

Cyclophosphamide-induced immunomodulation as a potential modifier of apical periodontitis: a hypothesis-based study

Imunomodulação induzida por ciclofosfamida como um potencial modificador da periodontite apical: um estudo baseado em hipótese

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ABSTRACT

Cyclophosphamide (CPD) is a widely used antineoplastic and immunosuppressive agent with well-established effects on adaptive immunity, particularly through the modulation of T lymphocyte populations. **Objective:** This study aimed to discuss the hypothesis that CPD-mediated immunomodulation may modify the development and progression of apical periodontitis (AP), influencing disease expression, bone resorption, and periapical healing. **Material and Methods:** A consultation of the scientific literature was conducted to develop and adequately support the proposed hypothesis. Articles related to the topic were identified using keywords referring to cyclophosphamide, apical periodontitis, immunomodulation, and T lymphocytes. The evidence retrieved was analyzed and integrated by considering the immunomodulatory effects of CPD, the immunopathogenesis of AP, and the role of T lymphocyte subsets in the regulation of inflammation, cytokine production, bone resorption, and tissue repair. **Results:** The available evidence indicates that CPD exerts dose-dependent immunomodulatory effects, including the selective regulation of regulatory T lymphocytes. T lymphocytes play a central role in the complex immune response involved in AP by influencing cytokine production, inflammatory regulation, and the balance between bone resorption and repair. Therefore, CPD-induced alterations in T lymphocyte subsets may modify the inflammatory response associated with AP and, consequently, influence its development, progression, and healing. **Conclusion:** CPD-mediated immunomodulation is biologically plausible as a potential modifier of AP. Experimental and clinical studies are needed to test this hypothesis and determine its implications for the diagnosis, treatment, and follow-up of endodontic diseases in patients undergoing CPD therapy.

KEYWORDS

Apical periodontitis; Cyclophosphamide; Endodontics; Immunomodulation; T lymphocytes.

RESUMO

A ciclofosfamida (CPD) é um agente antineoplásico e imunossupressor amplamente utilizado, com efeitos bem estabelecidos sobre a imunidade adaptativa, especialmente por meio da modulação das populações de linfócitos T. **Objetivo:** Este estudo teve como objetivo discutir a hipótese de que a imunomodulação mediada pela CPD possa modificar o desenvolvimento e a progressão da periodontite apical (PA), influenciando a expressão da doença, a reabsorção óssea e o reparo periapical. **Material e Métodos:** Foi realizada uma consulta à literatura científica para elaborar e fundamentar adequadamente a hipótese proposta. Foram consultados artigos relacionados ao tema, localizados por meio da busca de palavras-chave referentes à ciclofosfamida, periodontite apical, imunomodulação e linfócitos T. As evidências encontradas foram analisadas e integradas considerando os efeitos imunomoduladores da CPD, a imunopatogênese da PA e o papel das subpopulações de linfócitos T na regulação da inflamação, na produção de citocinas, na reabsorção óssea e no reparo tecidual. **Resultados:** As evidências disponíveis indicam que a CPD exerce efeitos imunomoduladores dependentes da

dose, incluindo a regulação seletiva dos linfócitos T reguladores. Os linfócitos T desempenham papel central na complexa resposta imunológica envolvida na PA, influenciando a produção de citocinas, a regulação da inflamação e o equilíbrio entre a reabsorção e o reparo ósseo. Dessa forma, alterações nas subpopulações de linfócitos T induzidas pela CPD podem modificar a resposta inflamatória associada à PA e, conseqüentemente, influenciar seu desenvolvimento, sua progressão e seu reparo. **Conclusão:** A imunomodulação mediada pela CPD apresenta plausibilidade biológica como potencial modificadora da PA. Estudos experimentais e clínicos são necessários para testar essa hipótese e determinar suas implicações para o diagnóstico, o tratamento e o acompanhamento das doenças endodônticas em pacientes submetidos à terapia com CPD.

PALAVRAS-CHAVE

Periodontite apical; Ciclofosfamida; Endodontia; Imunomodulação; Linfócitos T.

INTRODUCTION

Cyclophosphamide (CPD) is an immunosuppressive drug whose mechanism of action involves inducing apoptosis and reducing the homeostatic proliferation of regulatory T lymphocytes (Treg; Figure 1). CPD is used in the treatment of haematological malignancies, including lymphoma and leukaemia, as well as epithelial tumours such as those of the breast, ovaries, and small cell lung carcinomas [1,2]. In addition to its role in antineoplastic chemotherapy, CPD is also employed in the treatment of autoimmune and immune-mediated diseases, such as lupus nephritis, Wegener's granulomatosis, and multiple sclerosis. Moreover, it is part of the conditioning regimen preceding bone marrow transplantation for hematological malignancies and is used in treating aplastic anaemia. Prolonged use of CPD results in immune system suppression [3-5]. Discovered in 1958, CPD is one of the oldest anticancer drugs and is recognized as a highly successful chemotherapy agent, listed among the World Health Organization (WHO) essential medicines.

CPD can be administered orally or intravenously. High doses (generally exceeding 120 mg/kg) exert a direct cytotoxic effect on tumor cells. However, such dosages can cause numerous side effects, including haemorrhagic cystitis and, in more severe cases, cardiac toxicity [6]. In contrast, low-dose CPD is generally well tolerated, with a significantly reduced risk of side effects. At these doses, its therapeutic effects are primarily attributed to immunomodulatory mechanisms, particularly the selective induction of apoptosis in Tregs, resulting in enhanced antitumor immune responses [7,8].

Apical periodontitis (AP) is an inflammatory disease of endodontic origin that develops as a consequence of microbial infection of the root canal system, typically following carious lesions

or dental trauma [9]. Microorganisms and their byproducts gain access to the pulp space, leading to pulp necrosis and the establishment of a persistent infection that triggers an immunoinflammatory response in the periapical tissues [10-12]. This response is characterized by the recruitment and activation of innate and adaptive immune cells, including macrophages, dendritic cells, B lymphocytes, and T lymphocytes, along with the release of pro-inflammatory cytokines, chemokines, and immunoregulatory mediators [13,14]. The dynamic interaction among these immune components plays a central role in the progression, stabilization, or resolution of periapical lesions, with T lymphocytes emerging as key regulators of inflammation, bone resorption, and tissue repair in AP. However, the potential impact of CPD-induced immunomodulation on the development of apical periodontitis remains poorly understood (Figure 2).

BIOLOGICAL RATIONALE LINKING CPD AND AP

CPD is an antineoplastic and immunosuppressive agent with well-documented dose-dependent effects on the immune system, particularly on T lymphocyte populations. While high doses induce broad cytotoxicity, low doses selectively modulate immune responses by affecting Treg and altering cytokine secretion profiles [7,15]. Experimental and clinical studies indicate that CPD can reduce Treg homeostasis and function, thereby enhancing effector T lymphocytes activity and modifying immune regulation [16-18].

AP is a multifactorial inflammatory disease characterized by a complex interplay between innate and adaptive immune responses triggered by microbial infection of the root canal system. The establishment and progression of periapical lesions involve the coordinated activity of

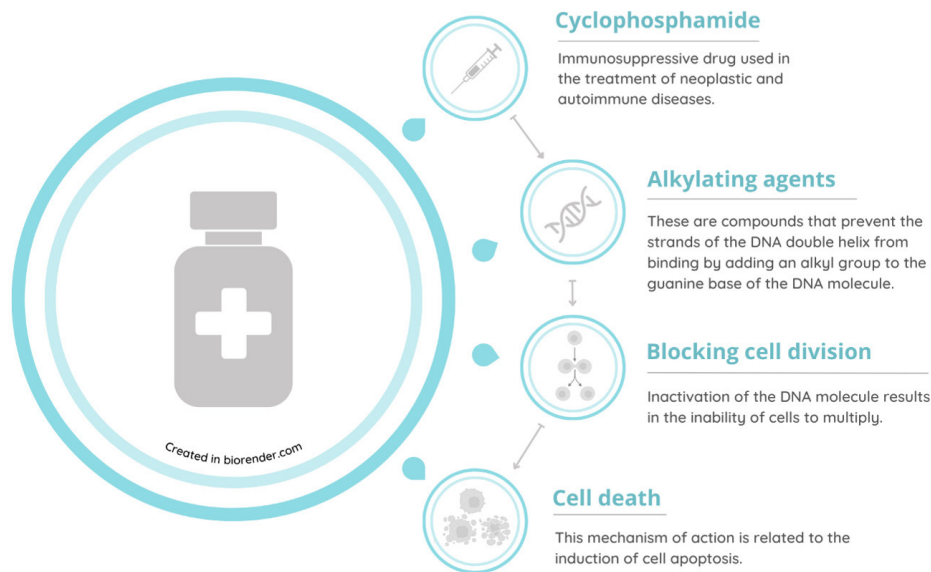


Figure 1 – Mechanism of action of cyclophosphamide. Cyclophosphamide is a drug used in the treatment of various autoimmune disorders and in chemotherapy regimens. After administration, cyclophosphamide is metabolized in the liver and is an alkylating agent belonging to the oxazaphosphorine group. It can be administered orally or intravenously, with the dose varying according to the clinical condition being treated. This alkylating agent acts through three main mechanisms: first, alkylation of DNA bases occurs, resulting in the fragmentation of deoxyribonucleic acid due to the action of repair enzymes attempting to replace the alkylated bases, thereby inhibiting DNA synthesis and ribonucleic acid transcription. Second, cross-links form between atoms in the affected DNA, preventing the separation of DNA strands necessary for synthesis or transcription. Third, cyclophosphamide induces incorrect nucleotide pairing, leading to mutations.

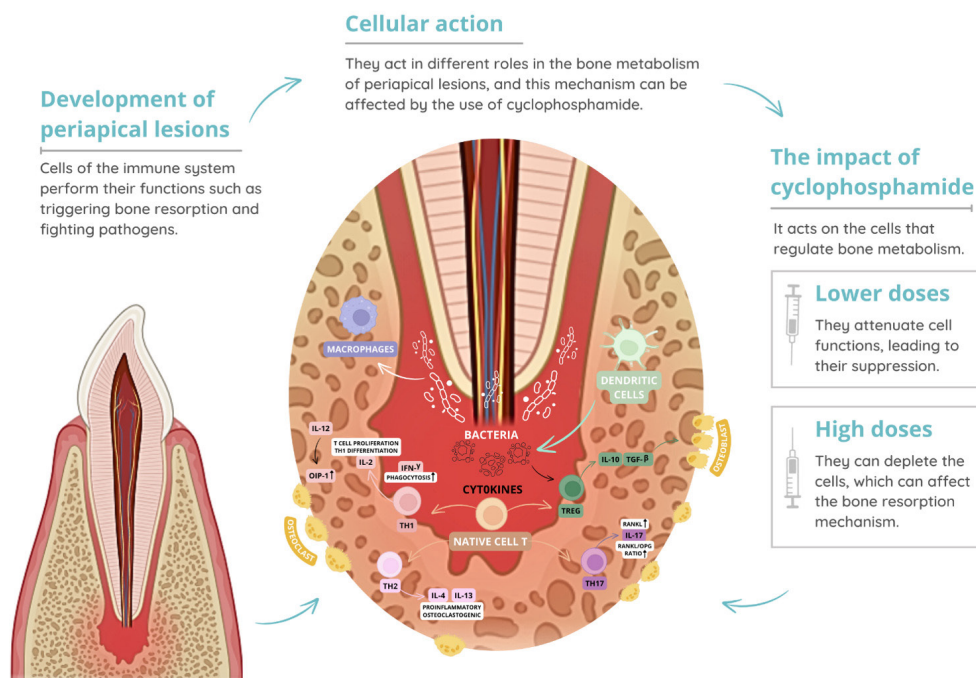


Figure 2 – Relationship between the development of periradicular lesion and the use of cyclophosphamide. Different types of injuries can lead to endodontic infections, resulting in periapical lesions. Following bacterial proliferation and the extension of their toxic products to the root apex, an immune response is triggered, recruiting inflammatory cells such as neutrophils, macrophages, and lymphocytes to the area to contain the bacterial infection. At this point, the cells release inflammatory mediators, such as cytokines and prostaglandins, which promote the inflammatory response, attract more defense cells, and cause degradation of the periapical tissues. The lesion then progresses through various stages until it becomes chronic. During this process, bone resorption occurs, driven by osteoclasts in response to the defense mechanisms acting to contain the infection. The hypothesis of this study explores how cyclophosphamide may affect this inflammatory response, given that this medication directly impacts cellular response and bone metabolism.

neutrophils, macrophages, dendritic cells, osteoclasts, and multiple cytokine networks that regulate host defense, bone resorption, and tissue repair. Within this complex osteoimmune environment, T lymphocytes play an important immunoregulatory role by modulating inflammatory responses and osteoclastogenesis rather than acting as the sole determinants of disease progression. T lymphocytes-mediated pathways contribute to periapical tissue destruction through the production of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)- α , which promote osteoclast differentiation and bone resorption via RANKL-dependent mechanisms [14,19,20]. Therefore, the present hypothesis focuses on one specific immunological pathway through which CPD may influence the biological behavior of AP.

Distinct T lymphocyte subsets, including Th1, Th2, Th17, and Treg, orchestrate the balance between destructive and reparative processes in AP. Th1 and Th17 responses are associated with enhanced inflammation and bone resorption, whereas Th2 and Treg-associated cytokines contribute to immune regulation and periapical healing [13,21-24]. Disruption of this balance has been implicated in lesion progression and impaired repair.

Low-dose CPD has been shown to shift immune responses toward a pro-inflammatory phenotype by increasing Th1-associated cytokines, such as interferon (IFN)- γ and IL-2, while reducing Th2- and Treg-related mediators, including IL-4 and IL-10 [8,25,26]. Given that these immune pathways are directly involved in the pathogenesis and healing of AP, CPD-induced modulation of T lymphocyte subsets may alter the inflammatory microenvironment of periapical tissues, influencing lesion development, progression, and repair.

Despite the widespread clinical use of CPD, its potential impact on apical periodontitis remains poorly explored. Understanding how CPD-mediated immune modulation affects periapical disease may provide important insights into endodontic diagnosis and treatment outcomes in immunosuppressed patients.

Beyond systemic immune modulation, the periapical region represents a unique immunological microenvironment in which local immune responses are continuously shaped

by microbial stimuli and tissue-derived signals. The balance between pro-inflammatory and regulatory pathways within this niche is critical for determining whether apical periodontitis progresses, stabilizes, or resolves. Disruption of this finely tuned equilibrium may result in altered inflammatory patterns, even in the absence of significant changes in microbial load.

CPD-induced immunomodulation may exert differential effects at systemic and local levels. While systemic immunosuppression is a recognized outcome of CPD therapy, local immune responses within periapical tissues may be selectively altered rather than uniformly suppressed. This selective modulation could influence immune cell recruitment, cytokine gradients, and osteoimmune signalling pathways, potentially modifying lesion behaviour and radiographic expression.

Particular attention should be given to the Treg/Th17 axis, which has emerged as a critical regulator of inflammatory bone diseases. Experimental evidence suggests that CPD-induced depletion or functional impairment of Treg cells may favour Th17-driven inflammation, leading to increased production of IL-17 and enhanced recruitment of neutrophils and osteoclast precursors. In the context of apical periodontitis, such shifts may exacerbate inflammatory bone resorption or interfere with the resolution phase of the lesion.

Importantly, immune-mediated modulation of periapical inflammation may contribute to a dissociation between clinical symptoms, radiographic findings, and histopathological activity. Evidence from other immunosuppressive conditions suggests that alterations in host immune responses may reduce the radiographic expression of apical periodontitis despite persistent inflammation within periapical tissues. Whether this also occurs during CPD therapy remains unknown and warrants further investigation.

It should be emphasized that these immunological effects are dose dependent. While low-dose CPD preferentially modulates Treg and enhances effector immune responses, high-dose CPD causes generalized lymphodepletion and systemic immunosuppression. These distinct pharmacological profiles may lead to different effects on AP. Therefore, the present hypothesis specifically addresses the biological consequences of low-dose CPD, since its selective modulation of T lymphocyte subsets provides the most plausible mechanistic link with AP immunopathogenesis.

To date, no direct experimental evidence has demonstrated that CPD induces modulation of the Treg/Th17 balance within AP lesions. Accordingly, the present hypothesis is based on the biological plausibility derived from the well-established immunomodulatory effects of CPD observed in other experimental and clinical settings, which warrant investigation in the context of AP.

THE HYPOTHESIS

Based on the selective immunomodulatory effects of low-dose CPD on Treg and Th1/Th17 responses, we hypothesize that low-dose CPD enhances the immunoinflammatory response associated with AP by promoting a Th1/Th17-skewed immune profile, resulting in increased inflammatory bone resorption and delayed periapical healing. Conversely, high-dose CPD, due to its broad immunosuppressive effects, may lead to a distinct biological response, which falls outside the primary scope of the present hypothesis.

Although CPD induces well-characterized systemic immunomodulatory effects, these changes may not be fully reproduced within the local periapical microenvironment. Immune responses in AP are continuously shaped by persistent microbial stimulation, local cell-cell interactions, and tissue-specific signaling pathways, which may modify or counterbalance systemic immune alterations. Therefore, the present hypothesis assumes that systemic immunomodulation may influence, but not necessarily determine, the local immune response within periapical lesions, highlighting the need for direct experimental investigation.

FUTURE DIRECTIONS

The hypothesis proposed in this study highlights several directions for future research aimed at clarifying the influence of CPD-induced immunomodulation on the development, expression, and healing of AP. Observational clinical studies, including cross-sectional, case-control, and cohort designs, may contribute to a better understanding of the association between CPD use and periapical disease, particularly regarding lesion prevalence, radiographic detectability, and treatment outcomes. Such studies may help identify whether systemic immunosuppression modifies the clinical and radiographic presentation of AP.

However, when designing future clinical studies, potential confounding factors should be carefully considered. Patients receiving CPD frequently undergo concomitant therapies, including corticosteroids, other chemotherapeutic agents, antibiotics, or immunomodulatory drugs, and may present systemic conditions and oral health characteristics that independently influence the development and progression of AP. Therefore, future studies should control for these variables through appropriate study design and statistical adjustment to better isolate the specific contribution of cyclophosphamide to periapical disease.

Experimental studies using immunosuppressed animal models represent an important approach to investigate the biological mechanisms underlying CPD-mediated modulation of periapical inflammation. Experimental studies should compare CPD-treated and untreated animals using micro-computed tomography to evaluate periapical bone loss, histological analysis to characterize the inflammatory infiltrate, and molecular approaches to assess Treg and Th17 cell populations, RANKL/OPG expression, and key cytokines involved in bone resorption and immune regulation, such as IL-1 β , IL-6, IL-10, IL-17, TNF- α , and IFN- γ . These models may clarify how alterations in T lymphocyte subsets and cytokine expression influence bone resorption and periapical tissue repair, providing mechanistic insights that are difficult to obtain in clinical settings. Complementary analyses focusing on inflammatory mediators and immune cell profiles could further elucidate the pathways involved in AP progression and healing under immunosuppressive conditions. The CPD regimen, including dose and treatment duration, should be defined according to the specific experimental objectives and clinical context, following multidisciplinary planning and established therapeutic protocols.

If confirmed, this hypothesis may have relevant clinical implications for endodontic diagnosis and treatment planning in patients receiving CPD. Emerging evidence from studies involving different immunosuppressive and immunomodulatory therapies suggests that these medications may influence the radiographic detectability of AP, although the findings remain heterogeneous and are not specific to CPD [27-29]. Therefore, reduced radiographic expression should not necessarily be interpreted as reduced disease activity, as ongoing inflammatory

processes may still be present at the tissue level. Given that the immune mechanisms involved in lesion formation also participate in periapical healing, CPD-induced immune modulation may affect both disease progression and post-treatment repair.

Understanding the impact of CPD on periapical immune responses may therefore support more individualized clinical monitoring strategies and encourage further translational research integrating immunology and endodontics.

Data availability

Research data is only available upon request.

Authors' Contributions

CAM: Conceptualization, Visualization. CAM, GAM, JAS, IFCP, BMG, WLFT, CREB, LCS, FB: Investigation. CAM, GAM, JAS, FB: Methodology. IFCP, BMG, WLFT, CREB, LCS, FB: Supervision. WLFT, CREB, LCS: Project Administration. CAM, GAM, JAS, IFCP, BMG: Writing – Original Draft Preparation. WLFT, CREB, LCS, FB: Writing – Review & Editing.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Regulatory Statement

Regulatory approval was not required for this study, as it did not involve human participants, human biological samples, or animals.

REFERENCES

- Ahlmann M, Hempel G. The effect of cyclophosphamide on the immune system: implications for clinical cancer therapy. *Cancer Chemother Pharmacol*. 2016;78(4):661-71. <https://doi.org/10.1007/s00280-016-3152-1>. PMID:27646791.
- Emadi A, Jones RJ, Brodsky RA. Cyclophosphamide and cancer: golden anniversary. *Nat Rev Clin Oncol*. 2009;6(11):638-47. <https://doi.org/10.1038/nrclinonc.2009.146>. PMID:19786984.
- De Jonge ME, Huitema ADR, Rodenhuis S, Beijnen JH. Clinical pharmacokinetics of cyclophosphamide. *Clin Pharmacokinet*. 2005;44(11):1135-64. <https://doi.org/10.2165/00003088-200544110-00003>. PMID:16231966.
- Fukushima H, Kudo T, Fuskushima T, Takahashi-Igari M, Shiigai M, Mori K, et al. An infant with life-threatening hemangioma successfully treated with low-dose cyclophosphamide. *Pediatr Int*. 2011;53(6):1073-5. <https://doi.org/10.1111/j.1442-200X.2011.03452.x>. PMID:22181565.
- Chung NG, Lee JW, Jang PS, Jeong DC, Cho B, Kim HK. Reduced dose cyclophosphamide, fludarabine and antithymocyte globulin for sibling and unrelated transplant of children with severe and very severe aplastic anemia. *Pediatr Transplant*. 2013;17(4):387-93. <https://doi.org/10.1111/petr.12073>. PMID:23551397.
- Stork CM, Schreffler SM. Cyclophosphamide. In: Wexler P, editor. *Encyclopedia of toxicology*. 3rd ed. Oxford: Academic Press; 2014. p. 1111-1113. <https://doi.org/10.1016/B978-0-12-386454-3.00720-X>.
- Waterman PA Jr, Torabinejad M, McMillan PJ, Kettering JD. Development of periradicular lesions in immunosuppressed rats. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998;85(6):720-5. [https://doi.org/10.1016/S1079-2104\(98\)90041-5](https://doi.org/10.1016/S1079-2104(98)90041-5). PMID:9638707.
- Madondo MT, Quinn M, Plebanski M. Low dose cyclophosphamide: mechanisms of T cell modulation. *Cancer Treat Rev*. 2016;42:3-9. <https://doi.org/10.1016/j.ctrv.2015.11.005>. PMID:26620820.
- Rittling SR, Zetterberg C, Yazig K, Skinner S, Suzuki N, Fujimura A, et al. Protective role of osteopontin in endodontic infection. *Immunology*. 2010;129(1):105-14. <https://doi.org/10.1111/j.1365-2567.2009.03159.x>. PMID:19824920.
- Bryant VL, Slade CA. Chemokines, their receptors and human disease: the good, the bad and the itchy. *Immunol Cell Biol*. 2015;93(4):364-71. <https://doi.org/10.1038/icb.2015.23>. PMID:25895814.
- Ricucci D, Siqueira JF Jr, Lopes WSP, Vieira AR, Rôças IN. Extraradicular Infection as the Cause of Persistent Symptoms: A Case Series. *J Endod*. 2015;41(2):265-73. <https://doi.org/10.1016/j.joen.2014.08.020>. PMID:25282379.
- Stashenko P. The role of immune cytokines in the pathogenesis of periapical lesions. *Endod Dent Traumatol*. 1990;6(3):89-96. <https://doi.org/10.1111/j.1600-9657.1990.tb00400.x>. PMID:2079017.
- Wang L, Yang F, Qiu Y, Ye L, Song D, Huang D. The Potential Roles of T Cells in Periapical Lesions. *J Endod*. 2022;48(1):70-9. <https://doi.org/10.1016/j.joen.2021.09.016>. PMID:34627784.
- Cavalla F, Letra A, Silva RM, Garlet GP. Determinants of Periodontal/Periapical Lesion Stability and Progression. *J Dent Res*. 2021;100(1):29-36. <https://doi.org/10.1177/0022034520952341>. PMID:32866421.
- Hughes E, Scurr M, Campbell E, Jones E, Godkin A, Gallimore A. T-cell modulation by cyclophosphamide for tumour therapy. *Immunology*. 2018;154(1):62-8. <https://doi.org/10.1111/imm.12913>. PMID:29460448.
- Lutsiak MEC, Semnani RT, De Pascalis R, Kashmiri SVS, Schlom LJ, Sabzevari H. Inhibition of CD4+25+ T regulatory cell function implicated in enhanced immune response by low-dose

- cyclophosphamide. *Blood*. 2005;105(7):2862-8. <https://doi.org/10.1182/blood-2004-06-2410>. PMID:15591121.
17. Engels CC, Charehbili A, van de Velde CJH, Bastiaannet E, Sajet A, Putter H, et al. The prognostic and predictive value of Tregs and tumor immune subtypes in postmenopausal, hormone receptor-positive breast cancer patients treated with adjuvant endocrine therapy: a Dutch TEAM study analysis. *Breast Cancer Res Treat*. 2015;149(3):587-96. <https://doi.org/10.1007/s10549-015-3269-7>. PMID:25616355.
 18. Le DT, Jaffee EM. Regulatory T-cell modulation using cyclophosphamide in vaccine approaches: a current perspective. *Cancer Res*. 2012;72(14):3439-44. <https://doi.org/10.1158/0008-5472.CAN-11-3912>. PMID:22761338.
 19. Yamaguchi-Yamamoto Y, Tomida M, Hozumi M. Pregnancy associated increase in differentiation-stimulating factor (D-factor)/leukemia inhibitory factor (LIF)-binding substance(s) in mouse serum. *Leuk Res*. 1993;17(6):515-22. [https://doi.org/10.1016/0145-2126\(93\)90127-7](https://doi.org/10.1016/0145-2126(93)90127-7). PMID:8505848.
 20. Stashenko P, Yu SM, Wang CY. Kinetics of immune cell and bone resorptive responses to endodontic infections. *J Endod*. 1992;18(9):422-6. [https://doi.org/10.1016/S0099-2399\(06\)80841-1](https://doi.org/10.1016/S0099-2399(06)80841-1). PMID:9796508.
 21. Maia CA, Chaves HGS, Benetti F, de Menezes GB, Antunes MM, Pinto KP, et al. Zoledronic Acid Modulates Cytokine Expression and Mitigates Bone Loss during the Development of Induced Apical Periodontitis in a Mice Model. *J Endod*. 2023;49(11):1522-8. <https://doi.org/10.1016/j.joen.2023.08.010>. PMID:37633518.
 22. Fukada SY, Silva TA, Garlet GP, Rosa AL, Da Silva JS, Cunha FQ. Factors involved in the T helper type 1 and type 2 cell commitment and osteoclast regulation in inflammatory apical diseases. *Oral Microbiol Immunol*. 2009;24(1):25-31. <https://doi.org/10.1111/j.1399-302X.2008.00469.x>. PMID:19121066.
 23. de Brito LCN, Fonseca Teles FR, Teles RP, Totola AH, Vieira LQ, Ribeiro Sobrinho AP. T-lymphocyte and cytokine expression in human inflammatory periapical lesions. *J Endod*. 2012;38(4):481-5. <https://doi.org/10.1016/j.joen.2011.12.010>. PMID:22414833.
 24. Colić M, Gazivoda D, Vucević D, Majstorović I, Vasilijć S, Rudolf R, et al. Regulatory T-cells in Periapical Lesions. *J Dent Res*. 2009;88(11):997-1002. <https://doi.org/10.1177/0022034509347090>. PMID:19828886.
 25. Schiavoni G, Mattei F, Di Pucchio T, Santini SM, Bracci L, Belardelli F, et al. Cyclophosphamide induces type I interferon and augments the number of CD44hi T lymphocytes in mice: implications for strategies of chemioimmunotherapy of cancer. *Blood*. 2000;95(6):2024-30. <https://doi.org/10.1182/blood.V95.6.2024>. PMID:10706870.
 26. Matar P, Rozados V, Gervasoni S, Scharovsky G. Th2/Th1 switch induced by a single low dose of cyclophosphamide in a rat metastatic lymphoma model. *Cancer Immunol Immunother*. 2002;50(11):588-96. <https://doi.org/10.1007/s00262-001-0237-3>. PMID:11807622.
 27. Ideo F, Niazi S, Mezzena S, Mannocci F, Cotti E. Prevalence of apical periodontitis in patients with autoimmune diseases under immunomodulators: a retrospective cohort study. *J Endod*. 2022;48(6):722-9. <https://doi.org/10.1016/j.joen.2022.02.008>. PMID:35257683.
 28. Allilhaibi M, Niazi SA, Farzadi S, Austin R, Ideo F, Cotti E, et al. Prevalence of apical periodontitis in patients with autoimmune diseases: A case-control study. *Int Endod J*. 2023;56(5):573-83. <https://doi.org/10.1111/iej.13902>. PMID:36747086.
 29. Ideo F, Niazi S, Chessa L, Miglianti M, Bardini G, Mannocci F, et al. Prevalence of apical periodontitis in patients with autoimmune liver diseases on immune suppressants and immune modulators: a cross-sectional study. *J Endod*. 2024;50(6):784-91. <https://doi.org/10.1016/j.joen.2024.02.026>. PMID:38527610.

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