

# TNF Inhibitors and Periodontal Inflammation in Psoriatic Arthritis

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*The link between immune mediated rheumatic disorders and oral health, particularly periodontal disease, is widely accepted, based on shared immune and inflammatory processes as well as local (articular, gingival) damage mediated by similar pro-inflammatory cytokine and destructive mediators. We aimed to evaluate periodontal status in psoriatic arthritis (PsA) before and after 24-weeks treatment with TNF inhibitors and to identify potential relation between disease activity, inflammatory parameters, therapeutic response and chronic periodontitis. Patients were prospectively assessed according to a standard protocol comprising a complex rheumatologic (PsA activity, inflammatory prolife) and dental evaluation (plaque and gingival index, bleeding on probing, periodontal pocket depth, clinical attachment level). Up to one third PsA presented with moderate to severe periodontitis at baseline, with high prevalence of sites with dental plaque, abnormal bleeding, increased periodontal pocket depth and clinical attachment loss. Higher levels of inflammatory parameters were described in the subset of PsA presenting with aggressive periodontal diseases, while significant correlation between dental pathology and CRP ( $p < 0.05$ ). A significant improvement in both PsA-related parameters and periodontal status was demonstrated after 24 weeks of anti-TNF therapy ( $p < 0.05$ ). Periodontal disease may develop in PsA and should be commonly evaluated, particularly patients with active disease. Benefits of TNF inhibitors, with significant response in articular and periodontal parameters, suggest common inflammatory pathways in both entities.*

**Keywords:** psoriatic arthritis, periodontal disease, TNF inhibitors

The association between immune mediated rheumatic disorders (e.g. rheumatoid arthritis, lupus, scleroderma, spondylarthropathies) and oral health, particularly periodontal disease, is widely accepted, based on shared immune and inflammatory processes as well as local tissue (articular, gingival) damage, mediated by complex network of similar pro-inflammatory cytokine and destructive mediators [1-5].

Psoriatic arthritis (PsA) represents a chronic inflammatory heterogeneous disease affecting predominantly the skin, joints, and entheses, with several distinct clinical profiles [6]. The pathologic process of skin and joint lesions reflects a complex interplay between immunologic and inflammatory events on a background of environmental factors (including a temporal relation with certain viral and bacterial infections) in a genetically predisposed host [6-10].

A closer look to the immunopathogenesis of the disease displays: abundant Th1-cell cytokines (e.g., TNF- $\alpha$ , IL-1  $\beta$ , IL-10) derived from activated T cells and other mononuclear pro-inflammatory cells (monocytes, macrophages); increased proliferative activity of fibroblasts (skin, synovial) and their ability to secrete IL-1, IL-6, and platelet-derived growth factors; excessive humoral immunity (autoantibodies against nuclear antigens, cytokeratins, epidermal keratins, heat-shock proteins); abnormal bone remodelling mediated by TNF- $\alpha$  and matrixmetalloproteinases (MMPs) [6, 8-10].

Periodontitis or periodontal disease is a chronic inflammatory infectious disease characterized by an immunologically mediated destruction of dental supporting

tissue leading to progressive attachment loss, bone resorption, periodontal pocket formation and/or gingival recession [1-5, 8-12].

Both psoriatic and periodontal disease share common pathobiological pathways including excess of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-1- $\beta$ , in target tissues (skin, joint, gingival microenvironment), exaggerated immune response to the microbiota residing at the epithelial surface (skin, periodontal tissue), abnormal bone remodeling and/or resorption [8- 10, 12].

Regardless of extensive interest in periodontitis and systemic disorders during the last decade, only few papers have addressed the link between PsA and chronic periodontitis, with still controversial conclusions [10, 12].

Thus, while certain papers considered there is no difference in periodontal profiles, though psoriatic patients had few teeth remaining [10, 12], others authors showed that psoriasis patients had poor periodontal status compared to controls [10, 12, 14] and periodontitis may be associated with psoriasis [8, 10, 12, 15]. Psoriatic patients had more bone loss and loss of teeth compared to controls according to a complex periodontal assessment including alveolar bone loss on bite-wing X-rays [10, 12, 16].

Furthermore, the prevalence of periodontitis is higher in psoriasis subjects as compared to controls as demonstrated by clinical attachment loss and alveolar bone loss [10, 12], more commonly reported in moderate/ severe psoriasis compared to controls [9, 10, 12]. The risk of severe periodontal disease in psoriasis was six times higher in smokers than in nonsmokers [10, 12,17]. Recent

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epidemiological studies suggested that periodontitis may be an independent risk factor for developing psoriasis: there is an increased risk for psoriasis among patients with chronic periodontitis [8-10, 12].

The relation among PsA and chronic periodontitis is bidirectional; increased risk for psoriasis, especially palmoplantar pustulosis, was reported among patients with chronic periodontal disease [10, 12, 18, 19-23], while periodontal bone loss may increase the risk of subsequent psoriasis [10, 12, 19].

The main objective of our study was to assess the periodontal status in PsA and to identify potential relation between disease activity, disability, inflammatory profile, therapeutic response and clinical periodontal parameters.

## Experimental part

### Material and method

41 consecutive PsA patients (30 women) fulfilling the CASPAR classification criteria were enrolled in a prospective short-term (24 weeks) observational study aiming to evaluate oral health, particularly periodontal disease. Patients were followed-up in the outpatient rheumatology department and qualified to initiate their first TNF inhibitor based on National Recommendation for Biologics in Active PsA refractory to synthetic drugs.

Patients with comorbidities potential overlapping periodontal issues such as diabetes and smokers (current, former) as well as those with a history of periodontal disease were excluded.

Standard assessments were performed by experienced examiners and covered a dual rheumatologic and dental, including: (i) *PsA-related parameters* - disease activity (DAS28-ESR, on 28 evaluable joints using erythrocyte sedimentation rate; and Disease activity in PsA, DAPSA score), disability scores (Health Assessment Questionnaire Disability Index, HAQ-DI) and inflammatory parameters (ESR analyzed by the Westergren method and C-reactive protein, CRP, by the classic method); and (ii) *periodontal parameters* - bleeding on probing (BOP), probing pocket depth (PPD), clinical attachment level (CAL), plaque index (PI) and gingival index (GI).

Clinical measurements were done at four sites of all teeth, respectively mesio- and disto-buccal, mesio- and disto-lingual, using a Williams probe for PPD and CAL. Either partial (at least 8 evaluable teeth excluding 3<sup>rd</sup> molar) or fully dentate patients were accepted for the study.

PPD was defined as the distance from the free gingival margin to the bottom of the sulcus or periodontal pocket, while CAL as the distance from the cement-enamel junction to the bottom of the sulcus or periodontal pocket.

A patient was considered as having chronic periodontitis if at least four teeth with a PPD  $\geq 5$  mm and with CAL  $\geq 2$  mm at the same time (1999 Consensus Classification of Periodontal Diseases) [24].

No periodontal therapy or invasive dental procedures (professional scaling and prophylaxis) were permitted during the study period; additionally, all participants were instructed not to change their oral hygiene routines.

**Table 1**  
DEMOGRAPHIC, RHEUMATOLOGIC AND DENTAL CHARACTERISTICS OF PATIENTS WITH RA AT BASELINE

<i>Rheumatologic and periodontal</i>	<i>characteristics</i>
<b><i>RA-related parameters</i></b>	
<i>Age (years; mean<math>\pm</math>SD)</i>	53.36 $\pm$ 18.27
<i>PsA duration (months; mean<math>\pm</math>SD)</i>	36.45 $\pm$ 24.57
<i>ESR (mm/h; mean<math>\pm</math>SD)</i>	47.65 $\pm$ 19.36
<i>Serum CRP levels (mg/dL; mean<math>\pm</math>SD)</i>	12.43 $\pm$ 6.37
<i>DAS28-ESR (mean<math>\pm</math>SD)</i>	5.25 $\pm$ 0.87
<i>DAPSA (mean<math>\pm</math>SD)</i>	22.57 $\pm$ 8.12
<i>NSAIDs (%) (n)</i>	87.80 (36)
<i>DMARDs (%) (n)</i>	100 (41)
<b><i>Periodontal status</i></b>	
<i>Number of present teeth (mean<math>\pm</math>SD)</i>	21.8 $\pm$ 4.3
<i>% of sites with plaque (mean<math>\pm</math>SD)</i>	32.85 $\pm$ 11.7
<i>Gingival index (mean<math>\pm</math>SD)</i>	0.93 $\pm$ 0.27
<i>% of sites with bleeding on probing (mean<math>\pm</math>SD)</i>	14.2 $\pm$ 7.1
<i>PPD (mm; mean<math>\pm</math>SD)</i>	3.42 $\pm$ 0.78
<i>% of sites with PPD <math>\geq 4</math> mm (mean<math>\pm</math>SD)</i>	12.45 $\pm$ 2.9
<i>CAL (mm; mean<math>\pm</math>SD)</i>	2.91 $\pm$ 0.92
<i>% of sites with CAL <math>\geq 4</math> mm (mean<math>\pm</math>SD)</i>	1.87 $\pm$ 0.23

The study comprised the baseline visit (V1), before starting biological therapy, and the end of study visit, after 24 weeks (V2).

The study protocol was approved by the local ethics committee and patients provided a written informed consent before their enrollment.

Statistical analysis was done in IBM SPSS-19 software,  $p < 0.05$ .

## Results and discussions

### Baseline (V1) characteristics

#### PsA-related parameters

Demographics, disease duration, inflammatory tests, concomitant medication (non-steroidal anti-inflammatory and immunosuppressive drugs), disease activity and disability scores as well as periodontal status at baseline are provided in table 1.

As expected, moderate to severe active PsA (DAS28-ESR:  $5.25 \pm 0.87$ ; DAPSA:  $22.57 \pm 8.12$ ), with high levels of inflammation (ESR:  $47.65 \pm 19.36$  mm/h, meaning around twice the upper normal limit; CRP:  $12.43 \pm 6.37$  mg/dL, respectively up to 3.75 times the upper normal limit) qualified for to receive TNF inhibitors. Concomitant NSAIDs and synthetic disease modifying anti-rheumatic drugs (e.g. methotrexate, leflunomide, sulfasalazine) were administered in the majority of cases (87.80% and 100%, respectively) at the time of investigation, either alone or in combination.

#### Periodontal parameters

48.78% (20) PsA patients presented with fewer teeth than normal for age and gender-matches healthy individuals, and the average number of evaluable teeth of  $21.8 \pm 4.3$ .

An increased prevalence of dental plaques ( $32.85 \pm 11.7$ ), abnormal gingival index ( $0.93 \pm 0.27$ ) and bleeding on probing ( $14.2 \pm 7.1$ ) were described at baseline in PsA. The mean pocket depth was  $3.42 \pm 0.78$  mm, with

a value  $> 4$  mm identified in  $12.45 \pm 2.9$  % of cases. Besides, a significant number of cases had advanced clinical attachment loss, with an average of  $2.91 \pm 0.72$  mm. All data are shown in table 2.

Up to one third of patients enrolled in our study (29.26%, 12 cases) presented with chronic periodontitis. Further, PsA with aggressive periodontitis (localized or generalized) displayed higher levels of inflammatory parameters as compared with PsA without periodontitis: mean CRP  $6.31 \pm 2.13$  mg/dL, mean ESR of  $59.23 \pm 12.37$  mm/h in patients with periodontitis vs. mean CRP  $3.74 \pm 0.63$  mg/dL and mean ESR of  $37.12 \pm 10.35$  mm/h in patients without periodontitis ( $p < 0.05$ ).

CRP levels correlated with the presence and severity of periodontitis ( $p < 0.05$ ) in studied patients.

### Changes in rheumatologic and periodontal status after TNF inhibitors (V2)

#### Disease activity and biochemical biomarkers

At 24 weeks of biological therapy, we demonstrated significant improvement in disease activity and inflammatory parameters regardless of the TNF inhibitor administered (monoclonal anti-TNF antibody or soluble TNF receptor). Patients in our study were treated with adalimumab, etanercept or golimumab. A rapid and consistent decrease in DAS28-ESR with low to moderate final DAS28-ESR was reported in all cases ( $5.25 \pm 0.87$  vs.  $3.1 \pm 0.56$ ,  $p < 0.05$ ). The same trend was registered for DAPSA:  $22.57 \pm 8.12$  vs.  $14.68 \pm 2.83$  ( $p < 0.05$ ).

Both ESR and CRP levels dramatically improved under TNF inhibitors - ESR:  $47.65 \pm 19.36$  mm/h vs.  $25.51 \pm 12.72$  mm/h,  $p < 0.05$ ; CRP:  $12.43 \pm 6.37$  mg/dL vs.  $5.27 \pm 1.09$  mg/dL,  $p < 0.05$  (table 2).

#### Periodontal status

Significant improvement in periodontal status was reported under TNF inhibitors at the end of the follow-up period ( $p < 0.05$ ) (table 2).

**Table 2**  
RHEUMATOLOGIC AND PERIODONTAL CHARACTERISTICS OF PATIENTS WITH RA BEFORE AND AFTER MEDICATION WITH TNF INHIBITORS

Characteristics	Baseline	6 months	P
<b>RA-related parameters</b>			
DAS28-ESR	$5.25 \pm 0.87$	$3.1 \pm 0.56$	$p < 0.05$
DAPSA	$22.57 \pm 8.12$	$14.68 \pm 2.83$	$p < 0.05$
Serum CRP levels (mg/dL)	$12.43 \pm 6.37$	$5.27 \pm 1.09$	$p < 0.05$
ESR (mm/h)	$47.65 \pm 19.36$	$25.51 \pm 12.72$	$p < 0.05$
<b>Periodontal status</b>			
% of sites with plaque	$32.85 \pm 11.7$	$31.9 \pm 12.4$	$p > 0.05$
Gingival index	$0.93 \pm 0.27$	$0.82 \pm 0.17$	$p > 0.05$
% of sites with bleeding on probing	$14.2 \pm 7.1$	$4.7 \pm 2.1$	$p < 0.05$
PPD (mm)	$3.42 \pm 0.78$	$1.96 \pm 0.41$	$p < 0.05$
% of sites with PPD $\geq 4$ mm	$12.45 \pm 2.9$	$7.9 \pm 2.7$	$p < 0.05$
CAL (mm)	$2.91 \pm 0.92$	$1.87 \pm 0.35$	$p < 0.05$
% sites with CAL $\geq 4$ mm	$1.87 \pm 0.23$	$0.95 \pm 0.26$	$p < 0.05$

We demonstrated substantial differences in PPD and CAL as compared to baseline ( $p < 0.05$ ); despite any specific periodontal therapy, mean PPD as well as patients with  $PPD \geq 4$ mm declined with biologics ( $3.42 \pm 0.78$  vs.  $1.96 \pm 0.41$ ;  $12.45 \pm 2.9$  vs.  $7.9 \pm 2.7\%$ , respectively;  $p < 0.05$ ).

Additionally, significant difference in CAL as compared to baseline was observed at 24 weeks:  $2.91 \pm 0.72$  mm vs.  $1.87 \pm 0.35$ ,  $p < 0.05$ ; significant lower number of sites with  $CAL \geq 4$ mm were shown ( $1.87 \pm 0.23$  vs.  $0.95 \pm 0.26\%$ ).

However, we have not demonstrated important modifications in plaque and gingival index with TNF inhibitors ( $p > 0.05$ ).

We prospectively assessed periodontal status in patients with moderate to severe active PsA and we evaluated the relationship between clinical periodontal parameters, CRP levels and disease activity in patients with PsA treated with TNF inhibitors.

Firstly, we showed that participants in the current study have impaired oral health and significantly higher number of missing teeth (described in up to half of analyzed PsA) and more periodontal disease as expected for age and sex-matched healthy individuals; we reported a high frequency of gingival plaques and gingival inflammation, but high PPD and CAL as well. Furthermore, up to one third of PsA had chronic periodontitis, and even severe periodontal involvement. Interestingly, a direct correlation between serum CRP levels as an indicator of active psoriasis-related inflammation, and periodontal disease was identified.

Secondly, we confirmed the benefits of biological therapy in PsA as supported by a rapid and sustained effect in active disease, refractory to synthetic immunosuppressive; a short-term (24 weeks) treatment with TNF inhibitors (adalimumab, etanercept, golimumab) resulted in significant decline in disease activity and inflammatory parameters (ESR, CRP).

Thirdly, we demonstrated an improvement of periodontal status (plaque index, gingival index, pocket depth and clinical attachment loss) during anti-TNF therapy, indirectly suggesting that controlling systemic inflammation could also influence local, gingival inflammation even during short-term (24 weeks) follow-up.

Though common inflammatory pathways of systemic and local (articular, gingival) inflammation and the key role of oral pathogens in modulating host inflammatory and immune response are widely recognized in rheumatoid arthritis and, to a lesser extent, in psoriatic arthritis, insufficient data is actually known about the interrelation between PsA and periodontal disease [1, 3, 10, 12].

We were able to talk about impaired periodontal health with an increased frequency of severe periodontitis in our PsA patients; however, data from literature is still controversial [8-23]. Certain studies failed to recognize a statistically significant prevalence of periodontitis in PsA as compared with healthy control subjects [10-12]. One potential explanation is the long-term use of medication known to have protective effects on periodontal damage in PsA cases enrolled in different studies [9, 10, 12, 18].

Conversely, different other papers [9, 10, 12, 16, 18] reported important association between moderate to severe psoriasis and oral health, particularly periodontal disease; patients with psoriasis have significantly fewer teeth and radiographic bone loss compared to controls [9, 10, 12]; the prevalence of moderate to severe periodontitis was also higher [10, 12].

Besides, a recent work demonstrated a significant association between PsA and severe chronic periodontitis [8]; although higher CAL, as the standard for evaluating

the severity of periodontitis assessing the past disease activity, was demonstrated in PsA, PPD (reflecting current disease activity) presented with high but not statistically significant values [8, 10].

Furthermore, parameters overlapping the accuracy of data analysis such as smoking, obesity and systemic diseases including diabetes and cardiovascular disease were not allowed in our protocol.

Additionally, we demonstrated an important improvement of PPD and CAL during biological therapy for active PsA, advancing the role of TNF inhibitors in suppressing not only articular inflammation and subsequent damage, but also periodontal inflammation and local, alveolar damage. It is reasonable to assert that a decrease in proinflammatory cytokines level in the periodontal microenvironment, induced by TNF blockade is also responsible for a positive outcome for periodontal parameters such as PPD, CAL, gingival index and bleeding on probing.

TNF inhibitors typically account for decrease in acute phase reactants (e.g. CRP) levels in PsA. We identified not only a strong positive correlation between CRP level and periodontal health (high CRP levels associated with more severe periodontitis) at baseline, but at 24 weeks of follow-up (V2).

Finally, we provided sufficient arguments for significant burden of periodontitis in patients with active PsA and the role of TNF inhibitors in controlling both PsA-related parameters and periodontal health in short term administration.

Further studies in larger cohorts of PsA patients as well as comparison with periodontal disease within other inflammatory immune rheumatic diseases, particularly rheumatoid arthritis patients are necessary in order to characterize periodontal health in patients with PsA and to validate the influence of biologic drugs in improving periodontitis in such patient population.

In another paper was studied the influence of TNF inhibitors in cardiovascular diseases [25].

## Conclusions

Psoriatic arthritis may be accompanied by comorbid periodontal disease. TNF blockade is efficient in patients with active RA and potentially able to modulate the gingival inflammation.

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