Randomized clinical trials and observational studies: which data from which studies in respiratory field?

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Randomized clinical trials (RCT) are recognized as 'gold standard' for evaluating drug efficacy in terms of clinical outcomes. We define efficacy the capability of a drug to produce the wanted effect in strictly controlled conditions. In this context, RCT are usually planned to test superiority or non-inferiority of new molecules in comparison with the reference drug or placebo in a well defined condition; randomization assures that pts are similar in different treatment groups (Saturni et al, 2014). In order to avoid other confounding factors, RCTs are carried over under optimal conditions: selected patients (pts), ideal settings, high level management. Thanks to their rigorous methods, RCTs have the greater level of evidence during the writing of a guideline by a scientific committee. Overall RCT have low generalizability but very high internal validity. On the other hand the main limitation of RCT is that they don't offer a real 'pictures' of the population that has to be treated and often, when used for the approval and reimbursement evaluation, they don't allow an extensive understanding of the real drug terms and condition use.

Recently the real world studies (RWS) have received a growing interest from investigators since they present conditions more similar to those clinicians operate in their real life. In these studies, pts are different than those enrolled in RCTs: they suffer from a number of diseases, assume other drugs, are managed in routine clinical practice and their care could be affected by a great attention to costs and resource consumption. Furthermore, the adherence to treatment is lower than in RCTs. Even the definition of efficacy between RCT and RWS is different: in the latter, effectiveness is the measure of the drug efficacy in real setting, that is always lower than the RCT efficacy because of the limitations of real management and patient adherence. The main issues of these approach is represented of the lack of randomization and often pts are managed 'as they are affect of one disease' instead of receiving 'a diagnosis of it'.

In order to compare RCT vs RWS and describe the 'state of art', we report here some observations. Published data state that asthmatic pts in RCTs represent less than 6% of asthmatic pts (Chetta et al, 2014), and 17% of COPD pts (Scichilone et al, 2014).

In RWS, safety aspects tend to be more consistent and generalizable, taking into consideration pts with comorbidities, and can give more defined information in terms of diseases management. On the other hand, even if they could provide useful data, often they miss quite a lot of them because the data collection is not so strict as that of RCT. The lack of data could compromise the understanding of relationship between a certain disease management and some important adverse effects (e.g. incidence of pneumonia related to the use of inhaled steroids, Janson et al, 2013) and sometimes not allow to draw definitive conclusion about the tested hypothesis.

Clinical data provided by RCTs could be a good starting point to include a certain drug in a formulary. Furthermore, clinicians should consider that adherence to a treatment has a crucial role in increasing efficacy. Adherence in RWS is certainly lower, and the effectiveness is lower than efficacy too. Age of pts, co-treatments and other pts characteristics can interfere with the choice of the correct treatment in real life setting. Finally, payers should pay attention in making decisions based only on RCTs. They risk to pay for a ideal efficacy, buying a lower effectiveness. Carrying out a real life study, corrected with a randomization list should be a good balance, in order to have real life procedures and adherence to a specific drug, with a sufficient internal validity. Some of those studies, called pragmatic trials, (e.g. the Salford Study) are ongoing and they offer a good option for investigators to balance weakness and strengths of RTCs and RWS.