Seminars in Arthritis and Rheumatism 43 (2014) 730–737

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

The comparison of effects of biologic agents on rheumatoid arthritis damage progression is biased by period of enrolment: Data from a systematic review and meta-analysis

Ennio Giulio Favalli, MD[a,*], Francesca Pregnolato, BSTT[b], Martina Biggioggero, MD[a,c], Pier Luigi Meroni, MD[a,c]

[a] Division of Rheumatology, Gaetano Pini Institute, Via Gaetano Pini 9, 20122 Milan, Italy
[b] Experimental Laboratory of Immunological and Rheumatologic Researches, IRCCS, Istituto Auxologico Italiano, Cusano Milanino, Italy
[c] Department of Clinical Sciences and Community, University of Milan, Milan, Italy

ARTICLE INFO

Keywords:
Rheumatoid arthritis
Damage progression
Biologics
Meta-analysis

ABSTRACT

Objectives: To indirectly compare the 12-month effects of available biologic agents in slowing RA radiographic progression.
Methods: A systematic review of literature of randomised, double-blind, controlled trials (RCTs) evaluating RA radiographic progression as end point was conducted using a PubMed searching of MEDLINE from January 1995 to May 2012. For each trial, the mean change from baseline of the standardised annual radiographic progression score (weighted for estimated annual progression rate) was estimated, and the effect size was calculated as the difference between biologic and non-biologic-treated groups. In order to optimise data homogeneity and improve RCTs comparison, a mixed-effect model was applied including previous responsiveness to methotrexate (MTX-experienced or MTX-naïve populations) and period of study enrolment as moderators.
Results: The PubMed search resulted in 183 references, and 14 were eligible for the meta-analysis. The analysis of study distribution in forest plots showed a high correlation between the study period of enrolment and the impact of biological therapy in both MTX-naïve and MTX-experienced subgroups. In particular, effect size was the highest for older trials and progressively decreased in the most recent ones, suggesting a highest propensity to radiographic progression in populations enroled in older trials. Some statistically significant differences among RCTs were found in both subgroups but were significantly biased by the different propensity to radiographic progression due to period of enrolment.
Conclusions: Our meta-analysis demonstrated that period of enrolment deeply influence study population propensity to radiographic progression in each trial. This finding does not allow the indirect comparison of various biologic agents, despite our mixed-model significantly reducing heterogeneity among RCTs.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory arthropathy whose progression is heterogeneous, and the outcome is difficult to predict. Some RA patients do not develop any erosion even after long-term disease, but the vast majority display bone erosions and cartilage breakdown, resulting in joint destruction, functional impairment, and increased mortality [1,2].

The outcome of the disease improved considerably in recent years with the availability of new effective therapies. In particular, biological agents displayed a rapid and sustained disease control, associated with impressive prevention of joint destruction [3]. Biological agents target several immune effectors that play a key role in local and systemic inflammation, including TNF, IL-6 receptor and IL-1 β, while rituximab is a MoAb against CD20 positive B-cells and abatacept is a fusion protein against CTLA-4, inhibiting T-cell co-stimulation.

The large number of currently available biologic drugs provides a rationale for comparing the efficacy of these agents on damage progression in order to make a reasonable therapeutic choice. To date, all these agents have been tested versus methotrexate (MTX) for efficacy on disease progression prevention in several randomised clinical trials (RCTs), whereas only few direct head-to-head comparisons have been conducted.

The purpose of this investigation is to indirectly compare the 12-month effects of all available biologic drugs in slowing radiographic progression in RCTs. In particular, we thought that RCTs

* Corresponding author.
E-mail address: ennio.favalli@gmail.com (E.G. Favalli).

0049-0172/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.semarthrit.2013.11.006

inclusion criteria have been subjected to gradual changes over the years making the reported radiographic damage progression much more related to the patients' characteristics than to the efficacy of the tested biologic agent.

Methods

Literature search and study selection

A systematic review of literature was conducted using a PubMed searching of MEDLINE from Jan 1995 to May 2012, according to standard reporting guidelines [4]. PubMed was searched using the medical subject heading (MeSH) terms ('arthritis, rheumatoid/radiography' OR 'disease progression') combined with 'arthritis, rheumatoid/drug therapy', and limited to 'randomised control trial' as article type, 'humans' as species, 'English' as language, 'adult' as age and a period between 1 January 1995 and 31 May 2012 as publication date. The last search was conducted on 1 June 2012.

Study quality assessment and data extraction

Two investigators independently reviewed the titles and abstracts from the literature applying the predefined inclusion criteria in a hierarchical manner. First, only randomised, double-blind, controlled trials that compared abatacept, anakinra, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab with any synthetic DMARD or placebo in adult patients with RA were included. Second, only trials that were published in a peer-reviewed medical journal, available as a complete study report, were included. Third, only RCTs with evaluation of radiographic progression as a primary or secondary endpoint were considered. Last, only trials with at least 1 year of follow-up period and at least 50 patients enroled were included.

Studies that pooled patients from different disease cohorts were also excluded. All publications identified as potentially relevant by at least one reviewer were retrieved. The reviewers examined all publications for duplication of study populations, discussed publications that were considered to be potentially relevant and came to a consensus on inclusion based on the inclusion criteria.

Statistical analysis

The radiographic progression in RCTs on biologic agents is usually assessed by using at least three different scoring methods: Sharp score [5] and its modifications by van der Heijde (vdH–Sharp) [6] and Genant (Genant–Sharp) [7]. The radiographic score (irrespective of the scoring system) was standardised by calculating the score as the percentage of the maximum score according to the formula: score percentage = (score/maximum possible score) $\times$ 100 [8]. The outcome was the mean change from baseline of the annual radiographic progression rate (calculated as the mean change from baseline of radiographic score divided by standardised annual estimated disease progression score). When the study was designed with more than one group of patients treated with different biologic drug schedules, data were extracted from the group treated with the licensed biologic agent schedule. The effect size was calculated as the difference between the two groups in each trial. Total score (TS), erosion score (ES) and joint narrowing space score (JSNS) were analysed separately. If standard deviation was not given, it was calculated from a 95% confidence interval, a standard error of the mean, a *P*-value and a T table, or from data estimated from figures [9].

Both random- and mixed-effects models have been applied and compared in order to estimate the average effect of biologic agents. Random-effects model assumes that different clinical trials are not exactly identical in their methods and/or in the baseline characteristics of the study population. Heterogeneity (defined as the variability generated by these study differences) can be modelled when treated as a purely random variable. A mixed-effects model includes one or more moderators that may account for at least part of the heterogeneity [10]. In our analysis, the moderator variables are previous DMARDs treatment and period of enrolment. Period of enrolment has been identified by year of publication, since we have found that it is linearly dependent from both the start and the duration of the study ($F = 3.02 \times 10^7$, $P \ll 0.05$). A likelihood ratio test was conducted in order to provide information about the fit statistics of two models, with and without moderators.

Heterogeneity among included studies was quantified as τ^2 (estimate of total amount of heterogeneity) and I^2 (percentage of total variability due to heterogeneity). Q-test was applied to assess the extent of heterogeneity [11]. For each trial, the effect was plotted according to its standard error in a forest plot showing a graphical overview of the results [12]. A *P*-value equal to or less than 0.05 was considered statistically significant. The meta-analysis was conducted in R programme with metafor package (Viechtbauer W, 2010).

Differences between study characteristics were evaluated by Wilcoxon rank-sum test for two independent samples.

Results

The PubMed search (Fig. 1) resulted in 183 references. Ninety-nine were excluded because they did not include any of the biologic agents under evaluation. Out of 84 remaining potentially relevant trials, 27 were excluded as not especially designed to evaluate radiographic progression in biologic versus non-biologic-treated patients, four because of the assessment of damage progression by MRI or ultrasound only, five because of the insufficient sample number and/or follow-up period, two because of the lack of sufficient radiographic data to calculate a radiographic progression rate [13,14] and 32 since they were extension studies [15] or post-hoc analyses [19] of otherwise included trials. Finally, 14 RCTs were evaluated for the meta-analysis [15–27]. Because of some missed values, the analysis of ES and JSNS was restricted to 10 RCTs [15–23].

Baseline population characteristics in the RCTs

The first identified paper was published in 2000, and the last in 2011. In order to optimise data homogeneity and improve RCTs comparison, studies were stratified in two subgroups according to previous DMARDs treatment (MTX-experienced or MTX-naïve populations).

Demographic and clinical characteristics were very similar among the included trials in both subgroups (Table 1). In particular, RCTs for the MTX-naïve subgroup enroled early RA (ERA) populations with a mean disease duration equal to or less than 2 years, whereas RCTs for the MTX-experienced subgroup involved late RA (LRA) patients (mean disease duration >2 years).

The standardised annual estimated disease progression score (SAEDP) significantly differed between MTX-naïve and MTX-experienced subgroups in TS and ES while JSNS displayed a *P*-value very close to a statistically significant threshold (Fig. 2).

Table 2 shows sample size and effect size characteristics of TS, ES and JSNS in subgroups treated with biologic agents and placebo in each included RCTs.