



Original article

Relationship between different anti-rheumatic drug therapies and complementary and alternative medicine in patients with rheumatoid arthritis: an interview based cross-sectional study



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ABSTRACT

Objectives: The use of complementary and alternative medicine (CAM) by patients with rheumatoid arthritis (RA) is highly prevalent. The relationship of these remedies with disease therapy are not fully studied. We aimed to explore the relationship between different anti-rheumatic drug therapy and CAM use in RA patients.

Methods: The study used an interview-based cross-sectional survey in two major referral centres in Riyadh, Saudi Arabia. Patients were adults with confirmed RA that attended rheumatology clinics. Information on the utilization of CAM, RA duration, drug therapy, and laboratory parameters were obtained. Descriptive statistics as well as adjusted odds ratio using bivariate logistic regression were used to explore the different factors related to CAM use, including drug therapy.

Results: A total of 438 adult patients with RA were included. The mean (\pm SD) age of the patients was 49 (\pm 15.0) years. The majority were women 393 (89.7%). Two hundred and ninety-two patients (66.7%) had used CAM. The CAM users who had a longer disease duration (AOR 1.041 [95% CI: 1.011, 1.073]; $p = 0.008$) were more likely to be female (AOR 2.068 [95% CI: 1.098, 3.896]; $p = 0.024$), and use methotrexate (AOR 1.918 [95% CI: 1.249, 2.946]; $p = 0.003$) as opposed to celecoxib (AOR 0.509 [95% CI: 0.307, 0.844]; $p = 0.009$) and biologic monotherapy (AOR 0.443 [95% CI: 0.224, 0.876]; $p = 0.019$). Other factors related

Abbreviations: CAM, complementary and alternative medicine; RA, rheumatoid arthritis; HAQ, health assessment questionnaire; MTX, Methotrexate; LEF, leflunomide; SSZ, sulfasalazine; HCQ, hydroxychloroquine; TNFi, tumour necrosis factor inhibitor.

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to CAM were meloxicam use (AOR 2.342 [95% CI: 1.341, 4.089]; $p = 0.003$) and traditional therapy (AOR 2.989 [95% CI: 1.647, 5.425]; $p = 0.000$). The remaining factors were not significant.

Conclusion: CAM use is prevalent in patients with RA. Understanding patients and disease related factors associated with higher use of CAM is warranted to improve RA management and provide more rational use of these remedies.

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1. Introduction

Complementary and alternative medicine (CAM) is reportedly used in between 9.8 and 76% of the population depending on settings, culture and disorders (Harris et al., 2012). CAM is defined as “any product, including herbal remedies, minerals, vitamins, and natural products, which may be purchased without a prescription for self-treatment” (Anderson et al., 2000). Many studies assert that patients with chronic conditions tend to use more alternative medicine than patients with more acute illness (Lee et al., 2004; Metcalfe et al., 2010). Of the commonly used CAM products in chronic diseases were garlic, aloe vera, ginger and turmeric (Peltzer and Pengpid, 2019).

CAM use is not only linked to the prevalence of chronic diseases but also the disease severity, inflammatory disorders, and chronic pain (Lin and Cheifetz, 2018; Samdup et al., 2006; Smith et al., 2004). Rheumatoid arthritis (RA) is a progressive inflammatory disorder that is chronic in nature and characterized by pain, disability and deformity (Singh et al., 2016). Patients with RA, similar to all other chronic illness, tend to use CAM more than the general population (Almuhareb et al., 2019; Ernst and Posadzki, 2011; Rao et al., 2003; Setty and Sigal, 2005). Recently, the American College of Rheumatology (ACR) published a review on natural products highlighting their possible impact on managing patients with RA (DeSalvo et al., 2019). According to a study conducted in Saudi Arabia, among the most commonly utilized CAM products in patients with RA were vitamin D, calcium, ginger, honey, turmeric, black seeds, and fenugreek (Almuhareb et al., 2019). CAM use is common among patients with RA due to multiple reasons. Some of these are patient un-satisfaction with their current therapy, affordability, added benefits to their current therapy regime, or a perception that natural products are less risky (Ernst and Posadzki, 2011). In a recent study conducted, it has been found that 67% of patients with RA use alternative medicine in addition to their current management to seek added benefits (Almuhareb et al., 2019).

Patients with RA are treated with disease-modifying anti rheumatic drugs (DMARDs) that can either be a biologics or traditional drug, corticosteroid and non-steroidal inflammatory drugs (Saag et al., 2008). Their management plan could be a single DMARD, double or triple therapy based on the severity of the disease and their symptoms (Singh et al., 2016). Failure to achieve the therapeutic goal of relieving patient’s symptoms could result in them seeking alternative treatment options (Anderson et al., 2000). Data exploring the use of different therapeutic modalities and its effect on the tendency to use CAM are currently lacking. Therefore, this work aimed to examine the effect of different therapeutic modalities and its relation to CAM use among patients with RA.

2. Material and methods

2.1. Study designs and settings

This study was a cross-sectional interview-based survey conducted at rheumatology clinics, in King Saud University Medical

City (KSUMC), and the Prince Sultan Military Medical City (PSMMC) located in Riyadh, Saudi Arabia. The study aimed to examine the effect of different therapeutic modalities and its relation to CAM use among patients with RA. The survey was conducted over ten months from 1st of May 2017 to the end of February 2018. The study included only patients aged over 18 years, patients with documented diagnosed of RA and at least three months disease period and receiving at least one pharmacological therapy.

2.2. Data sources and measurements

Patient interviews and a review of medical charts were used as the data collection sources for this study. The patient interviews using a purposefully designed survey for this study were conducted face to face by a research member in Arabic and lasted approximately 15-min. The survey was designed to identify information about the patient’s current RA medication, alternative medicine use, and functional disability. The developed questionnaire went through a validation and pilot testing process before the study commenced (Almuhareb et al., 2019). Functional disability was measured using the Arabic version of the Health Assessment Questionnaire (HAQ), the pain was assessed based on the presence or absence of morning stiffness through the visual analogue scale tool (El Meidany et al., 2003). Electronic medical records were used to extract patient demographics, social history, body mass index (BMI), medical history and laboratory information (Almuhareb et al., 2019). DMARDs were classified as either traditional or biologics. Traditional DMARDs include methotrexate (MTX), leflunomide (LEF), hydroxychloroquine (HCQ), and sulfasalazine (SSZ). Disease-modifying agents used by participants were further classified as mono, double or triple therapy according to the definition of ACR in RA management. Mono is defined as the sole use of MTX, SSZ, HCQ, or LEF. Double therapy is the use of MTX with SSZ, MTX with HCQ, SSZ and HCQ, or a combination with LEF. Triple therapy is the use of a combination of MTX, SSZ, and HCQ (Singh et al., 2016). Additionally, biologic therapy used by participants were classified as either tumor necrosis factor-alpha inhibitor biologics (TNFi biologics) or non-tumor necrosis factor-alpha inhibitor biologics (Non-TNFi biologics). TNFi biologics includes; etanercept, infliximab, adalimumab and certolizumab, while non-TNFi biologics includes: rituximab and abatacept.

2.3. Sample size and statistical analysis

Patients who met the study inclusion criteria using a simple convenience sampling were invited to participate. The required sample size was calculated based on the following formula $n = \frac{z^2 p(1-p)}{d^2}$, where z = level of confidence, p = expected prevalence, and d = precision. Based on the expected prevalence of 67% with a 95% confidence interval (CI) and 0.05 precision (d) (Anderson et al., 2000). This has yielded an estimated sample size of 363 patients.

Collected data were coded and entered using the Statistical Package for Social Sciences (SPSS software version 25). The mean (±SD) was calculated for quantitative data, while proportions were computed for categorical variables. An unpaired student *t*-test was used for comparing the means of continuous variables. Proportions were compared using Chi-square tests. The predictive values of alternative medicine users were calculated using a binary logistic regression analysis with a confidence interval 95%. The following variables were considered as confounding variables and adjusted for in logistic regression: age, gender and disease duration. Results were considered significant if the *p*-value was less than 0.05.

3. Results

The demographic characteristics of patients who completed the survey and were included in the final analysis (N = 438) are shown in Table 1 with a mean (±SD) age of the patients of 49 (±15.0) years. The majority were women 393 (89.7%). Two hundred and ninety-two patients (66.7%) had used CAM. The mean (±SD) duration of RA was longer in patients that used CAM; 11 (±8.0) years as compared to 9 (±7.0) years in non-users (*p* = 0.011). Demographical data and a bivariate analysis of the difference in baseline demographics between CAM users and non-users are in Table 1.

Table 1
Demographics and baseline characteristics with differences calculated using bivariate analysis (n = 438)

Demographics	CAM users (n= 292)	Non-users (n= 146)	P-value
Gender, n (%)			0.019*
Female	269 (92.1)	124 (84.9)	
Male	23 (7.9)	22 (15.1)	
Age (years), mean (±SD)	49 (±14)	48 (±16)	0.528
BMI (kg/m²), mean (±SD)	30.55 (±6.73)	30.28 (±7.36)	0.720
Duration of having RA (years), mean (±SD)	11 (±8)	9 (±7)	0.011*
Saudi nationality, n (%)	288 (98.6)	142 (97.3)	
Riyadh residence, n (%)	218 (74.7)	107 (73.3)	
Marital status, n (%)			0.885
Single	41 (14)	26 (17.8)	
Married	198 (67.8)	100 (68.5)	
Divorced	24 (8.2)	4 (2.7)	
Widowed	29 (9.9)	16 (11)	
Educational level, n (%)			0.043*
Low education (e.g. illiterate, elementary, high school)	194 (66.4)	84 (57.5)	
High education (e.g. Diploma, university degree, postgraduate degree)	98 (33.6)	62 (42.5)	
Smoking, n (%)	11 (3.8)	7 (4.8)	0.610
Monthly income, n (%)			0.320
<10,000 SAR	196 (67.1)	91 (62.3)	
≥10,000 SAR	96 (32.9)	55 (37.7)	
Erythrocyte Sedimentation Rate (mm/hr), mean (±SD)	28 (±21)	24 (±20)	0.022*
C-Reactive Protein (mg/L), mean (±SD)	8 (±12)	9 (±11)	0.802
Health Assessment Questionnaire score 0–3, mean (±SD)	1.14 (±0.82)	1.09 (±0.81)	0.605
Pain score 0–100, mean (±SD)	42 (±31)	45 (±31)	0.369
Morning stiffness, n (%)	129 (44.2)	61 (41.8)	0.633

SD: Standard deviation, BMI:Body mass index(kilogramper meter squared), RA: Rheumatoid arthritis, SAR: Saudi Riyals.

* Significant according to the significance level of 0.05

Table 2

Drug categories according to the 2015 American College of Rheumatology (ACR) recommendations for the treatment of RA (n = 438), stratified by CAM use with *p* value of difference

Drug category	CAM users (n= 292)	Non-users (n= 146)	P-value
Methotrexate, n (%)	176 (60.3)	66 (45.2)	0.003*
DMARDs monotherapy, n (%)	182 (62.3)	81 (55.5)	0.168
Double DMARDs therapy, n (%)	75 (25.7)	30 (20.5)	0.235
Triple DMARDs therapy, n (%)	5 (1.7)	1 (0.7)	0.383
TNFi biologics, n (%)	56 (19.2)	32 (21.9)	0.500
Non-TNFi biologics, n (%)	45 (15.4)	19 (13)	0.503
Biologics monotherapy, n (%)	20 (6.8)	19 (13)	0.033*
Biologics + DMARDs, n (%)	98 (33.6)	50 (34.2)	0.886
Glucocorticoid (e.g. prednisolone), n (%)	101 (34.6)	42 (28.8)	0.221
NSAIDs, n (%)			
Celecoxib	45 (15.4)	36 (24.7)	0.019*
Meloxicam	75 (25.7)	19 (13)	0.002*
Diclofenac	22 (7.5)	19 (13)	0.063
Methotrexate dose, n (%)			
<12.5 mg/day	56 (32.4)	19 (28.8)	0.594
≥12.5 mg/day	117 (67.6)	47 (71.2)	0.594
Glucocorticoid dose (e.g. prednisolone), n (%)			
Low-dose glucocorticoid (≤10 mg/day)	90 (89.1)	38 (90.5)	0.808
High-dose glucocorticoid (>10 mg/day)	11 (10.9)	4 (9.5)	0.808

DMARDs: Disease-modifying antirheumatic drugs, TNFi: tumour necrosis factor inhibitor, NSAIDs: Nonsteroidal anti-inflammatory drugs.

* Significant according to a significance level of 0.05

Among the 438 participants, MTX was the most frequently prescribed drug for 242 patients (55.3%) and 60.3% of them were CAM users (*p* = 0.003). With regards to the DMARD, the majority were on monotherapy followed by dual and triple therapy respectively. For biologics, the majority (20.1%) were on aTNFi among them 19.2% were CAM users. Drug therapies used by participants according to the ACR 2015 classification and the difference between CAM users and non-users are shown in Table 2. A non-significant difference was found for age, BMI, marital status, monthly income, pain, HAQ and morning stiffness.

Factors that were associated with CAM use among the study population were assessed using binary logistic regression adjusted for age, gender, and disease duration as displayed in Table 3. Factors that showed a significant association with higher CAM use included female gender (AOR 2.068 [95% CI: 1.098, 3.896]; *p* = 0.024), patients with longer disease duration (AOR 1.041 [95% CI: 1.011, 1.073]; *p* = 0.008), and traditional therapy (AOR 2.989 [95% CI: 1.647, 5.425]; *p* ≤ 0.001). RA patients who were on MTX were more likely to use CAM (AOR 1.918 [95% CI: 1.249, 2.946]; *p* = 0.003). Patients prescribed meloxicam were also more likely to use CAM (AOR 2.342 [95% CI: 1.341, 4.089]; *p* = 0.003), while patients on celecoxib were less likely to use CAM (AOR 0.509 [95% CI: 0.307, 0.844]; *p* = 0.009). Additionally, biologics monotherapy showed a significant association with lower CAM use (AOR 0.443 [95% CI: 0.224, 0.876]; *p* = 0.019). Non-significant factors associated to medication use were the use of mono, double or triple DMARDs therapy, educational level and the use of glucocorticoid therapy.

4. Discussion

Based on our definition, majority of participants were considered CAM users. The prevalence of CAM use was similar to literature from other countries, such as the United States of America

Table 3

Binary logistic regression analysis to determine factors associated with CAM use among the study population adjusted by age, gender and disease duration (reference group: non-users)

Factors	AOR	95% CI	P-value
Duration of disease^E (years)	1.041	[1.011, 1.073]	0.008*
Gender^S			
Male (Ref.)	2.068	[1.098, 3.896]	0.024*
Female			
Traditional DMARDs			
Yes	2.989	[1.647, 5.425]	≤0.001*
No (Ref.)			
Methotrexate			
Yes	1.918	[1.249, 2.946]	0.003*
No (Ref.)			
Celecoxib			
Yes	0.509	[0.307, 0.844]	0.009*
No (Ref.)			
Meloxicam			
Yes	2.342	[1.341, 4.089]	0.003*
No (Ref.)			
Biologics monotherapy			
Yes	0.443	[0.224, 0.876]	0.019*
No (Ref.)			
Non-Significant Factors			
Biologics + DMARDs	0.891	[0.578, 1.372]	0.600
DMARDs monotherapy			
Yes	0.787	[0.515, 1.203]	0.268
No (Ref.)			
Double DMARDs therapy			
Yes	1.393	[0.803, 2.417]	0.238
No (Ref.)			
Triple DMARDs therapy			
Yes	1.317	[0.135, 12.834]	0.813
No (Ref.)			
TNFi biologics			
Yes	0.844	[0.514, 1.385]	0.502
No (Ref.)			
Non-TNFi biologics			
Yes	1.046	[0.578, 1.894]	0.881
No (Ref.)			
Glucocorticoid			
Yes	1.308	[0.836, 2.045]	0.240
No (Ref.)			
Educational level			
High education	1.369	[0.886, 2.116]	0.158
Low education (Ref.)			

^E Disease duration is adjusted to age and gender only.

^S Gender is adjusted to disease duration and age.

* Significant according to the significance level of 0.05.

(Anderson et al., 2000). CAM users were more likely females, and of a comparable age, marital status, body mass index and monthly income to non-CAM users. To our knowledge, this study is considered the first of its kind to be conducted among patients with RA to assess the impact of anti-rheumatic medications and probability of CAM use. While CAM use is commonly linked to disease severity, poor health and lower quality of life (Jones et al., 2019), the link between RA therapeutic modalities and its relation to CAM has not been examined previously.

RA patients using MTX were more likely to be CAM users, and the same applied to meloxicam. On the other hand, participants using biologic monotherapy and/or celecoxib were less likely to be CAM users. Medications and their combinations were analyzed using bivariate analysis. Taking age, gender and disease duration into consideration; binary logistic regression was used to explore differences. CAM use was affected by gender, duration of the disease, the use of traditional DMARDs, MTX, biologic monotherapy, celecoxib, and meloxicam. Traditional DMARDs therapy in general and MTX in particular were more likely to be used in conjunction with CAM. This can be justified by, the results of a network meta-analysis that compared the efficacy and safety of various anti-rheumatic treatments for patients with RA. They concluded

that traditional DMARDs use alone was linked to low efficacy (Ma et al., 2019). Furthermore, our results revealed that participants on meloxicam were also more likely to be CAM users. Greater use of meloxicam among CAM consumers could indicate that patients were in active pain and had stiffness or fatigue. This supports our previously published work that CAM was used by participants to add benefit to their current therapy regimens (Almuhareb et al., 2019). Interestingly, participants using celecoxib and biologics monotherapy were less likely to use CAM although age was taken into consideration. Descriptive studies on RA patients in Saudi Arabia are scarce, with a small number of included participants. This study has the benefit of being conducted in the capital city of Saudi Arabia in two of the largest tertiary referral centres. As far as we are aware, this is the first study that explores the use of CAM and its relationship to different drug therapies among patients with RA. This study was a cross-sectional study with the limitation of a temporal association that should be interrelated with caution. However, as our findings were pertinent, this opens the door for further studies. MTX is one of the most popular and effective DMARDs (Weinblatt, 2013). Its use with CAM has never been previously explored. Therefore, our findings are novel and may warrant large-scale clinical trials being conducted.

5. Conclusions

In conclusion, CAM use is common in patients with RA. To improve RA management and provide more rational use of CAM, understanding patients and disease related factors associated with higher use of CAM is warranted. As far as we know, this is the first study that explores the use of CAM among patients with RA and its relationship to different drug therapies. In this study, CAM use was linked to female gender, duration of the disease, the use of MTX, traditional DMARDs, and meloxicam. Another interesting finding was the decreased odds of CAM use among patients using biologic monotherapy and celecoxib.

Ethical consideration

Ethical approval was obtained from both King Saud University Medical City (KSUMC), and the Prince Sultan Military Medical City (PSMMC) located in Riyadh, Saudi Arabia. Institutional Review Board (IRB) (project number E-17-2392 and HAP-01-R-015, respectively).

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors contributed extensively to the work presented in this paper and have approved the manuscript and agree with its submission.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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