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Original article

Efficacy of triple association methotrexate, sulfasalazine and hydroxychloroquine in early treatment of rheumatoid arthritis with insufficient response to methotrexate: Meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: To evaluate the efficacy of the triple synthetic Disease Modifying Anti-Rheumatic Drugs (sDMARD) combination methotrexate, sulfasalazine and hydroxychloroquine versus a biologic DMARD (bDMARD) in the treatment of early rheumatoid arthritis.
Methods: A systematic literature search was performed using the PubMed and Cochrane databases, and abstracts presented at rheumatology scientific meetings until December 2013. Randomized controlled trials comparing the efficacy and the safety of biologic DMARD with the triple combination were included. Outcome measures were Van der Heijde modified Sharp score (SHS), remission rate, ACR criteria response, adverse events.
Results: A total of 1225 abstracts were screened. We extracted data from 5 trials including patients (515 in the triple combination group and 710 in the bDMARD group). We showed higher ACR70 response (OR = 1.79, 95% CI [1.17, 2.72]) in patients treated with bDMARDs, whereas radiological progression was not different from patient with triple combination (OR = 1.10, 95% CI [−0.04, 0.28]). At year 2, ACR70 response and remission rate, the results were similar in both groups with respectively OR = 1.44 (95% CI [0.86, 2.43]) and SMD = 0.45 (95% CI [0.17, 0.72]). The proportion of serious adverse events was similar in both groups OR = 1.02 (95% CI [0.68, 1.52], $P = 0.92$, $I^2 = 0\%$). Gastro-intestinal adverse events were higher in the triple combination group (OR = 1.75, 95% CI [0.73, 4.21], $P = 0.21$, $I^2 = 75\%$). Infectious adverse events were more frequent in the bDMARD group (OR = 0.50, 95% CI [0.35, 0.70], $P < 0.0001$, $I^2 = 36\%$).
Conclusion: Biological treatment seems to be more efficient than triple combination in terms of radiological progression in RA with inadequate response to methotrexate.

1. Introduction

Current recommendations in early rheumatoid arthritis (RA) focus on achieving clinical remission as soon as possible. The concept of a window of opportunity has emerged in early RA, based on a time frame within there is a higher response to intensive treatment strategies leading to a better chance for sustained low disease activity and remission [1,2].

Methotrexate allows about 30% to 50% of early RA patients to achieve a low disease activity [3,4]. Among the several potential DMARD (Disease Modifying Anti-Rheumatic Drugs) combinations, the combination of methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ) has been shown to be the most effective [5]. In the T-REACH trial [6], the triple combination was superior to a single sDMARD (Synthetic DMARD) in the early RA with high probability of radiological progression. O'Dell et al. [7] and Calguneri et al. [8] also described the long-term interest of the triple combination in RA.

During the past few years, several studies comparing the effect of a single sDMARD versus medication triple combination were performed in patients suffering from Rheumatoid Arthritis [6,7]. Nevertheless, conclusions of those studies are often contradictory

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[9,10], and guidelines for prescribing the triple combination in early RA are still unclear [11,12]. Some studies showed that the triple combination achieved similar clinical results than a biologic DMARD [13] whereas some studies suggested that bDMARD is superior to the triple combination [14]. Moreover, discrepancies between clinical and radiological outcomes and between short-term and long-term endpoints have been shown [13].

Therefore, we performed a systematic literature review to compare the efficacy and the safety of triple combination and bDMARD (biological DMARD) in early rheumatoid arthritis with insufficient response to MTX.

2. Methods

We performed a systematic literature search of randomized studies comparing the efficacy and the safety of a triple combination MTX, SSZ and HCQ versus a bDMARD in the treatment of early RA.

2.1. Search strategy

An extensive search of Pubmed and Cochrane was made by two reviewers (A.M. and A.C.B.) concerning articles until December 2013. The following keywords were used for database screening ("Hydroxychloroquine" [Mesh] or "Methotrexate" [Mesh] or "Sulfasalazine" [Mesh]) and ("Arthritis, Rheumatoid" [Mesh] or "rheumatoid" [tw]). We completed our screening with a second combination: ("Hydroxychloroquine" [Mesh] or "Methotrexate" [Mesh] or "Sulfasalazine" [Mesh] or "Drug therapy, combination" [Mesh]) and ("Arthritis, Rheumatoid" [Mesh] or "rheumatoid" [tw]) not ("Hydroxychloroquine" [Mesh] or "Methotrexate" [Mesh] or "Sulfasalazine" [Mesh]) and ("Arthritis, Rheumatoid" [Mesh] or "rheumatoid" [tw]). The only limit of the search was "clinical trial". Another screening in the Cochrane database with the following keywords was performed: "([Methotrexate] explode all trees OR MeSH descriptor: Hydroxychloroquine explode all trees OR MeSH descriptor: [Sulfasalazine] explode all trees) AND MeSH descriptor: [Arthritis, Rheumatoid] explode all trees".

A hand search of references concerning included studies and abstracts presented at Annual Scientific Meetings of the American college of Rheumatology (ACR) the European League against Rheumatism, and the French Society of Rheumatology published from November 2009 to November 2013 completed the literature search. A search on the www.clinicaltrials.gov Web site was also performed to identify randomized studies that were not yet published.

2.2. Study selection

Inclusion criteria were (i) randomized controlled trials (RCTs) that included (ii) early (disease duration < 24 months) RA patients as defined by the 1987 ACR criteria [15] or the 2010 EULAR/ACR classification [16] with (iii) insufficient response to MTX and (iv) stable doses of non-steroid anti-inflammatory drugs (NSAIDs) and steroid (less than 10 mg/day at least 1 week before the inclusion), treated (v) either by the triple combination and bDMARD (vi) with stable doses of (NSAIDs) and steroids. MTX doses ranged from 10 mg/week to 25 mg/week, SSZ doses ranged from1 to 2 g/day and HCQ doses were 400 mg/day. Infliximab dose ranged from 3 mg/kg to 10 mg/kg etanercept intravenously dose was 50 mg/week subcutaneously and adalimumab 40 mg all 2 weeks subcutaneously.

2.3. Outcome measures

We applied the Cochrane Musculoskeletal Group recommendations to select outcome measures [17]. We reported ACR70 response [18], Sharp van der Heijde Score (SHS) [19], remission [20]. We reported the number of patient with an increase of SHS > 0.5 point at two years as a proxy for clinically significant radiological progression. We also reported the number of completers and the adverse events.

2.4. Quality assessment

Two authors (A.M. and A.C.B.) assessed the methodological quality of each study included in the meta-analysis on the JADAD scale (ranging from 0 to 5), where a high score indicates high quality methodology. When disagreements remained after discussions between both reviewers, a third reviewer (A.B.) was consulted.

2.5. Data extraction

Two investigators (A.M. and A.C.B.) independently selected articles among those screening with keywords previously reported and collected data using a predetermined form including patients characteristics (number, gender, age, Body Mass Index [BMI]), disease duration, current and past treatment with sDMARDs or bDMARDs, the use of NSAID or corticoids, rate of rheumatoid factors (RF) or Anti-citrullinated protein antibody (ACPA) positive patients, Health Assessment Questionnaire (HAQ) scale [21], Disease Activity Score in 28 joints (DAS 28) [22], SHS [19], remission rate (ACR/EULAR) [20], ACR criteria response [18], adverse events. Data were collected at several end points: 12 months, 24 months. When a trial was reported in several publications, the more informative publication was included in the meta-analysis. When studies reported more than 2 subgroups, we included only the first intervention group described in this study and its corresponding control group.

2.6. Statistical analysis

The efficacy of triple combination was compared to the bDMARD in each study by the calculation of the standardized mean difference (SMD; difference between both groups of mean outcome variation from baseline/SD at baseline) and 95% confidence interval (95% CI). Individual SMDs were pooled using the method of the inverse of variance. Intervention safety was assessed by the odds ratio (OR) and 95% CI. The results of individual trials were pooled by meta-analysis using the Mantel-Haenszel method. Heterogeneity was examined using an extension of the Q statistic, I^2 (and its 95% CI), which was considered to be statistically significant at values > 50%. Inter-reviewer reproducibility for study selection, data extraction and methodological quality assessment was calculated. Inter-reviewer reproducibility was considered to be moderate for kappa coefficients ranging from 0.21 to 0.59, good for kappa coefficients ranging from 0.60 and 0.80 and excellent for kappa coefficients > 0.80. Number needed to treat/harm (NNT/NNH) was calculated. Meta-analyses were performed with Review Manager 5 (Nordic Cochrane Centre, Rigshospitalet, Denmark) and additional statistical analyses were conducted with StatsDirect (StatsDirect, Cheshire, UK).

2.7. Heterogeneity analysis and publication bias

To explore heterogeneity, studies were combined into 2 or 3 subgroups according to the trial design (JADAD ≤ 3 or > 3), or country (US vs. European studies). Heterogeneity between the subgroups was tested using a chi-square test. Publication bias was assessed using funnel plots for meta-analysis comprising more than 3 studies. No funding was received for this study.