

RESEARCH ARTICLE

# Remember/Regeneration Treatment Method as A New Holistic Approach for Pain Management in Patients with Rheumatoid Arthritis: A Retrospective Case Series

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## ABSTRACT

**Background:** Rheumatoid arthritis (RA) is a chronic autoimmune disease that is well characterized by persistent synovitis followed by the destruction of the cartilage and bone in joints. Despite many novel therapeutic approaches and scientific studies, no treatment provides a cure for the disease yet.

The Remember/Regeneration Therapy Method (RTM) is a novel holistic medicine approach that targets physiopathological changes in quadruplet body structures and includes various complementary methods such as acupuncture, ozone therapy and phytotherapy, etc. in different combinations which are determined depending on the clinical features of the diseases affecting the patient.

**Method:** We retrospectively reviewed medical data of 61 patients with RA who were admitted to our clinic between the years of 2012 to 2018. In order to show the efficacy of RTM on RA, previous patient records including pain score, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were statistically evaluated.

**Results:** The pain scores of patients who received RTM phytotherapeutics decreased significantly, while ESR and CRP values did not show a significant difference compared to current medical agents.

**Conclusion:** RTM may provide permanent treatment for RA and many other similar diseases by using different RTM combinations which include various holistic methods with different doses, treatment durations and sessions. For that purpose, further scientific studies are needed.

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## KEYWORDS:

Rheumatoid arthritis,  
RTM, Holistic medicine, Pain score.

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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease that is characterized by the destruction of the cartilage and bone in joints, and eventually persistent synovitis [1]. RA is one of the major public health problems worldwide and affects 0.5%-1% of the world population [2]. Currently, disease-modifying antirheumatic drugs (DMARDs) and the biological agents which block some inflammatory cytokines such as tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1, and IL-6 are mainly used for the treatment of RA as well as steroidal anti-inflammatory agents and immunosuppressive drugs [3]. Despite novel therapeutic approaches, there is no cure for patients with RA currently. Therefore, chronic pain due to RA leads patients to use different options of complementary therapies [4]. Thus, many complementary and alternative medicine methods such as acupuncture and various phytotherapeutic agents have been studied to demonstrate their efficacies on RA [5,6].

Novel scientific discoveries in the sciences of biology and genetics have demonstrated that inheritance has a whole new dimension beyond the genes, not in the structure of the DNA. In this new dimension of inheritance called epigenetics, it has been shown that changes can be transferred to new generations [7,8]. The importance of epigenetic modifications in long-term memory performance has been demonstrated in the most extensive and comprehensive study on DNA methylation. The processes such as chromatin remodeling, histone modifications, and non-coding RNA are also other important changes that belong to epigenetic mechanisms [9].

The Remember/Regeneration Therapy Method (RTM) is a holistic approach which consists of diagnostic and treatment systems that include mainly phytotherapy and different combinations of various complementary and traditional medical methods such as acupuncture, cupping therapy,

hirudotherapy, ozone therapy, etc. Phytotherapy is the main and pivot part of the RTM while the other treatment modalities are used to support the effects of phytotherapy. Moreover, in phytotherapeutic applications of RTM, two main groups of phytotherapeutics called "Remember Herbs" and "Regeneration Herbs", which consist of different amounts of various medicinal herbs, are used. On the other hand, according to the RTM, diseases are seen as the reflection of epigenetic changes in the phenotype resulting from the gene-environment mismatch. The treatment strategy is based on the recovery of health by essentially improving the deteriorating structures. It has been considered that the pathological process of a disease can potentially be reversed by RTM, considering the epigenetic changes. It has been clinically observed that epigenetic changes and irregularities improved when appropriate treatment protocols were applied, as in the RTM [10]. Already, many phytochemicals are shown to be effective in conditions such as cancer chemoprevention and metabolic syndrome through epigenetic regulation [11,12].

In this study, we aimed to demonstrate the efficacy of RTM on RA. For this purpose, we present a case series consisting of 61 patients with RA who were admitted to RTM Clinic, Izmir, Turkey.

## METHOD

We retrospectively reviewed medical data of 61 patients with RA in total, who were admitted to our clinic between January 2012- January 2018. All patients were using various current therapeutic agents for RA when they were admitted. Pain scores of the patients were evaluated with a pain scale ranging from 1-5, 5 being the highest amount of pain. Pain scores of the patients at this initial stage were named as "Baseline Pain Score". All patients included in the study have been chosen randomly, without considering pain scores.

Twenty-two patients have been treated with current medical drugs plus RTM phytotherapeutics while 39 patients have been treated with RTM phytotherapeutics only. In other words, 22 patients continued to use their existing medicines together with phytotherapeutics while others accepted to use phytotherapeutics only.

Various parameters including pain scores, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) have been recorded at the time of initial admission, first follow-up visit and a second follow-up visit were evaluated. The period between each visit and recorded parameters was about four months. Finally, records of patient groups who received medical+phytotherapy or only phytotherapy were statistically compared in order to evaluate the efficacy of each one.

In this study, there were no exclusion or inclusion criteria such as gender of the cases, clinic status of the cases and the presence of concurrent disease. We included all the cases with RA we have treated. Because it has been considered that the existence of an additional disease or difference in clinical severity of the cases does not affect the efficacy of the treatment positively. So such factors have been ignored.

Statistical analysis was performed with IBM SPSS version 21.0 (IBM Corp. Released 2012. Armonk, NY, USA) package program. Descriptive statistics were presented as mean, standard deviation, percentages. Kolmogorov Smirnov test (Statistics=0.402,  $p<0.001$ ) was used to determine whether continuous variables were normally distributed or not. Mann Whitney U was used for comparisons between groups. Friedman and Bonferroni corrected Wilcoxon tests were used for comparisons in groups. A p-value of less than 0.05 was accepted statistically significant.

## Limitations

In this study, we could not use molecular methods to explain the mechanism of action of RTM. Since the cases were out of control of our clinic before RTM treatment, they applied to us without further analysis to support their diagnosis. Therefore, we could not study the effectiveness of treatment through these analyzes. Our treatment parameters were limited to pain score, ESR and CRP. The fact that the study was a retrospective study also contributed to this deficiency.

## RESULTS

In the current study, 61 patients (Male:Female 6:55; Mean Age  $42.2\pm 10.6$  years) who had suffered from RA for an average of  $52\pm 36$  months were evaluated retrospectively. The records of pain score, CRP and ESR were evaluated to demonstrate the efficacy of RTM on patients with RA. The pain scores showed a significance recovery statistically while there was no statistical difference in terms of CRP and ESR values detected at initial and follow-up visits (Table.1). The treatment period of the patients was  $120\pm 35$  days.

There was a significant difference between the baseline pain scores and the post-treatment pain scores. Based on percentage calculations, during the first admission of patients, the baseline pain scores had been rated between 1 and 5. At the initial stage, baseline pain scores of 50 (85%) patients were 5, while the baseline pain score of just 1 (1.6%) patient was 1. The baseline pain scores of the other 10 (14.4%) patients were detected between 2 and 4. According to the first follow-up visit performed after the start of therapy, the number of patients with a pain score of 5 decreased to 15 (24.6%) while the number of patients with a pain score of 1 was detected as 8 (13.1%). The pain scores of the other 38 (62.3%) patients were detected between 2 and 4. According to the second follow-up records, the number of patients who have a pain score of 5 decreased to 5 (8.2%) while the number of patients who have a pain score of 1 was detected as 8 (13.1%) again. And finally, the pain scores of the other 48 (78.7%) patients were detected between 2 and 4.

On the other hand, at the first follow-up visit, pain levels of 41 (67.2%) patients were found to be decreased, while only 1 (1.6%) patient's pain level was increased compared to baseline pain scores. At the second follow-up visit, pain levels of 50 (82%) patients were found to be decreased while 2 (3.3%) patients' pain scores were higher compared to baseline pain scores. Also, at the second follow-up visit, pain levels of 37 (60.6%) patients were found to be decreased while 5 (8.2%)

patients' scores were higher when compared to first follow-up scores.

As a result, the baseline mean pain score was  $4.7 \pm 0.8$  while the first and second follow-up mean pain scores were  $3.6 \pm 1.3$  and  $2.8 \pm 1.2$  respectively. (Table 1)

In terms of treatment groups, the combination of medical drugs and phytotherapeutics didn't provide an additional improvement on the pain scores. In fact, at the first follow-up visit, only the phytotherapy group had a statistically lower mean pain score than the medical+phytotherapy group ( $p=0.03$ ) (Table 2) (Figure). These results indicate that the improvement in pain scores in time is likely related to RTM phytotherapeutics independent from medical drugs.

## DISCUSSION

Despite intense scientific studies on RA, a curative treatment without side effects has not been found currently. To date, many treatment options such as DMARDs and the biological agents which block some inflammatory cytokines such as TNF- $\alpha$ , IL-1, and IL-6 are mainly used for the treatment of RA as well as steroidal anti-inflammatory agents and immunosuppressive drugs [13]. Nowadays, the biologic agents are considered as a promising treatment option for RA as well as almost all systemic rheumatic diseases by blocking various cytokines in inflammatory pathways [14]. However, inflammation is one of the most important mechanisms defending the body, and it achieves this by regulating the balance between different inflammatory processes which are called as both good and bad [15]. So, it can't be supposed that inflammation is harmful and completely unnecessary for the body. It is called good, because inflammatory cytokines have a crucial role in various mechanisms in tissue homeostasis as host defense, bone formation and remodeling, etc. [16-18]. Therefore, anti-cytokine therapies that target inflammation are not just useful for diseases, but also may cause various pathologies and side effects due to disruptions in the physiological mechanisms and homeostasis in which inflammation serves [19-22]. Thus, the consequences and side effects of the current biologic treatments have led scientists to seek harmless and effective treatment options, just as they do in all other areas of medicine. Many methods of holistic and alternative medicine have been studied to find the most proper treatment options for RA as well as almost all diseases [23,4].

Additionally, it has also been shown that various epigenetic modifications play important roles in the pathogenesis of RA to the extent that they are the subject of review articles [24,25]. Considering all scientific researches to date, it will not be very ambitious to say that almost every disease is related to epigenetic modifications more or less.

Many phytochemicals have been shown to have beneficial effects through epigenetic regulation on many pathological conditions such as metabolic syndrome and cancer chemoprevention [26,12]. Scientific discussions about epigenetic remedies, which are used for inflammatory skin disorders, still maintain up-to-date [27]. It is more likely that such a similar scientific discussion may also be applied for RA

which exhibits a strong inflammatory process.

As is known, modern medicine does not provide a complete recovery on diseases such as rheumatoid arthritis. One of the most important reasons for this is that it is suffocated in molecular research. Molecular-based therapies, which are currently in active use, continue throughout the life of patients. When treatment is discontinued, the disease exacerbates. This indicates that not only a few molecules of the patients but all body mechanisms are defective. And, it can be predicted that such a situation can only be the result of a permanent change. Ultimately, this problem may indicate that patients with RA are subject to an epigenetic change.

RTM is a holistic medicine method that describes the anatomical and physiological aspects of physiopathological changes in quadruplet body structures (QBSs). RTM phytotherapeutics consists of unique mixtures of different herbal ingredients in different proportions and they are placed at the center of the RTM. Also, when it is needed, many complementary medical methods such as acupuncture, ozone therapy, cupping therapy, hirudotherapy, etc. may be added to RTM phytotherapeutics and that is the major axis of the model. In the RTM, diseases are seen as the reflection of epigenetic changes in the phenotype resulting from the gene-environment mismatch. The treatment strategy is based on the recovery of health by essentially improving the deteriorating structures. Considering that many of the epigenetic changes which lead to disease can potentially be reversed, it has been clinically observed that epigenetic changes and irregularities improved with appropriate treatment protocols, as in the RTM. Thus, firstly, these extraordinary and abnormal conditions that lead to the gene-environment mismatch should be eliminated, and secondly, previous normal physiological processes should be reminded to the body. The name of RTM comes from the special treatment strategy that is composed of proper combinations of regenerative and reminder phytotherapeutic agents and holistic medicine methods [10]. The positive feedback from RTM treatment in the long-term follow-up results indicates that the treatment affects epigenetic mechanisms. Proof of such a hypothesis is of course possible with prospective and scientific studies with appropriately selected molecular parameters. The most important reason for not having enough deep analysis in this study is that we do not have enough parameters in this retrospective study.

In the current case series, the pain scores in almost all patients were significantly decreased by our treatment model. It is more likely that the efficacy seen on the pain scores is related to possible smart molecules that are found in RTM phytotherapeutics and regulate epigenetic modifications. However, there was no statistical difference in CRP and ESR values. CRP is one of the non-specific inflammatory markers and may retain its existence for a long time in the blood circulation. In similar, an increase in ESR may also retain existence for a long time just like CRP. Because the second follow-up of the patients was performed at the 8th month of the treatment, this period may not be enough for the recovery in CRP and ESR levels. Therefore, more long-term follow-up

periods may be needed to show the normalization of CRP and ESR levels. Thus, further studies with long term follow-up periods may be performed. Even though pain management is clinically more important than other parameters, the recovery of CRP or ESR levels is important in terms of indicating the performance of RA treatment.

## CONCLUSION

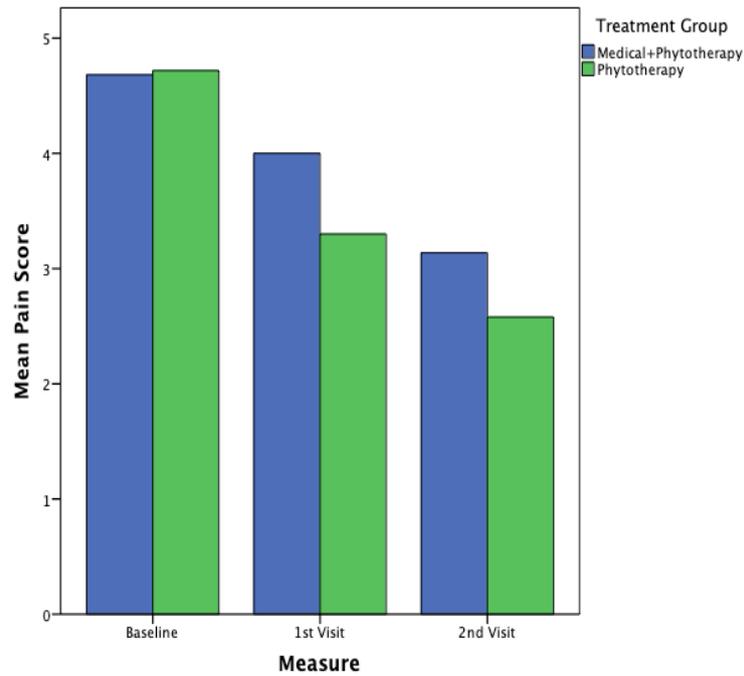
As a conclusion, the RTM was well tolerated by all patients with RA, and no side effects were observed. The identification of epigenetically regulated genes related to RA may be promising in order to develop epigenetic drugs for disease management. However, further functional studies might be required to determine epigenetically regulated genes in RA.

## DECLARATION OF INTEREST

The author declares no conflicts of interest.

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**Fig.1:** The changes in mean pain scores in the medical+phytotherapy and the phytotherapy groups over time.

**Table 1:** The changes of the mean CRP, ESR and pain score at different follow-up times.

	Baseline (A)	1st Control Visit (B)	2nd Control Visit (C)	p*	Statistically Significant Difference**
CRP	6.6± 11.1	6.6± 11.9	4.4± 7.9	0.750	
ESR	30.0± 21.5	31.7± 24.6	29.8± 18.0	0.313	
Pain Score	4.7± 0.8a	3.6± 1.3b	2.8± 1.2c	<0.001	A>B,C B>C

\* Friedman test

\*\*Posthoc Bonferroni corrected Wilcoxon signed ranks test

**Table 2:** The comparison of the mean pain scores according to the treatment groups.

	Medical+phytotherapy Mean± SD	Only phytotherapy Mean± SD	z	p*
Baseline Pain Score	4.7± 0.8	4.7± 0.8	-0.548	0.937
1st Follow-up Pain Score	4.0± 1.2	3.3± 1.3	-2.512	0.031
2nd Follow-up Pain Score	3.1± 1.3	2.6± 1.0	-1.692	0.091

\* Mann Whitney U test

SD=Standard Deviation