Predictive factors of treatment persistence in rheumatoid arthritis

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Abstract

1. Introduction. Randomised controlled trials (RCTs) are considered the “gold standard” to establish drug efficacy, but they have typically a short follow-up and include only a limited number of patients, which rarely allows to assess safety appropriately. In addition, RCTs generally include highly selected patients and use strict protocols, which may not be representative of the challenges patients and health professionals face in real-life. By contrast, non-randomised studies, such as observational studies or epidemiological studies, have typically large numbers of patients, long follow-ups and highly heterogeneous study populations, which may allow to study subgroup of patients with different characteristics or establish generalisability in a less homogenous population. Therefore, real-world studies are increasingly recognised as an important mean to evaluate drug safety and effectiveness, and pharmaceutical companies are now more than ever required to demonstrate a real-life perspective in the regulatory process [...].

Reference


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In this editorial, we do not aim to exhaustively review all predictive factors ever associated with drug persistence, but to provide the reader with some points to consider and “food for thoughts” when reading studies reporting drug persistence.

2. Treatment persistence of conventional synthetic DMARDs: the issue of confounding and the limitations of RCTs

A few studies sought to evaluate the persistence of csDMARDs, mainly with methotrexate. The persistence of methotrexate is highly variable. In a systematic review of observational and interventional studies, methotrexate persistence ranged from 50 to 94% at 1 year and 25 to 79% at 5 years, the main reason for discontinuation being intolerance [4]. Interestingly, treatment termination rates varied strongly by the rheumatologist, which could be related to the fact that different doctors' account differently for the intolerance attributed to methotrexate. Both younger age and older age seemed to be associated with higher risk of discontinuation, but no other variables were found associated with methotrexate persistence.

Persistence of leflunomide appeared to be comparable to methotrexate [5], but the analysis did not account for confounding factors, which could have biased these results as patients prescribed leflunomide have lower baseline disease activity and are less often DMARD-naïve than patients on methotrexate [6,7]. This allows discussing a second major treat to observational comparative effectiveness studies, namely confounding. When comparing patients prescribed different drugs in an observational setting, accounting for differences between groups is key, or the results may be wrongly attributed to the therapy, whilst it may be due to a confounding factor. In a subsequent study, matching for the number of previous DMARDs, age and erythrocyte sedimentation rate, the persistence of leflunomide was found to be inferior to methotrexate [7]. In the same study, sulfasalazine also demonstrated lower persistence than methotrexate [8]. Confounding bias, and in particular the factors associated both with the prescription of a particular drug and its outcomes, have to be taken into account in the study design and the analysis for a valid study result.

More recently, the persistence of triple therapy has been under scrutiny. While RCTs have demonstrated that triple therapy can be as effective as TNF-inhibitors and methotrexate, the real-world persistence of triple therapy appears to be lower, in particular related to higher discontinuation rates due to adverse events of sulfasalazine [9,10]. At 1 year, only 18% of patients were still on triple...
therapy compared to 45% of patients treated by methotrexate and TNF-inhibitors [9]. These results illustrate the need for real-world evidence to assess how therapies fare outside of the clinical trial context.

3. Treatment persistence of biological DMARDS and JAK-inhibitors: drug characteristics and the role of time-varying factors

The beneficial interaction of TNF-inhibitors with methotrexate co-medication has been described over a decade ago [11]. The proposed mechanism is thought to be related to a decrease in the immunogenicity of monoclonal antibodies and a reduced production of anti-drug antibodies when the TNF-inhibitors are prescribed with methotrexate [12]. Curiously patients with tocilizumab, and perhaps also abatacept and rituximab, do not display high levels of anti-drug antibodies [13], nor decreased persistence [14] in monotherapy, in contrast to TNF-inhibitors. The drug persistence of rituximab is particularly delicate to define, as treatment is generally given biannually, but often less frequently, making it incredibly difficult to compare it to other drugs. Only a few have dared to take on the challenge of evaluating and comparing the persistence of rituximab to other drugs [15]. JAK-inhibitors, having only been recently introduced in the market, real-world studies of its persistence are only just emerging but, as with non TNF-inhibitors, methotrexate does not seem to be associated with persistence [16].

Several other factors have been linked to decreased treatment persistence, mostly with TNF-inhibitors, but also with other bDMARDs, such as higher number of previous bDMARDs, female gender, and higher disease activity or lower function at baseline [17]. Higher body mass index seems to decrease the drug persistence of TNF-inhibitors, but interestingly this has not been evidenced for tocilizumab or abatacept [18,19]; although for abatacept, subcutaneous administration has not been evaluated to our knowledge. On the other hand, seropositivity seems to impact more the persistence of abatacept or rituximab, than other bDMARDs [20].

Most of the studies evaluating predictors of drug discontinuation in RA have examined simply the effect of baseline characteristics at treatment initiation, only a few have examined if factors evolving during the course of the treatment could influence persistence [21]. As expected, the absence of improvement in disease activity is the most important factor determining drug persistence, well before the disease activity at baseline [21], suggesting that the recommendations of adapting the treatment to response to therapy are followed. However, the influence of the patient global assessment was only weakly associated with treatment changes, well after the change of disease activity, baseline disease activity, change of physician global assessment and its baseline values, which would suggest that the patient perspective is currently still not enough taken into account when deciding to maintain a treatment or not.

4. Other challenges of the evaluation of drug persistence

Although treatment persistence is thought to reflect mainly a drug’s tolerance and its effectiveness, other reasons may lead to discontinuation of a treatment, such as pregnancies or remission. Ideally, the broad reasons for discontinuation should be analysed separately, when analysing drug persistence. Factors unrelated to the drug or the patient may also play a role, such as individual physician’s perception or increased availability of treatment choices. Several studies have shown that drug persistence decreases with calendar of year initiation [18]. For example, when comparing subcutaneous tocilizumab to intravenous tocilizumab, calendar year of treatment initiation was the main factor associated with drug persistence, with increasing rates of discontinuation more recently (Fig. 1). An example for the impact of new treatment choices is the introduction of a different JAK inhibitor, as with baricitinib a few years after the availability of tofacitinib, which lead in Switzerland to a sudden decrease in the persistence of tofacitinib (hazard ratio of discontinuation of 1.71 for tofacitinib after the introduction of baricitinib compared to before) [22]. National tenders (national negotiations with drug manufacturers) also influence drug prescription at the country level and thus measure of drug persistence [23]. Differences in health care systems will influence drug persistence and result in vastly different drug persistence figures between countries [24]. Persistence is thus a “fuzzy” composite outcome, which is driven primarily by the patient and the healthcare provider satisfaction with the drug, but also by pulls unrelated to the drug. We would suggest that any study comparing drug persistence between drugs, adjusts at least for the year of treatment initiation,
the presence of concomitant treatments, the line of therapy, patient and disease baseline characteristics, and country of origin in international studies.

5. Conclusion

Drug persistence is an important aspect of treatment effectiveness, providing complementary information to RCTs. For clinicians, it may be helpful to know about some predictive factors of persistence when choosing a new treatment (e.g., “What treatment is the best treatment choice as monotherapy for an obese patient with seronegative rheumatoid arthritis?”) (Table 1). Real-world evidence is necessary, firstly to evaluate rare outcomes, or outcomes that may appear only in the distant future; secondly, to provide evidence of generalisability. However, generalisability without internal validity is useless and researchers must acknowledge that several factors may influence results in observational studies, and perform their analyses and report their conclusions accordingly. Unadjusted or poorly adjusted analyses of persistence that overlook major confounding factors, can lead to wrong conclusions. To critically interpret the results, we must also be aware that several factors unrelated to a particular drug may influence drug persistence. If these conditions are met, drug persistence, as a robust and well-reported measure in observational settings, is a remarkable outcome, combining two key aspects of a medication, its effectiveness and its safety. Together with other outcomes, drug persistence can help to shape a comprehensive understanding of a treatment’s usefulness for our patients.

Disclosure of interest

The authors declare that they have no competing interest.

References


Table 1

Key factors associated with anti-rheumatic drug persistence in rheumatoid arthritis (RA), based on the current literature and discussed in this editorial (non-exhaustive list).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Factors associated with persistence</th>
<th>Factors not associated with persistence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probably all treatments</td>
<td>Ineffectiveness [3]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intolerance [3]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treating rheumatologist [4]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Higher number of previous bDMARDs, female gender, lower function at baseline [17]</td>
<td></td>
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<tr>
<td></td>
<td>Change of disease activity, disease activity at baseline, change of physician global assessment, baseline physician global assessment [21]</td>
<td></td>
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<tr>
<td></td>
<td>Calendar year of treatment initiation [18]</td>
<td></td>
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<tr>
<td></td>
<td>National tenders [23]</td>
<td></td>
</tr>
<tr>
<td>Health care system/country of origin [24]</td>
<td>Launch of an alternative competitor drug [22]</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Young and old age [4]</td>
<td></td>
</tr>
<tr>
<td>TNF-inhibitors</td>
<td>Co-medication with methotrexate [11]</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Higher body mass index [19]</td>
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<tr>
<td>Abatacept</td>
<td>Seropositivity [20]</td>
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<tr>
<td>Rituximab</td>
<td>Seropositivity [20]</td>
<td></td>
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<tr>
<td>Tofacitinib</td>
<td>Seropositivity [20]</td>
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