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CAFFEINE TO ALLEVIATE METHOTREXATE INTOLERANCE IN RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: In spite of its tolerance issues, methotrexate is still considered as the cornerstone among conventional disease-modifying antirheumatic drugs in rheumatoid arthritis. Some patients report a reduction of gastrointestinal side effects when they consume caffeine concomitantly. However, some studies suggest that caffeine can reduce the efficacy of methotrexate. **Objective:** To break through this paradox, the aim of this study was to evaluate the effects of caffeine consumption on efficacy and tolerance of methotrexate in patients with rheumatic diseases. **Methods:** A systematic review was performed following the PRISMA statement to identify all published clinical studies that evaluated the effect of caffeine on the efficacy and tolerance of methotrexate in patients with rheumatic diseases. PubMed, Google Scholar, ScienceDirect, and Cochrane Library databases were investigated from January 2000 until June 2020. **Results:** Among 34 identified studies, 7 fulfilled our criteria for inclusion: three studies were about efficacy, and four about tolerance. Taken together, these studies tend to show that caffeine consumption does not reduce the efficacy of methotrexate, and that caffeine consumption concomitantly with the weekly dose of treatment improves its tolerance. **Conclusion:** Available studies to date are limited but allow to draw clinical implications for the management of methotrexate intolerance. First, caffeine doesn't seem not reduce the efficacy of methotrexate. Second, caffeine may improve methotrexate tolerance when taken concomitantly with the medication weekly dose. The addition of 2 cups of coffee in the morning of the medication day, and another 2 cups 1-3 hours before taking the MTX may help in alleviating symptoms.

KEYWORDS: Caffeine; Methotrexate; Efficacy; Tolerance; Rheumatoid arthritis; Adenosine.

1. INTRODUCTION

Methotrexate (MTX) is currently considered as the anchor disease-modifying anti-rheumatic drug (DMARD) in rheumatoid arthritis (RA).[1,2] The American College of Rheumatology (ACR), as well as the European League Against Rheumatism (EULAR) recommendations both recommend MTX as a the first-line DMARD for most patients with established RA.[3,4]

The mechanism of action of MTX in RA and other inflammatory rheumatic diseases is still incompletely understood. Recent progress was made in the comprehension of its molecular and cytokines effects.[5,6] It has been shown that MTX participates in the cascade of adenosine, a molecule with anti-inflammatory property with the inhibition of proinflammatory cytokines production, when it binds to its receptors on inflammatory cells and in the central nervous system (CNS).[7–9] In doses used in the treatment of RA, MTX causes the accumulation of the enzyme 5-aminoimidazole-4-carboxamide ribonucleotide in animal models, and this accumulation is associated with raising intracellular levels of adenosine[7,10,11], and thus explaining the reduction of inflammation. Besides, it is also known that methylxanthines, including theophylline and caffeine, are adenosine receptor antagonists.[12,13] Theoretically, caffeine could consequently reduce the anti-inflammatory effects of MTX. In this way, some studies suggested that caffeine consumption may interfere with the efficacy of MTX.[11,14]

Furthermore, intolerance issues following MTX intake have been reported, causing a reduction of patients' therapeutic adherence, consisting of symptoms related to the gastrointestinal (GI) tract, and to the CNS with behavioral symptoms.[15–19] This is sometimes called the "methotrexate fog" or "methotrexate blah" according to the Arthritis Foundation.[20] These symptoms have been described in pediatric patients in which a validated score was published to assess MTX intolerance: the Methotrexate Intolerance Severity Score (MISS), classifying the symptoms as "associative", "anticipatory" or "behavioral".[21] This score has been validated and adapted to adult populations in RA.[22,23] In a recent study of 150 patients with RA under MTX, 33.3% of the cases exhibited intolerance, out of which the most recurring symptoms were behavioral (44%) and vomiting (11%).[16] There are several reported measures to

improve MTX-adherence (Figure 1). Firstly, given that MTX inhibits folate-dependent metabolic processes, it is generally admitted that side effects of MTX can be prevented with folic acid supplementation.[11,24] Other reported measures include splitting the oral MTX dose when they are superior to 15 mg/week.[25,26] or switching to subcutaneous route.[27] However, even with these measures, many patients still experience GI side effects after MTX intake.

Several studies linked the effect of MTX-induced adenosine release to its GI and behavioral intolerance.[8,12,28] As an antagonist of adenosine receptor, caffeine may inhibit receptors in the CNS, and consequently alleviate MTX intolerance. This assumption enters in contradiction with the above theoretical conclusion that caffeine reduces the anti-inflammatory effect of MTX, and raises questions about the potential role of caffeine in the management of RA under MTX.

In our daily practice, some patients reported a better tolerance of MTX when they consumed caffeine concomitantly with the weekly intake, and did not require higher doses of MTX to maintain disease remission compared to those who do not consume caffeine. To break through the above paradox and verify our observation, we conducted a systematic review with the aim of trying to answer the following two questions: 1) Can patients under MTX consume caffeine without interfering with the therapeutic effect? 2) Does caffeine consumption reduce GI and behavioral side effects of MTX?

2. METHODS

2.1 Search strategy

We followed the systematic review guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[29] The flow chart is detailed in Figure 2.

The search was performed by 3 independent reviewers, including all studies published in scientific journals in which patients with RA were given caffeine in association with MTX. The following databases were explored with no language restrictions from January 2020 until June 2020: PubMed, Google Scholar, ScienceDirect, and the Cochrane Library. The following combined terms were investigated: “methotrexate”, “caffeine”, and “rheumatoid arthritis”. The International Clinical Trials Registry Platform Search Portal and clinicaltrials.gov were searched to look for randomized controlled trials. Additional manual searches were also conducted to forage for conference abstracts and papers. The reference lists of retrieved articles were hand-searched to identify relevant additional studies.

Inclusion criteria comprised all the clinical studies in which patients with RA received both MTX and caffeine. There were no restrictions based on age, sex, race, or on the design of the study.

Exclusion criteria comprised studies in animals, in diseases other than RA, general reviews about caffeine, and studies that consisted in molecular and genetic explorations (non-clinical studies).

2.2 Study Selection

Two of the authors (ZE and KN) independently reviewed the titles and abstracts retrieved by the search, performed a dual-blinded data extraction with the assessment of its comprehensiveness, and selected potentially eligible studies. Disagreements were resolved by consensus discussion with a third author (SJ). One investigator was requested by email to provide supplementary data to his conference abstract, but with no response.

A structured data abstraction form was used by one of the authors (ZE) to ensure the consistency of the appraisals of each study. It included publication data (first author name, date of publication, country, study design, sample and duration), demographic data (sample size, sex ratio), caffeine intake evaluation methods, disease evaluation measures (functional and clinical signs, laboratory tests, disease activity scores), and outcomes. Folic acid supplementation and the administration of other DMARDs were also taken into account as possible bias for analysis. Any discrepancies were resolved by consensus between the 3 authors.

2.3 Outcome measures

Primary objective

To evaluate the efficacy of MTX when combined to caffeine, i.e. to determine if caffeine consumption reduces the therapeutic effect of MTX on the disease activity. Efficacy was judged on the criterion of maintaining the same dose of MTX with an intake of caffeine. Measures to evaluate disease activity searched were: 1) Functional symptoms: duration of morning stiffness (DMS), patient’s assessment of joint pain using a Visual Analog Scale (VAS), Patient Global Assessment (PGA) of disease activity, the Multidimensional Health Assessment Questionnaire (MDHAQ). 2) Physical signs: Swollen Joint Counts (SJC), Tender Joint Counts (TJC). 3) Laboratory tests: Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP). 4) Disease activity scores: Disease Activity Score in 28 joints (DAS28).

Secondary objective

To evaluate the tolerance of MTX when combined to caffeine, i.e. to see if caffeine consumption reduces GI and behavioral side effects of MTX. Tolerance improvement was judged on the reduction of MTX side effects after caffeine intake. Symptoms of intolerance considered were those of, but not limited to, the MISS questionnaire[21]: abdominal symptoms (stomachache, nausea, discomfort, heaviness, acidity, cramps, constipation), behavioral symptoms including

anticipatory symptoms (anxiety, depression, aversion to its name, sight, thought, aversion to food, unpleasant taste and smells, insomnia, headaches, difficulty in concentrating), or general, non-specific symptoms (loss of appetite, weakness and fatigue, the whole body feeling hot, burning in the chest).

2.4 Risk of bias assessment

The methodological quality of included studies was assessed independently by two authors (ZE and KN) using a validated checklist of items for cohort, case-control, and cross-sectional studies in epidemiology: the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for cohort, case-control, and cross-sectional studies, and for conference abstracts.[30] Any discrepancies were resolved by consensus with a third reviewer (SJ).

3. RESULTS

3.1 Search results

34 articles were identified as potentially relevant and were analyzed. Most of the retrieved studies failed to meet our inclusion criteria. 7 studies were finally included in this systematic review, of which 4 were journal articles[31–34] and 3 were conference abstracts.[35–37] Three studies were about efficacy[31,32,35] (summed up in Supplemental Table 1) and three were about tolerance[33,36,37] (summed up in Supplemental Table 2).

3.2 Studies about efficacy

In the cross-sectional study (congress abstract) of Silke et al.[35], 91 patients were interviewed about their caffeine intake and their MTX dose. There was no data about the concomitant use of other DMARDs or folic acid. The evaluated criterion was the correlation between the withdrawal of MTX due to treatment failure and caffeine intake. Patients were classified in 2 categories: minimal and regular coffee drinkers based on a threshold of 7 cups of coffee per week. Doses of MTX varied from 5 to 15 mg/week (mean = 10.3 ± 2.75). The proportion of people who discontinued MTX is higher in regular coffee drinkers (p value = 0.02). Treatment failure was the reason for discontinuing in 80% of cases. 90% of patients still on MTX, and 74% of those who discontinued MTX were minimal coffee drinkers.

In the cohort study of Nesher et al.[31], 39 patients with recent-onset RA were included. MTX was started at the dose of 7.5 mg/week, without folate supplementation, and without other DMARDs. Patients reported their daily diet and were divided in 3 groups depending on their amount of daily caffeine (Supplemental Table 1). Five disease parameters were assessed at baseline (before initiation of MTX therapy), and at monthly intervals for 3 months: DMS, VAS, TJC, SJC, and ESR. The percentage of improvement in each parameter between visits 0 and 3 was calculated. Patients in group C (high caffeine intake) experienced significantly less improvement in DMS (p = 0.013) and VAS (p = 0.028) compared with patients in group A (low caffeine intake). They also experienced less improvement in other parameters, but the difference with the other 2 groups was not statistically significant. There were no significant differences between the responses of group B (medium caffeine intake) compared with those of the other 2 groups.

In the cohort study of Benito-Garcia et al.[32], a sample of 264 patients with RA under MTX were drawn from a prospective observational cohort of 900 RA patients. The number of ongoing and past DMARDs, and folates supplementation were taken into account. Patients filled a food questionnaire, providing information about their average consumption of beverages containing caffeine over the previous year. The daily caffeine intake for each participant was determined by multiplying the frequency of consumption of each beverage unit by the caffeine content of the specified unit, individualizing three caffeine groups (Supplemental Table 1). The mean weekly dose of MTX was 17.1 mg (± 5.8) for low caffeine consumers, 15.4 mg (± 5.7) for moderate consumers, and 15.5 (± 5.2) for high consumers (p = 0.08). 29.2% of the patients were taking folic acid, 26.3% leucovorin, and 51.2% either leucovorin or folic acid. The average disease duration was 10 years or more in 62% of the patients in the low group, 66% of the patients in the moderate group, and 52% of those in the highest group, with no significant difference between the three groups (p = 0.12). There were also no significant differences between the groups in terms of duration of MTX use (p = 0.35) or in the number of current or past DMARDs taken (p values respectively = 0.29 and 0.16). Patients with moderate and high caffeine intakes had more elevated DAS28, PGA, and SJC, but the differences were not statistically significant. DAS28 levels did not differ significantly between the 3 groups in the fully adjusted model: for moderate caffeine intake, odds ratio (OR) = 1.6, 95% CI: 0.8–3.2; for high caffeine intake, OR = 1.6 95% CI: 0.8–3.4. There was also no significant change in DMS, MDHAQ scores, and CRP levels between the 3 groups. Furthermore, folic acid and leucovorin did not confound results.

3.3 Studies about tolerance

In the cohort study of Malaviya[33], 855 patients with RA were included over a period of 11 months. All the patients were receiving a monotherapy of MTX with folate supplementation. MTX intolerance was considered if patients presented GI and behavioral symptoms. MTX intolerance was classified arbitrarily into 3 categories: 1) Minimal intolerance if patients were able to manage it by themselves in various ways including taking sugar candy or plain sugar, adjusting the MTX timing and reassurance from the rheumatologist. 2) Moderate intolerance if the patients required antiemetics/antacids, dose/route of adjustment in addition to antiemetics, antacids. 3) Severe intolerance if the patient was inclined to discontinue MTX despite these measures. Patients with moderate to severe MTX intolerance (a total of 120) were included in the caffeine protocol plan. Caffeine

protocol plan is given in Supplemental Table 2. The efficacy of the intervention was evaluated in their follow-up visit (between 3 and 6 months). Participants were asked to grade the response to caffeine in 4 categories: 1) Complete relief if symptoms of MTX intolerance improved so much that the antiemetic and other drugs for its control were discontinued. 2) Partial relief if the symptoms were better, but antiemetics/antacids were still needed. 3) Minimal relief if there was no improvement of symptoms. 4) Worse if caffeine caused similar aversion as did MTX. The results of the intervention are presented in Supplemental Table 2.

In the cohort study of Baghel et al.[36], 600 patients with RA were enrolled and asked to take their weekly MTX dose along with coffee. The coffee schedule comprised 3 servings detailed in Supplemental Table 2. Only the patients who moderate or severe MTX intolerance (n = 115) were included in the caffeine protocol. The results of the intervention are presented in Supplemental Table 2.

In a second cohort study of Malaviya et al.[34], 410 patients were included, of which 396 (96.58%) with RA, 4 (0.97%) with SpA, and others 10 (1.21%) other diseases (MCTD, SLE, SjS). All the patients were receiving a weekly dose of MTX with a maximum of 25 mg/week. The intolerance severity was measured using a standard 0–100 numeric rating scale with 21 small circles from 0 to 100, at 5-unit increments. Patients with moderate to severe MTX intolerance were included in the caffeine protocol plan with the same schedule as the study of Baghel et al. Patients with severe MTX-intolerance were also advised to take palonosetron 0.5 mg, 30 min before the MTX dose and repeated after 12h. There is no information about the concomitant use of other DMARDs or folic acid. The results of the intervention are presented in Supplemental Table 2. Furthermore, 103 (52.02%) patients who had relief with coffee continued taking it for > 1 year, while another 63 (31.81%) patients who had relief with coffee stopped taking it and remained free of symptoms after 3–6 months. 9 patients (4.54%) did not like coffee and gave it up immediately and managed MTX-intolerance with other means (chocolates, sweet candies, anti-emetics, and avoiding a few meals).

In the prospective, randomized and controlled cohort study of Fehr et al.[37] (abstract only), 60 patients with RA experiencing moderate to severe MTX-intolerance were included and randomly assigned into 2 groups of 30 individuals each. Group A was prescribed caffeine: coffee or dark chocolate (no details regarding the dose), while group B continued MTX regimen without addition of any extra caffeine. The MTX-intolerance was assessed using the MISS questionnaire, and was evaluated at baseline before initiation of study, then at the next 3 months consecutively. After 3 months, 80% of the patients showed full improvement of symptoms of MTX-intolerance with statistically significant difference all over the study period (p = 0.005). 50% of study group patients discontinued anti-emetic and other drugs, while none in control group did.

Tables

Table 1: Summary of the included studies for the evaluation of caffeine and methotrexate efficacy.

Author, year, country [ref]	Design, duration, sample size	Caffeine intake	MTX efficacy evaluation measures	Outcomes
Silke et al., 2001, Ireland [35]	Cross-sectional, 10 months, N=91	< 7 cups/week: minimal drinker ≥ 7 cups/week: regular drinker	Withdrawal of MTX	*Regular coffee drinkers are most likely to discontinue treatment (p value = 0.02), the main reason being failure of treatment (80%) *90% of patients still on MTX were minimal drinkers *74% of patients who discontinued MTX were minimal drinkers
Nesher et al., 2003, Israel [31]	Cohort, 3 months, N=39	3 groups depending on intake (mg/day): A: low < 120 B: medium 120-180 C: high > 180	TJC, SJC, VAS DMS, ESR	*Group C: significantly less improvement in morning stiffness and joint pain compared with group A; less improvement in other parameters as well but insignificant *Group B: insignificant differences between their responses and those of the other 2 groups
Benito-Garcia et al., 2006, United States [32]	Cohort, N=264	3 groups (Gaussian distribution), mg/day: Low: < 105 Moderate: 106-260 High: > 260	DAS28, CRP, PGA, SJC, MDHAQ, DMS	*DAS28 did not differ significantly between the 3 groups *Insignificant change in CRP levels between the 3 groups *Insignificant differences in DMS and MDHAQ score *Moderate and high caffeine group had higher DAS28 scores, PGA, and SJC, but differences were insignificant

CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; DMS: duration of morning stiffness; ESR: erythrocyte sedimentation rate; MDHAQ: Multidimensional Health Assessment Questionnaire; MTX: methotrexate; PGA: Patient Global Assessment; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SJC: swollen joint count; TJC: tender joint count

Table 2: Summary of the included studies for the evaluation of caffeine and methotrexate tolerance.

Author, year, country [ref]	Design, duration, sample size	MTX intolerance evaluation, [included in the caffeine protocol]	Caffeine intake	Outcomes
Malaviya, 2016, India [33]	Cohort, 11 months, N=855	No MTX intolerance: 313 (36.6 %) Minimal intolerance: 422 (49.3%) [Moderate intolerance: 103 (12%)] [Severe intolerance: 17 (2%)]	For non-coffee-drinking patients: 90-135 mg/24h synchronized with MTX weekly dose (early in the morning, after dinner, and the next day morning) For coffee-drinking patients: a few extra cups on the day of MTX similar to the above schedule Coffee alternative: 40 g serving of 50% dark-rich in cocoa chocolate 1h before MTX dose, and another serving after 8-12h if intolerance symptoms persisted	Complete relief: 66 (55%) Partial relief: 16 (13.3%) Minimal relief: 9 (7.5%) Worse: 12 (10%) Not participated: 17 (14.2%)
Baghel, 2018, India [36]	Cohort, ? N=600	No MTX intolerance: 285 (47.5%) Minimal intolerance not requiring any intervention: 200 (63.5%) [Moderate or severe MTX intolerance: 115 (36.5%)]	On the MTX dose day: 2 strong cups of coffee early in the morning, repeated in the late evening 1–3 hours before the dose of MTX. + 2 cups of strong coffee the next morning	Complete relief: 52/115 (45.2%) Partial improvement with continuation of MTX but only with antiemetics: 17/115 (14.8%) Minimally better but somehow managing: 14/115 (12.2%) Did not get any relief and discontinued MTX: 14/115 (12.2%) Not participated: 18/115 (15.6%)
Malaviya, 2019, India [34]	Cohort, open, N=410	Minimal intolerance not requiring any intervention (< 10%): 212 patients (51.7%) [Moderate to severe MTX intolerance (> 10%): 198 patients (48.3%)]	MTX day: 2 strong cups of coffee early in the morning, repeated in the late evening 2–3 hours before the dose of MTX. + 2 cups of strong coffee the next morning	Complete relief: 30 (15.15%) 70-95% relief: 15 (7.57%) 10-60% relief: 89 (44.94%) Managing without coffee: 26 (13.3%) No relief: 38 (19.19%)
Fehr, 2020, Egypt[37]	Prospective, randomized controlled cohort, 15 months, N=60	MISS questionnaire (numerical data not provided)	Group A (study group): 30 patients with prescribed caffeine (coffee or dark chocolate) Group B (control group): 30 patients under MTX without addition of any extra caffeine	Number of patients with full improvement of symptoms: At 1-month: 7 patients (23%) At 2 months: 10 patients (33.3%) At 3 months: 24 patients (80%) Discontinuation of antiemetics: 50% of the study group, none in control group

MTX: methotrexate

Figures

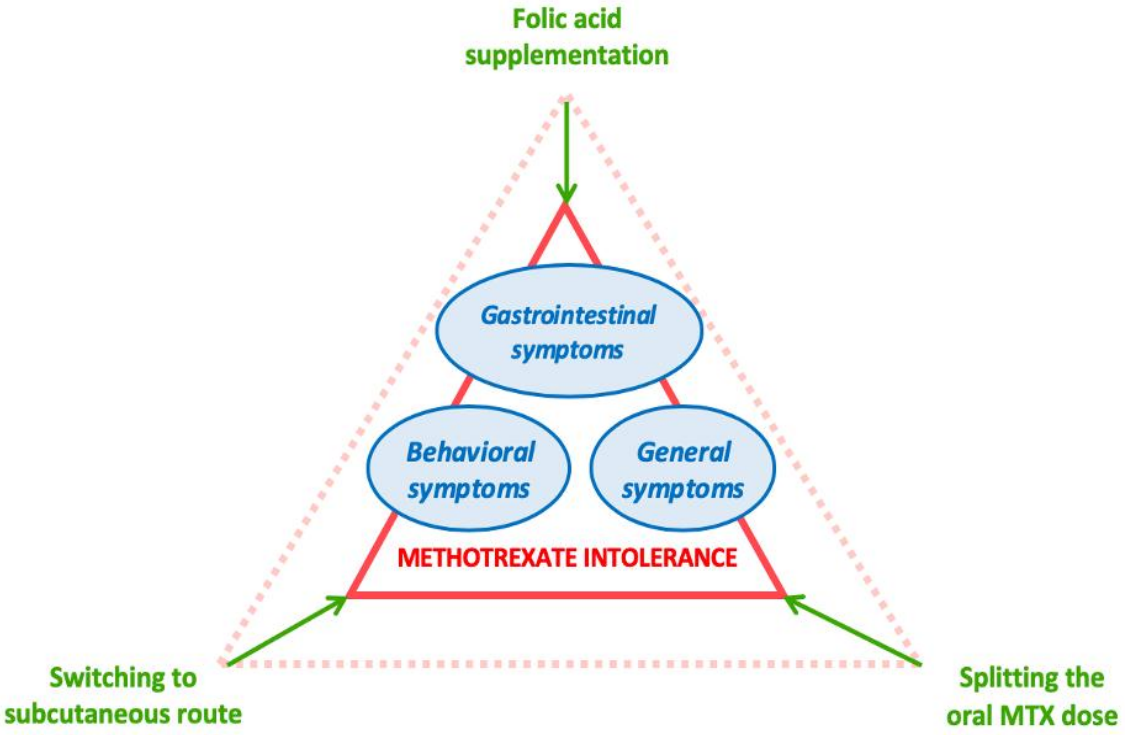

Figure 1: Summary of the reported measures to reduce methotrexate intolerance.

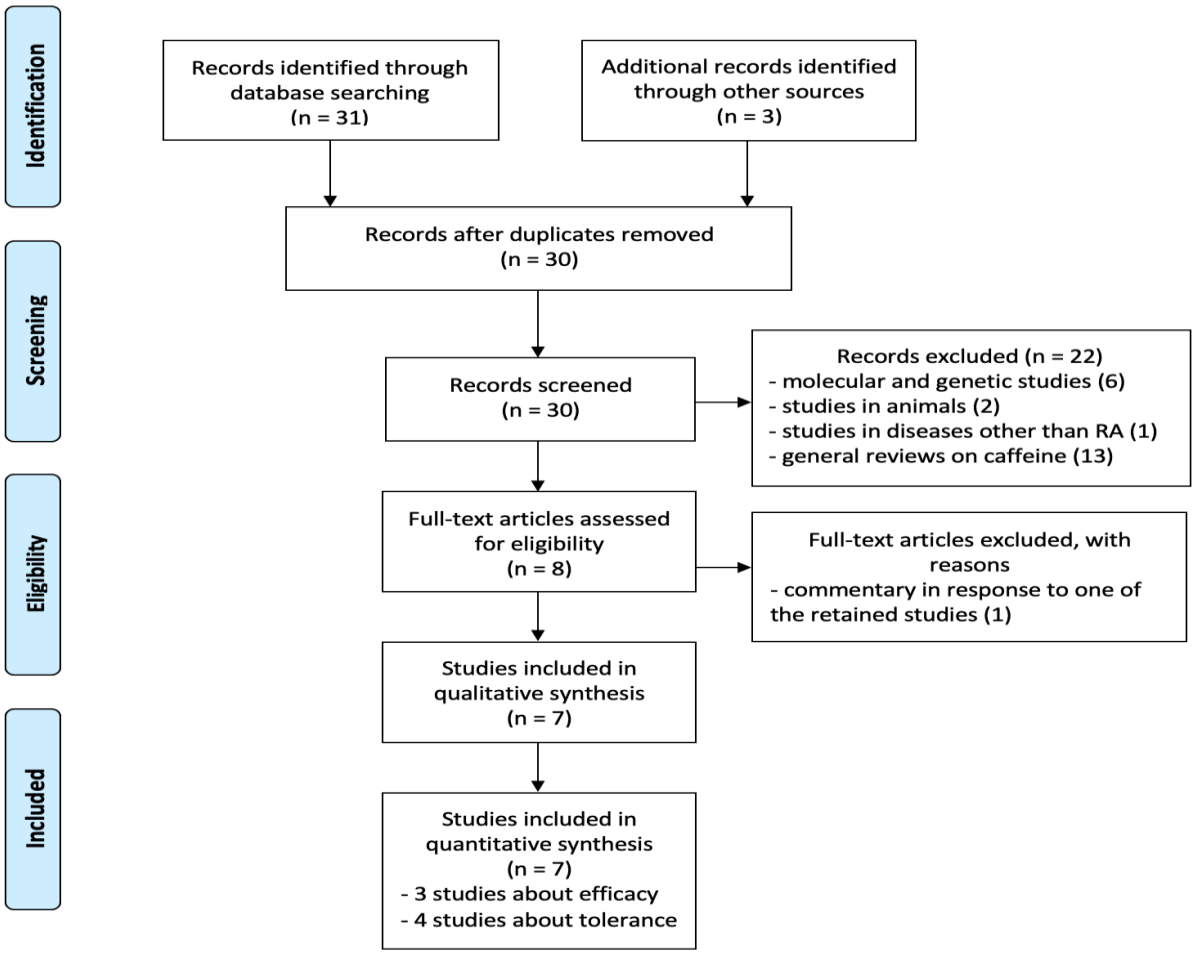

Figure 2: PRISMA flow diagram of the studies included in the systematic review.

4. DISCUSSION

This systematic review shows that caffeine in the management of RA under MTX is experiencing renewed interest in the last few years. The first papers published in the 2000s decade investigated the question of efficacy of the association MTX-caffeine, whereas more recent studies focused on the interest of caffeine in the management of MTX-induced GI and behavioral side effects. The retrieved studies were either cross-sectional or cohort studies. Only one randomized study was found, being about caffeine and MTX tolerance. Due to the heterogeneity in the studies, an analysis in this setting was difficult to perform, and therefore a meta-analysis was not conducted.

Regarding caffeine and MTX efficacy, the first study of Silke et al. found that regular coffee drinkers were most likely to discontinue MTX because of treatment failure. However, the criterion of "regular drinker" was arbitrarily established based on the threshold of 7 cups of coffee per week, instead of taking into account a precise dose of caffeine, unlike the other studies. The work of Nesher et al. presents the advantages of being prospective, individualizing 3 groups of patients depending on their caffeine intake. The major finding was that patients with high caffeine consumption (> 180 mg/day) experienced significantly less improvement in the subjective parameters of VAS and DMS than patients with low caffeine consumption (< 120 mg/day). However, the objective parameters of TJC, SJC, and ESR that either rely on the physician's examination or on the laboratory tests, did not show significant differences between the groups. Furthermore, no disease activity scores were evaluated in this prospective study. Finally, in the study of Benito-Garcia et al., patients were also divided in 3 groups depending on their caffeine intake, and the primary outcome for MTX clinical response was the DAS28. Besides, the other parameters that were evaluated were rather objective: DMS, PGA of disease severity, MDHAQ score, SJC, and CRP. The main finding was that the DAS28 did not differ significantly between the 3 groups, contradicting the initial conclusions of Silke et al. A drawback needs to be highlighted in these studies: the lack of specification of folic acid supplementation. This data is important to evaluate because of the proven existence of single-nucleotide polymorphisms in genes coding for folate pathway enzymes, resulting in interindividual variability in both MTX response and toxicity.[38,39] The same limitation concerns data about the consumption of other DMARDs, which is not specified in all the studies, and can cause bias in terms of drug accountability.

Considering the tolerance of MTX, the major findings of first work of Malaviya were that 55% of the patients who followed the caffeine protocol experienced an improvement of symptoms and discontinued antiemetics/antacids, 13% had symptoms improvement but were still consuming antiemetics/antacids. That is to say that about 68% of the patients experienced at least an improvement of symptoms according to this first study. However, these positive conclusions are weakened by some limitations. First, the MTX intolerance was assessed with a subjective scale that has not been validated by former studies. The use of the MISS questionnaire[21] could give a more accurate information. Secondly, some patients were interviewed on the phone rather than on a face-to-face interview, which may also have affected the results. The study of Baghel also reported satisfactory results, with a total improvement of MTX intolerance of 45.2%, confirming the findings of the previous study. By adding partial and minimal improvement rates, almost 72.2% of the patients included in the study experienced an improvement of symptoms thanks to the caffeine. However, the shortcomings of this study are the lack of validated tools to assess the MTX intolerance, and the lack of specification of the duration study and outcome delays. The second study of Malaviya relied on a scale to assess the intolerance, which may result in a slightly different interpretation of the outcomes: 15.15% of the included patients experienced a complete relief, 7.57% experienced 70-95% relief, and 44.94% presented 10-60% relief. Taken together, about 67.66% of the patients improved their symptoms with caffeine, which globally is in accordance with the initial study of the same author. Finally, the most recent study of Fehr et al. presents the advantages of being prospective, randomized, and controlled. At 3 months after inclusion, the proportion of patients showing full improvement of symptoms reached 80%, which corroborates the above findings.

5. CONCLUSION

Available studies about the role of caffeine on efficacy and tolerance of MTX are limited but allow to draw some practical learning points from their results. Taken together, they tend to show that caffeine consumption does not reduce the efficacy of MTX, and that caffeine consumption concomitantly with the weekly dose of MTX improves its tolerance. The best suggested caffeine regimen may be the addition of 2 cups of coffee in the morning of the medication day, another 2 cups 1-3 hours before taking the MTX, and 2 other cups in the next morning. The encouraging results of this review reinforce the opinion that the association of caffeine with MTX should benefit from further studies in the treatment of RA. There is a need for studies with a larger-scale, and randomized prospective protocols with rigorous statistic methods. Quantifiable outcome measures should be used for more accuracy, such as the DAS28, ACR criteria (ACR20, 50 and 70), EULAR criteria, or the Simple Disease Activity index (SDAI) for efficacy; and validated tools to assess MTX intolerance, such as the MISS questionnaire. However, patients with MTX intolerance may already benefit from these encouraging results, in order to improve their adherence to the treatment, currently considered as the gold standard among conventional DMARDs in RA.

Key Messages

*Clinical studies on the effect of caffeine on methotrexate are experiencing renewed interest in recent years.

*Caffeine consumption doesn't seem to reduce the efficacy of methotrexate. There is no need for higher doses of methotrexate to maintain disease activity.

*Caffeine consumption concomitantly with the weekly dose of methotrexate may reduce its intolerance. The best suggested caffeine regimen would be adding 2 cups of coffee in the morning of the medication day, another 2 cups 1-3 hours before taking medication, and 2 other cups the next morning.

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Code availability. Not applicable.

Authors' contributions. All the authors were involved in data curation, analysis, interpretation, and writing of the manuscript. All authors have approved the final version of the submitted manuscript.

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