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Review

Safety of biologic DMARDs in RA patients in real life: A systematic literature review and meta-analyses of biologic registers

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ABSTRACT

Objectives: In daily practice, safety in rheumatoid arthritis (RA) patients receiving biological treatment is an important issue. Unlike randomized controlled trials, biologic registers provide long-term real life safety data. To identify all biologic registers worldwide, to extract and analyze data regarding safety in RA patients under biologics.
Method: Systematic review was performed independently by 2 rheumatologists using PUBMED, COCHRANE Library and EMBASE databases, up to December 2014. Worldwide biologic registers and related publications were identified. Data on safety issues in RA patients were extracted for meta-analyses. Random-effect meta-analyses were performed to estimate risk ratios (RRs) of mortality, cardiovascular events, cancer, including lymphoma and melanoma and serious infections between (1) biological and non-biological DMARD (cDMARD), (2) between biologics when data were available.
Results: Forty-three biological registers were identified worldwide and 27 publications were included for safety meta-analyses on anti-TNFs. Compared to cDMARD, mortality and cardiovascular events were significantly decreased in patients treated with anti-TNFs: RR = 0.60 [95% CI 0.38–0.94] and RR = 0.62 [0.44–0.88], respectively. Anti-TNFs did not increase the risk of solid cancer in patients without or with prior malignancy (RR = 0.84 [0.60–1.18] and RR = 0.77 [0.29–2.03], respectively), lymphoma (RR = 0.90 [0.62–1.31]) and melanoma (RR = 1.17 [0.86–1.59]). As expected, serious infections were significantly increased during anti-TNF treatment (RR = 1.48 [1.18–1.85]) compared to cDMARD. No significant difference was found between soluble receptor to TNF and monoclonal antibodies (RR = 0.55 [0.22–1.35]).
Conclusions: By reducing dramatically chronic inflammation in RA patients, anti-TNFs decrease mortality, cardiovascular events without increase significantly the risk of cancer, compared to cDMARDs.
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1. Introduction

Anti-TNFs and other biologic agents (bDMARD for biologic disease modifying anti-rheumatic drug) are major therapeutic advances in the management of rheumatoid arthritis (RA). Although they are efficacious, there still are concerns about long-term safety. Randomised controlled trials (RCTs) are not capable to detect rare or delayed-onset events, such as infections, solid cancers and lymphoma. Moreover, results from RCTs may not be transposable to "real life" because patients eligible for RCTs may have less comorbidities than those from our daily practice.

Since the approval of anti-TNFs in 2000, many countries have set up national and local biologics registers, which are longitudinal observational prospective cohort studies, to evaluate long-term outcomes (safety and efficacy) in clinical practice.

Our objectives were first to identify and describe worldwide registries on RA patients under biological agents, and then to perform meta-analyses of safety issues.

2. Methods

A systematic literature review was performed independently by 2 rheumatologists (MDLFD, CS) according to the

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Cochrane Collaboration Guidelines (http://www.handbook.cochrane.org/ version 5.1.0 updated March 2011) and PRISMA statement (Preferred reporting Items for Systematic reviews and Meta-analyses) [1].

2.1. Data sources and searches

With the help of 2 librarians, a systematic review search was performed in PUBMED, EMBASE and Cochrane Library databases until the end of December 2014 with no limitation of time and journal.

The first search (search 1) identified registries using the following combination of keywords in MeSh terms (PUBMED): "Arthritis, Rheumatoid" "AND" "Registries".

After identification of all registries, a second search (search 2) was performed to identify, all publications related to registries. The following combination of keywords was used in PUBMED: "Arthritis, Rheumatoid" "AND" the name of the registry.

In EMBASE, we used "Rheumatoid arthritis" and "Disease registry" (non-human and pediatric studies were excluded). We completed the review by hand search using reviews previously published.

2.2. Study selection

The selection was performed independently by 2 rheumatologists (MLFD and CS) as well. Published data were selected by screening the titles and abstracts, and then by reading the complete paper of potentially relevant studies.

We included all registries and related publications with data on RA adult (> 18 years) under biological agents. Only articles in English, French and Spanish were included.

2.3. Data extraction and synthesis for meta-analyses

From complete reading of selected publications, we extracted the following data:

- baseline registries' characteristics: country or area, year of start, inclusion criteria, population(s), effectives, treatments, biological agent(s), duration of follow-up, number of publications, comparator groups (general population and/or non biological DMARD group);
- data on safety regarding cancer (including lymphoma and melanoma), serious infections, cardiovascular events and mortality: number of events, risk factors in biological and non biological (control) groups of patients.

2.4. Quality assessment

Studies selected for safety meta-analyses were assessed for quality using Newcastle-Ottawa Scale [NOS, ref: Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses (Ottawa: Department of Epidemiology and Community Medicine, University of Ottawa; 2009, accessed at www.ohri.ca/programs/clinical_epidemiology/oxford.htm)]. This scale is validated to assess the quality of non-randomised studies such as cohorts and case-control studies. It allocated points in three domains: participant selection (0–4 points), comparability (0–2 points) and exposure or outcome (0–3 points).

2.5. Statistical analysis for meta-analyses

Extracted data were combined for meta-analyses. For all outcomes, Mantel–Haenszel random-effects method was applied. This assumes that studies were estimating different intervention effects and partly explains the heterogeneity between studies. Forest plots were created to summarize risk ratios (RR) estimates and their 95% confidence intervals (95% CI). These figures present measures of heterogeneity across observational studies (Cochrane Q statistic noted as Chi^2 and the I^2 statistic) and a test for overall effect (Z). Funnel plots were also produced to help to detect publication bias.

We used RevMan version 5.3 (Review Manager, Copenhagen, The Nordic Cochrane Centre, 2003) statistical software.

3. Results

The literature search is summarized in the flowchart (Fig. 1). From 813 abstracts, we selected 309 publications from 36 registers. Sixteen published reviews allowed us to identify 7 other registries with no publication identified in databases (hand search) [2–17].

Thus, 43 worldwide registers were identified. Their main characteristics are summarized in the supplemental file (Table S1; See the supplementary material associated with this article online).

Briefly, 23 registries biologic registers are European, 9 from North America, 4 from South America, 4 from Asia, 1 from The Emirates and 1 from Australia. Thirty-seven registers were national and 6 were regional.

Twenty-one registers included exclusively RA patients, the others included patients with other chronic inflammatory disorders (such as spondyloarthritis, psoriatic arthritis. . .).

Inclusion criteria were mainly RA patients who start their first or a new biological or non-biological DMARD, excepted in RATIO and AERS. In these 2 registers, patients with inflammatory diseases (such as Crohn disease, ankylosing spondylitis, rheumatoid arthritis or psoriatic arthritis) were included when they developed a serious safety event under anti-TNF (serious infection or lymphoma). Some registers are limited to one biologic, such as ORA for abatacept, AIR-PR and MIRA for rituximab, REGATE for tocilizumab.

Baseline collected data were age, gender, RA characteristics (duration, seropositivity, diseases activity measures, previous biologic and non-biologic DMARDs), concomitant treatments (cDMARDS, oral steroids) and important comorbidities. During the follow-up, data were collected at regular time intervals either by patients, physicians or nurses reported outcomes. Recorded outcomes were adverse events, changes of treatments and disease activity.

Published results were mainly about the first 3 licensed anti-TNFs (infliximab, adalimumab and etanercept) for 128 publications from 39 registers. Other biologics were less represented: rituximab (4 registers and 5 publications), anakinra (2 registers and 2 publications), tocilizumab (6 publications from 3 registers) and abatacept (2 registers and 2 publications).

Thirteen registers collected also data on comparison cohorts of patients with RA being treated with cDMARD. Three used general population as comparator (i.e. BIOBADASER, RATIO, and LORHEN).

From these 43 registers, we identified 324 publications on RA: 25 assessed epidemiology/register description, 139 assessed biologic efficacy, 124 safety, 24 were about drug survival and 12 on cost effectiveness of biological agents.

3.1. Safety of biological agents in RA patients

From 124 publications on safety, we included 27 from 13 registers in the meta-analyses [18–45,51]. These publications were included because they provided data on safety issues (mortality, cardiovascular events, serious infections, cancer included melanoma and lymphoma) in biological and non-biological RA patients.

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