CONTENT

SECUNDARY KINETOPROPHYLAXIA IN ARTHROPATIC PSORIASIS

Keywords: Physical Therapy, Arthropathic Psoriasis, Pain, Quality of Life

Introduction

Arthropathic psoriasis is a disease 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. Despite major advances in PsA and psoriasis in recent years, 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 guidelines 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. Patients who remain untreated could develop resistant inflammation, joint damage, physical disabilities and higher mortality. 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. Acutisations and remittance are more frequent; majority of the patients with PsA reported at least an acutisation in the last two years. 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. Physical function worsens while the number inflamed joints

and disease activity increases. 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.

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". WHO has developed and approved a standard language and classification system for functionality and disability: International Classification of Functionality, Disability and Health (ICF). 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. Due to skin damage, patients with PsA may also have a greater impairment of psychosocial function, manifested in embarrassment and, in some cases, depression. 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. Patients with PsA usually complain of fatigue and sleep disturbances, which can contribute to a poor HRQoL score.

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. 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. 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 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

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 physical therapy). In addition, pain intensity was assessed daily using a journal throughout the study.

Results

To obtain the number of subjects eligible for the study, 254 patients were evaluated. Of those who did not meet the inclusion criteria, the majority refused to participate in the study (11 subjects), 3 had severe or unstable cardiovascular disease. Thus, a number of 120 PsA patients aged 18+ were enrolled in 2 centers. 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]; 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 [-.58 to 3.13], P≥.5, 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 CRP> 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 CRP> 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 factor[26]. 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. 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) III 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 associated with endothelial dysfunction, such as soluble intracellular and vascular adhesion molecules. 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. 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. 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; Exercise induces an increased level of beta-endorphins and their euphoric effect determines the perception that the person is less tired***.

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 fatigue. Aerobic exercise

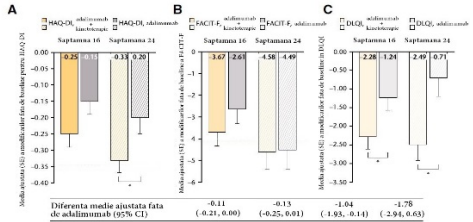
can reduce fatigue and improve physical function by breaking the cycle of lack of physical activity, impaired functions and fatigue.

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

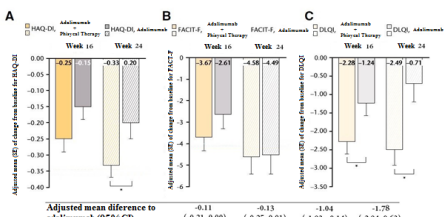
In conclusion, individualized physical therapy added to adalimumab therapy improves quality of life after 16 weeks in patients with PsA with several sustained effects and after 24 weeks (8 weeks of individual physiotherapy). Both the effect of aerobic exercise on CRP concentration, combined with the 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.

Annexes



Diferenta medie ajustata fata de 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 + Kineta n	120	120	120	120
Adalimumab n	120	120	120	120

Fig. 1 HAQ-DI (A), FACIT-F (B), DLQI (C) modificare fata de baseline (saptamanile 16 si 24). *Diferenta semnificativ statistica. CI interval de confidenta, DLQI Dermatology Life Quality Index, FACIT-F Functional Assesment of Chronic Iliness Thepy-Fatigue scale, HAQ-DI Health Assessment Questionnaire-Disability Index, SE eroare standard



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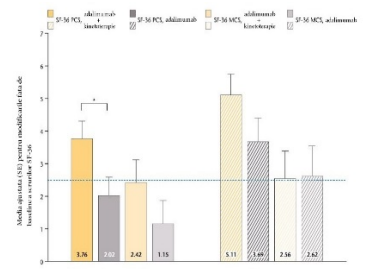
Adalimumab + Ph.Th n	120	120	120	120
Adalimumab n	120	120	120	120

Fig.1 HAQ-DI (A),FACIT-F (B), DLQI (C) baseline change (week 16&24). *Statistical significant difference, CI confidence iterval, DLQI Dermatology Life Quality Index, FACIT-F Functional Assesment of Chronic Iliness Therapy-Fatigue scale, HAQ-DI Health Assessment Questionnaire-Disability Index, SE standard error



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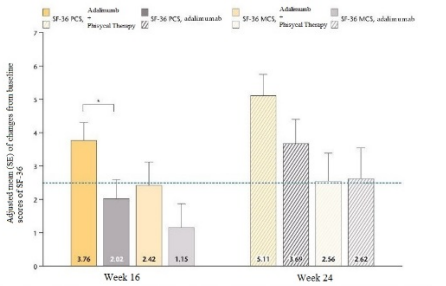
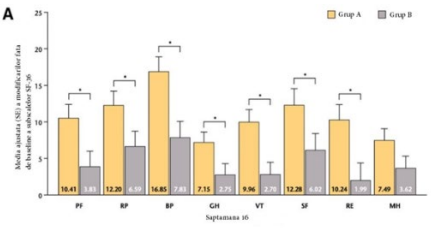
Adalimumab + Kineta n	120	120	120	120
Adalimumab n	120	120	120	120

Fig.2 SF-36 PCS si MCS modificare fata de baseline (saptamanile 16 si 24). *Diferenta semnificativ statistic. Linia punctata reprezinta MCID mai mare de 2.5. CI interval de confidenta, MCID diferenta minima clinic semnificativa, MCS componenta mentala, PCS componenta fizica

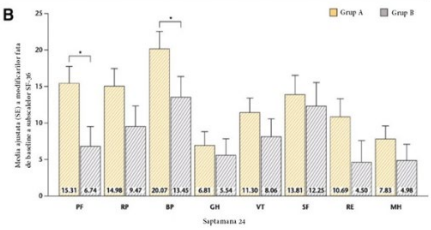


Adjusted mean difference to Adalimumab (95%)	-0.11 (-0.21, 0.00)	-0.13 (-0.25, 0.01)	-1.04 (-1.93, -0.14)	-1.78 (-2.94, 0.63)
Adalimumab + Ph.TH n	120	120	120	120
Adalimumab n	120	120	120	120

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 clinicel significant difference, MCS mental component, PCS phisycal component

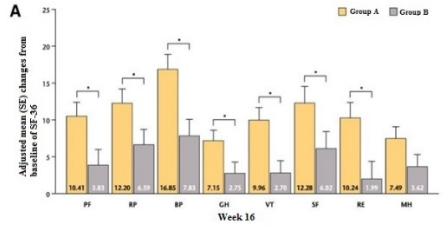


Diferenta medie ajustata fata de Grup B (95% CI)	6.58 (1.45, 11.70)	5.61 (0.57, 10.65)	9.02 (3.91, 14.14)	4.40 (0.79, 8.02)	7.26 (2.00, 11.63)	6.26 (0.59, 11.93)	8.25 (2.00, 13.80)	3.87 (-1.6, 7.90)
Grup A, n	41	41	41	41	41	41	41	41
Grup B, n	39	39	39	39	39	39	39	39

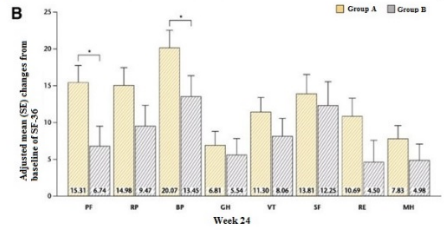


Diferenta medie ajustata fata de Grup B (95% CI)	8.57 (2.15, 14.99)	5.51 (-1.04, 12.06)	6.62 (0.15, 13.09)	1.27 (-3.99, 6.53)	3.24 (-2.40, 8.89)	1.56 (-5.76, 8.88)	6.19 (-0.79, 13.18)	2.85 (-2.25, 7.95)
Grup A, n	41	41	41	41	41	41	41	41
Grup B, n	39	39	39	39	39	39	39	39

Fig. 3 Modificarile fata de baseline pentru subscale ale CRP >ULN saptamana 16 (A) si 24 (B). *Diferenta semnificativ statistica. BP durere corporala, CI interval de confidenta, CRP proteina C-reactiva, GH sanatate generala, MH sanatate mentala, PF functia fizica, RE rol-emotional, RP rol-fizic, SE eroare standard, SF functia sociala, SF-36 Short Form-36, VT vitalitate



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 (2.00, 11.63)	6.26 (0.59, 11.93)	8.25 (2.00, 13.80)	3.87 (-1.6, 7.90)
Group A, n	41	41	41	41	41	41	41	41
Group B, n	39	39	39	39	39	39	39	39



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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 viatality