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Subcutaneous administration of methotrexate at high doses makes a better performance in the treatment of rheumatoid arthritis compared with oral administration of methotrexate: A systematic review and meta-analysis

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ABSTRACT

Objectives: This study was conducted to determine whether subcutaneous (SC) methotrexate (MTX) makes better performance on bioavailability, clinical efficiency, side effects occurrence, and treatment failure in the treatment of RA compared with oral MTX.

Methods: The databases PubMed, Web of Science, Embase, and Cochrane Library were systematically searched. Seven studies involving 1335 patients were eligible for data extraction and meta-analysis. The outcomes of meta-analysis were presented as mean difference (MD) or odd ration (OR) with 95% confidence interval (95% CI).

Results: Meta-analysis showed that SC MTX can significantly increase the AUC_{0-t} (area under plasma concentration curve from administration to last observed concentration at time t) (MD = 506.84; 95% CI: 80.80–932.89), shorten the time to reach maximum observed concentration (T_{max}) (MD = −0.13; 95% CI: −0.25 to −0.01) and the apparent terminal elimination half-life ($t^{1/2}$) (MD = −0.39; 95% CI: −0.70 to −0.08), reduce the occurrence of nausea (OR = 0.53; 95% CI: 0.28–0.97) and diarrhea (OR = 0.43; 95% CI: 0.20–0.95), improve the American College of Rheumatology criteria for 20% improvement (ACR20) (OR = 1.68; 95% CI: 1.09–2.61) and ACR70 (OR = 1.52; 95% CI: 1.02–2.26), and relieve the pain (MD = −0.65; 95% CI: −0.93 to −0.37) compared with oral MTX. However, the differences in maximum plasma concentration (C_{max}), the occurrence of headache, vomiting and dyspepsia, ACR50, treatment failure were not significant between the two groups.

Conclusion: SC route of MTX at high doses made better performance on improving the bioavailability and clinical efficacy, reducing the GI disorders, but it cannot decrease the treatment failure when compared with oral administration of MTX.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease occurring in each decade of life [1]. This disease is globally distributed with a prevalence of 0.5–1%, but the exact pathogenesis is still unknown [2,3]. RA is a progressive disease that could deprive patients of a healthy workforce and significantly increase the burden to the family [4]. So, it is necessary to take antirheumatic measures to treat the disease as early as possible. Methotrexate (MTX) is a drug of choice for RA worldwide with a favorable efficacy to control symptom, increase long-term safety and improve survival over time [5–7]. Oral MTX is the most commonly prescribed treatment for RA and has been used in clinical for ages. A systematic review found evidence that higher doses would improve clinical outcomes [8]. However, with the dose increasing, oral MTX have shown bioavailability variations and frequent gastrointestinal (GI) side effects, which limit optimal use [9]. Accordingly, parenteral MTX was put into research. Studies [10,11] suggest that the bioavailability of MTX is improved with intravenous and intramuscular injection of MTX, particularly at doses > 15 mg/week. At the same time, subcutaneously (SC) administered of MTX has attracted more and more rheumatologists' attention in recent years with well absorbed and tolerated clinical results, which may be more effective than oral MTX at the high doses [12,13]. Furthermore, SC injection of MTX could be accomplished with a prefilled autoinjector pen, which made it more convenient for patients to administrate drug than other parenteral methods [14].

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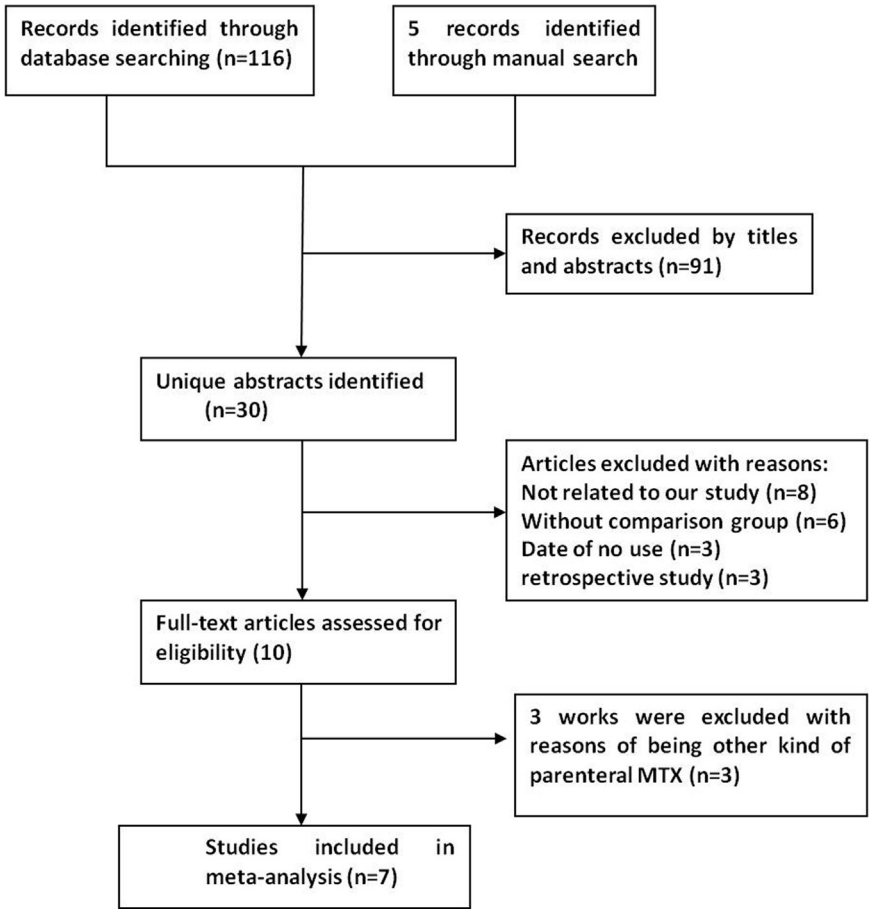

Fig. 1. Flow chart of study selection.

In order to compare SC MTX with oral MTX in the treatment of RA on bioavailability, clinical efficiency, the occurrence of adverse events, and treatment failure systematically, we conducted a systematic review and meta-analysis to determine whether SC MTX makes better performance than oral MTX.

Materials and methods

Search strategy

We identified randomized controlled trials (RCT) or randomized crossover studies from 1974 to September 15, 2015 by searching the databases including PubMed, Web of Science, Embase, and Cochrane Library using the following terms: (Rheumatoid arthritis) and (Methotrexate) and (Subcutaneous and oral). Besides, the reference lists of review articles, all reports and additional trials are also included by manual search.

Inclusion criteria

RCTs, randomized crossover studies and cohort studies that compared the SC MTX with oral MTX were included. The doses $\geq$ 15 mg/week were regarded as high doses in our study. Eligible studies were selected based on criteria aforementioned by two reviewers. Any disagreement between them was resolved by consensus.

Data extraction

We extracted the following data from the included articles: publishing date, location of study, numbers of patients in each group, demographic data of participants including age, gender, dosages of drug administrated, primary outcomes bioavailability assessments including area under plasma concentration curve from administration to last observed concentration at time t (AUC_{0-t}), maximum plasma concentration (C_{max}) of MTX, drug elimination expressed as time to reach maximum observed concentration (T_{max}) and apparent terminal elimination half-life ($t^{1/2}$) were evaluated; secondary outcomes we analyze adverse events containing GI side effect, headache, bronchitis, nasopharyngitis, etc.; third outcomes is clinical efficacy, which includes American College of Rheumatology criteria for improvement (ACR) and visual analog scale (VAS) score; the last outcome is to evaluate treatment failure (defined as serious adverse event resulting in change in therapy or treatment inefficacy). If necessary, we attempted to contact the author of the original reports to obtain further details. The data extraction was made by two reviewers. Likewise, any disagreement between them was resolved by consensus.

Study quality

Each study that was included in the analysis was assessed independently by each author. The assessment was performed using the modified Jadad scale for systematic reviews [15]. Studies achieving a score of $\geq$ 4 points were considered to be of high quality.