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Omalizumab for severe allergic asthma in clinical trials and real-life studies: What we know and what we should address

Marco Caminati [a, *], Gianenrico Senna [a], Massimo Guerriero [b], Anna Rita Dama [a], Fulvia Chieco-Bianchi [c], Giorgia Stefanizzi [a], Marcello Montagni [d], Erminia Ridolo [d]

[a] Allergy Unit, Verona University and General Hospital, Verona, Italy
[b] Department of Computer Science, University of Verona, Verona, Italy
[c] Respiratory Pathophysiology Division, University-City Hospital of Padua, Padua, Italy
[d] University of Parma, Department of Clinical and Experimental Medicine, Parma, Italy

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ABSTRACT

Randomized clinical trials (RCTs) are the gold standard for the assessment of any therapeutic intervention. Real-life (R-L) studies are needed to verify the provided results beyond the experimental setting. This review aims at comparing RCTs and R-L studies on omalizumab in adult severe allergic asthma, in order to highlight the concurring results and the discordant/missing data.

The results of a selective literature research, including "omalizumab, controlled studies, randomized trial, real-life studies" as key words are discussed.

Though some similarities between RCTs and R-L studies strengthen omalizumab efficacy and safety outcomes, significant differences concerning study population features, follow-up duration, local adverse events and drop-out rate for treatment inefficacy emerge between the two study categories. Furthermore the comparative analysis between RCTs and R-L studies highlights the need for further research, concerning in particular long-term effects of omalizumab and its impact on asthma comorbidities.

1. Introduction

Randomized controlled trials (RTCs), besides meta-analysis, have had a key role in the development of the Evidence Based Medicine and they are considered the gold standard for the assessment of any therapeutic intervention [1]. In fact the evaluation of the clinical outcomes is performed at the best conditions such as the high selection of patients and an optimal medical setting which assures an accurate clinical assessment and follow-up. Aim of RCTs is the evaluation of the clinical efficacy and safety of any drug, avoiding any possible confounding factor. Furthermore recently the experimental design, the data analysis and the results explanation have been standardized by the Consolidating Standards of Reporting Trials (CONSORT) [2], strengthening their high internal validity, under specific controlled conditions. According to very strict exclusion criteria, patients with co-morbidities or taking drugs which can interfere with the results of the study are commonly excluded. Randomization is another key tool in the RCTs protocols as it assures the comparability of active and placebo groups. Moreover the regular assessment of each patient according to the schedule of the protocol can minimize the risk of non-adherence to the treatment. Therefore the evaluation of the efficacy in RCTs is the essential premise for a widespread use of any drug in clinical practice [3]. On the other hand the same criteria applied to the protocols in order to avoid confounding factors limits the feasibility of the results observed in RCTs in the daily practice [4]. Actually patients enrolled in controlled clinical trials are representative for a little sample of the "real" patients. It is particularly true when considering experimental studies for anti-asthmatic drugs. Recent studies have observed that less than 5% of asthmatics treated in daily practice can satisfy the inclusion criteria of clinical trials [5–7]. In fact potential confounding factors that can influence the investigated outcomes and therefore represent exclusion criteria in RCTs are very common in the daily routine.

* Corresponding author. Allergy Unit, Verona University Hospital, Piazzale Aristide Stefani 1, 37126 Verona, Italy. Tel.: +39 045 8123525; fax: +39 045 8122048.
E-mail addresses: ma.caminati@gmail.com (M. Caminati), gianenrico.senna@ospedaleuniverona.it (G. Senna), massimo.guerriero@univr.it (M. Guerriero), annarita.dama@ospedaleuniverona.it (A.R. Dama), fulvia.chiecobianchi@gmail.com (F. Chieco-Bianchi), giorgia.stefanizzi@libero.it (G. Stefanizzi), marcello.m1@hotmail.it (M. Montagni), erminia.ridolo@unipr.it (E. Ridolo).

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This is the case of concomitant diseases (i.e. rhinitis, sinusitis) or treatments (i.e. beta-blockers), as well as smoking habits. These conditions concern most of treated patients in clinical practice and their impact on the treatment safety and efficacy is unknown and not always easily predictable.

Furthermore, though an increasing amount of evidences highlights that elderly account for a significant proportion of asthmatic patients and experience a high number of exacerbations and hospitalizations, they are usually not included in RCTs [8]. The use of biological treatments for asthma in the elderly is generally unexplored, in real-life studies as well. It arises a major concern if we consider that asthma in the elderly presents a specific "phenotype" and its management usually deals with a complex polypharmacotherapy. For safety reasons at first the effect of biologicals in this setting needs to be accurately known.

Another important difference between RCTs and real-life concerns the clinical setting. Usually the study population of experimental trials is followed in specialized centres, where high technology and specialists are available, differently from the general practice settings [9]. Asthmatic patients enrolled in clinical trials are also regularly assessed and instructed about the correct use of inhalers. It improves their adherence to the treatment, which is usually high, as it is a pre-requisite to be included in the study. From this perspective too, the "controlled trial setting" is likely to be quite far from the real-life, where a poor technique of the use of inhalers as well as a low adherence to the treatment are common drawbacks.

When balancing efficacy and costs, RCTs do not provide reliable data as the experimental setting does not deal with accessibility and price/reimbursement issues, which represent a crucial aspect in clinical practice and often differ by country.

Moreover the short duration of RCTs does not reproduce the usual treatment timeframe for chronic respiratory diseases. This aspect is not negligible, as it's known that treatment duration importantly affects in general disease management [4].

For all the reasons mentioned above, once that the clinical efficacy has been assessed in RCTs, the "effectiveness" of any therapeutic intervention should be evaluated. In other words, to what extent the clinical efficacy demonstrated in RCT is confirmed in real-life, should be verified beyond the experimental setting [1]. In Table 1 the different aspects of RCTs are summarized and evaluated in the light of their relevance to efficacy, primary outcome of RCTs, and effectiveness, which is usually better explored by R-L studies.

The need for data concerning the daily clinical setting may account for the growing interest currently paid to the "real-life" (R-L) studies, as they address the effectiveness of any drug [4]. Fig. 1 show the trend of published RCTs and R-L studies on omalizumab for asthma in adults and children published between 1997 and 2014 [10].

Omalizumab is a humanized recombinant anti-IgE monoclonal antibody approved for therapeutic use both in adults and in children aged 6–12 years with severe allergic asthma. The coexistence of severe asthma refractory to the conventional pharmacological approach and sensitization to at least one perennial allergen represent the current indications for Omalizumab prescription. Its efficacy and safety as an add-on therapy is sustained by several data coming from both clinical trials and real-life experiences [11–35] and showing a significant reduction of yearly exacerbation-rate, a steroid sparing effect and an improvement of Quality of life (QoL)-related outcomes [36,37]. As biological drugs are used only in few selected cases, every specialist experiences their efficacy and safety usually on a small group of patients, so that it is crucial getting from the literature clear and univocal messages. To our knowledge it has never been investigated to what extent the results of RCTs and real-life studies overlap. Furthermore few evidences concern adherence to the treatment with omalizumab, its impact on lung function and on asthma comorbidities, long-term follow-up and non-responders profile.

The aim of the present review is to provide a descriptive comparative analysis of RCTs and R-L studies on omalizumab in adult severe allergic asthma, in order to highlight the concurring results as well as the discordant and missing data.

Table 1
Comparative relevance of different study parameters (RCTs) concerning efficacy and effectiveness.

	Efficacy	Effectiveness
Patients selection	🙂	😐
Medical setting and equipment	🙂	☹
Experimental design	🙂	☹
Exclusion of confounding factors (smoke, drugs, comorbidities)	🙂	☹
Regular follow-up	🙂	😐
Exclusion of elderly patients	😐	☹
Patient education	🙂	😐
Short study duration	😐	☹
Patient reported outcomes	🙂	🙂
Functional/biological outcomes	🙂	😐
Economic issues	😐	☹

RCTs = randomized clinical trials.
🙂 High relevance.
😐 Medium relevance.
☹ Low relevance.

2. Material and methods

2.1. Search strategy

A complete search of the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE and Pub Med up to December 2013 was carried out. The search strategy retrieved citations containing the subject heading omalizumab and was restricted to randomized, double-blind, placebo-controlled trials and "real life studies" for severe allergic asthma in patients ≥18 years old. The key words used were "omalizumab, asthma, controlled studies, randomized trial, real life studies". No language restrictions have been applied. All published studies up to 31 December 2013 were included in the present study. Outcomes of the study were to compare the population studies and clinical results in RCT and "real life studies".

2.2. Data collection and statistical analysis

Two independent authors analyzed all included papers according to the before-mentioned criteria and recorded the relevant data concerning the study populations, the clinical efficacy and the safety of the treatment. Comparison was then made between the data recorded by the two researchers. In case of disagreement, the original paper was re-analyzed and a consensus decision reached.

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