Background: The approval by medicines regulatory agencies of new therapeutic agents in rheumatoid arthritis (RA) is based on results of phase III randomized controlled trials. The RA trials have been mainly used ACR20 response as primary endpoint. Conversely, this outcome is not clinically relevant for significant improvement of patients’ quality of life.

Objectives: We aimed to explore the surrogacy between ACR20 and ACR70 in rheumatoid arthritis.

Methods: We performed a systematic review search by screening randomized clinical trials registered in MEDLINE, EMBASE and the Cochrane Library between January 1990 and June 2021. We included all randomized trials (phase II and III trials, including multiamd design) that compared biotherapies or JAK inhibitors with csDMARDs or placebo with available ACR20 and ACR70 response. The coefficient of determination R²trial between these two outcomes were estimated using weighted meta-regression. To validate the surrogacy, the coefficient of determination (R²trial) should be superior to 0.65 and close to 1. The lower limit of 95% prediction interval needed to be upper than 0.5 to predict a weak surrogacy and upper than 0.72 to predict a strong surrogacy. The 95% prediction interval for R²trial was calculated with the percentile bootstrapping method.

Results: We included 189 randomized trials totaling 81,734 patients. Using 322 coefficients, the comparison of determination R²trial for estimating the relation between ACR20 on ACR70 responses is 0.55 (95% prediction interval 0.47-0.63). In subgroup analyses, the R²trial for the anti-TNFα therapeutic class was 0.69 (95% prediction interval 0.56-0.78). The R²trial in other subgroup analyses (double-blind design, superiority studies, multicentric studies, year of publication, corticosteroid use, small-study effect, and other therapeutic classes) were not relevant for surrogacy.

Conclusion: There is no surrogacy between ACR20 and ACR70 in RA. The use of ACR20 as primary outcomes should be limited to phase II trials and is not suitable for health technology assessment of benefit-risk ratio.

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RISK-BENEFIT ASSESSMENT OF THE USE OF RITUXIMAB FOR RHEUMATOID ARTHRITIS IN REAL LIFE: FINDINGS FROM 1984 PATIENTS FROM THE FRENCH AUTOIMMUNITY AND RITUXIMAB REGISTRY

Keywords: Rheumatoid arthritis, bDMARD, Safety

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Background: Most randomized clinical trials (RCTs) are explanatory studies examining whether a therapy can work under ideal circumstances. Rituximab (RTX) has been approved for treatment of rheumatoid arthritis (RA) following the results of three RCTs [1–3], including about 1000 patients. However, less than 10% of real-life patients was found to be eligible to these registration trials, because of restrictive inclusion criteria or exclusion criteria such as co-morbidities or undesired co-medication, which questions external validity of these RCTs. Whether the efficacy, tolerance or safety data obtained in highly selected RCTs patients can be extrapolated to a more heterogeneous sample of patients receiving RTX in daily practice, remains to be elucidated.

Objectives: We aimed to identify the main reasons limiting the eligibility of routine care patients in RTX-registration RCTs, and to investigate the relationships between the number of eligibility (both inclusion and exclusion) criteria and RTX efficacy and safety in a real-life scenario.

Methods: The AIR registry is a French nationwide, multicentre, prospective cohort study aiming at investigating efficacy and safety of RTX in a real-life setting. We retrieved eligibility criteria of the drug-registration trials evaluating rituximab for RA and applied them to our population. We compared the EULAR response (moderate-to-good) at 12 months and the incidence of serious adverse events (AEs, including severe infections, malignancies, major adverse cardiovascular events, and death) at 12 months between eligible and non-eligible patients. We modeled the risk-benefit ratios according to the number of fulfilled critical eligibility, defined by those associated with response and severe AEs, respectively, after backward stepwise variable elimination.

Results: Among 1989 RA patients included in the AIR registry, only 9 to 12% fulfilled all main eligibility criteria for the 3 drug-registration trials. The main unfilled inclusion criteria were an elevated CRP or ESR level (67.5%), erosive changes on bone X-ray (68.1%), and a swollen joints count ≥4/28 (74.6%). The main exclusion reasons were a history of severe or recurrent infection (35%), another severe uncontrolled disease (16%), neoplasia (14%), a high prednisone dose (≥ 10 mg/day for 26%), the use of another DMARD than methotrexate (16%) and ACR functional class IV disease (15%). Compared with RCT-eligible patients, non-eligible patients had less frequently moderate-to-good EULAR response (40.3% versus 46.9%, P=0.044), and had a smaller change in DAS-28 (-1.2 vs -1.4; 95% CI 0.1 to 0.5; P=0.005) at 12 months. Compared to patients with no exclusion criterion, patients with at least one critical exclusion criterion had a higher risk of severe AEs (HR 3.03, 95% CI 2.25–4.06 for ≥ 3 exclusion criteria compared to none). While the probability of EULAR response decreased with the number of unmet critical inclusion criteria, the probability of severe AEs increased with the number of exclusion criteria (Figure 1), highly decreasing the incremental risk-benefit ratio.

Conclusion: Few RA patients treated with rituximab fulfilled the eligibility criteria of the main drug-registration trials. Non-eligible patients had less chance of treatment response, and a higher risk of severe adverse events. This suggests that the efficacy and safety data from those trials cannot be extrapolated to RA patients in daily practice.

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