Anti-Tumor Necrosis Factor Alpha Therapy and Periodontal Inflammation in Rheumatoid Arthritis

A clinical and biochemical approach

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Although the relationship between periodontal disease and rheumatoid arthritis (RA) is widely documented, centered by common pathobiologic pathways, the effect of various tumor necrosis factor alpha (TNF) antagonists in modulating not only inflammatory and immune articular damage, but also periodontal microenvironment remain debatable. We aimed to evaluate the periodontal status with and without TNF inhibitors in RA patients and to identify potential relation among these entities. We performed a prospective longitudinal 6-months analysis on 96 RA initiating their first biological therapy. Standard assessments included a dual rheumatologic (RA activity, disability, serological, inflammatory prolife) and dental evaluation such as plaque index (PI), gingival index (GI), bleeding on probing (BOP), pocket depth (PD), clinical attachment level (CAL). More than half of RA presented at baseline with chronic periodontitis, as suggested by high prevalence of sites with dental plaque, abnormal BOP, PD and CAL. Advanced inflammatory (CRP, ESR) and immune (anti-cyclic citrullinated peptide antibodies, ACPA) markers were described in RA subsets presenting with aggressive periodontal diseases, while significant correlations between dental pathology, RA activity and ACPA levels were also reported ($p<0.05$). Furthermore, we revealed significant improvement in both RA-related characteristics and periodontal status after 6 months of anti-TNF therapy ($p<0.05$). RA, particularly active severe, ACPA positive disease, is essentially accompanied by comorbid periodontal disease. TNF blockade is efficient in patients with active RA and potentially able to modulate the inflammatory process in the periodontal tissue.

Key words: rheumatoid arthritis, periodontal disease, TNF inhibitors, anti-cyclic citrullinated peptide antibodies

Rheumatoid arthritis (RA) and periodontal disease are chronic inflammatory entities, classically characterized by a complex pathobiology comprising synovium and periodontal inflammation, joint damage and alveolar bone loss [1-9].

The relationship between these two disorders is directed by common genetic susceptibility (HLA-DR) as well as environmental factors (smoking), together with an excessive activation of pro-inflammatory cytokines (e.g., tumor necrosis factor - TNF-α, and interleukins - IL-1β, IL-6, IL-11, IL-17) and mediators (prostaglandin E2, nitric oxide), osteoclast activation (RANKL overregulation) with active bone destruction and periodontal lesions, exposure to antigens generated by peptidylarginine-deaminase and citrullination [1-9].

Furthermore, underlying link between rheumatologic and dental pathology via citrullination is actually dependent on several gingival microorganisms, particularly *Porphyromonas gingivalis* (*P.gingivalis*) [1-9].

Recent reports hypothesized that early aggressive RA management with synthetic disease modifying anti-rheumatic drugs (DMARDs) and/or biologic agents not only result in sustained disease remission according to treat-to-target strategy, but also might hamper periodontal damage in active periodontitis [1, 2, 10-17]. Thus, several authors have demonstrated that regular DMARDs are able to retrieve periodontal status in RA with periodontitis [10-17]; typically, both gingival inflammation and periodontal destruction are positively influenced by specific remissive drugs, while corticosteroids and anti-TNFs are also able to clinically improve periodontal parameters in RA patients [1, 2, 10-17]. However, the effect of various TNF antagonists in modulating not only inflammatory articular damage, but also periodontal disease seems to remain debatable [10-17].

On the other hand, it was advocated that specific therapies (classic professional scaling, adjuvant photo-activated toluidine) for chronic periodontitis prevent periodontal infection and gingival inflammation [11-14], but also improve RA activity and severity, as well as response to different DMARDs [10-17].

The main objectives of our study were to evaluate the periodontal status in RA patients with and without TNF inhibitors and to identify potential relation between different RA parameters (activity, disability, serological and inflammatory profile, therapeutic response) and periodontal disease.

Experimental part

Material and method

We performed a prospective longitudinal 6 months analysis on 96 consecutive RA patients initiating their first

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biological anti-TNF agent, recruited in a single academic center. All patients have attended the outpatient rheumatology department and were selected to receive biological therapy according to the national protocol, meaning moderate-to-severe disease activity sub-optimally controlled under maximal doses of synthetic DMARDs (at least two remissive drugs, one of them being methotrexate). Individuals with diabetes mellitus and smokers (current, former) were excluded, due to potential overlapping periodontal issues.

Standard assessments comprised a dual rheumatologic and dental evaluation performed by trained examiners, as follows: (i) *RA-related parameters* - disease activity (disease activity on 28 evaluable joints using erythrocyte sedimentation rate, DAS28-ESR) and disability scores (Health Assessment Questionnaire Disability Index, HAQ-DI), inflammatory (ESR and C-reactive protein, CRP) and serological parameters (rheumatoid factor, RF, and anti-cyclic citrullinated peptide antibodies, ACPA; ACPA were detected using the fluorescence enzyme immunoassay (FEIA) for anti-cyclic citrullinated peptide autoantibodie with values <7 U/mL classified as negative; 7-10 U/mL as equivoque and >10 U/mL as positive; Synevo Lab); and (ii) *periodontal status* including several parameters such as plaque index (PI), gingival index (GI), bleeding on probing (BOP), pocket (probing) depth (PD) and clinical attachment level (CAL).

Only partial (meaning at least 8 evaluable teeth excluding 3rd molar) or were fully dentate patients were enrolled. Clinical measurements were done at four sites of all teeth, such as mesio- and disto-buccal, mesio- and disto-lingual; a Williams probe was used for measurements of PD and CAL.

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.

The study comprised two visits, at baseline (V1), before starting TNF inhibitors, and at the end of follow-up interval (V2), after 6 months of biological therapy.

All participants have signed a written informed consent before their enrollment and the study received Ethics Committee approval.

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

Results and discussions

Baseline characteristics

RA- related parameters

Demographics, RA history (disease duration), sero-positivity (RF, ACPA), disease staging, functional status (HAQ-DI), inflammatory syndrome (ESR, CRP), disease activity (DAS28-ESR), concomitant medication (DMARDs, corticosteroids) as well as periodontal status were recorded in all patients at baseline and summarized in table 1.

We enrolled patients aged between 23 and 60, with both early and established RA, with positive immune profile (RF+, ACPA+) in the majority of cases and moderate to high RF and ACPA levels.

As expected, biological therapy was proposed for patients with highly active RA (mean DAS28-ESR of 4.95±1.54), with high levels of inflammation (mean ERS of 58.3+21.9, respectively more than twice the upper normal limit; mean CRP of 4.43±2.89, respectively up to 3.2 the upper normal limit) and aberrant immune response (mean RF level of 145.8±122.5, mean ACPA of 145.8 ±116.2). Concomitant synthetic DMARDs (methotrexate, leflunomide, sulfasalazine or antimalarials) were administered in all cases, while low dose corticosteroids in about one third of RA.

Supplementary, in a limited number of RA (32) we were able to perform seriate analysis of serum TNF alpha levels (ELISA, normal values <8.1pg/mL; Synevo Lab), before

Rheumatologic and periodontal	*characteristics*
RA-related parameters	
Age (years; mean±SD)	49.2±25.7
Duration of RA (months; mean±SD)	56.5±32.1
RF positivity (%) (n)	83.3 (80)
Serum RF levels (IU/mL; mean±SD)	145.8±122.5
ACPA positivity (%) (n)	78.1 (75)
Serum ACPA titer (U/mL; mean±SD)	145.8±116.2
ESR (mm/hour; mean±SD)	58.3±21.9
Serum CRP levels (mg/dL; mean±SD)	4.43±2.89
DAS28-ESR (mean±SD)	4.95±1.54
Corticosteroids (%) (n)	37.5 (36)
DMARDs (%) (n)	100 (96)
Periodontal status	
Number of teeth present (mean±SD)	23.7±9.7
% sites with plaque (mean±SD)	34.9±15.2
GI (mean±SD)	0.98±0.16
% sites with BOP (mean±SD)	13.9±8.7
PD (mm; mean±SD)	2.75 ±0.51
% sites with PD ≥4 mm (mean±SD)	11.9±2.4
CAL (mm; mean±SD)	2.62±0.49
% sites with CAL ≥4 mm (mean±SD)	2.51±0.53

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

and after 6 months of anti-TNFs. High levels of serum TNF were demonstrated at baseline in all patients, with a mean concentration of 16.25 + 5.31 pg/mL

Periodontal parameters

57.29 % (55) RA presented with fewer teeth than normal for age and gender-matches healthy individuals, with a mean number of evaluable teeth of 23.7± 9.7. We reported an increased prevalence of sites containing dental plaques (34.9± 15.2), abnormal gingival index with a mean value of 0.98±0.16 and 13.9 ±8.7 % sites with bleeding on probing. Also, RA patients had a mean pocket depth was 2.75 ± 0.51 mm, while important PD (> 4 mm) was identified in 11.9 ± 2.4 % of cases. Furthermore, a significant number of cases (%) had advanced clinical attachment level, with a mean value of 2.62 ± 0.49 mm and common attachment loss. All data are shown in table 1.

In subgroup analysis, higher inflammatory tests (both CRP and ESR) and immune abnormalities (ACPA, but not RF) were demonstrated in RA with either localized or generalized aggressive periodontitis, as follows: for RA with periodontitis – mean CRP of 6.31+2.13 mg/dL, mean ESR of 64.41+17.62 mm/h, mean ACPA levels of 256.23+ 54.19 U/mL, while in RA without periodontitis - mean CRP of 3.27+1.75 mg/dL, mean ESR of 32.52+4.85 mm/hour, mean ACPA concentration of 93.61+14.23 U/mL, respectively ($p<0.05$).

In addition, we revealed statistical significant positive correlations between periodontitis, RA activity, and ACPA levels ($r=0.86$, $p<0.05$; $r=0.83$, $p<0.05$).

Changes in rheumatologic and periodontal status after TNF inhibitors

Disease activity and biochemical biomarkers

6 months of biological therapy, irrespective of the specific TNF inhibitor administered (monoclonal anti-TNF antibodies, soluble TNF receptor) resulted in significant improvement in disease activity, inflammatory and immune parameters. Thus, a significant decrease in mean DAS28-ESR levels with low to moderate final DAS28 was reported in all cases (4.95 ± 1.54 vs 2.65 ± 0.81, $p<0.05$). Statistical significant fall in both ESR and CRP levels was reported (ESR: 58.3+21.9 vs 23.12+10.2, $p<0.05$; CRP: 4.43 ± 2.89 vs 1.4 ± 0.73, $p<0.05$), together with reduction in ACPA levels (145.8±116.2 vs 101.0 ± 54.5, $p<0.05$) (table 2).

In the subgroup of patients with available serum TNF evaluation, a significant decrease was registered in the majority of patients, particularly in those achieving low disease activity status or remission; mean serum TNF was 8.84+3.63pg/mL ($p<0.05$).

Periodontal status

Although no periodontal therapy was permitted during the follow-up, and patients were instructed to maintain their dental behavior, overall a statistically significant improvement in periodontal status was demonstrated after 6 months of biological therapy with TNF inhibitors ($p<0.05$) (table 2).

Our results showed significant differences in PD and CAL as compared to baseline ($p<0.05$). Mean pocket depth significantly decreased under TNF inhibitors (2.75 ± 0.51 vs 1.36±0.29, $p<0.05$), as well as the mean number of RA with PD > 4 cm (11.9 ± 2.4 vs 8.2± 3.5 % sites with severe PD).

The same tendency was described for clinical attachment level: significant difference as compared to baseline for the study group (2.62 ± 0.49 vs 1.92± 0.23, $p<0.05$), with 2.51± 0.53 vs 1.4±0.42 % of sites with CAL > 4 mm, even clinical attachment loss.

Not surprisingly, both plaque and gingival index were not significantly influenced under biological DMARDs (% sites with plaque: 34.9± 15.2 vs 31.9±12.4, $p>0.05$; GI: 0.98±0.16 vs 0.63 ±0.11, $p>0.05$).

We were also interested in assessing changes (Δ) in periodontal parameters in our RA patients treated with TNF antagonists; thus, we reported slightly changes in gingival plaques ($p>0.05$) and a Δ% sites with plaque of -3.0± 3.8, accompanied by the same trend in gingival index registered as Δ GI of -0.35±0.05 ($p>0.05$), and Δ % sites with BOP -3.7±9.3. However, TNF antagonists resulted in significant change in PD with a Δ PD (mm) of -1.49± 0.22 ($p<0.05$) and Δ % sites with PD ≥4 mm of -3.7 ±6.9 ($p<0.05$), while Δ CAL (mm) (-0.5 ± 0.26) and Δ % sites with CAL ≥4 mm (-1.11± 0.11) were similarly significant ($p<0.05$).

Our study demonstrated rapid and sustained efficacy of anti-TNF agents among active RA patients sub-optimally

Characteristics	Baseline	6 months	p
RA-related parameters			
DAS28-ESR	4.95±1.54	2.65±0.81	p<0.05
Serum ACPA titer (U/mL)	145.8±116.2	101.0±54.5	p<0.05
Serum RF levels (IU/mL)	145.8±122.5	96.6±45.8	p<0.05
Serum CRP levels (mg/dL)	4.43±2.89	1.4±0.73	p<0.05
ESR (mm/hour)	58.3±21.9	23.12±10.2	p<0.05
Periodontal status			
% sites with plaque	34.9±15.2	31.9±12.4	p>0.05
GI	0.98±0.16	0.63±0.11	p>0.05
% sites with BOP	13.9±8.7	3.3±1.8	p<0.05
PD (mm)	2.75 ±0.51	1.36±0.29	p<0.05
% sites with PD≥4mm	11.9±2.4	8.2±3.5	p<0.05
CAL (mm)	2.62±0.49	1.92±0.23	p<0.05
% sites with CAL≥4mm	2.51±0.53	1.4±0.42	p<0.05

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

controlled by synthetic DMARDs; short-term TNF inhibition resulted not only in significant decrease of disease activity globally assessed by DAS28-ESR, but also improved inflammatory (ESR, CRP) and serologic (ACPA) parameters as well. It is widely recognized that TNF antagonists reasonably control inflammation pathway in moderate-to-severe active RA, and our results generally support the evidences in integrative literature reviews [12-18].

Furthermore, our results revealed significant association between TNF antagonists used to treat RA (infliximab, adalimumab, etanercept) and the periodontal status (plaque index, gingival index, pocket depth and clinical attachment loss), even during short-term (6 months) follow-up.

In fact, we already established the dual efficacy of anti-TNF therapy in a pilot study performed on a limited number of RA and periodontitis [15].

Actually, in the current study, we observed that RA patients tend to have more gingival plaques, possible related to different degrees of hand disability, as well as high prevalence of gingival inflammation, as shown by GI; however, TNF inhibition had no significant effect neither on PI nor on GI ($p>0.05$), although modestly ameliorated such periodontal parameters. The decrease in GI and BOP may be related to decrease in gingival inflammation with TNF agents.

The other parameters defining the periodontal status including pocket depth and clinical attachment loss improved significantly from baseline, supporting the role of anti-TNF therapy in suppressing periodontal inflammation and delaying local alveolar damage. Thus, the difference in PD and CAL during follow-up was thought to be related to decrease in local (periodontal micro-environment) of pro-inflammatory mediators / cytokines levels induced by TNF blockade.

A closer look to the RA-periodontal disease relation and the benefits of TNF antagonists in both conditions revealed conflicting data [14-18]. Treatment with a TNF inhibitor was shown in a several previous research papers to control both RA and periodontitis [14-18]. On the other hand, different authors noticed only modest influence of TNF inhibition in periodontal disease in the absence of surgical procedures or other periodontal specific therapeutic protocols [12-19].

Interestingly, a recent report advanced the hypothesis that tocilizumab, a recombinant humanized antihuman interleukin-6 receptor monoclonal antibody, may ameliorate periodontal inflammation in RA with periodontitis [19]. In fact, the study has demonstrated that patients in both TNF inhibitor and tocilizumab groups present with a significant improve in rheumatologic parameters and decrease in periodontal inflammation as assessed by probing depth and clinical attachment loss, while gingival index as well as bleeding on probing were modestly influenced [19]. Moreover, none of these two drugs was associated with significant changes in plaque index [19].

As in our study, IL-6 and TNF blockade may not only decrease RA activity but also ameliorate systemic inflammation, which subsequent recover of periodontal inflammation [15, 19].

Furthermore, TNF inhibition is responsible for consistent decrease in serum inflammatory mediators and antibody profile as well, providing an excellent impact on all RA related characteristics and positively influencing oral health.

Conclusions

Rheumatoid arthritis, particularly severe active, ACPA positive disease subsets, is essentially accompanied by comorbid periodontal disease.

TNF blockade is efficient in patients with active RA and potentially able to modulate the inflammatory process in the periodontal tissue.

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