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Editorial

Lessons learned from rheumatoid arthritis registries

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1. Introduction

Following the introduction of biological anti-rheumatic treatments, numerous European countries have implemented national registries to evaluate the long-term effectiveness of these therapies and to verify the safety of their use [1]. The contribution of these registries and in a more general manner of observational research, has been increasingly recognized by academic societies, the pharmaceutical industry and health authorities. Indeed, current international treatment guidelines for rheumatoid arthritis (RA) on the tolerability and the safety of therapies are based largely on observational data [2]. Furthermore, registration authorities require pharmaceutical companies to compile post-registration registries for the collection of data regarding the effectiveness and tolerability of new therapies, as they are no longer satisfied with just the results of randomized studies.

A registry is a structured collection of data regarding patients who are generally followed in a prospective manner in a geographically defined population [3]. Registries are a specific type of cohort study and are part of observational studies. Unlike the latter, registries does not have a date for the end of the study and they often only collect clinical data normally obtained during a medical examinations. It is useful to distinguish between two types of registries: disease registries, such as a registry (RA registries) for example and drug registries, which are specific for a medication. Traditionally, for RA, the preference in France has been for registries of medications (e.g. ORA, AIR, REGATE, etc.), while other European countries have generally opted for disease registries. Disease registries enable internal comparisons of the effectiveness or the tolerability between therapies. The criteria for inclusion/exclusion vary among disease registries according to the objective being pursued by the investigators, with for example registries of early RA ("inception cohort"), or studies focused on the safety and the tolerability, which a priori link with other national databases, such as cancer or infection registries. There are also different models for recruitment: in Denmark, Sweden and Switzerland recruitment is integrated with routine care of RA patients, while in the United Kingdom and Spain only the patients of certain participating centers receiving biological treatments are included.

2. Reliability and benefits of registries

To establish the effectiveness of a new treatment, the gold standard for evidence is still randomized controlled studies [4]. Non-randomized studies can nonetheless be very useful in specific situations. First of all, the randomization can be counter to ethics criteria (for example, if the results are predictable or the extent of the effect in preliminary studies is very strong). Secondly, the outcome studied can be very rare or far into the future, making a randomized study impossible due to a lack of time and resources. For example, the detection of an increase in the risk of cancer over 20 years from one patient out of 10,000 to five patients out of 10,000 (relative risk of 5) would require that 58,848 patients are followed, randomized into two treatment groups over a period of 20 years. Thirdly, the generalization of the results of a randomized trial can be too limited. Over time, the treatments are used by an increasing number of patients and particularly by patients with less severe disease and with a larger number of comorbidities than generally accepted in randomized clinical trials. The generalization of the results of clinical trials to more complex patients can then become problematic. Lastly, it is often relevant to explore modifiers of effects, or subgroups effects in the authorized indication. These groups (for example, immunopositive versus immunonegative patients) are not usually randomized in the clinical trial. Moreover, in RA, concerns in terms of costs and safety of new therapies continue to be major considerations. Furthermore, comparative research of effectiveness becomes more and more important and it is unlikely that randomized studies can provide answers to numerous important questions regarding the comparative effectiveness. In a more general sense, it has been estimated that only ~15% of medical questions can be adequately addressed by a randomized study, which leaves ~85% to be addressed through observational studies.

Following, we will provide some examples illustrating clinical situations in which the study of registries can provide valuable clinical information:

Interestingly, it was studies of registries, rather than randomized studies that allowed methotrexate to acquire its current status as the gold standard of anti-rheumatic agent. Indeed, randomized placebo-controlled studies with methotrexate in the early 1980s failed to reveal a better effectiveness compared to other synthetic therapies in use at that time. It was observational studies that

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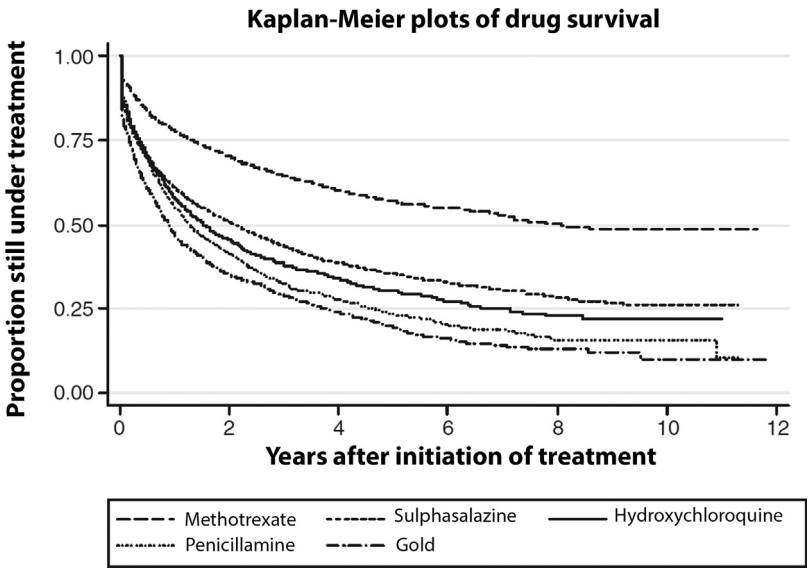

Fig. 1. Drug survival for anti-rheumatic maintenance therapies. Drug survival of methotrexate for patients with RA was more than double relative to other anti-rheumatic maintenance therapies in the 1980s. Reproduced with permission from the Journal of rheumatology [5].

subsequently showed that drug survival was much better than with other therapies: 50% of the patients had to suspend the treatment after only 10 months for gold salts, 20 months for hydroxychloroquine, 21 months for penicillamine and 27 months for azathioprine. For methotrexate, this duration was more than 60 months [5] (Fig. 1).

More recently, biological treatments have led to lasting changes in the management of patients suffering from severe RA. However, recognition of the main secondary effects and particularly the risk of opportunistic infections with anti-TNF treatments, came about through observational studies and not as a result of the numerous prior randomized studies [6,7]. The incidence of tuberculosis with infliximab in patients afflicted with RA was determined to be between 1 and 2% per year prior to 2001 in Spain, which was significantly more than in the RA population not treated with anti-TNF [6]. Interestingly, studies of registries have also provided proof of the effectivenesseffectiveness of preventative measures and of pretreatment anti-tuberculosis screening assessments [6].

Modulators of effects, also called interactions or subgroup effects, can be illustrated by studies of registries in regard to changes of bDMARDs. Thus, in the Swiss registry, a switch to a bDMARD with a different mode of action (rituximab) was not beneficial unless the previous anti-TNF treatment had been discontinued due to a lack of effectiveness. By contrast, if the reason for discontinuation of the prior anti-TNF treatment was due to intolerance or an adverse event of the treatment, the effectiveness of a second or a third anti-TNF treatment was comparable to a switch to a bDMARD with a different mode of action [8]. These results have since been confirmed by a large randomized French study [9]. Another subgroup effect identified by studies of registries was the discovery that certain bDMARDs, such as rituximab or abatacept, are associated with better results in seropositive patients than in seronegative patients [10–12].

3. Limitations of registries

Studies of registries have at times yielded contradictory results, either by finding different effect sizes, or by reaching distinctly divergent conclusions. This is what led a work group of the EULAR to propose guidelines in regard to the analysis and the report of results derived from registries [13]. A detailed comparison of the characteristics of these registries can often provide insights regarding the reasons that underlie these heterogeneous results [14]. This is what is referred to as confounding factors or factors that blur the association between the exposure and the disease. A confounding factor needs to be associated both with the exposure and the outcome of the study. In other words, a confounding factor must on its own have an impact on the outcome of the study. It is possible to control for a confounding factor when the study is being planned and when the statistical analysis is being carried out. However, sometimes the confounding factors vary over time (for example, the introduction of new treatment instructions), which can make interpretation of the results difficult, even though it is theoretically possible to correct or adjust the analysis for time-varying confounders.

The most serious source of errors in observational studies is selection bias, which is also called “confounding by indication” or “channelling bias”. Selection bias is linked to the recruitment of patients in the study or the fact of receiving one treatment rather than another. There is selection bias when, for example, the reasons that led a rheumatologists to prescribe a particular treatment also influenced the expected results. For example, it would make little sense to compare the effectiveness of biologic treatments with conventional synthetic drugs in a registry, as bDMARDs are generally given to the most severe patients and hence, no matter what, there should be a less favorable progression for this subgroup. The problem is that very often the reasons that drive practitioners to prescribe one treatment over another are not known and it is, therefore, impossible to adjust or correct for these effects. This is one of the reasons that lead to randomized and double-blind studies to be carried out for effectiveness, as this is the only method to limit selection bias. Studies of registries must take into account the possibility of selection bias and propose sensitivity analyses to test the robustness of the results of the study. It should be pointed out that selection bias can also occur in randomized trials when the patients assigned to an arm of the study leave the study more than the patients assigned to the other arm, for example if the secondary effects of the treatment are particularly severe.

A well-known example of selection bias is the use of hormone replacement therapy (HRT) in menopausal women. Most cohort studies have suggested a lower risk for cardiovascular disease in HRT users relative to those who did not receive HRT [15,16]. This result has been interpreted as supporting the existence of a protective effect of HRT against the risk of coronary disease. However, in a large randomized clinical trial, Manson et al. found a higher

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