An Overview on Biologic Medications and Their Possible Role in Apical Periodontitis

Elisabetta Cotti, DDS, MS, Elia Schirru, DDS, MS,*† Elio Acquas, PhD,‡ and Paolo Usai, MD§*

Abstract

Introduction: Apical periodontitis (AP) is the expression of a deficient balance between infection and the host immune response. **Methods:** If reducing the bacterial load from the root canal and preventing its reinfection may lead to clinical success, then the integrity of the nonspecific immune system has a relevant influence on the outcome of endodontic treatment. **Results:** Compromised immune systems and/or genetic alterations of the host's response may as well play an important role on the development, progression, and healing of AP. Thus, immunomodulatory drugs might have the potential to influence both the severity of AP and the outcome of endodontic treatment. Biologic medications are a new class of drugs of monoclonal antibodies or fusion proteins that include fragments of a peculiar cytokine receptor. Specific inflammatory molecules or cells, such as tumor necrosis factor, interleukins, and T or B cells, are the selective targets of these drugs. They modulate the altered immune response and perform an important role in the short-term treatment of chronic inflammatory diseases such as rheumatoid arthritis, refractory Crohn disease, or ulcerative colitis. Despite the clinical positive outcomes and their widespread use, the consequences of administering biologic medications on the development of the dental diseases have not been adequately investigated. **Conclusions:** The aim of this review was to give an overview of biologic medications, their composition, their mechanisms of action, and their possible implications on endodontic and other dental diseases. *(J Endod 2014;40:1902–1911)*

Key Words

Apical periodontitis, biologic drugs

From the *Department of Conservative Dentistry and Endodontics, School of Dentistry, ‡Department of Life and Environmental Sciences, School of Pharmacology, and §Department of Gastroenterology, School of Medicine, University of Cagliari, Italy; and the †Department of Endodontology, Kings College Dental Institute, London, United Kingdom.

Address requests for reprints to Dr Elisabetta Cotti, Department of Conservative Dentistry and Endodontics, University of Cagliari, School of Dentistry, 09124 Cagliari, Italy. E-mail address: cottiend@tin.it

0099-2399/$ - see front matter

http://dx.doi.org/10.1016/j.joen.2014.08.013

The aim of endodontic therapy is to treat or to prevent apical periodontitis (AP). AP is a coordinated sequence of host responses to the presence of a microbial infection originated from the root canal system and invading the local tissues (1). If reducing the microbiota from the root canal and preventing its reinfection may lead to clinical success, then host factors must have a critical role in determining the severity of the disease as well as in determining how a specific patient responds to treatment (1).

The so-called "integrity of the nonspecific immune system" has an influence on the outcome of endodontic treatment, which may be as important as other patient- and treatment-related variables (ie, technical quality of root canal treatment) (2). The role of the immune system may be reflected in the delayed or impaired resolution of AP, the response to treatment of immunocompromised patients, diabetic patients, and the degree of severity of the clinical manifestations of AP (2–8). Within this overall scenario, genetic factors from the host that influence immune modulation must also play a very important role on the development, progression, and healing of AP (9–11).

Strindberg (4) had already included in his classic study the "general health status of the patient" as an explanatory variable, but he had not found a significant impact of this variable on periapical health.

Marending et al (2) for the first time in recent years assessed the importance of the immune system on endodontic initial treatment and retreatment outcome in 132 teeth of subjects seeking endodontic therapy within a medical center in Switzerland.

They scored periapical health using the periapical index (PAI) system, had the same operator perform the standardized treatments on teeth, and followed up patients for an average of 46 months. Their overall success (defined as a PAI score at recall ≤ 2 without symptoms) was 88% with a recall rate of 79%. Using a regression model, 3 significant predictors for treatment outcome were found in that cohort:

1. Integrity of the nonspecific immune system ($P = .05$)
2. Dichotomized initial PAI score ($P = .04$)
3. Quality of root filling ($P = .01$)

The stepwise logistic regression analysis indicated an odds ratio of 8.25 for the role of immune system versus an odds ratio of 12.77 for the quality of root canal filling; this is a remarkable finding because it suggests that the status of the immune system is almost as important as the technical quality of endodontic treatment.

Fouad and Burleson (5) in a retrospective study on diabetic versus nondiabetic patients have come to similar conclusions, showing that diabetic patients with preoperative AP had significantly reduced success on endodontic treatment. Studies have shown the trend toward a higher risk for the spreading of periapical infection and for the development of larger periapical lesions on immunocompromised animals (6, 7).

Furthermore, in terms of the host response, the delayed or impaired resolution of periapical lesions has been attributed to the persistent state of activation of macrophages after the initial cause of AP has been removed with the consequent continuous production of bone-resorbing cytokines (8).

Genetic factors were first associated with the development of symptomatic apical abscesses (9), with the occurrence of external root resorption (12), and in a recent case-control study on AP refractory to endodontic treatment. Morsani et al (10) found that a specific genotype in the interleukin (IL)-1β gene cluster is associated with the persistence of AP. Because monocytes from people homozygous for the IL-1β gene

(allele 2) produce 4 times more IL-1β and heterozygous cells produce 2-fold more IL-1β (11), this situation could contribute to the creation of a stronger immune-inflammatory response at the periapical area of a tooth affected by AP and the consequent persistence of AP even after a state-of-the-art root canal treatment.

Although the importance of the initial periapical status and the technical quality of the root canal treatment on endodontic success has been reviewed several times, the most important conclusion from these studies is the definite impact that an impaired nonspecific immune system has on the efficacy of endodontic treatment (3).

The clinical implications of these conclusions suggest the novel concept that new immunomodulatory drugs have the potential to influence endodontic treatment outcome. This review provides a foundation to understand this new hypothesis for the modulation of endodontic outcome.

Models for Chronic Inflammatory Diseases

Inflammation is the usual response to harmful exogenous or endogenous elements. It is a protective response that helps to destroy, dilute, or wall off detrimental agents, and at the same time it initiates a variety of events that generate the healing and repair or replacement of the damaged tissue. Inflammation and repair are also potentially harmful; the inflammatory response is the cause of hypersensitive reactions and a variety of diseases ranging from asthma to rheumatic pathologies. The current belief is that inflammation represents part of the nonspecific immune response with typical signs that include alteration of blood flow, vasodilation, upraising of cellular metabolism, release of cellular mediators, cellular influx, and extravasation of fluids (13).

Mediators are the major effector system of innate inflammatory reaction; they come from plasma proteins, inflammatory cells, and tissue cells. Mediators from plasma proteins are kinins, proteases activated during coagulation and activation of the complement; mediators from inflammatory cells are histamine, serotonin, prostaglandins, leukotrienes, platelet-activating factor (PAF), reactive oxygen species, nitric oxide, neuropeptides, chemokines, and cytokines (Table 1) (14–20).

Major cytokines include tumor necrosis factor (TNF), IL-1/12, and interferon gamma (14). TNF-α is a cytokine released by activated monocytes, macrophages, and T lymphocytes that contributes to the immune response, growth regulation, differentiation, survival, and physiological function of a variety of different cells together with the production of other cytokines, inflammatory mediators, and enzymes (21, 22). It is a potent inducer of bone resorption, which stimulates the differentiation and activation of osteoclasts (23). TNF-α functions are mediated by 2 receptors: TNF-R1 (receptor type 1, CD120a, and p55/60), which is expressed in most tissues, and TNF-R2 (receptor type 2, CD120 b, and p75/80), which is highly regulated and typically expressed in immune system cells (22) (Table 2) (24–35).

Acute inflammation is a prompt response designed to support a site of damage with leukocytes and plasma proteins. Chronic inflammation is a complex event characterized by the simultaneous presence of active inflammation, the tissue injury and healing process, vascular changes, and infiltration of white blood cells; it represents the base of complex pathologies (14, 36).

AP is an inflammatory disease. The pathologic changes of the periapical tissues in AP are caused by microbes, their toxins, and metabolic byproducts; these irritants are capable of either inducing nonantigenic pathways or serve as antigens to activate adaptive responses. Thus, the pathogenesis of AP involves an innate and adaptive immune response (37–39) (Fig. 1). The development of acute AP reflects the innate immune response and represents the immediate defense reaction to irritants; characteristic features of acute AP are similar to typical acute inflammation. If pathogens in the root canal are not defeated, acute AP progresses to chronic inflammation (37–39). The specific conditions from the infected pulp tissue and root canal play a regulatory role in controlling the local immune-inflammatory process (40). Primary endodontic infection is a potent activator of toll-like receptor-4 (TLR-4) and stimulates macrophages to produce cytokines that establish different network interrelationships implicated in the development of the variety of clinical and radiographic features of AP (41, 42). IL-6 and IL-10 have been positively associated with the radiographic size of the lesion and with the inflammation of the periodontal ligament. Higher levels of TNF-α were correlated to the presence of exudation; on the other hand, IL-10, which counterbalances the production of inflammatory cytokines, was negatively correlated to the presence of clinical symptoms (41, 42). The network between different cytokines regulates the formation of both initial and chronic AP. Chronic inflammatory forms of AP are characterized by a balance between anti- and proinflammatory cytokines (41). The response of periapical tissues to injuries is similar to that of the other connective tissues in the body and the other inflammatory diseases. The role of IL-6 in human resorptive chronic diseases such as rheumatoid arthritis (RA) has been reported (43).

RA and Crohn disease (CD) are, in fact, well-known models of pathologies strongly related to chronic inflammation (43–45). RA affects 0.3%–1% of the entire world's population (46, 47), and it presents, as a major feature, the excessive production of proinflammatory cytokines, their primary localization into synovia, and their eventual spread to the entire joints. TNF seems to be the predominant cytokine involved in the pathogenesis of RA (48); the other cytokines implicated in this disease are the allelic variations of IL-1 and IL-1Ra (receptor antagonist), noticeable in animals but still controversial in humans, (49, 50), and IL-6 (51). Inflammatory cells are represented by T cells, dendriticlike cells, and macrophages. The progression of RA also includes the degeneration process of cartilage and bone through the activation of the receptor activator of nuclear factor κB (Rank)–receptor activator of nuclear factor κB ligand (RankL) system. Rank-RankL system is based on 3 different elements: Rank, its ligand RankL, and osteoprotegerin (52). Rank is a membrane protein receptor expressed on preosteoclasts; RankL is a protein of the TNF superfamily expressed by stromal cells, synovial fibroblasts, and T cells (53).

Once secreted, RankL binds to its own receptor RANK on osteoclast progenitor cells (preosteoclasts) (54); the activated receptor then stimulates the differentiation of the osteoclasts and eventually the resorption of bone (55). RANKL activity is regulated by osteoprotegerin, a decoy receptor of RANKL that blocks osteoclastic formation. Thus, cytokines such as TNF-α, IL-1, IL-6, and IL-17; hormones; and growth factors increase the expression of RANKL in the joints and promote osteoclastogenesis (56).

CD involves potentially the whole alimentary tract with a predilection for the distal small bowel and proximal large bowel. The defective production of defensins in patients and the IL-23 pathway are associated with this disease (57). IL-12 and IL-23 promote the differentiation of naive CD4+ T cells into Th1 effector cells (that produce interferon gamma), the generation of memory T cells, and the differentiation of Th17 cells (58). T-cell products IL-2 and activated antigen-presenting cells amplify the immune response with the production of IL-2 (T-cell growth factor), IL-1, and TNF. Besides inflammation, aphthous ulcers and granulomas are the early clinical hallmark of CD; CD granulomas are sarcoidlike lesions with epithelioid histiocytes and inflammatory cells, and TNF is the key cytokine involved in its formation (57). Genetics and environment have been advocated as important factors in the pathogenesis of rheumatic diseases (RA) (59, 60); yet, the