

CORRELATIONS BETWEEN SYSTEMIC THERAPY WITH CONVENTIONAL (SYNTHETIC) AND BIOLOGICAL DMARDS, RHEUMATOID ARTHRITIS AND PERIODONTAL INDICES OF CHRONIC PERIODONTITIS

Maria Alexandra Martu¹, Elena Rezus², Cristina Popa^{3*}, Sorina Mihaela Solomon^{4*}, Ionut Luchian⁴, Arina Ciocan Pendefunda⁵, Ioana Sioustis⁴, Diana Anton⁶, Silvia Martu⁴, Liliana Foia⁷.

¹Grigore T. Popa” University of Medicine and Pharmacy, Faculty of Dental Medicine. Iași, Romania

²Grigore T. Popa” University of Medicine and Pharmacy, Rheumatological Department, Iasi, Romania

³Grigore T. Popa” University of Medicine and Pharmacy, Oral Medicine Department, Iași, Romania

⁴Grigore T. Popa” University of Medicine and Pharmacy, Periodontal Department, Iasi, Romania

⁵Grigore T. Popa” University of Medicine and Pharmacy, Prosthodontics Department, Iași, Romania

⁶PhD Student Gr. T. Popal University of Medicine and Pharmacy, Iași, Romania

⁷Grigore T. Popa” University of Medicine and Pharmacy, Faculty of Medicine, Biochemistry Department, Iași, Romania

Corresponding authors: Cristina Popa, E-mail: dr.cristinapopa@gmail.com

Sorina Solomon, E-mail: drsolomonro@yahoo.com

Summary.

The purpose of the study. This study proposes an analysis of local inflammatory status by evaluating Quigley Hein indices, papillary bleeding indices (PBI) and gingival Lõe and Silness indices, accompanied by a detailed assessment of systemic status (VSH, CRP) in patients with rheumatoid arthritis and *synthetic and biological DMARDs therapy*.

Results and discussions. DMARDs determine the level of CRP and FR markers, the rate of erythrocyte sedimentation, and cartilage and bone damage. In the present study, serum levels of VSH and CRP recorded individual values higher than the maximum reference limit for 48.2% and respectively 46.3% of the patients, the mean level being significantly higher in the advanced stages of the disease. Measurement of oral markers revealed the the lowest average level of Quigley Hein score in patients treated with Sulfasalazine + Rituximab, while the highest values were recorded for Leflunomide + Etanercept therapy. The lowest average level for GI score was seen in patients treated with Methotrexate + Adalimumab and Leflunomide + Adalimumab, and the largest was found in patients treated with Leflunomide + Rituximab and Methotrexate + Rituximab. Regarding the treatment of RA, we could not establish a clear effect on oral health ratios of conventional and synthetic DMARDs combined therapy. However, it is important to note that, in contrast, in patients receiving biological DMARDs treatment, the average level of oral health indices was significantly lower. Thus, we can note the positive influence that this class of drugs, especially those that act on TNF- α , generates it on local status.

Conclusions. To maintain oral health, patients with AR are encouraged to achieve proper oral hygiene. Consultation of the periodontist is necessary to determine the course of treatment.

Keywords: *chronic periodontitis, rheumatoid arthritis, periodontal index, synthetic and biological DMARDs therapy.*

Introduction.

There is a strong association between RA and periodontitis. Interventions for the prevention, reduction or treatment of periodontitis in

patients with arthritis will certainly promote a better health status for these patients. [1]

Given the similarities between pathogenesis of periodontitis and rheumatoid arthritis, there

is a pertinent concern in the periodontology research community to optimize the therapeutic options available in the RA. [2-5] Rheumatoid arthritis and periodontal disease share similar inflammatory pathways and environmental mechanisms. This potential association has generated new ideas about possible links between these two common conditions.[6]

Although early mechanisms that have as a result impaired immune tolerance and progression to AR signs and symptoms are not known, the inflammatory cascade plays a key role in all stages of the pathogenesis of this disease, from initiation of autoimmunity to articular localization and destruction of joints and bones [7-9].

Treatment modalities in patients with RA and periodontitis can include medications, efforts to reduce joint stress, physical therapy and surgery. [3]

Non-steroidal anti-inflammatory agents (NSAIDs) and so called anti-rheumatic disease-modifying drugs (DMARDs) are commonly used to treat RA.

Significant evidence suggests that citrulline can bind RA to periodontitis. Genetic factors lead the host's responses to chronic diseases with a complex pathogenesis. In the future, more effective therapeutic approaches will include multiple synergistic host response modulation therapies combined with treatments that target microbial etiology. [10-13]

Additional studies are needed to better understand these mechanisms and help maintain general health, oral health parameters requiring close monitoring in RA patients. [7]

The term DMARDs is used to name a group of drugs that are generally unrelated, but differ from NSAIDs that reduce inflammation but do not treat RA and steroids that reduce the immune and inflammatory response but do not slow the progression of the disease. In other words, while NSAIDs and steroids are used to control RA symptoms, only DMARDs influences the progression of the disease. [14]

DMARDs determine the reduction of the level of CRP and FR markers, the rate of erythrocyte sedimentation, and cartilage and bone damage. In the treatment of rheumatoid

arthritis, the therapy with biological DMARDs are often prescribed in combination with a conventional agent in those patients that presented a limited response to conventional anti-rheumatic disease-modifying therapy. Biological DMARDs include a number of anti-cytokine agents that block the activity of specific cytokines and are usually monoclonal antibodies that bind to the target cytokine.

Tumor necrosis factor-alpha (TNF- α) is particularly important and therefore one of the primary objectives of the development of anti-cytokine therapies that have been introduced in the treatment of rheumatoid arthritis has been the development of anti-TNF α agents. Other cytokines that play a role in the pathogenesis of rheumatoid arthritis include interleukin-1, interleukin-6, interleukin-17, interleukin-15 and later interleukin-23. [15-18]

Since these two pathologies have several common pathogenic mechanisms and since the treatment of periodontitis can have a beneficial effect on RA, we could expect that treatments that are effective in AR will also contribute to the improvement of periodontal status.

There is substantial evidence regarding the utility of prostaglandin inhibitors, of NSAIDs in the treatment of both conditions, without the latter having demonstrated their modulating effects in RA therapy.

Numerous studies have recorded low levels of probing depth, a reduced rate of alveolar bone loss, and a lower degree of gingival inflammation in patients that utilise NSAID over long periods of time compared to control groups. [1,19]

In a cross-sectional study in which were compared 20 patients with RA that received infliximab treatment for an average of 40 months with 20 subjects who had not previously received infliximab, the treatment with infliximab was associated with a significant increase of the gingival inflammation without affecting the severity of periodontitis. [20]

Modulation of T cell activation provided another therapeutic target in RA with the use of abatacept, and inhibition of alveolar

bone loss suggested that RA treatment with it could also improve the progression of periodontitis, until this date studies being only experimental, without clinical trials conducted on human subjects. [21]

From the data analyzed, as the rheumatic affection increases, the oral status is proportionally altered at the level of all indexes, but especially regarding GI and PBI, which are relevant oral indicators for an exacerbated systemic inflammatory status, as confirmed also by [1].

Several studies have shown that non-surgical periodontal treatment is able to reduce serum levels of TNF- α , IL-1 β , IL-6, IL-10, MMP-8 and C-reactive protein and to moderate RA activity in patients with moderate to severe periodontal disease [22-27].

Some research have shown that patients with autoimmune disorders (including AR) exhibit much more severe periodontal inflammation than patients who do not suffer from autoimmune disease, anti-TNF- α therapy decreasing inflammation in periodontal tissues. [2,3, 28]

Thus our study represents an opening towards the clinical correlation between periodontal inflammatory status and the degree of rheumatic involvement.

The purpose of the study.

This study proposes an analysis of the local inflammatory status by evaluating Quigley Hein indices, papillary bleeding (PBI) index and gingival index L \ddot{o} e and Silness, accompanied by a detailed assessment of systemic status in patients with rheumatoid arthritis and *synthetic + biologic DMARDS therapy*.

Materials and method

The treatment for RA was mainly based on the following (Figure 1):

- most commonly Leflunomide (46.4%) and Rituximab (44.5%);
- Methotrexate was also noted to be administrated with a frequency of 23.6%;
- Adalimumab and Tocilizumab were also reported to be administrated with a frequency of 18.2% and 15.5%, respectively.

Results

Correlation of RA medication with the effect on systemic and oral health indices

The lowest mean VSH level is seen in Hydroxychloroquine + Rituximab and Metotrexate + Adalimumab treated patients, and the highest is seen in subjects receiving Hydroxychloroquine + Tocilizumab (Figure 2).

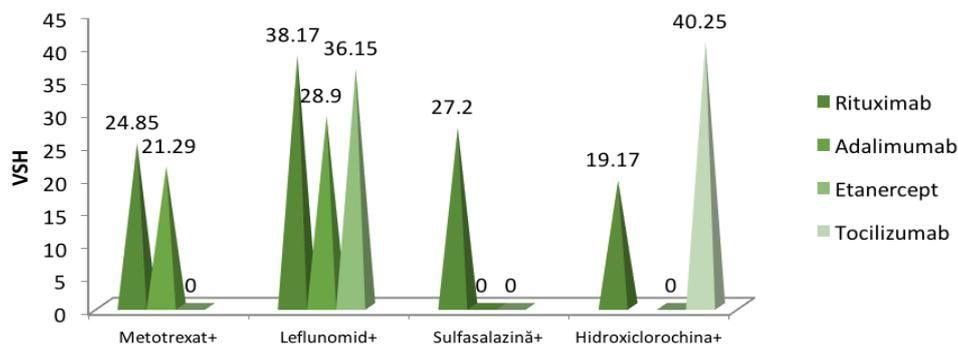


Fig. 1. Average VSH level based on combined synthetic and biological DMARDS treatment

Regarding the classical inflammatory marker, the lowest average CRP score is seen in patients treated with Methotrexate +

Adalimumab, and the highest in subjects treated with Hydroxychloroquine + Tocilizumab (Figure 2).

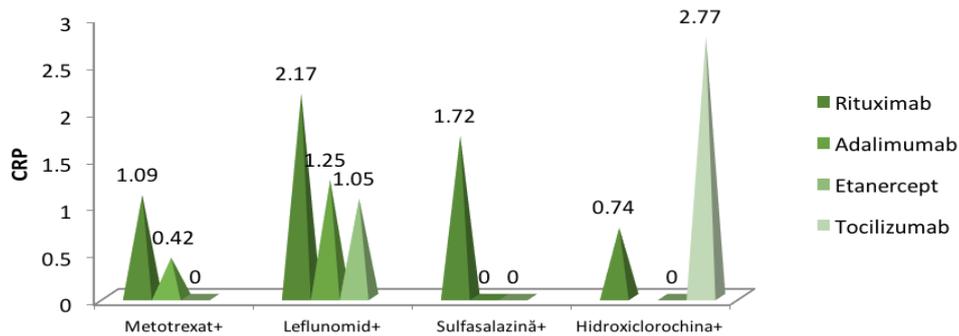


Fig. 2. Average CRP level based on combined synthetic and biological DMARDS treatment

Measurement of oral markers revealed the lowest median Quigley Hein score in patients treated with Sulfasalazine +

Rituximab, while the highest values were recorded in Leflunomide + Etanercept therapy (Figure 3)

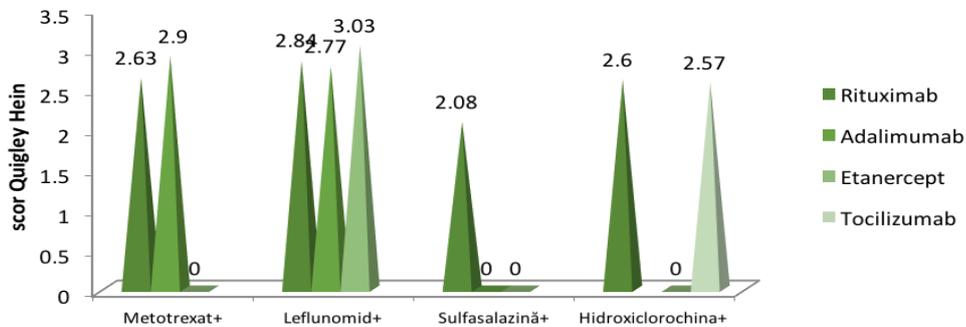


Fig. 3. Average Quigley Hein's index level according to synthetic + biological DMARDS combined treatment

The lowest average GI index level was seen in patients treated with Methotrexate + Adalimumab and Leflunomide + Adalimumab, and the largest

was found in patients treated with Leflunomide + Rituximab and Metotrexate + Rituximab (Figure 4).

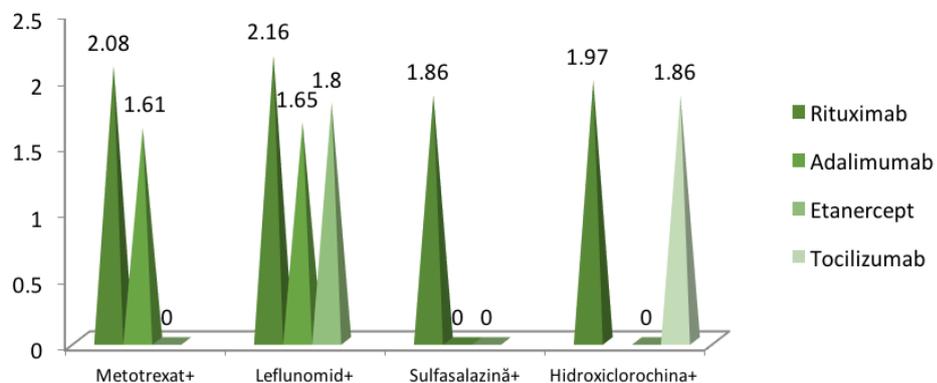


Fig. 4. Average GI index level according to synthetic and biological DMARDS combined treatment

The lowest average PBI level was observed in Leflunomide + Etanercept treated

patients, and the highest in patients treated with Leflunomide + Rituximab (Figure 5).

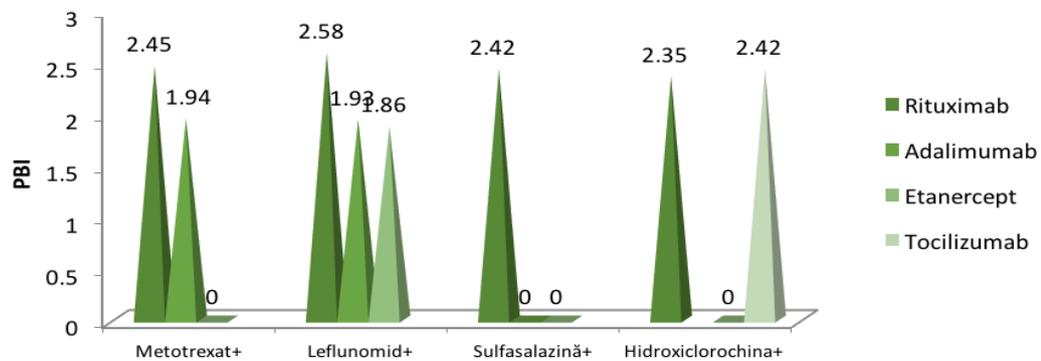


Fig.5. Average PBI level based on synthetic and biological DMARDs combined treatment

Discussions

Together, periodontitis and AR are responsible for significant functional loss and morbidity in a large proportion of the population worldwide. That's why, for many years, scientists have tried to find a link between the mechanisms of both diseases, hoping to facilitate the development of an effective treatment. [1,23]

RA is an autoimmune condition diagnosed as chronic inflammatory arthritis when five or more joints are affected. The diagnosis is based on clinical history, physical examination, increase in C reactive protein (CRP) and rheumatoid factor (RF). Imaging methods are used to evaluate different associations. RA is typically manifested with signs of inflammation, the affected joints being swollen, warm, painful and rigid. This inflammation leads to tendon ossification, erosion and destruction of joint surfaces [3, 22]

In the present study, serum levels of VSH and CRP recorded for 48.2% and 46.3% of the patients individual values higher than the reference maximum, the mean level being significantly higher in the advanced stages of the disease. This quantification of inflammatory markers, witnesses of an exacerbated inflammatory status, may be extremely relevant and with negative influences at the level of periodontal homeostasis.

RA is a complex disease associated with an increased prevalence of multiple comorbidities, which may precede or accompany RA, but can also be caused by the complex therapy used. Substantial evidence indicate that systemic inflammation continues and immune dysfunction characteristic to RA plays a critical role in the development and acceleration of comorbidities. Comorbidities most commonly observed in RA patients include cardiovascular disorders, pulmonary disorders, neoplastic disorders, osteoporosis, body composition changes and neuropsychiatric disorders [29]. Patients with RA often present two or more comorbidities that exacerbate their precarious systemic status, as observed in this study. [30]

Assessing the presence of comorbidities has highlighted in our study a significant association between hypertension and osteoporosis. [31-33]

These two chronic diseases can produce adverse effects, affecting the quality of life of patients; in addition, the literature offers numerous evidence of the negative influence they may produce in the periodontal status, exacerbating inflammatory status and accelerating tissue destruction.

Rheumatoid factor (RF) was found positive in RA and other chronic inflammatory diseases, including periodontitis. RF could be quantified at the gingival level, in the subgingival plaque and in the serum of patients with periodontitis.

Patients with RF-positive periodontal disease had a high titre of IgG and IgM antibodies against oral microorganisms compared to seronegative patients. The rheumatoid factor of HIV-positive patients has a cross-reaction with oral bacterial epitopes. [34]. Proteinases are considered to be important virulence factors because they make possible the growth of *P. gingivalis* and can lead to the degradation of the host tissue. Researchers have identified lysine and arginine amino acid sequences for Fc regions of the IgG molecule. Since *P. gingivalis* decomposes in particular lysine and arginine, and the IgG3

CH2 and CH3 domains are processed by *P. gingivalis* proteinase, they take on a key function in FR production in cells. [10,12,35]

In our study, the altered values of the oral and periodontal health indices analysed were significantly correlated with a stage III or IV of RA. Very likely the motor restrictions encountered by these patients make it difficult to achieve adequate oral hygiene, the burden of disease in general and the influence on the quality of life may be additional factors in the existence of a precarious periodontal condition. (Fig. 6,7)



Fig. 6. Deformation of fingers in RA context



Fig.7. Clinical aspects and gingivo-periodontal changes in RA and periodontal disease patients

In conclusion, there are no conclusive data in human subjects to evaluate the effects of DMARDs on periodontitis due to the small number of patients studied and the lack of randomized, double-blind, placebo-controlled trials. The use of anti-TNF antibodies did not consistently prevent alveolar bone loss and generated aggravated or improved gingival inflammation, depending on the drug used.

The biological reason for using DMARDs treatment as a modulator of periodontitis expression in animals was

confirmed by studies that showed that mice with TNF- α deficient p55 receptor developed less severe periodontal inflammation (reduced bone loss and low inflammatory response) in response to inoculation with *A. actinomycetemcomitans* [11,36]

Using the same experimental periodontitis model induced by *A. actinomycetemcomitans*, the researchers found that antigen-induced arthritis exacerbated alveolar bone loss, while anti-

TNF- α therapies improved the development of periodontitis. [13,37]

Until this date, most research on the use of anti-cytokine therapies for periodontitis in humans has been limited to small clinical trials evaluating periodontal status in patients with rheumatoid arthritis under treatment. [1,3]

In our study, the combination of methotrexate and adalimumab recorded the lowest VSH and CRP values, consistent with multiple studies demonstrating the systemic anti-inflammatory effect of methotrexate in particular [38,39] Leflunomide and adalimumab associations, as well as leflunomide with etanercept, recorded the most marked decreases in both rheumatic and oral health indices, similar to those of [40] which identified that patients with rheumatoid arthritis that received anti-TNF- α treatment experienced statistically significant improvements of the probing depth, probing bleeding and gingival inflammation compared to patients that did not receive anti-TNF- α therapy after non-surgical periodontal treatment.

The combination of leflunomide with rituximab or methotrexate with rituximab was associated with the highest values of GI and PBI indices, coinciding with similar literature studies. [41]

However, it is important to note that, in contrast, in patients receiving biological DMARDs treatment, the average level of oral health indices was significantly lower. Thus, we can note the positive influence that

this class of drugs, especially those that act on TNF- α , generates on local status.[42]

In order to maintain oral health, patients with RA are encouraged to achieve proper oral hygiene. Consultation of the periodontist is necessary to determine the course of treatment. Reducing the oral contribution to the overall inflammatory burden due to the favorable outcome of periodontal treatment is an important desideratum. Maintaining the full health of RA patients should be a collaborative effort. This dentist-rheumatologist partnership will definitely influence the oral and global health of these patients.

Interventions to improve oral pathology may have direct and indirect systemic benefits. Considerations include the patient's ability to maintain adequate oral hygiene, xerostomia and the related complications, patient susceptibility to infections, haemostasis alterations, and drug actions and interactions.

Conclusions

Regarding the treatment of RA, we could not establish a clear effect on oral health indices of the conventional and synthetic DMARDs combined therapy.

Periodontal parameters (hygiene index, gingival inflammation index, papillary bleeding index) significantly correlated with severe RA status.

From the point of view of anti-rheumatic therapy, the best values of systemic and oral indices were observed in patients treated with a combination of anti-TNF- α with leflunomide or methotrexate.

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