Observational studies: friend or foe?

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Randomised controlled trials (RCTs) are the holy grail when aiming at testing the effect of one of more interventions, typically one or more treatments. Advantages of RCTs are that both random allocation of patients into treatment-groups and blinding of the allocated intervention make it possible to effectively reduce many biases when testing the efficacy of interventions. These aspects together with the typically stringent inclusion criteria of RCTs (homogeneity) contribute to their high internal validity. Internal validity means how well a study can rule out alternative explanations for its findings, usually sources of bias. These strengths of RCTs are offset by some limitations. RCTs are the most adequate study design to analyse the short-term efficacy and short-term safety of interventions. However, many relevant questions for daily clinical practice fall out of this scope; examples of these are outcomes studies, studies about the consequences of a disease, effectiveness of interventions over the long-term and especially safety over the long-term. Questions that are relevant for daily clinical practice more often pertain to the long--term. Moreover, in contrast to their high internal validity, RCTs often lack external validity or generalizability. By including a selected population of patients, the results of an RCT cannot easily be transferred to another context, to another population of patients reflecting our daily clinical practice.

How can limitations of RCTs be overcome? Observational studies can offer here an attractive alternative. Particularly if methodologically well-conducted, they can sometimes even be superior to RCTs in answering certain types of research questions, as previously mentioned.

Let us go through the example of a specific research question and the steps that have been taken to address it. The question is whether treatment with tumor necrosis factor-alpha inhibitors (TNFi) inhibits the progression of structural damage in axial spondyloarthritis. As this is a question on the efficacy of an intervention, an RCT would be the preferable study design to address it. However, this is challenged by the fact that from an ethical perspective placebo-controlled trials cannot be conducted for a period longer than 24 weeks, while the progression of structural damage, as measured with the imaging and scoring method currently considered most adequate, cannot be measured in a period shorter than 2 years. This led researchers to explore a best alternative to an RCT, namely a comparison between the treatment arm of an RCT and an historical cohort of patients not treated with TNFi, reflecting the natural history of the disease. The same study was conducted with data from three different TNFi from three different trials, that all yielded the same result: no inhibition of structural damage progression with TNFi compared to no TNFi[1-3]. However, such comparisons with a historical cohort are not free of bias. It was obvious that RCTs could not give a clear and definite answer to this research question, which changed the focus of researchers towards methodologically optimizing such an analysis within an observational context. The Swiss Clinical Quality Management cohort, the Swiss cohort of patients with axSpA, a prospective cohort study, has been used. A total of 432 patients have been followed up throughout a period of up to 10 years with imaging assessments every 2 years[4]. In a beautiful and methodologically sound approach, consisting of a longitudinal analysis making use of all the data available for each patients, the authors have concluded that TNFi are associated with a reduction in the progression of spinal structural damage and that this effect seems to be 'mediated' through the inhibiting effect of TNFi on disease activity. This study illustrates the value of an observational study in answering a research question, very relevant for daily clinical practice, that was not possible to answer in the context of an RCT, even though that would have been desirable.

The choice of the study design is based on the research question. Observational studies are popular and

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good solutions to answer several questions relevant for daily clinical practice. Several registries contain already collected and 'ready-to-use' information that may be tempting to analyse in order to answer 'almost any research question'. Still the first step, after formulating the research question, is to assess whether such a study design is appropriate to answer the corresponding research question. If yes, then one needs to ensure that not only the appropriate data have been collected, but also that they are properly taken into account in the analyses. Confounding is one of the largest pitfalls in observational studies. The non-random allocation of patients into groups that are eventually to be compared is inherently associated with bias that needs to be controlled to the highest possible extent. A confounder is a variable that influences both the dependent variable and independent variable, and thus causing a spurious association. For example, coming back to the above-mentioned study on the effect of TNFi on structural damage progression, male gender is a factor known to be associated with the outcome (males have more structural damage progression), but also related to the uptake of TNFi (males with axSpA are preferably treated with TNFi, while female axSpA is sometimes ignored). It therefore needs to be adjusted for in such an analysis, as it was the case in the above-mentioned Swiss study[4]. That implicitly means that important potential confounders should have been measured in the observational study, which is not rarely an issue in analyzing observational studies. If analyses are not adjusted for relevant confounders, results can be flawed and uninterpretable. At the phase of starting data collection, it is therefore very important to carefully consider which research questions will be analysed and, hence, which potential confounders also need to be measured.

At the stage of the data analysis, it is important to make the best use of the data available. Having data from multiple time points throughout follow-up may importantly enrich the possibilities of the researcher/analyst. For example, if we take the mentioned study of the Swiss cohort: when analysing the effect of TNFi on structural damage progression, the authors did not look at the effect of TNFi at baseline (baseline predictor) on the outcome, structural damage, at a given time point, e.g. 10 years. Rather than that, the authors made use of all data collected, with continuous information on TNFi and data on structural damage from every 2 years. This allowed for a longitudinal analysis, with the effect of TNFi being analysed per 2-year period (i.e. between 0-2 years, 2--4 years, 4-6 years, 6-8 years and 8-10 years) and then its effect analysed on the outcome, reflecting the change in structural damage progression in the period of 2 years. This means, for example, that the effect of 'being on a TNFi' in the period 0-2 years on the change in structural damage in the period of 2-4 years was analysed (we speak of 'time-lagged analysis'). In addition, one single patient contributed with multiple intervals, which illustrates also why such an analysis has much more statistical power: it makes optimal use of all available data.

All in all, observational studies can be excellent sources from which evidence is generated that expands our knowledge on a disease and its outcomes. Proper methodological considerations need to be made when 'designing' an analysis within an observational study, to ensure that as many sources of bias as possible are considered and controlled.

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