SECUNDARY KINETOPROPHYLAXIA IN ARTHROPATIC PSORIASIS

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Summary

Despite major advances made in the recent years in relation with arthropathic psoriasis (PsA) and psoriasis(PsO), including epidemiological, genetic and pathogenetic data, information including therole of inflammatory cytokines, especially TNF-α and IL-17, which have led to the development of targeted therapies, from which have largely benefited patients with PsA and PsO, there is insufficient scientific evidence related to the influence of physical therapy in PsA. The only data come from studies in patients with ankylosing spondylitis (AS). This creates difficulties in standardizing therapeutic guidelines in the field. Given the above, we performed a multicenter, open-label, controlled study comparing the effects of Adalimumab + Physical Therapy (Group A) with the effects of Adalimumab alone (Group B).

The main objective of the study was to evaluate the effectiveness of physical therapy in reducing pain in patients with PsA.Secondary objective was to evaluate the influence of physical therapy on the quality of life (QoL) of patients with PsA. The assessment of the effects were made according to the recommendations of the guide of the European Society of Rheumatology. The study followed the evolution of patients over 3-6 months of therapy and addressed exclusively to patients with PsA.

***Results.** Of the total population studied, a greater improvement was observed, compared to baseline in most applied PROs scales, in the group that benefited from adalimumab add-on physical therapy both at the end of week 16 and at the end of the 8 weeks of unassisted physical therapy.*

Conclusions. Individualized physiotherapy added to adalimumab therapy improves quality of life after 16 weeks in patients with PsA with several sustained effects and after 24 weeks (8 weeks of individualized physical therapy).

***Keywords:** physical therapy, arthropathic psoriasis, pain, quality of life.*

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Introduction

Arthropathic psoriasis is adisease with pshicological and physical manifestations which has a great negative effect on QoL affected person. In addition, among those with PsA, more than half report progressive erosive arthritis and majority of them have also functional impairment. The functional deficit associated with PsO and PsA results in an increase in healthcare costs, a reduction in the quality of life, including here a low employment rate. In an effort to improve treatment options for patients suffering from these diseases, research has led to the discovery of several therapies that directly target the immune response that leads to PsO/PsA. A specific protein that has been shown to be an effective target for therapy is tumor necrosis factor (TNF-α). Adalimumab is the first fully humanized monoclonal antibody to target TNF-α. It has demonstrated significant improvements in cutaneous and articular manifestations, diminishing disabilities caused by joint damage, inhibiting structural damage at the radiographic level and improving the quality of life among patients with PsA. However, not all patients have a positive response to Adalimumab in addition, there are limited data on the remission of the disease.

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Despite major advances in PsA and psoriasis in recent years, including epidemiological, genetic and pathogenetic data, information including the role of inflammatory cytokines, especially TNF-α and IL-17, which have led to the development of targeted therapies, which has largely benefited patients with PsA and PsO, there is insufficient scientific evidence for the influence of physical therapy on PsA, the only data coming from studies on patients with AS. This creates difficulties in standardizing therapeutic guide-lines in the field.

The clinical burden. The evolution of PsA can be variable and unpredictable, ranging from mild and non-destructive disease to erosive and deforming arthritis, observed in 40% to 60% of patients with PsA.1Patients who remain untreated could developresistant inflammation, joint damage, physical disabilities and higher mortality. [1] In a prospective cohort of 100 PsA patients who were observed for approximately five years (mean duration, 11 years), and it was reported that the joint lesions progressed to an average of 0.42 peripheral joints per year [2]. Acutisations and remittance are more frequent; majority of the patients with PsA reported at least an acutisation in the last two years. [3] The burden of physical disability is substantial in patients with PsA. The HAQ Disability Index (HAQ-DI) is commonly used to assess physical function in PsA. A score from 0 to 1 represents a mild to moderate disability, 1 to 2 is a moderate to severe disability, and 2 to 3 represents a severe to very severe disability. [4] Physical function worsens while the number inflamed joints and disease activity increases. [5]

In addition to skin and joint damage, PsA has been associated with other inflammatory conditions, including autoimmune disorders (such as irritation and uveitis) and increased risk factors for cardiovascular disease (CVD). Salaffi et al. showed that more than half of the patients reported at least one comorbidity, such as high blood pressure, heart disease, gastrointestinal (GI) and chronic respiratory disorders. [6] Autoimmune bowel disorders are more common in patients with PsA. The intestinal mucosa of patients with PsA without intestinal symptoms shows microscopic lesions even when the mucosa appears normal macroscopically, this may support a pathogenic connection between skin, joints and intestine in psoriatic patients with arthritis, even in the absence of intestinal symptoms. [7, 8] The prevalence of inflammatory bowel disease is also higher in patients with PsA (3.9%) than in the general population (0.4%) (P <0.001). [9]

Quality of Life (QoL) of patients with PsA. The topic that interests us most in this research is the quality of life of patients with PsA or more precisely how much the quality of life of PsA is affected. World Health Organization (WHO), considers that QoL is "the individual's perception of his or her position in life, in the context of the culture and value systems in which he or she lives and in relation to his or her goals, expectations, standards and concerns. It is a broad concept, influenced in a complex way by physical health, mental state, personal beliefs, social relationships and its relationship with the relevant characteristics of its environment "10. WHO has developed and approved a standard language and classification system for functionality and disability: International Classification of Functionality, Disability and Health (ICF) [11].

PsA is a major burden for patients, diminishing their ability to perform daily activities and reducing their QoL. Physical function and health-associated quality of life (HRQoL) scores are lower in patients with PsA than in healthy individuals and patients with other inflammatory arthritis. [12] Due to skin damage, patients with PsA may also have a greater impairment of psychosocial function, manifested in embarrassment and, in some cases, depression. [13] The activity of the disease (joints and skin) is associated with worsening QoL; the psychological domains of HRQoL are also related to disease activity and pain scores [12]. Patients with PsA usually complain of fatigue and sleep disturbances, which can contribute to a poor HRQoL score. Almost 50% of psoriasis patients report some level of sleep discomfort; the presence of PsA is a strong predictor of sleep disorder (proportional ratio 3.27; P <0.001) [14]. The degree of fatigue observed in patients with PsA is significantly higher than that of the general population and comparable to that of patients with systemic lupus erythematosus;

approximately 50% of patients complain of moderate to severe fatigue and 29% complain of severe fatigue [14].

The economic burden. The costs associated with PsA can be considerable. Because the data collection methods are very different it is difficult to compare costs in all reported studies but it is clear that PsA comes with a substantial economic burden. In the US, they estimated a direct healthcare cost for PsA of $ 1.9 billion, based on an average patient cost of $ 3,638 (from 1999 to 2000), multiplied by the estimated prevalence of 520,000 PsA patients. in the US in 2000. [15] These costs were probably underestimated because patients receiving biologic therapy were excluded from the analysis.16 Average direct costs range from $ 4,008 in Hungary to $ 5,646 in the US. The total indirect costs associated with PsA represent 52% to 72% of the total costs. As expected, the direct and indirect costs of PsA increase as physical impairment and disease activity worsen. For example, total direct and indirect costs increase (in euros, converted to 2008 US dollars) from ∈ 2,331 (~ $ 3,800) and ∈ 5,599 (~ $ 9,155) in patients with low HAQ scores (below 1.2) to ∈ 5,721 (~ $ 9,350) and EUR 37,440 (~ $ 61,220) in patients with HAQ scores (1.7 or higher), according to 2002 reports. [17]

In addition to associating PsA with other "expensive" comorbidities for society, things can be even worse. Thus diabetes mellitus has multiple disabling complications such as bone and joint fragility [18] which together with the potential disability caused by PsA we can say that we have a real financial black hole for the public health system.

In summary, we can say that: psoriatic arthritis includes not only joint disease, but also psoriasis; the literature reveals that the number of patients with affective disorder caused by PsA may be higher than that of other arthritic conditions; similar to other inflammatory rheumatic diseases, PsA is progressive, erosive and destructive, leading to decreased functional capacity and poor quality of life; patients with PsA may also have an increased risk of comorbidities, especially cardiovascular disease, compared to the general population; PsA imposes a substantial economic burden on patients and society; the clinical burden of PsA contributes to direct medical costs; indirect costs, including lost productivity and incapacity caused by limitations in the functioning and activities of daily living, also contribute to the total costs of PsA.

We can also list some fundamental issues that PsA raises for society in general and patients in particular:

- Psoriatic arthritis (PsA) is a multifaceted disease, including variable associations of musculoskeletal involvement (peripheral arthritis, dactylitis, enthesitis, inflammation of the spine), skin and nail diseases or extra articular manifestations;
- Qol is profoundly altered in PsA, due to both the physical aspects of the impact and the changes in the psychological domains and functional / social consequences of the disease.
- QoL changes appear to be due to both the arthritic / rheumatological component and the psoriasis / skin component.
- The physical areas of health and especially **PAIN** are mentioned as patient priorities.
- **TIREDNESS** is a key problem for patients, although its causality is multifactorial.
- **Obesity** and **Diabetes** are aggravating comorbidities for PsA.
- In the medium and long term we should expect an increase in the number of people diagnosed with PsA taking into account the predisposing factors and increasing risk (diabetes, obesity, autoimmune deficiencies - thyroiditis).

Material and method

From the fundamental problems stolen from the PsA study, we consider that through physical therapy we can intervene on **PAIN**, **OBESITY** and **TIREDNESS**. That's why we decided to implement a study that examined the impact of secondary kinetoprophylaxis in Arthropathic Psoriasis. In this sense, a multicenter, open, controlled study was implemented that compared the effects of standard therapy (ADALIMUMAB) + physical therapy - Group A with the effects of standard therapy (ADALIMUMAB) - Group B.

The main objective of the study was to evaluate the impact of customized kinetic programs on PROs (patient-reported outcomes) in patients with PsA patients. **The secondary objective** of the study was to evaluate the impact of individualized kinetic programs on pain reduction in patients with PsA. The research included 120 patients with psoriatic arthropathy. They were randomized 1: 1 to receive standard adalimumab therapy and personalized physical therapy programs (active group - Group A) or only standard adalimumab therapy (control group - Group B). The tools used to assess the impact on PROs were: ***HAQ-DI – Health Assessment Questionnaire-Disability Index*** [19, 20], ***SF-36 componenta fizica (PCS) și component mentala (MCS)*** [21, 22]**,** ***FACIT-F – Functional Assesment of Chronic Illness Therapy-Fatigue*** [23]**,** ***DLQI – Dermatology Life Quality Index*** [24]**,** ***the Numerical Pain Intensity Scale was also used (NPRS)*** [25]**.**

The research activity took place between November 2017 and July 2019 in 3 private dermatology or rheumatology offices (in Galati, Brăila and Bucharest) and 2 gyms (in Gala<i and Bucharest). Subjects were assessed for eligibility for the screening visit two weeks before radomization. During the screening visit all patients were instructed to use HAQ-DI, SF-36, FACIT-F, DLQI and NPRS as well as other types of questionnaires. Prior to inclusion in the study, patients had to give their consent to enter the study.

The statistical analysis was descriptive, being expressed continuous variables such as means and medians with statistical significance estimation and two-sided 95% CIs as well as qualitative variables (either dichotomous or ordinal) expressed as proportions with a CI of 95%. For continuous variables, subgroup analyzes were performed with the ANOVA test. To estimate the required number of subjects we assumed a 30% prevalence of PsA among the population with psoriasis and we took into account a population of 360000 patients with psoriasis in Romania at a percentage of 2% of the general population, and for a range of 95% confidence the number of patients who had to be enrolled was 120.

The study took place for a 16-week period of assisted physical therapy followed by a further 8-week period in which subjects in the active Group A group were asked to continue the recommended kinetic programs individually. After randomization, the patients in one group followed a personalized kenetic program added to the background therapy, and the other group continued their usual therapy. During and after the therapeutic intervention, the effectiveness of the treatment was evaluated until the 24th week of the study (8 weeks after the end of the assisted kinetotherapeutic intervention). In addition, pain intensity was assessed daily using a journal throughout the study.

Results

To obtain the number of subjects eligible for the study, 154 patients were evaluated. Of those who did not meet the inclusion criteria, the majority refused to participate in the study (31 subjects), 3 had severe or unstable cardiovascular disease. Thus, a number of 120 PsA patients aged 18+ were enrolled in 2 centers. The main demographic and clinical characteristics of the study population are summarized in Table 1. Average age 47.3 years, living predominantly urban (78.8%) and having generally secondary or higher education (87.8% graduated at least high school). The percentage of patientswith full-time jobss was 85.4%. About 50% were obese, with a mean BMI of 26.7. and an average PsA duration of more than 3 years. There are differences between patients with the age of the disease under 5 years and over 5 years. Thus in table 1 it can be seen that the treatment with biological agents was started later in patients with the disease older than 5 years (46.2 years) compared to 43.2 years in those with the disease less than 5 years. Also, patients with disease older than 5 years have a higher percentage of hypertension (43%) and type I diabetes (10%) compared to those with disease less than 5 years (21.9% hypertension; type I diabetes 4.8%).

Table 1. Demographic and clinical characteristics of the study population

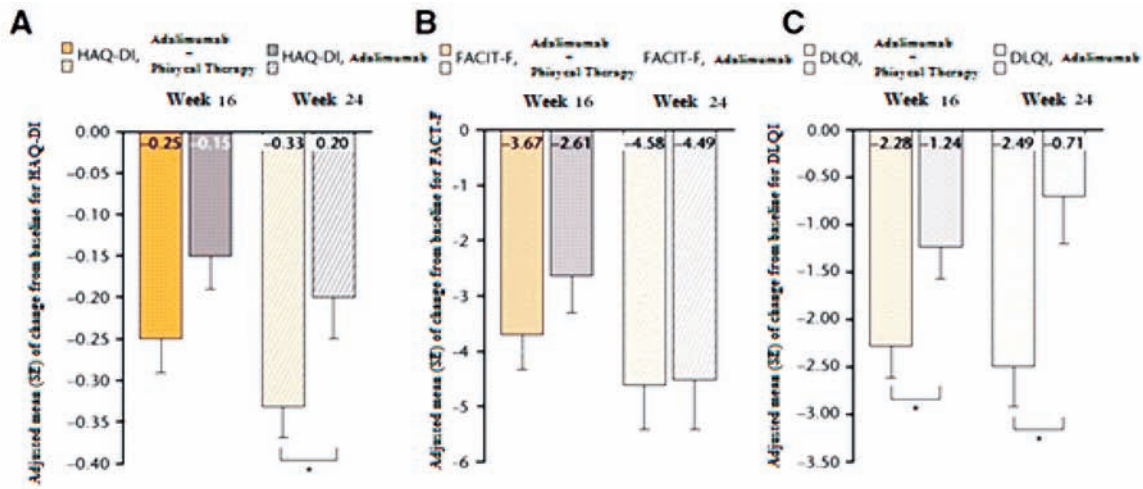
	PsA < 5 years	PsA ≥ 5 years	P value
Age, mean (SD)	47.3 (11.5)	53.3 (10.9)	0.032
Male sex, n (%)	23 (56.1)	29 (33.67)	0.214
Age at the diagnosis, years, mean (SD)	42.1 (11.4)	39.2 (11.3)	0.04
Age at the time of treatment initiation with biologic agent, years, mean (SD)	43.2 (11.0)	46.2 (11.2)	<0.001
Age of desease at the initiation of biological treatment, years, mean, (SD)	2.7 (1.4)	13.9 (8.3)	"1
Urban, n (%)	31 (78.0)	63 (79.7)	"1
Profesional Status, full-time job, n (%)	35 (85.4)	79 (89.9)	0.044
Secundary/higher education, n (%)	36 (87.8)	79 (89.9)	"1
Smokers, n (%)	12 (29.2)	25 (31.6	0.89
Type of PsA			
Symmetrical polyarthritis	34 (82.9)	66 (83.5)	
Predominatly distal arthritis, interphalangeal joints	2 (4.8)	4 (5.0)	
Asymmetric oligoarthritis	4 (10.0)	9 (11.4)	
Destructive arthritis (mutilans)	0 (0)	0 (0.0)	
BMI, kg/m^2, mean (SD)	26.7 (4.2)	28.2 (5.0)	0.062
Nail dystrophy, n (%)	11 (26.8)	22 (27.8)	0.278
Dactylitis, n (%)	11 (26.8)	22 (27.8)	0.278
Comorbidity			
Hyperuricemie, n (%)	0 (0)	3 (3.79)	0.341
Hypertension, n (%)	9 (21.9)	34 (43.0)	0.005
Diabetes mellitus, n (%)	2 (4.8)	8 (10.1)	0.005
Dyslipidemia, n (%)	3 (7.31)	11 (13.9)	0.561
Concomitant csDMARD, n (%)	39 (95.1)	75 (94.9	0.158
Oral steroids, n (%)	24 (82.9)	49 (62.0)	0.641

Until the end of the 16 weeks of assisted physical therapy intervention, no withdrawal from the study was registered. Regarding adherence to physical therapy after week 16 to week 24, it was not evaluated because it was not part of the objectives of this study. Compliance with physical therapy could be the subject of further research.

Of the total population studied, a greater improvement was observed, compared to baseline in most applied PROs scales, in the group that received adalimumab + add-on physical therapy both at the end of week 16 and at the end of the 8 weeks of unassisted physiotherapy (week 24 - fig.1).

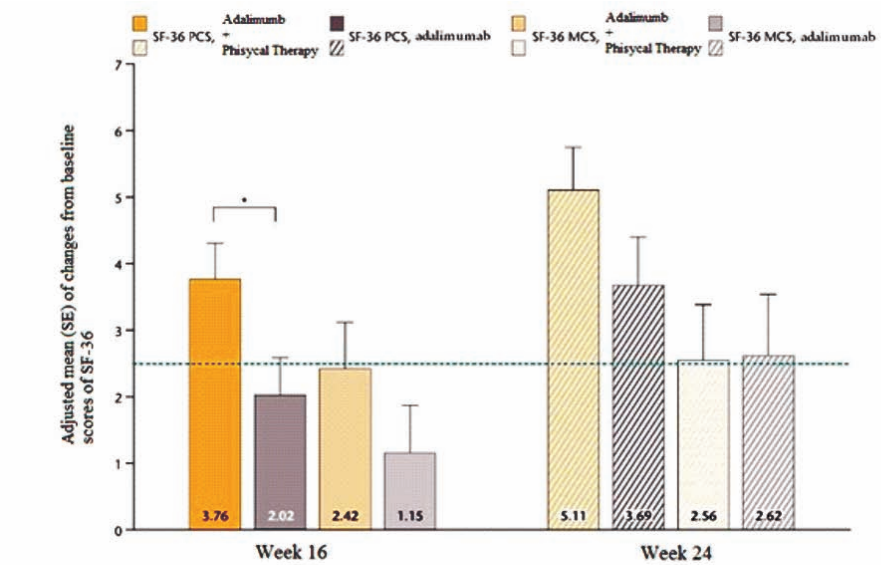
Statistically significant differences (95% CI Vs group B) were observed for baseline improvements in the physical therapy group compared to the adalimumab-only group:

- at 24 weeks for HAQ-DI scores (fig. 1a);
- at 16 weeks for SF-36 PCS scores (physical component - fig.2)
- at 16 and 24 weeks for physical pain sub-scores (DLQI) 5.36 [1.40-9.33]
- at 16 and 24 weeks for sub-scores related to vitality (energy) FACIT-F 4.07 [0.67 -7.47]



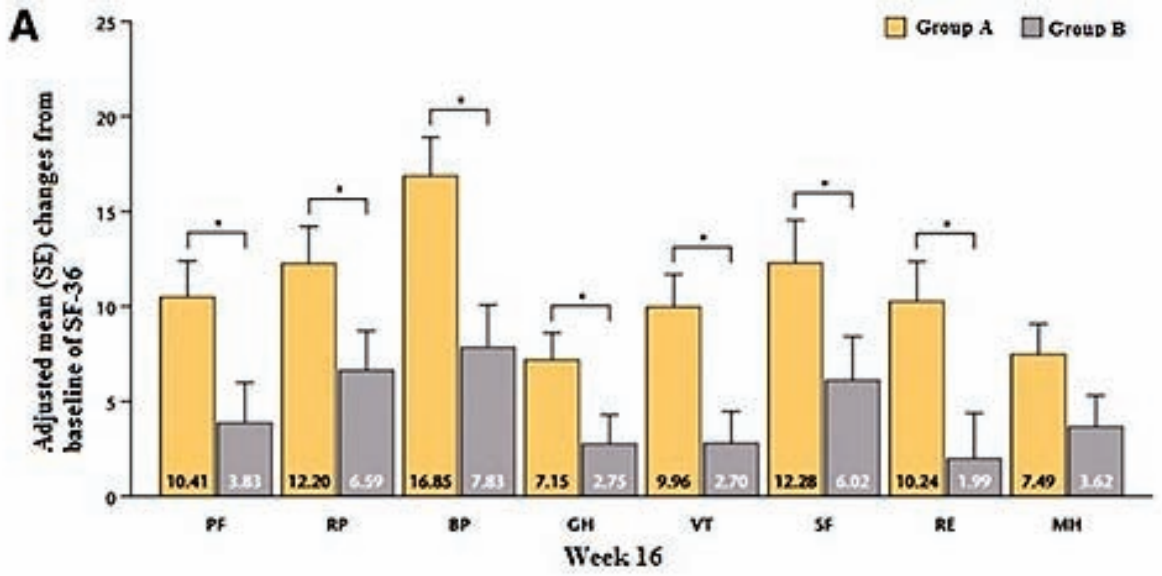
Adjusted mean diference to adalimumab (95%CI)		-0.11 (-0.21, 0.00)	-0.13 (-0.25, 0.01)	-1.04 (-1.93, -0.14)	-1.78 (-2.94, 0.63)
Adalimumab + Ph.Th	n	120	120	120	120
Adalimumab	n	120	120	120	120

Fig.1 HAQ-DI (A),FACIT-F (B), DLQI (C) baseline charge (week 16&24). *Statistical signifficant diference, CI confidence iterval, DLQI Dermatology Life Quality Index, FACIT-F Functionaal Assesment of Chronic Iliness Therapy-fatigue scale, HAQ-DI Health Assessent Questionnaire-Disability Index, SE trandard error

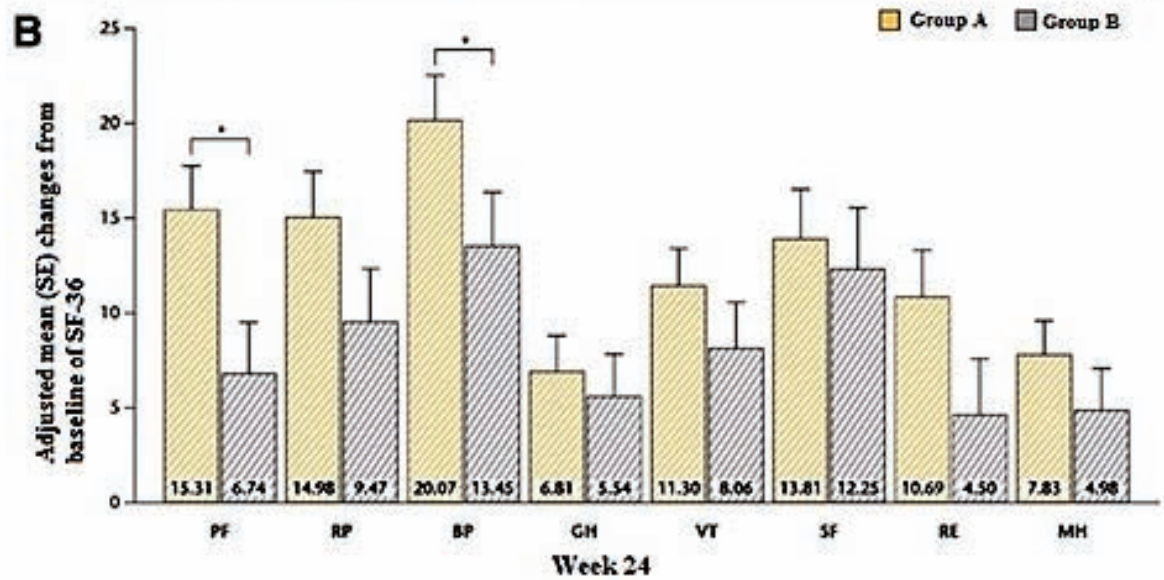


Adjusted mean difference to Adalimumab (95%)		-0.11 (-0.21, 0.00)	-0.13 (-0.25, 0.01)	-1.04 (-1.93, -0.14)	-1.78 (-2.94, 0.63)
Adalimumab + Ph.TH	n	120	120	120	120
Adalimumab	n	120	120	120	120

Fig. 2 PCS and MCS changes from baseline (week 16 and 24). * Significant Statistical Difference. Dotted line represents the MCID bigger than 2.5. CI confidence interval, MCID minimal clinical significant difference, MCS mental component, PCS phisycal component



Adjusted mean difference to Group B	6.58 (1.45, 11.70)	5.61 (0.57, 10.65)	9.02 (3.91, 14.14)	4.40 (0.79, 8.02)	7.26 (2.90, 11.63)	6.26 (0.59, 11.93)	8.25 (2.60, 13.89)	3.87 (-16, 7.90)
Group A, n	41	41	41	41	41	41	41	41
Group B, n	39	39	39	39	39	39	39	39



Adjusted mean difference to Group B	8.57 (2.15, 14.99)	5.51 (-1.04, 12.06)	6.62 (0.15, 13.09)	1.27 (-3.99, 6.53)	3.24 (-2.40, 8.89)	1.56 (-5.76, 8.88)	6.19 (-0.79, 13.18)	2.85 (-2.25, 7.95)
Group A, n	41	41	41	41	41	41	41	41
Group B, n	39	39	39	39	39	39	39	39

Fig. 3 Changes from baseline for subjects with CRP≥ULN: week 16 (A) and 24 (B). *statistically significant difference, BP body pain, CI confidence interval, CRP c-reactive protein, GH general health, MH mental health, PH phisycal function, RE emotional role, SE standard error, SF social function, SF-36 Short-Form-36, VT vitality

- at 16 and 24 weeks for DLQI (fig.1c)

Baseline changes in SF-36 mental component (MCS) scores did not show statistically significant differences but were numerically larger than the control group at week 16:

- Baseline-adjusted mean (SE) 2.42 [0.70] vs 1.15 [0.73]
- adjusted mean difference (95% CI) 1.28 [-0.58 to 3.13], P?0.05, but there were no relevant differences at week [24].

Analyzing baseline improvements in all PROs by C-reactive protein (CRP) level, a positive trend of Group A versus Group B was observed. For all scales (PROs), baseline improvements at week 16, although not reached statistical significance, were numerically higher in patients with baseline CRP above the upper limit of normal (ULN) versus lower CRP ULN in both groups studied (Group A, Group B) In the CRP subpopulation > ULN improvements reported in Group A versus Group B were significantly higher for the HAQ-DI, SF-36 PCS, MCS, FACIT-F and DLQI scales (fig.3). For all SF-36 sub-scales except mental health (MH), greater improvements were reported at week 16 for Group A versus Group B in patients with CRPș ULN (Fig. 3). Significant improvements (mean adjusted difference [95% CI]) for DLQI scales (-2.32 [- 3.80 to - 0.83]; II.6.6) and SF-36 PF (8.57 [2.15 to 14.99]) and BP (6.62 [0.15) and 13.09]) (Fig. 3A) were reported for CRP > ULN Group A versus Group B subpopulation at week 24.

Discussions

These results demonstrated that individualized physical therapy intervention generally improved the quality of life (PROs) of patients with PsA, especially those with initial CRPș ULN at baseline. In addition to the analysis of the general population, the effect on quality of life (PROs) was also analyzed according to the CRP level, the CRP level being identified as a negative prognostic factor26. A statistically not significant trend of improvement in PROs was observed in patients with elevated CRP at baseline regardless of group at the end of week 16. However, among patients with elevated CRP, those who underwent physical therapy reported greater improvements compared to those in Group B. These results suggest that the CRP level should be taken under consideration when assessing the indication for physical therapy. This can also be explained above by the long-term anti-inflammatory effect of physical activity.

Analyzing the literature, we found that cross-sectional studies have shown an inverse relationship between regular physical activity and serum concentration of inflammatory markers [27, 35]. In one of the first studies on this topic [27], the initial levels of CRP in athletes - 356 men and 103 women were compared with those of 45 male and 40 female subjects. Interestingly, among athletes, the effects of training on CRP varied by type of exercise, and values were significantly lower than control subjects in swimmers (-80% for men and -72% for women, p <0.001 for both) and rowing (-48%, p <0.01 in men and -28%, but not significant in women), while in football players, CRP did not differ significantly from control subjects. The effects of different forms of exercise on inflammatory markers were also examined on 4,072 participants in the National Health and Nutrition Examination Study (NHANES) III28 which showed that those who practiced jogging (ratio [OR] = 0, 33) and aerobic dancers (OR = 0.31) showed a significantly lower level of CRP compared to cyclists (OR = 1.30), swimmers (OR = 0.62) and weightlifters (OR = 0.83) . The amount of physical activity in leisure time was also inversely associated with CRP levels (p <0.001) in 13,748 adults in NHANES III [29]. Similarly, between 1,732 men and 1,101 women in the PRINCE30 study, intense aerobic activity was associated with lower CRP values in men (p = 0.007), but not in women (p = 0.38). The reason for this gender discrepancy is not clear, but it may be related to low physical activity in women. Physical activity can also reduce inflammation by improving endothelial function. Physical training reduces peripheral inflammatory markers asso-

ciated with endothelial dysfunction, such as soluble intracellular and vascular adhesion molecules36. Although exercise acutely increases oxidative metabolism and therefore induces oxidative stress, there is evidence that long-term physical activity increases antioxidant defense by increasing the concentration of antioxidant enzymes [37]. The decrease in PRO scores in the field of physical fatigue, demonstrated in this research, have been demonstrated by numerous studies that have evaluated the effect of different types of physical activity on fatigue in various chronic diseases. It is known that after a period of training it becomes easier and exercise can be tolerated more easily. This training effect results from physical and chemical changes that occur during muscle contractions and involves an increase in the maximum volume of tissue oxygen due to increased cardiac output and more efficient use of oxygen by contraction of muscle cells [38]. Research has been conducted on the impact of exercise on fatigue related to various chronic conditions. Some of the exercise regimens were studied in the laboratory, while others at home. All studies have shown that exercise significantly reduces fatigue in patients with chronic conditions. Fatigue is recognized as being in a significant correlation with the level of functional disability [39]. Moreover, research indicates an inverse relationship between levels of physical activity and fatigue [40-42]. Although the mechanism of how exercise reduces fatigue and increases energy levels remains unclear, research shows that exercise, especially aerobic exercise, can be beneficial in relieving fatigue and energy levels. Two hypotheses have been proposed:

- The effect of aerobic exercise is to increase cardiac output and thus oxygen infusion, as long as the individual maintains the level of daily physical activity [43].
- Exercise induces an increased level of beta-endorphins and their euphoric effect determines the perception that the person is less tired [44].

In addition to the muscle deconditioning related to the disease and the types of treatment, fatigue is aggravated by prolonged inactivity, contributing to muscle catabolism. As a result, patients need a greater degree of effort to carry out daily activities (fatigue). A consequence of this is a persistent and self-perpetuating decrease in daily activities caused by fatigue45,46. Aerobic exercise can reduce fatigue and improve physical function by breaking the cycle of lack of physical activity, impaired functions and fatigue.

Although PsA is sometimes considered a benign disease, the signs and symptoms of patients with PsA are highly variable, as the disease may include, for example, limited or fairly severe skin damage and limited or fairly severe joint involvement. These various implications alter the QoL of patients. Recent studies have shown that QoL is altered in PsA to similar levels as in other chronic diseases, including RA. An important aspect is that the endpoints used in PsA studies to assess QoL do not always reflect patients' opinions and perceptions about the impact of disability. Currently, in the PsA literature, there is a lack of qualitative studies that could provide the opportunity to explore in detail the perspective of patients. It would be of particular interest to use the qualitative methodology to deepen knowledge about the impact of PsA on areas that are not so well studied, but which are of high importance for patients with PsA, e.g. social participation, family and intimate relationships, work, emotional problems, fatigue or confrontation.

A number of limitations of the study should be considered. First, subpopulation comparisons and finding of scores ≥ MCID values and ≥ 1999 US Standards were post-hoc in nature. Second, due to the particular design of the study, the therapeutic benefits were evident at week 16. As such, the analyzes at week 24 were limited by the inconsistency of the subjects following the kinetotherapeutic program, suggesting that the kinetotherapeutic intervention should be done in a organized framework. Finally, certain PROs may improve less rapidly over time, and thus week 16 may not have allowed maximum effects of physical therapy.

Conclusions

Individualized physical therapy added to adalimumab therapy improves quality of life after 16 weeks in patients with PsA with several sustained effects and after 24 weeks (8 weeks of individual physiotherapy).

Both the effect of aerobic exercise on CRP concentration, combined with the decontracting effect of stretching technics associated with an increase in cardio-respiratory effort capacity (fitness), can explain the results of this research on PRO indicators.

Bibliography

1. Gottlieb A, Korman NJ, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis, Section 2. *J Am Acad Dermatol* 2008;58:851–864.
2. McHugh N, Balachrishnan C, Jones SM. Progression of periph- eral joint disease in psoriatic arthritis: A 5-year prospective study. *Rheumatology* 2003;42:778–783
3. Remicade (infliximab), package insert. Malvern, Pa.: Centocor OrthoBiotech, Inc.; 2008
4. Kavanaugh A, Fransen J. Defining remission in psoriatic arthri- tis. *Clin Exp Rheumatol* 2006;24(Suppl 43):S83–S87
5. Husted JA, Tom BD, Farewell VT, et al. A longitudinal study of the effect of disease activity and clinical damage on physical function over the course of psoriatic arthritis: Does the effect change over time? *Arthritis Rheum* 2007;56(3):840–849
6. Salaffi F, Carotti M, Gasparini S, et al. The health-related quality of life in rheumatoid arthritis, ankylosing spondylitis, and psori- atic arthritis: A comparison with a selected sample of healthy people. *Health Qual Life Outcomes* 2009;7:25
7. Ritchlin C. Psoriatic disease—from skin to bone. *Natl Clin Pract Rheumatol* 2007;3(12):698–706.
8. Schatteman L, Mielants H, Veys EM. Gut inflammation in psori- atic arthritis: A prospective ileocolonoscopic study. *J Rheumatol* 1995;22:680–683
9. Williamson L, Dockerty JL, Dalbeth N, Wordsworth P. Gastro- intestinal disease and psoriatic arthritis. *J Rheum* 2004;31(7):1469.
10. WHOQOL Group. Development of the WHOQOL: rational and cur- rent status. Int J Mental Health. **;23:24–56**
11. World Health Organization. International Classification Of Functioning, disability and health (ICF) [Internet]; [cited 2017 Dec 2]. Available from:
12. Borman P, Toy GG, Babaoglu S, et al. A comparative evaluation of quality of life and life satisfaction in patients with psoriatic and rheumatoid arthritis. *Clin Rheumatol* 2007;26(3):330–334
13. Mease PJ. Assessing the impact of psoriatic arthritis on patient function and quality of life: Lessons learned from other rheuma- tologic conditions. *Semin Arthritis Rheum* 2009;38(4):320–335
14. Callis DK, Wong B, Horn EJ, Krueger GG. Psoriatic arthritis is a strong predictor of sleep interference in patients with psoriasis. *J Am Acad Dermatol* 2009;60(4):604–608
15. Williams JP, Meyers JA. Immune-mediated inflammatory dis- orders (I.M.I.D.s): The economic and clinical costs. *Am J Manag Care* 2002;8:S664–S681
16. Brodszky V, Balint P, Geher P, et al. Disease burden of psoriatic arthritis compared to rheumatoid arthritis, Hungarian experi- ment. *Rheumatol Int* 2009;30(2):199–205
17. Huscher D, Merkesdal S, Thiele K, et al. Cost of illness in rheuma- toid arthritis, ankylosing spondylitis, psoriatic arthritis, and sys- temic lupus erythematosus in Germany. *Ann Rheum Dis* 2006; 65(9):1175–1183.
18. Wang, Shu-Hui et al. Increased risk for incident thyroid diseases in people with psoriatic disease: A cohort study, Journal of the American Academy of Dermatology, Volume 80, Issue 4, 1006 – 1012, DOI: https://doi.org/10.1016/j.jaad.2018.11.049
19. Colberg SR(1) et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Physician Association: joint position statement. 2010 Dec;33(12):e147-67. doi: 10.2337/dc10-9990.
20. Husted JA, Gladman DD, Long JA, Farewell VT. A modified version of the Health Assessment Questionnaire (HAQ) for psoriatic arthritis. Clin Exp Rheumatol. 1995;13(4):439–43
21. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. Health Qual Life Outcomes. 2003;1:20

22. Husted JA, Gladman DD, Farewell VT, Long JA, Cook RJ. Validating the SF-36 health survey questionnaire in patients with psoriatic arthritis. J Rheumatol. 1997;24(3):511–7
23. Mease PJ. Measures of psoriatic arthritis: Tender and Swollen Joint Assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/ Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). Arthritis Care Res (Hoboken). 2011;63(Suppl 11):S64–85
24. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210–6.
25. Langley GB, Sheppeard H. The visual analogue scale: its use in pain measurement. Rheumatol Int 1985;5:145–8
26. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 2003;1:79
27. Sluka KA, O'Donnell JM, Danielson J, Rasmussen LA. Regular physical activity prevents development of chronic pain and activation of central neurons. J Appl Physiol 2013;114:725–733. [PubMed: 23271699]
28. Stifani N. Motor neurons and the generation of spinal motor neuron diversity. Front Cell Neurosci. 2014;8:293. Published 2014 Oct 9. doi:10.3389/fncel.2014.00293
29. Besier TF, Lloyd DG, Cochrane JL, et al: External loading of the knee joint during running and cutting maneuvers. Med Sci Sports Exerc. 2001;33:1168–1175.
30. Hall CM, Brody LT. Therapeutic exercise: moving toward function. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2005
31. Patrick G De Deyne, Application of Passive Stretch and Its Implications for Muscle Fibers, *Physical Therapy*, Volume 81, Issue 2, 1 February 2001, Pages 819–827, https://doi.org/10.1093/ptj/81.2.819
32. Dufaux B, Order U, Geyer H, Hollmann W. C-reactive protein serum concentrations in well-trained athletes. Int J Sports Med 1984;5: 102– 6.
33. King DE, Carek P, Mainous AG III, Pearson WS. Inflammatory markers and exercise: differences related to exercise type. Med Sci Sports Exerc 2003;35:575– 81.
34. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. Epidemiology 2002;13:561– 8.
35. Albert MA, Glynn RJ, Ridker PM. Effect of physical activity on serum C-reactive protein. Am J Cardiol 2004;93:221–5.
36. Shamsuzzaman AS, Winnicki M, Wolk R, et al. Independent asso- ciation between plasma leptin and C-reactive protein in healthy humans. Circulation 2004;109:2181–5.
37. Mayer-Davis EJ, D'Agostino R Jr., Karter AJ, et al. Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. JAMA 1998;279:669 –74.
38. Powers SK, Ji LL, Leeuwenburgh C. Exercise training-induced alterations in skeletal muscle antioxidant capacity: a brief review. Med Sci Sports Exerc 1999;31:987–97.
39. Dimeo, F., Rumberger, B.G., and Keul, J. (1998) Aerobic exercise as therapy for cancer fatigue. Medicine & Science in Sports & Exercise, 30, 4758.
40. Brull DJ, Serrano N, Zito F, et al. Human CRP gene polymorphism influences CRP levels: implications for the prediction and pathogen- esis of coronary heart disease. Arterioscler Thromb Vasc Biol 2003; 23:2063–9
41. Morris, R.W. (1975) The physiology of exercise and its clinical implications in coronary heartdisease. South African Medical Journa~ 14(June), 999-1004.
42. Astrand, P.O. (1973) Physiology of exercise and physical conditioning in normals. Schweizerische Medizinische Wochenschrift, 103(2), 41-5.
43. Shern-Brewer R, Santanam N, Wetzstein C, White-Welkley J, Parthasarathy S. Exercise and cardiovascular disease: a new perspec- tive. Arterioscler Thromb Vasc Biol 1998;18:1181–7.

44. Porock, D. (2001) Fatigue. In: Palliative Care Nursing: a Guide to Practice, 2nd edn (ed. S. Aranda and M. O'Connor) AUSMED Publications, Melbourne, pp. 137-52.
45. McMurdo, M.T. and Bwnett, L. (1992) Randomized controlled trial of exercise in the elderly. Gerontology, 38, 292-8.
46. Porock, D., Kristjanson, L., Tinnelly, K., and Blight, J. (2000) The effect of exercise on fatigue in patients with advanced cancer: a pilot study. Journal of Palliative Care, 16(3), 30-6.

Conflict of interest
NONE DECLARED

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