreover, only 38% of the RCTs were double-blinded, and intention to treat analysis was not applied [20]. During the ensuing years, significant improvements were made in all methodological aspects of RCTs in respiratory medicine. One of the most recent published RCT on respiratory infections [21] evaluated macrolide maintenance treatment with azithromycin in adults with bronchiectasis not due to cystic fibrosis (CF) [21]. This study meets the criteria for a well-conducted RCT. It has an appropriate design, randomization, double blinding, placebo control and analysis by intention-to-treat (ITT) [21].

The validity of RCTs is built around precise requisites (Table 1), starting from a careful and rigorous experimental plan. Scientists must establish the aim, the primary and secondary outcomes, size

Table 1
Advantages and disadvantages of RCTs and real life studies.

	RCTs	Real life studies
Advantages	• Rigorous experimental design • Randomization • Blinding • Control • Rigorous analysis methods	• Non-selected population • Refer to the usual inhaler techniques • Realistic therapy adherence • Logistical and ethical feasibility • Able to evaluate complex therapies • Useful to detect rare or late side effect • Routine practice setting • Long duration
Disadvantages	• Selected patients • Setting and monitoring bias • Economical limitations • Logistical and ethical restrictions • Unsuitable for complex treatments studies • Inappropriate for thorough evaluation of side effects • Short duration	• Lack of patient selection brings confounding factors • Lack of randomization • Absence of blinding • Residual monitoring bias • Confounding by indication • Economical limitations • Logistical problems • Immortality bias

Table 1 describes the main advantages and disadvantages of both RCTs and real life studies. Advantages and disadvantages of RCTs are associated to their strict design and population selection, which make their conclusion robust but distant from real life conditions. On the other side, real life studies reflect more closely related to usual care, but they provide results obtained in sub-optimal treatment conditions.