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Research Article

The Effect of Onabotulinum Toxin-A on Frequency of Headache, Severity of Headache and Health Related Life-Quality at Patients With Resistant Chronic Migraine

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Summary

Introduction: Resistant chronic migraine (RCM) causes a considerable decline in the quality of life and work efficiency of the patients and ultimately might even decrease their socio-economic level because of severe and permanent headaches. In addition, migraine attacks force patients to rush to the emergency rooms, which leads to overcrowding and exhaustion of medical resources. In this study, the effect of onabotulinum toxin A (OBoNT-A) treatment was assessed in terms of efficiency and the quality of life retrospectively at patients with RCM.
Method: 15 patients with RCM who were given 155 IU OBoNT-A treatment twice in 12 weeks have been studied retrospectively in terms of change of headache frequency, severity, and the health related quality of life scores (physical function, physical restriction, pain, general health, vitality, social function, emotion and mental health categories) for 24 weeks. Response to treatment is identified as ≥30% decrease in headache frequency while the change in the quality of life was determined with short form-36 before and after treatment.
Findings: Average headache frequency was 26.3 day/month before treatment. After 24 weeks, 93% of the patients were responsive to the treatment. After OBoNT-A treatment average headache frequency decreased to 16,6 day/month in 12 weeks and to 17,8 day/month in 24 weeks ($p<0.001$). Average health related quality of life scores before treatment were under 50%, while all the health related quality of life scores improved after treatment($p<0.001$). At the end of 24 weeks, headache severity significantly decreased ($p<0.001$).
Conclusion: OBoNT-A is an effective treatment in patients with RCM and it must be considered a first line treatment for RCM patients considering the cost-effectiveness researches.

Key words: Onabotulinum toxin-A,resistant chronic migraine, quality of life

Onabotulinum Toksin Tip-A Tedavisinin Dirençli Kronik Migren Hastalarında Baş Ağrısı Sıklığı, Baş Ağrısı Şiddeti ve Sağlığa Bağlı Yaşam Kalitesi Üzerine Etkisi

Özet

Giriş: Dirençli kronik migren(DKM), yaşam fonksiyonlarında kısıtlılığa neden olan bir hastalıktır. Baş ağrısı ataklarında hastaların acil servislere başvurması, sağlık kaynaklarının meşgul etmesi ve yine hastaların sağlığa bağlı yaşam kalitesi ve üretkenliklerinin kaybı gibi nedenlerle sosyoekonomik yük getirir. Bu çalışmada retrospektif olarak onabotulinum toksin A (OBoNT-A) tedavisinin DKM hastalarında etkinliği ve yaşam kalitesine olan etkisi değerlendirildi.
Yöntem: Kliniğimizde 12 hafta arayla iki kez uygulanan 155 IU OBoNT-A tedavisi alan, modifiye DKM kriterlerini karşılayan, 15 hastanın retrospektif olarak 24 haftalık süreçte baş

ağrısı sıklığı, şiddeti, yaşam kalitesi (fiziksel fonksiyon, fiziksel rol kısıtlanması, ağrı, genel sağlık algısı, enerji, sosyal fonksiyon, emosyonel durum ve mental sağlık) skorlarında değişimi incelendi. Tedavi yanıtı her 12 haftada bir baş ağrısı sıklığında ≥%30 azalma olarak tanımlandı. Tedavi öncesi ve tedavi sonrası Kısa Form-36 ile yaşam kalitesinde değişim değerlendirildi.

Bulgular: 15 hastanın tedavi öncesi baş ağrısı sıklığı 26,3 gün/aydı. Hastaların %93,3'ü 24 hafta sonunda tedaviye yanıtlıydı. OBoNT-A enjeksiyonu sonrası bazale göre baş ağrısı sıklığında ortalamada 12 haftada 16,6 gün/ay ve 24 haftada 17,8 gün/ay azalma izlenmiş oldu ($p<0.001$). Tedavi öncesi yaşam kalitesi skorları ortalamada %50'nin altındaydı, tedavi sonrası sosyal fonksiyon, fiziksel rol kısıtlanması ve enerji kategorilerinde başta olmak üzere tüm kategorilerde sağlık ilişkili yaşam kalitesi skorlarında iyileşme izlendi ($p<0.001$). Baş ağrısı şiddetinde 24 hafta sonunda anlamlı azalma saptandı ($p<0.001$).

Sonuç: DKM hastalarında OBoNT-A etkin bir tedavidir. Maliyet-etkinlik araştırmaları yapılarak DKM hastalarında öncelikli tedavi olarak düşünülmelidir.

Anahtar Kelimeler: Onabotulinum toksin-A, dirençli kronik migren, yaşam kalitesi

INTRODUCTION

Chronic migraine (CM) causes disability and restricted health related quality of life and affects approximately 1,4-2,2% of the general population[5,20,21]. International Classification of Headache Disorders (ICHD-3) defined CM as headache on ≥15 days per month for >3 months, with ≥8 days meeting criteria for migraine or demonstrating response to migraine-specific treatment[13]. Patients with CM have inadequate response to abortive and protective treatment[5,9].

Patients who are resistant to four groups of protective agents of migraine (including antiepileptic drugs), often need to change their life style because of the headache and those unresponsive to abortive treatment are defined as having resistant chronic migraine (RCM)[17]. Compared to CM, RCM brings more socio-economic burden on the patients by restricting their social life and by reducing further their quality of life[7]. Such problems marked the beginning of the research on methods for effectively treating RCM where onabotulinum toxin type A (OBoNT -A) was found to be an effective, safe and well tolerated method at both treatment of CM and RCM[2,8].

Mechanism of OBoNT-A is unclear; some research claims that it probably inhibits secretion of nossiseptive mediators (glutamat, substance P, CGRP) from peripheral afferent terminals[1].

Health related quality of life at patients with CM lowers as the severity and frequency of headaches increase[7]. More than 50% of the patients are reported to be incapable of working and in need of bed rest because of severe headaches. Patients with CM suffer from significantly more disease-related disability compared to episodic migraine.

The objective of this study is to assess the efficacy of OBoNT-A therapy on RCM treatment and on the health related quality of life of patients with RCM and to investigate potential predictors of response to treatment.

MATERIAL AND METHODS

Clinical Configuration

Our clinic has approximately 2500 registered migraine patients. A form is filled for each migraine patient depending on their answers, which contains categories on the demographic characteristics of patients and medical characteristics of migraine, while the treatment response is monitored with a migraine dairy during clinic follow-up. Patients with CM are monitored for effect of treatment on the health related quality of life with short

form-36 (SF-36). In 2013, patients with RCM followed up by our clinic were offered to have OBoNT-A injection. Off-label drug request forms were filled for patients who accepted the therapy, and the forms were sent to the Turkish Ministry of Health Medical Devices Agency for approval. Because it is an invasive application, all patients were informed of the complications arising from the injection of the drug in writing with a consent form, the clinic started the procedures following upon receiving their consent.

Patients:

Patients' files which fulfilled the RCM criteria suggested by Schulman et al.[17] and received OBoNT-A injection between January 2013 and December 2013 were studied. Our team examined medical records, migraine characteristics forms, SF-36 health related quality of life forms, migraine dairies, migraine protective agents patients used, migraine subtype, severity of headache by visual analogue scale(VAS) score, and migraine abortive drugs patients used during OBoNT-A treatment retrospectively. Study included patients who received OBoNT-A injection with 6 month follow-up.

Migraine attack frequency and headache days per month were calculated on the basis of 3 monthly migraine dairy before the OBoNT-A injection. Non-steroidal drug usage had been castrated for 2 months before injection to eliminate CM from analgesic-overuse headache. SF-36 was used to evaluate headache induced restriction of life. Assuming that the injection day is day-zero; the same dose of injection was repeated at week-12 regardless of the patients' symptoms. Frequency and severity of headache were calculated depending on the migraine dairies which were kept for 6 months. As requested by HIS clinical study subgroup committee, patients with $\geq$ 30% reduction from baseline in headache frequency were considered as clinically responsive, at week-12 and -24 after OBoNT-A injection[11]. Change in the quality of life before and after treatment was evaluated with SF-36 scores. SF-36 is a multiple-choice form that consists of 36 questions and that evaluates health related quality of life in 8 categories (physical function, physical restriction, pain, general health, vitality, social function, emotion and mental health). Each category is separate and evaluated independently. 100 points show a good quality of life and a decrease in points is in direct correlation with the decrease in quality.

Therapy Application

A total of 155 units of OBoNT-A, 5 units for each 31 points on the head and neck muscles, was applied to all patients as recommended in PREEPMT study[6]. A fix dose of OBoNT-A was injected to two corrugator, one proceus, four frontal, eight temporal, six occipital, four paraspinal and six trapesius muscles. Abortive and protective treatment was not ceased during OBoNT-A treatment. Second injection was applied at the same injection points with the same fixed dose after 12 weeks.

Statistical Analysis

Statistical analysis was made by using SPSS program (18.0 windows; SPSS Inc., Chicago, IL, USA). Student's t test was used for the comparison of normally distributed continuous data, and Mann-Whitney U was used to test for the comparison of abnormally distributed continuous data. $p<0.05$ was considered significant at two-tailed tests.

RESULTS

20 patients with a diagnosis of RCM were injected OBoNT-A in the examined time period. 5 patients were excluded because of incomplete migraine dairies, SF-36 forms or migraine forms at retrospective survey. 15 patients (1 male, 14 female; mean age 44.6±10.9 years) were included in the analyses. Only one patient had migraine with aura, other patients had migraine without aura; no patient had other

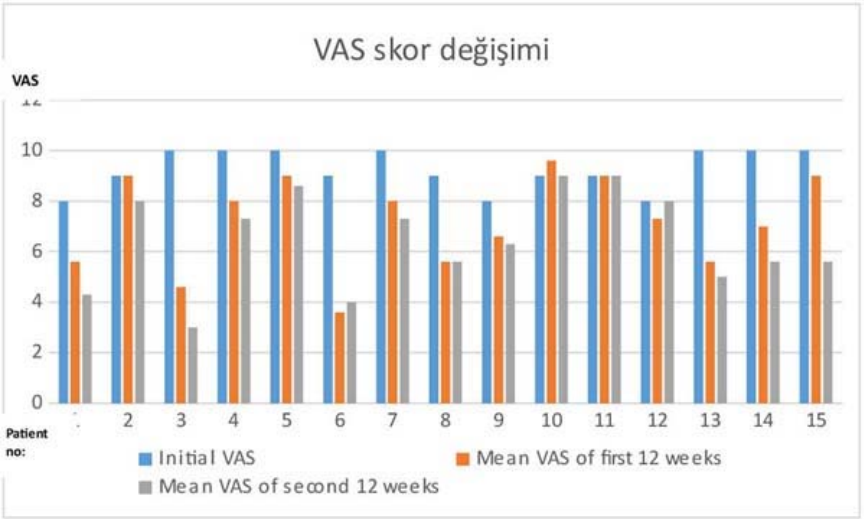
subtype of migraine. Mean CM time was 2.5±1.8 years.

5 of the 15 patients had been coming to the emergency room at least 3 times a month for parenteral therapy before treatment. 3 patients had quit their jobs because of migraine headaches. Patients had been receiving three groups of prophylactic agent on the injection day; B-blocker (4 patients were on propranolol), antiepileptic (1 patient was on valproate), antidepressant (1 patient was on amitriptilin, 9 patients were on venlafaxine). No patient used combination therapy. 8 patients had cut prophylactic treatment 2 months after first OBoNT-A injection by themselves and was able to keep headaches under control with abortive treatment alone during 24 weeks. 2 patients using propranolol and 5 patients using venlafaxine continued their prophylactic drugs. 4 patients did not need triptan for abortive treatment, only the use of nonsteroidal analgesic drugs in the 24 weeks period after the first OBoNT-A injection. While the highest VAS scores recorded in the migraine diary were compared to the average of pre-treatment, the first 12 weeks after the first injection and 12 weeks after the second injection, both VAS scores after treatment were found to be a statistically significant improvement compared to the baseline(respectively $p<0.001$ and $p<0.001$).(Graphic 1)

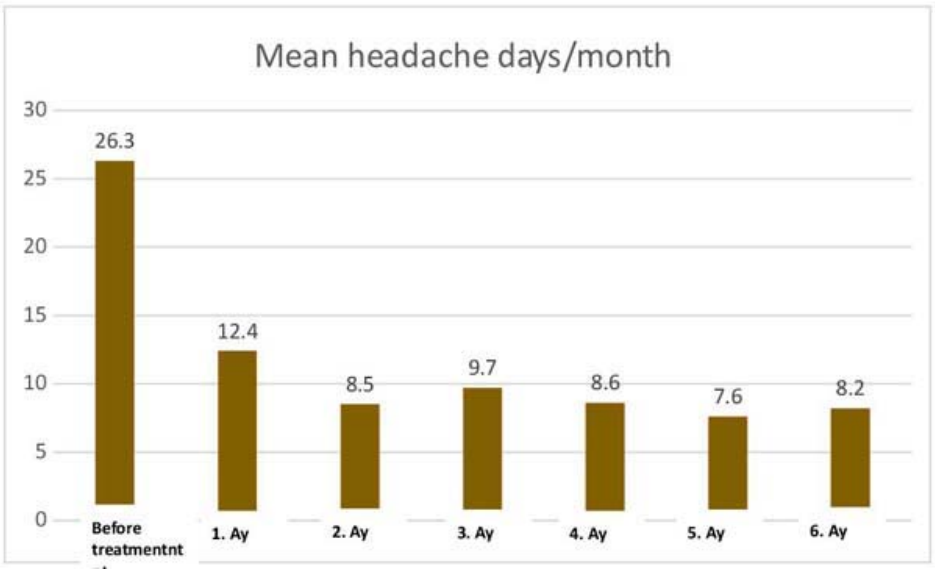
Baseline average headache frequency before OBoNT-A injection was 26.3±4.1 days/month. Average headache frequency decreased to 9.7 ± 7.1 days/month in period of the 12-week and 8.2 ± 7.5 days/months at the end of 24 weeks. Reduction from baseline was observed to be 16.6 days at week-12 and 17.8 days at week-24 ($p<0.001$). (Graphic 2)

12 of the 15 patients were considered as responders to treatment in terms of frequency of headache days at week-12 and 14 patients at week-24 after the injection of OBoNT-A. No patient had side effects.

The health related quality of life was evaluated with SF-36 scores before and after 24 weeks of the first OBoNT-A injection. Physical function, physical role restriction, pain, general health, vitality, social function, emotion and mental health scores were found to be significantly improved at the end of 24 weeks in comparison with scores before treatment ($p<0.001$). (Table 1, Graphic 3). Most obviously improved pre-treatment headache related loss of quality of life categories were observed to be social function, physical role restriction and vitality. Average quality of life scores in these categories increased from 16.6%, 8.3%, 17.4% to 55.6%, 70.0%, 74.1% respectively ($p<0.001$).



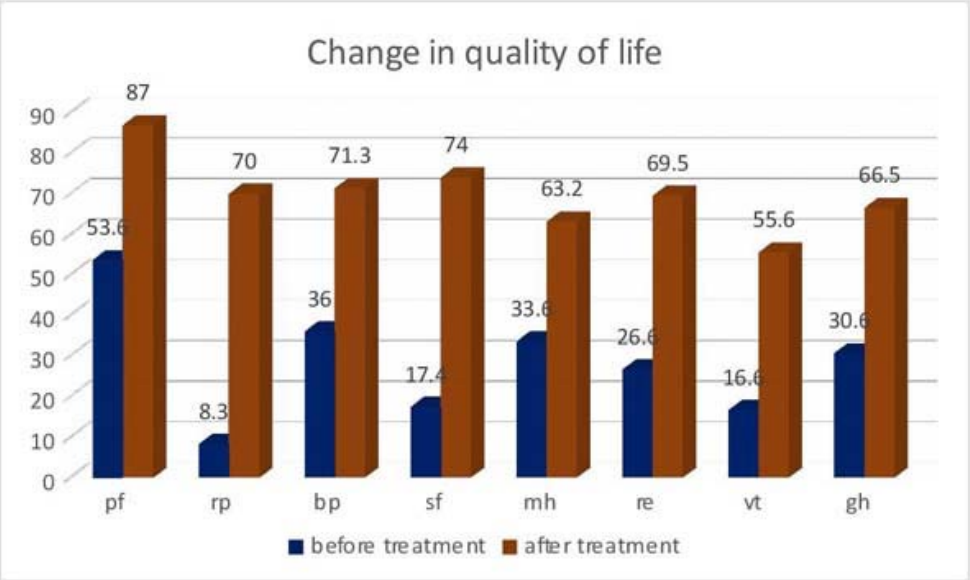
Graphic 1: *VAS scores of 15 patients before treatment, after first injection in 12 weeks and after second injection in 12 weeks*



Graphic 2: *Mean neadache days per month before injection and 6 months follow up after injection. At 12 nd week, second injection was applied.*

Table 1: Quality of life subcategories have a significant improvement compare to before treatment at patients with RCM.

	Tedavi öncesi kf-36 skoru	Tedavi sonrasi kf-36 skoru	*p*
Physical function	53,6	87,0	<0.001
Physical restriction	8,3	70,0	<0.001
Body pain	36,1	71,3	<0.001
General health	30,67	66,5	<0.001
Vitality	16,6	55,6	<0.001
Social function	17,4	74,1	<0.001
Emotion	26,6	69,5	<0.001
Mental health	33,6	63,2	<0.001



Graphic 3: *Change in quality of life evaluated with SF-36 at patients with RCM after OBONT-A injection. Pf: physical function; rp: physical restriction; bp: body pain; gh: general health;vt: vitality; sf:socialfunction; re: emotion; mh: mental health*

CONCLUSION

Resistant chronic migraine (RCM)patients followed up by our clinic who were restricted from physical and social activities due to their severe and permanent headaches, had been injected a fixed dose of 155 IU OBoNT-A for 2 cycles with 12 weeks interval and their patient files were studied to determine treatment effectiveness. At the end of week-24, 93.3% (14 patients) of 15 patients were observed to have ≥ 30% reduction in headache frequency and they were considered as responders. Average headache frequency decreased to 9.7 days/month at week-12 and 8.2 day/month at week-24. From a statistical point of view, the average SF-36 quality of life scores in all eight sub-categories significant improved, while the severity of migraine headache decreased significantly.

Patients with RCM are usually identified as patients who cannot provide sufficient pain control despite receiving appropriate prophylactic dose of treatment for ≥2 months and have to change their life style because of pain[17]. All patients included in the study were using one migraine prophylactic agent before OBoNT-A treatment. They had all been a patient in our clinic for at least 3 years and tried all four groups of migraine prophylactic agents for an adequate time period. Their average headache frequency was quite high (26 days/month) considering they had been using appropriate drugs. 3 of them had quit their jobs because of headaches. Physical restriction, pain, general health, vitality, social function, emotion and mental health scores evaluated by SF-36 were <%50. These data indicate that life functions of our patients was quite restricted despite adequate treatment. Therefore, this study provides a clinical observation for prophylactic effectiveness of OBoNT-A injection at patients with RCM.

With RCM, headache related disabilities lead to restrictions in daily life and health related quality of life decreases[7]. Today, effective treatment is limited for patients with RCM[3,15,16]. Although there are oral prophylactic agents for episodic migraine, none of them has been approved for RCM. OBoNT-A is the single agent that has been specifically approved to be an effective and safe agent for prophylaxis of CM by

PREEMPT study[2,3,8,10]; and safety and effectiveness for long term prophylaxis have been supported at a 56 week 5 cycles program[4] No cumulative toxic effect and plateau effect were detected after 5 cycles.

Our study differs from the PREEMPT study in several points. Firstly, our patients do not only fit for CM criteria but also fit for RCM criteria. Secondly, our study is retrospective, not a randomized controlled study. Thirdly, since our study has not been prospective, patients continued to use their prophylactic drugs during the OBoNT-A treatment. Our patient follow-up period was 24 weeks, similar to PREEMPT study. Since the number of headache days reduction was reported as 8.4 days /month at week-12 and 8.4 days/month at week-24 compared to baseline at PREEMPT study[3,10]; 6,5 headache days reduction at week-12 was observed with continuing prophylaxis in patients with RCM at study of Lin et al.[14]. In our study, it was determined that there was a more significant reduction in the number of headache days compared to the previous studies (16.6 days/month at week-12, 17.8 days/month at week-24). This reduction may be related to injecting a fixed dose of 155 IU to all patients, whereas other studies used variable doses (75-155 UI). There is no statistical difference between patients treated with 75 IU and 150 IU, yet patients treated with 75 IU were observed to be less responsive[14].

Our 8 patients gave up the prophylactic treatment on their own accord after 2 months following the first injection because they deemed it no longer necessary. 7 patients continued to use their prophylactic drugs (2 propranolol, 5 venlafaxine users). Continuing to use of prophylactic oral drugs during OBoNT-A treatment may provide further reduction in headache days compared to OBoNT-A alone, yet there has been no evidence in the literature to support this argument. As mentioned above, at the study of Lin et al.[14] OBoNT-A injection was applied while using oral prophylactic drugs yet headache days reduction was not as high as ours (6,5 days/month vs 16.6 days/month reduction at week-12). Depending on this observation it is understood that randomized controlled studies were needed to determine whether adding oral prophylactic agents on to OBoNT-A treatment would be a more effective treatment.

Previous studies did not examine the correlation between the severity of headache and the OBoNT-A treatment; however, when the OBoNT-A injection was increased from 2 cycles to 5 cycles, it is observed that frequency of triptan usage was further reduced (reduction-3,4 pills /month after 2 cycles, -4,6 pills/month after 5 cycles)[4]. In our study, severity of headache was found to decrease significantly at both first and second three months periods after the injection, 4 patients did not need to use the triptan in the period.

At PREEMPT studies, adverse events have a 29.4% of occurrence and ptosis has a 3.6% chance with a total dose of 35 IU OBoNT-A injection to frontal, corrugator and proceus muscles[10]. None of our patients with application of the same dose at the same locations had adverse events.

Abortive drug overuse was reported as 65.5% at CM patients[19]. To determine whether the headache is related to CM or drug overuse, nonsteroidal drug usage was ceased at all patients. Drug overuse leads to a more aggressive disease biology and turns episodic migraine into RCM. For this reason, we excluded the drug overuse. Previous studies have reported that OBoNT-A treatment provides significant improvement in the reduction of headache frequency and the quality of life compared to the placebo in patients with drug overuse on the association of CM[4]. The extension of the treatment to 56 weeks results in a prolonged state of well-being and in further improvement in the quality of life scores.

Patients with RCM have more reduction in the health related quality of life, severe social, emotional and physical disability and suffer more from economic problems compared to episodic migraine patients[7]. Quality of life scores provide a better understanding of the many burdens the disease brings. Physical restriction, pain, general health, vitality, social function, emotional and mental health scores evaluated with SF-36 of all our patients which were under 50% before treatment showed a significant improvement. In addition, previous studies showed a correlation between reduction of headache frequency and improvement of the quality of life scores[15]. Improvement of the health related quality of life scores reflect a clinical functional improvement.

Central hypersensitivity was thought to have an important role at CM pathophysiology[11]. It has been suggested that the mechanism of OBoNT-A at CM prophylaxis leads to the inhibition of sensitization of peripheral trigeminal sensory fibers, thus to the indirect inhibition of migraine headaches by regulating the activity of the central trigeminal neurons (1, 12). Previous studies have reported that ocular type and migraine with aura responded better to OBoNT-A injections[12,14]. No correlation has been found between therapy response and sex, age BMI≥25, dose of injection, Beck depression scale, and drug overuse[14]. Due to lack of migraine subtypes in our patient group (only 1 migraine with aura, others without aura), no relationship could be established between the demographic structure and the migraine subtypes.

There were certain restrictions in our study. Firstly, it is a retrospective study and there is no placebo group for correlation. Secondly, we used modified RCM criteria because the parenteral products of dihidroergotamin and triptans do not exist in Turkey[17]. In addition, treatment was applied only to the patients who received off-label drug usage approval from the Health Ministry because OBoNT-A is a costly treatment. Further studies should be made in order to compare OBoNT-A and drug cost-effectiveness of other treatment options in RCM patients who frequently use emergency services exhausting the health resources and who suffer from a reduction of the health related quality of life and loss of productivity due to attacks.

Finally, RCM restricts daily activities, social, physical and emotional functionality of the patients, which, in turn might result with unemployment, and severe economic problems. In our study, RCM patients responded to the treatment of OBoNT-A 24-week follow-up with 2 cycles of 155 IU injection. It is observed that headache frequency and severity markedly decreased, the health related quality of life scores of patients improved, and the need for the triptan was reduced. No adverse effect was determined. Although OBONT-A is an expensive treatment, it should be considered a priority in RCM patients' treatment due to its high therapeutic efficacy and its positive effect on the improvement of disease-induced decrease in the quality of life. This study will enhance our understanding of RCM treatment and its costly effects on patients; and, will lead to developing more effective and efficient approaches in the future.

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