Ozone Therapy for The Treatment of A Patient with Rheumatoid Arthritis and Hashimoto's Thyroiditis Who Had Insufficient Respond To Multidrug Therapy. 4 Years Follow Up

Romatoid Artrit ve Hashimoto Tiroiditi Olan Bir Hastanın Tedavisinde Ozon Tedavisi

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Abstract

Introduction	Rheumatoid Arthritis (RA) with insufficient respond to multidrug-therapy combinations constitutes a challange in therapeutic planning. Ozone therapy (OT) may bring new dimensions in the management.
Case Presentation	A 53-year-old woman had different multidrug-therapy combinations (non steroid anti inflammatory drugs (NSAID), Hydroxychloroquine, Sulphasalazine, Metothrexate (MTX), Cortico steroids (CS) and Leflunomide) in 22 years but still had swollen and painful joints with multipl deformities due to moderate activity of RA. Disease Activity Score (DAS 28 - CRP) was found to be 4.48. She also had pangastritis, low vitamin B12 levels and euthyroid Hashimoto's thyroiditis. She was unwilling to carry on with her medicines. She received medical intravenous ozone application starting as 2/week, 2000 gamma/session for 8 weeks, then lowered gradually to 1/month for a year. She stopped taking CS and Leflunomid after the 1st and 5th months of OT. She also stopped taking her pangastritis medications. After 4 years of initial OT, the last 3.5 years were free from medication and complaints. DAS 28 - CRP value difference was 2.26 (decrease > 1.2) wich denotes to a "major improvement". X-ray control of hands showed minimal increase in deformities. Decrease in Anti-Tiroglobulin levels has been found to be worth investigating.
Result	Appropriate ozone therapy may bring new horizons for patients with insufficient respond to multidrug-therapy combinations in Rheumatoid arthritis.
Keywords	Ozone Therapy, Rheumatoid arthritis, corticosteroids, csDMARD, Hashimoto's thyroiditis.

Öz

Giriş	*Çoklu ilaç kombinasyonlarına yetersiz yanıt gösteren Romatoid artrit (RA), tedavinin planlanmasında zorluk oluşturmaktadır. Ozon tedavisi (OT) mücadelede ümit verici olabilir.*
Olgu Sunumu	*53 yaşında kadın hasta. 22 yıl içerisinde farklı, çoklu-ilaç kombinasyonları kullanmasına rağmen (non steroid antiinflamatuar ilaçlar - (NSAID), hidroksiklorokin, Sulfasalazin, Metotreksat (MTX), Kortiko steroid (KS) ve Leflunomid) orta düzey RA aktivitesine bağlı eklemlerde şişlik, ağrı ve deformasyon şikayetleri ile müracaat etti. Hastalık Aktivite Skoru (DAS 28 – CRP) 4.48 bulundu. İlave olarak pangastrit, düşük B12 seviyesi ve Hashimoto tiroiditi mevcuttu. İlaçlarını kullanmakta isteksizdi. Intravenöz tıbbi OT uygulanmasına 2/hafta, 2000 gamma/seans, 8 hafta süre ile başlandı. Daha sonra 1/ay olacak şekilde uygulama kademeli azaltılarak 1 yıla tamamlandı. OT başlangıcından 1 ay sonra KS, 5 ay sonra Leflunomid alımı durduruldu. Daha sonra hasta ihtiyacı kalmadığını belirterek pangastrit ilaçlarını durdurdu. OT başlangıcından 4 yıl sonra yapılan değerlendirmede son 3.5 yılın komplikasyon olmadan ve ilaç kullanılmadan gerçirildiği görüldü. DAS 28 – CRP değer farkı 2.66 (düşüş > 1.2) bulundu ki bu "majör düzelmeyi" göstermektedir. Ellerin X-Ray kontrollerinde, deformitelerde minimal artış görülmüştür. Anti-Tiroglobulin seviyesindeki azalma incelenmeye değer bulunmuştur.*
Sonuç	*Çoklu-ilaç tedavisine yetersiz yanıt gösteren Romatoid artititli hastalarda uygun şekilde yapılan ozon terapi yeni ufuklar açabilir.*
Anahtar kelimeler	*Ozon terapi, Romatoid artrit, kortikosteroidler, csDMARD, hashimoto tiroiditi*

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune, progresively destructive inflammatory disease with an uncertain course and the global age standardized prevalance rate of RA was found to be 0.246% in 2017 which indicates to a 7.4% increase when compared with the values given in 1990.[1] It is much more common in women than in men. Usually it occures between the ages of 20 to 40 and main involvement sites are joints, connective tissues and tendones causing pain and leading to progresive disability and lost of function due to malformations and deformations.[2] 50% of the patients in developed countries loose their jobs in 10 years after the onset of the disease.[3] This leads to healthcare consequences with direct and indirect global cost burden. According to the Zion Market Research report, the global RA drug market value was $22.6 billion in 2018.[4]

There is no cure for RA in modern medicine even in today's practice. Many different methods and combination therapies are being carried out to modify the disease to reach to a remission state so that it prevents disability and anatomic damage. Today, this goal is attainable around 42% only in early RA patients.[5] More than 80% of traditional (conventional synthetic) Disease Modifying Antirheumatic Drugs (csDMARDs) applications are discontinued within two years, predominantly because of either their toxicity or lack of efficacy.[6,7] Median time for the discontinuation or modification of biologic DMARDs (bDMARDs) treatment was found to be as high as 50% within a mean period of 25.1 months.[8]

There is currently no uniform definition of sustained remission in RA. We used American College of Rheumatology, Rheumatoid Arthritis Disease Activity measuries with tender and/or swollen 28 joint conditions and C-Reactive Protein to measure Disease Activity Score (DAS 28 - CRP).[9]

The objective of this case report is to put forward a different approach in terms of complementary medicinal applications namely, ozone therapy, in patients with insufficient respond to multidrug-therapy combination for the treatment of RA.

Case Report

A 53-years-old woman applied to our clinic in November 2015. She had complains of heartburn, nusea, bloating, burping, stomach pain, tender and swollen joints with deformities. At the age of 31 (22 years ago) she was diagnosed to have RA. In the following years she had osteopenia, pangastritis, low B12 level and Hashimoto's Thyroiditis. On our first examination she had 5 tender joints, 10 swollen joints with CRP level being 11mg/L, Patient Global Activity: 35mm and DAS 28 – CRP value was 4.48 indicating to "Moderately Active RA"

Since her first diagnosis 22 years ago she used CS+Hydroxychloroquine+Sulphasalazine till 1995. Between 1995 to 2000 she used CS+MTX + Sulphasalazine + Naproxen/Etodolac. Between 2010 to 2011 she used CS + Salazopyrine + Alendronate + Naproxen/Etodolac. Later in between 2011 to 2012 she used CS+MTX+Leflunomide+ Cyanocobalamine + Alendronate + Naproxen/Etodolac. Last treatment period before initiation of OT was between 2013 and 2015. During these years she was also diagnosed to have euthyroid Hashimoto's thyroiditis and low vitamin B12 levels of unknown etiology. Lately she was on a medication with Prednisolon 5 mg 1/d + Leflunomide 20 mg 1/d + Cyanocobalamine 1mg/month + Rabeprazole 1/d and Naproxen/Etodolac 200mg 1/d as needed because she also had heartburn, nusea, bloating, burping and stomach pain due to pangastritis since 2013 wich started as an antral gastritis in 2011.

During those tretment years she had had an extensor tendon rupture on her 3rd finger in her right hand in 2013 and was on different multi drug combination therapies, where the drugs were administered by modifying the doses due to ups and downs in her clinical outcomes by the

rheumatologist until we initiated ozone therapy (OT) in 11/2015. She was very keen on her self healthcare and she carefully applied every treatment recommended to her. In her treatment history every discontinuation of a medicine was due to its side effects. As she had had insufficient respond to multi drug therapy for her RA she was very upset and was unwilling to cary on with her medicines and was eager to integrate OT into her treatment protocol.

She received medical intravenous ozone application for RA, starting as 2/week, 2000 gamma/session for 8 weeks, which was then modified to 1/week for 8 weeks, 2/month for 2 months, 1/month for a year. As her clinical outcome improved she stopped taking CS and Leflunomid after the 1st and 5th months from the commencement of ozone therapy respectively. She also stopped taking her medications for her pangastritis as she declared that she did not have any symptoms for gastritis any more. On January 2020 her DAS - 28 - CRP score was found to be 2.22 with Tender joints:0, Swollen Joints: 3, CRP: 6 mg/L, Patient Global Activity: 5mm indicating to the REMISSION in DISEASE ACTIVITY. 4 years difference in DAS 28 - CRP value was: 4.48 – 2.22 = 2.26. Reduction more than 1.2 represents "Major Improvement".[10]

Discussion

In contemporary medicinal applications, we have better diagnostic facilities and more effective drugs wich make long term prognosis of RA much better than previous decades but it is still, for sure, far behind the desired level. Most of the DMARDs have wide range of side effects. Modifying immune system through bone marrow makes patients more susceptible to infections. Liver, kidneys and gastrointestinal organs are under risk so that close monitoring is imperative. The patients' quality of life is low and unfortunately their life expectancy is shorter due to increased incidence of cardiovascular diseases, infections, bone fructures and malignancies.[11,12] These problems increase not only the morbidity and mortality but they also, directly or indirectly, impose an economic burden on the patients and their families. It is not a suprise that 75.9% of RA patients use complementary medicine in search for a solution for the treatment of this big problem.[13]

This case is a typical example for years of modified multi drug therapy for RA, despite which she had had moderate disease activity with significant loss in quality of life both due to the active disease itself and obviously to the side effects of the drugs. Insufficient respond to different multidrug therapy combinations with many execerbation attacs made her to search for new treatment modalites.

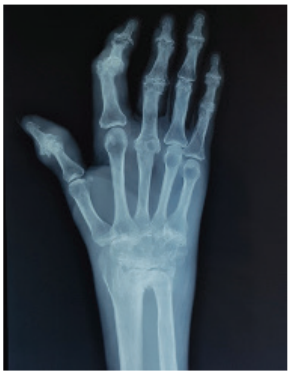
Although different methods of treatments are forwarded in the literature, ozone therapy stands to be a rising method with, if any, almost no side effects in the management of the RA.[14]

Our case puts forward a dramatic fall in her DAS 28 - CRP values from 4.48 to 2.22. This value was a good indicator of "remission". The fall in the DAS 28 - CRP value was more than 1.2 marks (difference found was = 2.26 - more than twice) underlines a "major improvement".[10]

Auto-reactive T cells that infiltrate the synovial tissue promote the immune response, resulting in an overproduction of pro-inflammatory cytokines. In Chronic diseases, inflammatory cytokines stimulate reactive oxygen species (ROS) formation which stimulates proteolitic activity which is mainly responsible from cartilage and bone destruction in RA. Leon and Viebahn applied MTX + OT to a study group and MTX to a control group and they found that protective redox markers (superoxide dismutase, Catalase and Glutathione) were higher in ozone grup and injury redox markers (nitrogenoxide, Advanced Oxidation Protein Products, Total Hydroperoxides ,Malondialdehyde) were lower. They also foud that there was a significant difference between DAS28 score in MTX-OT group.[15] This mechanism of action of OT might be the answer for the outcomes of our patient's results. It look likes that we had better results and this might be because of different treat-

ment protocol used for the OT.

The radiographic images of the patient did not put forward any anatomic healing, on the contrary indicated to a minimally deteriorating results from the time of admission and after OT however clinical symptoms and scoring was significantly better (Figures 1 and 2).



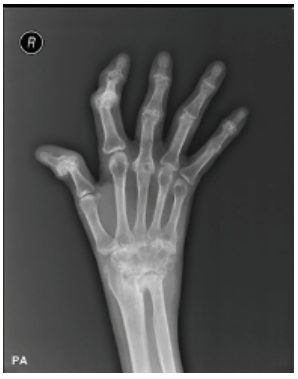


Figure 1: Hand X-ray in 2016.
Figure 2: Hand X-ray in 2020.

This may lead us to comment that despite raidological improvments may not be achived with OT clinical improvments still helps to improve, and improve well, the quality of life of patients with RA, however randomized controlled studies should be conducted to be able to make this decision precisely but it was what happened in our case.

In conclusion our patient discontinued all of her medication due to being symptom free 6 months after the initiation of OT and she is still semptom free after 4 years of follow up. We believe that it will be beneficial to carry out larger studies on the application of OT, especially in RA patients who do not respond to multidrug therapy and recommend the use of this method of treatment in failing patients who are on multi-drug regimes.

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