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Original article

Efficacy of baricitinib on periodontal inflammation in patients with rheumatoid arthritis

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ABSTRACT

Objective: Despite a widely recognized bidirectional pathobiologic relationship between rheumatoid arthritis (RA) and periodontal disease, the impact of innovative anti-rheumatic drugs in modulating not only inflammatory and immune articular damage, but also periodontal microenvironment remains debatable. We aimed to evaluate the periodontal status in RA with and without baricitinib, a Janus kinase (JAK) inhibitor, and to better describe association between these entities.
Methods: We performed a prospective longitudinal 24-weeks study in 21 active RA initiating baricitinib. Standard assessments included a dual rheumatologic (RA activity, disability, serological, inflammatory profile) and dental evaluation comprising plaque index, gingival index, bleeding on probing, probing depth, clinical attachment level.
Results: More than half of RA presented at baseline with chronic periodontitis, as suggested by high prevalence of sites with dental plaque, abnormal bleeding on probing, probing depth and clinical attachment level. Aggressive periodontal disease was reported particularly in disease subsets with excessive inflammatory (serum C reactive protein level) and serologic biomarkers (anti-citrullinated peptide antibodies). Furthermore, significant correlations between dental pathology, disease activity and ACPA levels were also reported ($P < 0.05$). Consistent improvement was noticed in both rheumatoid arthritis characteristics and periodontal status after 24 weeks of baricitinib ($P < 0.05$).
Conclusion: RA, particularly severe active ACPA-positive disease, is basically associated with altered periodontal health. JAK blockade through oral baricitinib may be efficient in patients with active RA and potentially able to modulate the inflammatory process in the periodontal tissue.

1. Introduction

The bidirectional relationship between periodontal disease and systemic disorders such as diabetes, cardiovascular and neurodegenerative disorders, chronic kidney disease, chronic obstructive airways disease, and immune-mediated rheumatic pathology, particularly rheumatoid arthritis (RA), is widely documented [1,2].

RA and chronic periodontitis are multifaceted chronic inflammatory conditions characterized by complex cytokine signature, with joint inflammation and damage, periodontal inflammation with subsequent periodontal ligament and alveolar bone loss and gradual increase in tooth mobility, respectively [3,4].

Both entities share multifactorial pathways including similar genetic background (HLA-DR antigens) and environmental factors (smoking), unbalanced activation of proinflammatory

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cytokines (TNF-α, IL-1β, IL-6, IL-17) and proinflammatory mediators (prostaglandin E2, nitric oxide), osteoclast activation (RANKL overexpression) and dynamic articular and alveolar bone damage [1–9]. Furthermore, exposure to oral, lung and gut microbiota, particularly to antigens generated during citrullination related to peptidylarginine-deaminase enzyme produced mainly by *Porphyromonas gingivalis* but also by *Aggregatibacter actinomycetemcomitans* may contribute to both RA and periodontal disease; hypercitrullination breaks the immune tolerance with induction of anti-citrullinated protein antibodies (ACPA) and promotes chronic inflammatory response in periodontal and synovial microenvironments [1,2,10–12].

Increased risk of periodontitis is already reported in patients with RA, irrespective of disease duration [1–3], with a rate of 1.13 *vs.* controls according to a recent review [4]; overall, it seems that RA patients are prone to develop moderate periodontitis, with worsen periodontal status and more severe and aggressive lesions if early untreated compared to established disease [1,2]. On the other hand, an association between chronic periodontal inflammation and the risk to develop RA was also advanced, new data proposing that periodontitis associated with *P. gingivalis* is more likely to be present in ACPA-positive at-risk adults without arthritis [11–13].

The emerging concept of dynamic link between RA and periodontitis suggests that aggressive management of rheumatic condition not only control articular inflammation and following damage, but also might modulate periodontal inflammation [1,2,14,15]. Different papers investigated TNF and non-TNF biologics in periodontal disease with controversial and provocative results; indeed, TNF inhibitors, IL-6 receptor antagonist and even B-cells depletive agents are all able to improve periodontal status in early and established RA with periodontitis by reducing gingival and periodontal inflammation as well as tissues loss [1,2,15–22].

We assumed that innovative small-molecule drugs that reversibly inhibit Janus-activated kinase (JAK)-dependent cytokine signaling (tofacitinib, baricitinib) recently approved for the management of moderate-to-active RA [23], may also have dual impact, on articular and periodontal disease, as they target intracellular pathways and modulate multiple cytokines [23]. However, only one paper has documented the benefits of tofacitinib on periodontitis in RA [24].

The aim of this study was to evaluate the influence of baricitinib on periodontal health in patients with RA and to describe the interplay between clinical, biologic and serologic RA characteristics and periodontal status.

2. Methods

We performed a prospective longitudinal study in twenty-one RA patients starting baricitinib for their moderate-to-severe active disease, followed-up in one academic rheumatology department in North-East Romania. Baricitinib was prescribed according to local recommendation for biologic and targeted synthetic therapy aligned with European League Against Rheumatism (EULAR) guidelines; before the study, patients presented inadequate response or intolerance to conventional synthetic antirheumatic drugs (csDMARDS) or biologics.

A dual rheumatologic and full mouth assessment was performed before starting baricitinib and reassessed after 24 weeks.

RA-related variables comprised disease activity based on DAS28-CRP (Disease Activity Score on 28 evaluable joints using C-reactive protein) and SDAI (Simplified Disease Activity Index), and serological markers (rheumatoid factor, RF, and ACPA).

Periodontal status was clinically evaluated using the number of teeth, full mouth plaque index (PI), gingival index (GI) and bleeding on probing (BOP) for the assessment of gingivitis, probing pocket depth (PD) and clinical attachment level (CAL) for current periodontitis and cumulative periodontal disease, respectively. Measurements of PD and CAL were performed with a Williams probe at four sites around each tooth and recorded to the nearest millimetre, every data close to 0.5 mm being rounded to the lower whole number. PI and BOP were reported as percentage (positive sites: all sites ratio). The missing and mobile teeth were clinically assessed and alveolar bone loss was measured on panoramic dental X-ray.

Case definitions for gingivitis and periodontitis as well as severity classifications were used according the new 2017 classification criteria [25]: level 1 (mild) – CAL ≥3 mm in ≥2 nonadjacent teeth and level 2 (severe) – CLA ≥ 5 mm in ≥30% of teeth; we considered level 0 – healthy periodontal status or up to one proximal site with CAL ≥3 mm.

Patients were instructed to maintain their oral hygiene habits the entire follow-up; any aggressive periodontal treatment (professional scaling, root planning) was avoided as we anticipated to evaluate the true impact of baricitinib on periodontal health.

As multiple confounders may interfere with correct interpretation of periodontal status [25], we excluded ex- or current smokers, patients with diabetes, patients receiving antibiotics or periodontal treatment within the previous 3 months, as well as patients having fewer than eight evaluable teeth.

2.1. Statistical analysis

Results were expressed as median and interquartile range 25–75% (IQR 25–75) or number (%), correlations by Spearman rank tests, while comparisons between baseline and 6 months of baricitinib were performed by Wilcoxon test. Statistics were done with SPSS software (version 19), *P*-values less than 0.05 being considered as statistically significant.

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

3. Results

3.1. Baseline RA and periodontal assessments

Demographics, rheumatologic and periodontal parameters as well as concomitant RA medication including glucocorticoids and DMARDs at baseline are summarized in Table 1 and Table 2.

We enrolled mainly seropositive longstanding RA, with moderate-to-severe active disease insufficiently controlled by csDMARDs or failing to respond to at least one biologic.

We described impaired oral health in the majority of patients ($n = 19$), as follows: 15 had fewer teeth than normal for age and gender-matches healthy controls, 9 gingivitis (abnormal GI and increased prevalence of sites with BOP), and 19 patients had different degrees of chronic periodontitis (level 1 + 2). Furthermore, advanced loss of attachment was reported in one out of five patients, while increased prevalence of sites containing dental plaques in 9 cases.

Subgroup analysis showed higher biological (CRP, ESR) and serologic (ACPA but not RF) activity in patients with severe, either localized or generalized, periodontitis, compared to RA patients without periodontitis ($P < 0.05$). In addition, significant direct association was demonstrated between the periodontitis level, RA activity and ACPA levels ($r_1 = 0.78$, $p_1 = 0.001$, $r_2 = 0.76$, $p_2 = 0.002$, respectively): patients with more active RA and higher ACPA had more severe periodontitis (tooth loss, advanced CAL, severe PD).

Table 1
Demographic and rheumatologic characteristics of RA patients before and after baricitinib therapy.

Characteristics	Baseline	24 months	*P*-values*
Gender (female/male)	18/3		
Age (years)	60.00 [53.25–64.5]		
RA duration (months)	117.16 [49.25–159.00]		
Concomitant medication			
Corticosteroids (*n*)	6		
Methotrexate (*n*)	13		
Leflunomide (*n*)	4		
Antimalarials (*n*)	2		
Without DMARDs (*n*)	2		
Previous biologics			
Bio-naïve RA/bio-experienced RA (*n*)	3/18		
Serology	17		
RF positive (*n*)	265.9 [128.5–321.2]	202.3 [127.1–272.5]	
RF titer (IU/mL)	12		0.27
ACPA positive (*n*)	321.17 [89.3–441.2]	175.67 [58.2–201.3]	**0.01***
ACPA titer (IU/mL)			
Inflammation			
CRP (mg/dL)	4.61 [3.60–7.99]	2.57 [1.49–3.2]	**0.02***
ESR (mm/hour)	48.63 [38.50–55.50]	25.00 [23.25–32.75]	**0.01***
Disease activity			
DAS28-CRP	5.53 [4.91–6.00]	3.97[3.74–4.37]	**0.02***
SDAI	21.00 [18.18–27.38]	11.5 [10.00–13.75]	**0.01***

RA: rheumatoid arthritis; DMARDs: Disease-Modifying AntiRheumatic Drugs; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibody; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28-CRP: Disease Activity Score including 28 joints using C-reactive protein; SDAI: Simplified Disease Activity Index; (*n*): number of patients; all data are presented as median and IQR values [25%–75%]; the bold values show the statistical significance.
* Significantly different from the baseline, as assessed by Friedman and Wilcoxon signed rank tests ($P < 0.05$).

Table 2
Periodontal status in RA patients before and after oral baricitinib.

Parameter	Baseline	24 months	*P*-values
Teeth count (*n*)	22.00 [20.25–23.75]	22.00 [20.25–22.75]	NS
% sites with plaque	31.00 [29.25–33.75]	30.00 [28.25–31.75]	NS
GI	0.98 [0.95–1.10]	0.82 [0.80–0.86]	$P < 0.05$
% sites with BOP	11.15 [10.12–12.10]	7.00 [6.50–8.1]	$P < 0.05$
PD (mm)	2.85 [2.80–2.90]	2.00 [1.90–2.20]	$P < 0.05$
% sites with PD ≥ 4 mm	12.7 (2.4)	8.3 (2.9)	$P < 0.05$
CAL (mm)	3.4 [3.1–3.7]	3.00 [2.9–3.2]	NS
% sites with CAL ≥ 4 mm	12.5 [11.05–13.0]	12.00 [11.05–12.25]	NS

Values are indicated as % or median [1st and 3rd quartiles]. RA: rheumatoid arthritis; GI: gingival index; BOP: bleeding on probing; PD: probing depth; CAL: clinical attachment level; NS: not significant ($P > 0.05$).

3.2. Effects of baricitinib on rheumatologic and periodontal parameters

Modifications in the periodontal status, clinical and biological RA activity were reassessed after 24 weeks, looking for the benefits of baricitinib.

As expected, all RA parameters significantly decreased; DAS28-CRP and SDAI strongly improved reaching moderate-to-low values, with a change of more than 1.2 points (EULAR-responders) *vs.* baseline, irrespective of the presence and severity of periodontitis. However, there was a trend to better improve in RA with periodontitis, although not significantly. Similarly, we reported a consistent decline in inflammation markers (both ESR and CRP), as well as a considerable immunologic response, particularly for ACPA levels, but also for RF (Table 1).

Patients with chronic periodontitis showed also a significant decrease in periodontal inflammation as suggested by improved GI, sites with BOP, PD and sites with PD ≥ 4 mm *vs.* baseline ($P < 0.05$) (Table 2).

Overall, clinical attachment level presented only slight changes without statistical significance; teeth count and bacterial plaque were also not significantly influenced by medication ($P > 0.05$) (Table 2).

Changes (Δ) in periodontal parameters after short-term baricitinib were calculated: significant change in PD −0.8[0.7–0.9] and Δ % sites with PD≥ 4 mm −3.5 [2.25–5] together with significant modifications in GI −0.15[0.13–0.28] and sites with BOP −3.8[3.2–4.95]; nevertheless, we showed only minor changes in periodontal parameters such as Δ CAL 0.3[0.4–0.5] and Δ % sites with CAL ≥ 4 −0.6[0.2–0.97] as well as gingival plaque and % of sites with gingival plaques ($P > 0.05$).

No significant correlations between variation of periodontal parameters with variation of RA were described ($P > 0.05$).

Since local periodontal treatment was not indicated during the short−term follow−up, we considered that improvement in all parameters investigating the degree of local gingival and periodontal inflammation is related to JAK blockade.

4. Discussion

We performed this study aiming to evaluate the influence of tsDMARDs on periodontal health in RA patients; we assumed that baricitinib, a JAK inhibitor blocking the subtypes JAK1 and JAK2, might decrease the levels of pro−inflammatory mediators in the periodontal microenvironment via the decline in systemic inflammation.

Before emphasizing the benefits of baricitinib on periodontal condition, we focused on oral health status in our RA cohort.

Firstly, we confirmed compromised oral health in the majority of cases, particularly a high rate of moderate-to-severe periodontal disease, confirming the already known risk of periodontitis in established RA [2,4–6,11]. Although we discussed only about

longstanding RA, several other studies have already noticed excessive periodontal disease nevertheless of RA settings (age, disease duration, serology profile, activity) *vs.* general population [2,4,11,12]. We identified abnormal periodontal parameters (increased PD, CAL) as well as high levels of gingival involvement confirmed by increased percentage of sites with plaques and inflammation, supporting data from literature [1,2]. Moreover, we recognized positive correlations between the severity of periodontitis, inflammatory parameters (especially CRP), serology (ACPA status and titres) and RA activity; indeed, recent studies suggest worst periodontal status in active untreated RA, and higher CRP if RA is associated with severe periodontitis [1,2,4,11,12]. Finally, it seems that ACPA-positive patients had severely impaired periodontal health, while disease activity correlated with periodontitis degree as well [1–4,11,12].

Secondly, we registered a rapid and consistent response to baricitinib, regardless of patient's previous medication (bio-naïve or bio-experienced RA); short-term JAK inhibition is able to result in significant improvement in clinical, biologic and, surprisingly, serologic RA activity (especially for ACPA, and here one can comment about the implications via citrullination at the periodontal and synovial microenvironment). Our results reasonably confirm the efficacy of baricitinib in controlling inflammation pathways in active established RA [23].

Thirdly, short-term course of baricitinib significantly reduced gingival and periodontal inflammation as suggested by improvement in GI, BOP, PD, paralleling the articular improvement. However, only minor changes in CAL were noticed, while the bacterial PI remained stable after 24 weeks of baricitinib ($P > 0.05$). That means a positive reaction of gingiva related to baricitinib, despite the fact that bacterial plaque index remained the same; that is really encouraging.

All patients continued background medication, their dental hygiene behaviour remained unchanged, and no periodontal therapy was practiced; accordingly, we concluded that the decrease in GI and BOP might be related to decrease in gingival inflammation induced by baricitinib.

Recent reports offer suitable arguments to reinforce that early aggressive RA management with csDMARDs and/or biologics not only promote sustained remission, but also impact periodontal damage [1,2,14,15,23]. It seems that regular treatment with biologics or non-biologics may retrieve periodontal status in RA with periodontitis [1,2,16–22]. Additionally, innovative biologics acting by blocking the TNF and IL-6-mediated signalling are also able to promote reliable decrease in inflammatory cytokines and antibodies with dramatic effect not only on clinical, biological and serological activity of RA, but also on oral health [14–21].

A closer look for evidences concerning TNF inhibitors in improving chronic periodontitis showed inconsistent results [1,2,16–22]. Several papers clearly demonstrated the efficacy of TNF blockade in controlling both RA and periodontitis [16–22], but others recognized only uncertain advantages unless concomitant specific periodontal treatment, even surgical procedures [16]. Interestingly, it seems that infliximab, a monoclonal antibody targeting TNF, enhances gingival inflammation, while improving alveolar bone destruction [1,2,26]; besides, infliximab dissociates response of severe periodontal destruction biomarkers (e.g. matrix metalloproteinase 3) in RA [26]. In contrast, both tocilizumab and rituximab promote a significant down regulation of gingival inflammation and gingival damage in RA associated with periodontitis related to decrease in serum inflammatory mediators [20,22].

The influence of intensive periodontal treatment on RA is similarly controversial. Several publications [27–30] have successfully demonstrated that specific therapies for chronic periodontitis (e.g. non-surgical professional scaling or root planning with or without antibiotics) may ameliorate local inflammation, improve RA activity and response to different anti-rheumatic drugs. However, other reports [30] fail to demonstrate successful RA outcomes with periodontal treatment; indeed, ESPERA trial emphasized improved periodontal health with periodontal treatment in RA, but no effect on clinical parameters assessed by DAS28 [30].

Data about JAK inhibitors in periodontitis are scarce; only one recent publication already mentioned the role of tofacitinib in two cases of RA and comorbid periodontal disease [24]. As suggested, efficacy of tofacitinib seems to be related to the suppression of systemic inflammation promoted by high levels of IL-6 through a sustained inhibition of IL-6 signalling [24]. Unfortunately, the level of IL-6 or its receptor in gingival crevicular fluid was not assessed, although serum concentration showed a significant and rapid decline.

Our main results are focused on baricitinib efficacy for joint and periodontal disease as well. In short-term we registered a significant decrease in clinical, biologic and serologic RA activity; we also noticed improvement of periodontal condition especially related to decrease in gingival inflammation (as supported by decreased in gingival index, bleeding on probing, sites with bleeding), but also on probing depth. That means a positive reaction of gingiva related to baricitinib, despite the fact that bacterial plaque index remained the same.

However, we failed to describe any significant correlations between variation of periodontal and rheumatologic parameters.

To the best of our knowledge, this is the first report to compare periodontal condition in patients with RA and chronic periodontitis before and after baricitinib therapy; our results showed beneficial effects of baricitinib on levels of periodontal inflammation, which might be related to inhibition of IL-6 and JAK-mediated cytokine signalling.

Further studies in larger number of RA patients and chronic periodontitis are necessary to confirm our results, with longer follow-ups and, eventually, with control group. Moreover, it would be interesting to explore cytokine level in gingival crevicular fluid and the influence of oral baricitinib.

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Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Rutter-Loche Z, Fuggle N, Orlandi M, et al. Periodontal disease and autoimmunity: what we have learned from microbiome studies in Rheumatology. In: Arjunan P, editor. Periodontitis–A useful reference. InTech; 2017. p. 113–41.
[2] Äyräväinen L, Leirisalo-Repo M, Kuuliala A, et al. Periodontitis in early and chronic rheumatoid arthritis: a prospective follow-up study in Finnish population. BMJ Open 2017;7:e011916.
[3] Koziel J, Mydel P, Potempa J. The link between periodontal disease and rheumatoid arthritis: an updated review. Curr Rheumatol Rep 2014;16:1–7.
[4] Fuggle NR, Smith TO, Kaul A, et al. Hand to mouth: a systematic review and meta-analysis of the association between rheumatoid arthritis and periodontitis. Front Immunol 2016;7:1–10.
[5] Choi IA, Kim YM, Lee JY, et al. Periodontitis is associated with rheumatoid arthritis. A study with longstanding rheumatoid arthritis patients in Korea. Korean J Intern Med 2016;31:977–86.
[6] Kobayashi T, Yoshie H. Host responses in the link between periodontitis and rheumatoid arthritis. Curr Oral Health Rep 2015;2:1–8.
[7] Ceccarelli F, Saccucci M, Di Carlo G, et al. Periodontitis and rheumatoid arthritis: the same inflammatory mediators? Hindawi. Mediators of Inflammation; 2019. Article ID 6034546, 8 pages.
[8] Thilagar S, Theyagarajan R, Sudhakar U, et al. Comparison of serum tumor necrosis factor-α levels in rheumatoid arthritis individuals with and without chronic periodontitis: a biochemical study. J Indian Soc Periodontol 2018;22:116–21.

[9] Rangil JS, Bagan L, Silvestre FJ, et al. Periodontal, salivary and IL-6 status in rheumatoid arthritis patients. A cross-sectional study. Med Oral Patol Oral Cir Bucal 2017;22:595–600.
[10] Eriksson K, Guozhong F, Lundmark A, et al. Periodontal health and oral microbiota in patients with rheumatoid arthritis. J Clin Med 2019;8:630.
[11] Mankia K, Cheng Z, Do T, et al. Prevalence of periodontal disease and periodontopathic bacteria in anti–cyclic citrullinated protein antibody–positive at-risk adults without arthritis. JAMA Netw Open 2019;2, http://dx.doi.org/10.1001/jamanetworkopen.2019.5394, e195394.
[12] Gonzales SM, Patne JB, Yu F, et al. Alveolar bone loss is associated with circulating anti-citrullinated protein antibody (ACPA) in patients with rheumatoid arthritis. J Periodontol 2015;86:222–31.
[13] de Oliveira Ferreira R, de Brito Silva R, Baraúna Magno M, et al. Does periodontitis represent a risk factor for rheumatoid arthritis? A systematic review and meta-analysis. Ther Adv Musculoskel Dis 2019;11:1–16.
[14] Jung GU, Han JY, Hwang K, et al. Effects of conventional synthetic disease-modifying anti-rheumatic drugs on response to periodontal treatment in patients with rheumatoid arthritis. BioMed Res Int 2018 [Article ID 1465402, 7 pages].
[15] Romero-Sanchez C, Rodríguez C, Santos-Moreno P, et al. Is the treatment with biological or non-biological DMARDS a modifier of periodontal condition in patients with rheumatoid arthritis? Curr Rheumatol Rev 2017;13:139–51.
[16] Savioli C, Ribeiro AC, Campos Fabri GM, et al. Persistent periodontal disease hampers anti-tumor necrosis factor treatment response in rheumatoid arthritis. J Clin Rheumatol 2014;18:180–4.
[17] Mayer Y, Balbir-Gurman A, Machtei EE. Anti-tumor necrosis factor-alpha therapy and periodontal parameters in patients with rheumatoid arthritis. J Periodontol 2009;80:1414–20.
[18] Kadkhoda Z, Amirzargar A, Esmaili Z, et al. Effect of TNF-α blockade in gingival crevicular fluid on periodontal condition of patients with rheumatoid arthritis. Iran J Immunol 2016;13:197–203.
[19] Sikorska D, Orzechowska Z, Rutkowski R, et al. Diagnostic value of salivary CRP and IL-6 in patients undergoing anti-TNF-alpha therapy for rheumatic disease. Inflammopharmacol 2018;26:1183–8.
[20] Kobayashi T, Yokoyama T, Ito S. Periodontal and serum protein profiles in patients with rheumatoid arthritis treated with tumor necrosis inhibitor adalimumab. J Periodontol 2014;85:1480–8.
[21] Kobayashi T, Ito S, Kobayashi D, et al. Interleukin-6 receptor inhibitor tocilizumab ameliorates periodontal inflammation in patients with rheumatoid arthritis and periodontitis as well as tumor necrosis factor inhibitors. Clin Exp Dent Res 2015;1:63–73.
[22] Coat J, Demoersman J, Beuzit S, et al. Anti-B lymphocyte immunotherapy is associated with improvement of periodontal status in subjects with rheumatoid arthritis. J Clin Periodontol 2015;42:817–23.
[23] Kawalec P, Śladowska K, Malinowska-Lipień I, et al. New alternative in the treatment of rheumatoid arthritis: clinical utility of baricitinib. Ther Clin Risk Manag 2019;15:275–84.
[24] Kobayashi T, Ito S, Murasawa A, et al. Effects of tofacitinib on the clinical features of periodontitis in patients with rheumatoid arthritis: two case reports. BMC Rheumatol 2019;3:1–4.
[25] Caton J, Armitage G, Berglundh T, et al. A new classification scheme for periodontal and periimplant diseases and conditions–Introduction and key changes from the 1999 classification. J Clin Periodontol 2018;45:S1–8.
[26] Rinaudo-Gaujous M, Blasco-Baque V, Miossec P, et al. Infliximab induced a dissociated response of severe periodontal biomarkers in rheumatoid arthritis patients. J Clin Med 2019;8:751, http://dx.doi.org/10.3390/jcm8050751.
[27] Ortis P, Bissada NF, Paloma L, et al. Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factor inhibitors. J Periodontal 2009;80:535–40.
[28] Yang NY, Wang CY, Chyuan IT, et al. Significant association of rheumatoid arthritis-related inflammatory markers with non-surgical periodontal therapy. J Formos Med Assoc 2018;117:1003–10.
[29] Calderaro CD, Correa JD, Ferreira DA, et al. Influence of periodontal treatment of rheumatoid arthritis: a systematic review and meta-analysis. Rev Bras Rheumatol 2017;57:238–44.
[30] Monsarrat P, Fernandez de Grado G, Constantin A, et al. The effect of periodontal treatment on patients with rheumatoid arthritis: the ESPERA randomised controlled trial. Joint Bone Spine 2019;86:600–9.