ORIGINAL ARTICLE

Phototherapy Induces an Improvement in Clinical and Biochemical Scores in Patients with Rheumatoid Arthritis

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ABSTRACT

Objective: *Rheumatoid arthritis (RA) is a common autoimmune disease for which there is no known cure. Ultraviolet light can induce immunosuppressive effects. Our main objective was to ascertain whether a complementary treatment with phototherapy would improve changes in functional scales in patients with RA.*

Methods: *Seven women with RA were enrolled for this study and submitted to phototherapy sessions with a 425–650 nm lamp.*

Results: *The Karnofsky scale changed from requiring frequent medical care to being capable of normal activity with few symptoms or signs of disease (*p *= 0.018), the rheumatoid arthritis-specific quality of life questionnaire decreased abruptly from 29 to 0 points (*p *= 0.018), the Steinbrocker functional capacity rating changed from limited to little or none of the duties of usual occupation or self-care to complete ability to carry out all the usual duties without handicaps (*p *= 0.017). The pain was remitted after the treatment period. The acute inflammation variables showed a significant decrease after the indicated sessions, C-reactive protein (*p *= 0.042) and erythrocyte sedimentation rate (*p *= 0.018).*

Conclusion: *The evaluated scales clearly show a benefit with the phototherapy in patients with RA. Thus, phototherapy seems to be a plausible complementary option to reduce the symptoms of RA.*

Keywords: C-reactive protein, functional scales, phototherapy, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a common autoimmune disease for which there is no known cure. A diverse number of biological pathways are altered in patients with RA, which impinge on a wide variety of cell types, tissue types and organ systems—innate immune cells (*eg*, dendritic cells, mast cells, neutrophils, platelets), adaptive immune cells (*eg*, B and T cells), bone, cartilage, synovial fibroblasts, vascular cells, brain, muscle, and fat (1). The chronic manifestations of RA are primarily manifested in the synovial tissues, with symptoms of pain, stiffness, swelling and progressive joint destruction (2).

Drugs used for the treatment can be divided into four broad categories: non-steroidal anti-inflammatory drugs, glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs), and biologic agents. Since 2002, treatment recommendations for RA have suggested an aggressive approach to inhibit the progression of joint damage and other complications that may develop soon after diagnosis (3–5). This aggressive approach includes the initiation of DMARDs and biologic agents as soon as possible.

Among complementary alternatives to treat RA, we find the use of light. In this respect, the frequency, wavelength and energy of an electromagnetic wave are related to one another, with wavelength being inversely proportional to both frequency and energy. The huge spectrum of electromagnetic radiation can therefore be

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organized conceptually by decreasing wavelength into radio waves, microwaves, terahertz radiation, infrared radiation, visible light, ultraviolet (UV) radiation, X-rays, and gamma rays.

Phototherapy is defined as the use of UV radiation in the treatment of skin disease. There are many types of phototherapy, including broadband ultraviolet B (UVB) (280–320 nm), narrowband UVB (311–313 nm), ultraviolet A (UVA) (340–400 nm) and combination therapy of psoralen plus UVA.

Although UV light can induce strong inflammatory responses in susceptible individuals, under chronic or minimally erythematogenic doses, its immunosuppressive effects are dominant. The mechanism of this immunosuppression involves both cellular components and soluble mediators (6). For example, Langerhans cells are very sensitive to UV radiation. These cells express molecules such as MHC class II, lymphocyte function-associated antigen-3, intercellular adhesion molecule (ICAM)-1, ICAM-3, B7, CD1a, and CD40. Ultraviolet radiation induces these cells to migrate out of the skin to draining lymph nodes (7, 8), and there is a dramatic reduction in the previously mentioned markers following UV exposure (9).

Our main objective was to evaluate the changes in functional scales, biochemical and inflammatory variables in patients with RA submitted to phototherapy within a range of 425–650 nm (visible light spectrum) and 11.33 J/cm^2.

SUBJECTS AND METHODS

In this descriptive, prospective, longitudinal and quasi-experimental clinical study, women who attended the Research Department of the Maternal-Perinatal Hospital 'Mónica Pretelini Sáenz' (HMPMPS), Health Institute of the State of Mexico (ISEM), Toluca, State of Mexico, Mexico, and met the criteria established by the American College of Rheumatology (10) for the diagnosis of RA were included in the study. Patients with previous fractures, chronic diseases that limit the functional capacity, other arthropathies or overlap syndromes were not included.

An essential aspect of the study was the absolute respect to the management, evaluation and subsequent citations instituted by the treating rheumatologist. Only in cases where the patient was not receiving specialized care or that their problem was recently installed and did not have an opportunity to apply this specialized care did we initiate the pharmacological management in conjunction with phototherapy.

We obtained general personal data from the patients' medical history; anthropometry, biochemical evaluations and clinical scales were conducted weekly to assess the RA affection.

Anthropometric measures were assessed in the Research Laboratory of the HMPMPS. Bodyweight was measured in an overnight fasting status without shoes in a minimal clothing state by the use of a digital scale (Seca, Hamburg, Germany) to the nearest 0.1 kg. Height was measured using a non-stretched tape measure to the nearest 0.1 cm. Body mass index was calculated as weight in kilogram divided by height in meters squared.

We applied the following clinical evaluations: Karnofsky scale, Quality of life-rheumatoid arthritis, rheumatoid arthritis-specific quality of life (RA-QoL) instrument, Steinbrocker functional capacity rating, and the visual analogue scale. Also, we evaluated these items: spontaneous pain, pressure pain, movement pain and inflammation (fluorosis) with the following parameters: 0 (absent), + (light), ++ (moderate), +++ (severe); functional limitation and temperature rise were classified as follows: 0 (absent), 1 (present); and strength (excluding hands) was evaluated as follows: 1 (normal), −1 (diminished), −2 (very diminished).

Fasting blood samples (10 ml) were taken at the HMPMPS laboratory in the early morning after an overnight fast. Serum samples were analysed for serum total proteins, albumin, globulin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, bilirubin, creatinine, blood urea nitrogen, urea, uric acid (Dimension Rx L Max, Dade Behring, USA), hemogram (Advia 120, Bayer Health, USA), fasting plasma glucose (Dimension Rx L Max, Dade Behring, USA), erythrocyte sedimentation rate (ESR), creatine phosphokinase, electrolytes (Na, K, Ca, P, Mg, Cl), Venereal Disease Research Laboratory, C-reactive protein (CRP), rheumatoid factor, and urine test and cyclic citrullinated antibody test. All these tests were measured according to standardized procedures recommended by the International Federation of Clinical Chemistry and Laboratory Medicine.

The phototherapy lamp developed by our research team (Federal Ministry of Health registration number: 1694E95) used the electromagnetic spectrum within a range from 425 to 650 nm (visible light spectrum), 11.33 J/cm^2. With the patient in supine position, after registering vital signs (blood pressure, heart rate, respiratory rate and temperature), weight, height and capillary glucose determination, we proceeded to place the phototherapy device 30 cm above the chest.

The phototherapy scheme was: (a) 45-minute daily sessions from Monday to Friday for two to three months, (b) three sessions per week of 45 minutes each for one to two months, (c) twice-a-week sessions of 45 minutes each for one to two months, and (d) a weekly session for one to two months until completion. Weekly frequency and progressive reduction of the phototherapy sessions were determined according to the patients' own improvement.

The protocol was approved by the Research Committee of the HMPMPS (November 2010). We followed the Helsinki Declaration, Fortaleza, Brazil, and all patients were asked to sign and give written informed consent.

Statistical analysis was performed using SPSS version 19. Firstly, descriptive analyses were performed. Then, we compared if the group presented differences through the time by Wilcoxon test. A difference of $p \leq 0.05$ was considered significant.

RESULTS

A total of seven female patients with RA, with a median age of 44 years (range 21–56), were enrolled for this study. Four patients were already in treatment with a rheumatologist, and three were naïve to any kind of treatment.

The median of anti-rheumatic drugs that the patients were taking at the time of starting the protocol was of 2.2. The median of time within the protocol was of 140 ± 7.7 (SE) days, and the median of prescribed phototherapy sessions was of 66 (range 34–77) (Table 1). The clinical characteristics of the studied women are shown in Table 2.

Table 3 shows the results of the evaluated scales. All the median scores were significantly better rated after the treatment period. Karnofsky changed from requiring frequent medical care to being capable of normal activity with few symptoms or signs of disease. The RA-QoL questionnaire decreased abruptly from 29 to 0 points. Steinbrocker functional capacity rating changed from limited to little or none of the duties of usual occupation or self-care to complete ability to carry out all the usual duties without handicaps. The pain was remitted after the treatment period.

The acute inflammation variables declined notoriously after the indicated sessions. The erythrocyte sedimentation rate diminished more significantly than CRP, although both reached a statistical difference. Metabolically speaking, albumin increased and cholesterol decreased after the survey.

DISCUSSION

There are many research lines searching for a better prognosis in RA. In spite of the great advances with biological drugs, there is still not a cure, and the cost of such therapy is not easily affordable for most patients. In this line of explorative options, there is scarce information related to the treatment of RA with light exposure. In this respect, the described techniques are extracorporeal photochemotherapy, photodynamic therapy, photopheresis and UVA.

Table 1: General characteristics of the patients

Variables	Patient						
	1	2	3	4	5	6	7
Age (years)	21	49	41	34	56	46	44
Familial cases of RA	0	0	0	1	0	0	5
State of origin	State of Mexico	State of Mexico	State of Mexico	Guerrero	Hidalgo	State of Mexico	Mexico City
Occupation	Student	Worker	Worker	Dentist	Housemaker	Housemaker	Worker
Disease duration (months)	4	56	43	80	73	39	116
Drugs at the beginning	Dc Cl Mtx Sz	Dc	Cl Dc Pred Mtx Pc	Dc Hcq Mtx Pc	Pc RtD	Dc	Cl Mtx Pxc Sz
Co-morbidities		Obesity HT				Sjogren syndrome HT HC	

Cl = chloroquine; Dc = diclofenac; HC = hypercholesterolemia; Hcq = hydroxychloroquine; HT = hypertriglyceridemia; Mtx = methotrexate; Pc = paracetamol; Pred = prednisone; Pxc = piroxicam; RA = rheumatoid arthritis; RtD = delayed action diclofenac; Sz = sulfasalazine

Table 2: Anthropometric and clinical characteristics

Variable	Initial	Final	*p*
Spontaneous pain	6 ± 2.9	0 ± 0.14	0.028
Movement pain	25 ± 4.3	0	0.018
Pressure pain	32 ± 4.8	0 ± 0.72	0.018
Inflammation	4 ± 1.6	0 ± 0.56	0.028
Affected joints	35 ± 1.6	0 ± 1.5	0.018
Deformed joints	0 ± 1.5	0 ± 1.5	
Functional limitation	10 ± 1.9	0 ± 0.14	0.018
CRP (mg/L)	80 ± 19.5	0 ± 29.5	0.042
ESR (mm/min)	40 ± 6	26 ± 3.9	0.018
RF (IU)	80 ± 172	0 ± 29.5	
Total proteins (mg/dL)	7.8 ± 0.23	7.6 ± 0.25	
Albumin (mg/dL)	3.7 ± 0.13	3.9 ± 0	0.018
Globulins (mg/dL)	4 ± 0.27	3.6 ± 0.23	
Cholesterol (mg/dL)	188 ± 11	177 ± 13	0.018
Triglycerides (mg/dL)	104 ± 15	108 ± 6	

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor.

Table 3: Scales of evaluation

Scale	Initial	Final	*p*
Karnofsky	50 ± 4.7	90 ± 2.6	0.018
QoL-RA	12 ± 2.6	77 ± 1.8	0.028
RA-QoL	29 ± 0.75	0 ± 1.1	0.018
Steinbrocker functional classification	3 ± 0.21	1 ± 0.14	0.017
VAS	9 ± 0.6	0 ± 0.4	0.018

QoL-RA = quality of life-rheumatoid arthritis scale; RA-QoL = rheumatoid arthritis-specific quality of life; VAS = visual analogue scale.

Extracorporeal photochemotherapy has been applied in refractory RA with clinical improvement, a decline in CRP and no adverse reactions recorded (11). Photodynamic therapy is based on the use of light-sensitive molecules called photosensitizers. This photoactivation causes the formation of singlet oxygen, which produces peroxidative reactions that can cause cell damage and death (12).

The use of photosensitizers is not a new topic in medicine (13). Experimentally, incubation with chloroquine or methotrexate and subsequent laser irradiation at a wavelength of 351 nm resulted in an at least 20-fold enhanced cytotoxicity. Both substances therefore may serve for a photodynamic therapy of RA (14). We cannot exclude the possibility of some patients being benefitted under the photodynamic effect of either of both drugs.

Ultraviolet A light may be effective in the treatment of patients with RA, but elucidation of its precise role requires further study including double-blind trials (15). Photopheresis is an extracorporeal form of photochemotherapy with 8-methoxypsoralen and UVA radiation. This therapeutic option leads to the induction of antigen-specific immune suppression directed to the pathogenic clone of T cells (16). In 1991, Malawista *et al* (17) conducted a study in seven patients with RA who were treated with extracorporeal photopheresis. After a treatment period of between 12 and 16 weeks, positive responses were obtained in four of seven patients, noting a decrease in number and degree of joint involvement and in morning stiffness and pain.

Our approach differs in many senses in relation to the above-mentioned works. Firstly, we used visible wavelength, which, to our knowledge, is the first study demonstrating a clinical benefit in RA. In evaluating the clinical benefits with any treatment in patients with RA, the use of functional scales is mandatory. Our group has evaluated not one but five scales, all of which with an evident demonstration of success in managing patients with RA with phototherapy.

As is well known, an objective way to probe the benefit of any treatment is the decrease in inflammatory variables. Our results showed a decrease in CRP and ESR. As an initial attempt, we did not quantify TNF-α expression that had been included in a new protocol that had already begun.

A critical point to be considered is the role of vitamin D as its shortage in the diet added to a low sunlight exposure could predispose to several diseases including RA (18). In this respect, the fact that we used the 425–650 nm wavelength could stimulate the vitamin D synthesis and, as a consequence, obtain a clinical benefit derived from this vitamin pathway. Whether phototherapy induces a clinical improvement by reducing oxidative stress, changing isomerization or any other molecular effect was beyond the scope of the present study.

This study has its limitations. The low number of cases does not give us enough power to extrapolate the results to a more diverse population. Also, it was not a randomized clinical trial as it was impossible to enrol enough naïve patients with RA and successfully integrate comparative groups. This last attempt has to be developed in a hospital with considerable RA incidence. Despite the above-mentioned limitation, our study has a strong point in reporting the results of five clinical scales and not only one.

Another point to be considered is the placebo effect. Without any doubt, this effect contributes to a feeling of welfare, but it would not be as definite as has been documented using five different clinical scales. Moreover, the placebo effect is conditioned by the personality (19), being extremely difficult that the seven patients had the

same factors influencing placebo response. Finally, the mechanism that underlies the phototherapy has yet to be elucidated, although there has been documentation of isomer changes and immunosuppression with this technique.

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