Cyclosporine A–induced gingival overgrowth: A comprehensive review

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Cyclosporine A, an extremely effective immunosuppressant, is also associated with various untoward effects, including gingival overgrowth. Despite intense clinical and laboratory investigation, the cellular-molecular mechanism through which cyclosporine A simultaneously acts as a selective immunosuppressant while it elicits a connective tissue reaction in the gingiva remains poorly understood. In recent years, cellular and molecular biologic techniques have elucidated a variety of growth factors that control connective tissue homeostasis. Two growth factors known to be major elements in wound repair and connective tissue homeostasis are platelet-derived growth factor and transforming growth factor-β1. Increased gingival levels of these factors may be responsible for promoting fibroblastic proliferation and fibroblastic production of extracellular matrix constituents in overgrown gingival tissues. Expression of these factors has recently been shown to be upregulated in these tissues. The results of these recent studies may provide a foundation for understanding the molecular mechanism involved in the pathogenesis of cyclosporine A–induced gingival overgrowth. (Quintessence Int 1999;30:775–783)

Key words: cyclosporine A, cytokine, gingival overgrowth, macrophage

Cyclosporine A (CsA) is an immunosuppressant drug that selectively affects the cell-mediated immune response. Cyclosporine A interferes with the early stages of T-cell activation, inhibiting the production of interleukin-2, thereby preventing delivery of signals essential to T- and B-cell maturation. Although CsA suppresses humoral immunity to a much lesser extent, increasing evidence suggests that B-cell differentiation and proliferation are also affected. Cyclosporine A has been widely celebrated for its ability to act as a safe, low-toxicity immunosuppressant and for its potential application in the management of a wide variety of systemic disorders.

Cyclosporine A can be administered orally, intramuscularly, or intravenously in a formulation known as Sandimmune (Sandoz). To maintain immunosuppression, an oral therapeutic dose of 10 to 20 mg per kilogram of body weight per day is required. This dose results in a serum concentration of 100 to 400 ng/mL. Because of large individual variations in drug bioavailability, ranging from 20% to 50% in adults, and a relatively narrow therapeutic range of the drug, the selection of an optimum treatment dose must be based on individual measurements of CsA blood levels; this approach is now regarded as an essential aid to patient treatment. The goal is to titrate each patient’s CsA dose to the lowest effective level. Despite such efforts, individual serum levels remain proximal, gravitating toward the range of 100 to 250 ng/mL.

Recently, a new formulation of CsA, Neoral (Sandoz), has become widely available. This microemulsion oral formulation overcomes the interpatient and intrapatient biopharmaceutic and pharmacokinetic variability of Sandimmune. It offers improved bioavailability and an enhanced therapeutic index, reducing the potential side effects of the drug.

The major use of CsA is for prevention of graft rejection after major organ transplantation procedures. Cyclosporine A has also been shown to reduce the morbidity and mortality from graft-versus-host disease in bone marrow transplant recipients. In addition, CsA has been used successfully to treat a variety of disorders in which the immune system may be involved, such as insulin-dependent diabetes mellitus, psoriasis, and erosive lichen planus. Other dermatologic and autoimmune disorders that have responded favorably to CsA include rheumatoid arthritis, bullous pemphigoid/pemphigus, multiple sclerosis, lupus erythematosus, ulcerative colitis, myasthenia gravis, and acquired immunodeficiency syndrome.
Despite its unequivocal success as a truly selective immunosuppressant drug, CsA is also associated with various adverse effects. Most of these effects are dose dependent and are frequently reversible without sequelae on a decrease in dosage or discontinuance of the drug. The main adverse effects of CsA include nephrotoxicity,\textsuperscript{16} hepatotoxicity,\textsuperscript{17} hypertension,\textsuperscript{18} neurotoxicity,\textsuperscript{19} a predisposition to bacterial, fungal, and viral infections,\textsuperscript{20} and fibrosis of pulmonary, pericardial, and renal tissues.\textsuperscript{21} The most notable adverse effect of CsA therapy is gingival overgrowth.

**Cyclosporine A–Induced Gingival Overgrowth**

**Incidence**

Drug-induced gingival enlargement was described more than 50 years ago.\textsuperscript{22} Presently, it is believed that more than 20 currently prescribed medications may act as etiologic factors in gingival enlargement.\textsuperscript{23} Three major drug categories have been associated with iatrogenic gingival overgrowth: anticonvulsants, especially phenytoin;\textsuperscript{24} calcium channel-blocking agents, such as nifedipine;\textsuperscript{25} and the immunosuppressant CsA.\textsuperscript{22,26}

As early as 1983, it was reported that CsA elicited enlargement and overgrowth of gingiva in human organ transplant recipients,\textsuperscript{26} corroborating earlier clinical observations.\textsuperscript{27} The reported incidence of CsA-induced gingival overgrowth varies among studies. Recent investigations reveal incidences from 15% to 85%, depending on the criteria used.\textsuperscript{28,29} However, a review of the few relatively well-controlled studies reported thus far suggests that the overall incidence may be approximately 25% to 50%.\textsuperscript{30}

Thus, the occurrence of CsA-induced gingival enlargement appears to be approximately half as frequent as that of phenytoin-induced gingival overgrowth\textsuperscript{31,32} and about the same as the occurrence of gingival enlargement elicited by the calcium channel blockers.\textsuperscript{33} This frequency is independent of whether the CsA therapy is instituted for prevention of graft rejection or whether it is prescribed for control of other systemic disorders.\textsuperscript{34} However, there is some evidence to suggest that the incidence of gingival overgrowth is as low as 2% when the drug is used in bone marrow grafting.\textsuperscript{35} Determination of the true incidence is difficult, because of numerous confounding variables within and between subject populations, including differences in drug dosage; plasma concentration of CsA; duration of therapy; method of assessing gingival enlargement; underlying periodontal status (especially the inflammatory component); age of the patients; medical condition for which the drug is being used; overall health of the patients; and concomitant use of other medications (especially those associated with gingival overgrowth).

**Clinical Characteristics**

In the susceptible patient, gingival overgrowth usually develops within 1 month\textsuperscript{36} to 3 months\textsuperscript{37} after initiation of CsA therapy. Cyclosporine A–induced gingival overgrowth commences as a papillary enlargement that is more pronounced on the labial aspects of the gingiva than on the palatal or lingual surfaces.\textsuperscript{38} The amount of overgrowth ranges from slight contour changes in the papillary tissues of the gingiva to complete coverage of the teeth. Overgrowth is restricted to the width of attached gingiva but can extend coronally and interfere with occlusion, mastication, and speech. Cyclosporine A–induced gingival overgrowth has not been observed in edentulous subjects.\textsuperscript{38}

The enlarged gingival tissues often show marked inflammatory changes. Affected tissues bleed readily on probing and are generally more hyperemic than the gingival tissues associated with phenytoin-induced gingival overgrowth.\textsuperscript{34} All segments of the dentition may be affected, but the anterior segment appears to be a predilection site.\textsuperscript{39}

In addition to esthetic problems, the overgrowth may result in uncleasible areas that are more prone to caries, development of periodontitis, and infections that could result in septicemia. The gingival overgrowth often leads to nutritional difficulties, especially in children, in whom the overgrowth may alter normal tooth eruption.\textsuperscript{40,41}

**Histologic Characteristics**

The overall histologic features of all drug-induced gingival overgrowths are comparable, consisting primarily of connective tissue with an overlying irregular, multi-layered, parakeratinized epithelium of variable thickness. Epithelial ridges are seen penetrating deep into the subepithelial connective tissue, creating irregularly arranged collagen fiber bundles. The connective tissue is highly vascularized, and focal accumulations of infiltrating inflammatory cells have been observed.\textsuperscript{22} The predominant cell type in the inflammatory infiltrate is the plasma cell; lymphocytes are observed to a lesser degree.

Some authors have noted acanthosis and parakeratinization of the epithelium with pseudoepitheliomatous proliferation. This finding, together with the presence of foci of periodic acid–Schiff–positive material within the epithelium and stroma, has led to the view that the tissue redundancy is due to epithelial acan-
thosis and an accumulation of noncollagenous extracellular substance.\textsuperscript{42} Ultrastructural studies, however, have demonstrated that the dimensional increase of gingival mass is primarily a connective tissue response, and, more precisely, the result of a highly increased production of amorphous ground substance by fibroblasts.\textsuperscript{45}

Some studies have noted a degree of fibroplasia within the gingival connective tissue, characterized by the presence of increased numbers of fibroblasts.\textsuperscript{26} Most studies, however, have failed to demonstrate an increase in the numerical density of fibroblasts, reporting a volume density of fibroblasts and extracellular collagen similar to normal gingiva.\textsuperscript{44-46} This indicates that CsA-induced gingival enlargement may not be a true hyperplasia; therefore, the term \textit{gingival hyperplasia} has been replaced by more accurate descriptions, such as \textit{gingival overgrowth} or \textit{enlargement}.

Other ultrastructural studies have demonstrated that gingival fibroblasts in CsA-induced overgrowth show characteristics of active protein synthesis and secretion, with reduced cytotoxic or degenerative changes. An increased proportion of specialized fibroblasts containing microfilament bands with semi-periodic dense nodes, termed \textit{myofibroblasts}, have also been observed.\textsuperscript{47} These myofibroblasts have also been demonstrated in phenytoin-induced gingival overgrowth.\textsuperscript{48} Because myofibroblasts are usually associated with the later stages of tissue turnover, the presence of these specialized fibroblasts in drug-induced overgrown connective and gingival tissues suggests that these drugs exacerbate the normal tissue turnover and wound-healing signals responsible for the appearance of myofibroblasts.

\textbf{Potential cellular mechanisms}

The mechanism through which CsA simultaneously acts as a selective immunosuppressant while it elicits a connective tissue reaction in the gingiva remains poorly understood. Because not all patients who take CsA develop gingival overgrowth, the terms \textit{responders} and \textit{nonresponders} have been used in the literature to identify, respectively, the existence or lack of individual susceptibility and perhaps a genetic predisposition. It has been demonstrated that gingival fibroblasts exhibit functional heterogeneity in response to various stimuli.\textsuperscript{49} Based on this finding, it was demonstrated that CsA could react with a phenotypically distinct subpopulation of gingival fibroblasts and cause an increase in protein synthesis and cellular proliferation rate.\textsuperscript{30,31}

Fibroblast heterogeneity has also been investigated with respect to the collagenolytic response to CsA.\textsuperscript{32} Various fibroblast strains demonstrated marked individual and interstrain differences in the activity of collagenase and tissue inhibitor of metalloproteinase both before and after exposure to CsA. These results indicate that the heterogeneity of the collagenolytic response of different gingival fibroblast strains and their subpopulations to CsA treatment may partly explain the variable gingival response noted in patients taking this drug.

Other examples of a potential genetic predisposition are (1) genetic polymorphisms (cytochrome P-450 genes) that result in individual variation in levels of CsA metabolism\textsuperscript{53}; and (2) type of human lymphocyte antigen (HLA) gene expression.\textsuperscript{54} (Apparently, HLA-DR1 apparently affords some degree of protection against the development of CsA-induced overgrowth, while HLA-DR2 is associated with an increased risk for gingival overgrowth.\textsuperscript{54})

The age and sex of the patient may be additional factors that can influence the incidence and severity of CsA-induced gingival overgrowth. Clinical studies suggest that children, especially adolescents and young females, appear to be more susceptible to drug-induced gingival overgrowth than adults.\textsuperscript{55-57} This may be related to a unique fibroblastic phenotype in younger patients or to the influence of sex hormones. An increase in the biologically active form of testosterone has been found in the overgrown tissues of patients with drug-induced gingival enlargement.\textsuperscript{58} Such alterations of androgen metabolism may account for the increased propensity for CsA-induced gingival enlargement in children and adolescents.\textsuperscript{53}

The relationship between the incidence and severity of CsA-induced gingival overgrowth and various drug pharmacokinetic variables is a controversial issue. Animal studies indicate that lower CsA blood levels are associated with decreased incidence and severity of gingival lesions.\textsuperscript{59} This has been corroborated in some human studies, which have reported that the incidence of overgrowth is related to either high doses of CsA\textsuperscript{44,60} or high blood concentrations of CsA.\textsuperscript{37,61} Most studies, however, have failed to confirm such positive correlations.\textsuperscript{36,36a} It has been postulated that a certain threshold concentration of the drug (trough level) is required to induce the gingival reaction and that increased levels of the drug above this threshold do not increase the severity of the lesion.\textsuperscript{37,56} Changes in severity would therefore result from other factors.

Local concentrations of the inducing drugs in saliva, gingival crevicular fluid, or plaque could also influence the expression and pathogenesis of drug-induced gingival enlargement. Because of its lipophilic nature, the free fraction of plasma CsA may enter saliva by passive diffusion. Several studies have reported a positive correlation between CsA concen-
tation in simulated saliva and the extent of gingival overgrowth. Other studies, however, have reported a lack of correlation between unstimulated salivary CsA levels and gingival overgrowth. These conflicting findings may be explained by the fact that dental plaque may act as a reservoir for CsA, which is then released by the actions of a stimulated salivary flow. This hypothesis is supported by the finding that concentrations of CsA in dental plaque are much higher than those found in blood or other tissues.

There is considerable epidemiologic evidence that plaque-induced gingival inflammation exacerbates the expression of CsA-induced gingival overgrowth. Furthermore, most studies suggest that effective plaque control and removal of local irritants can diminish the severity of CsA-induced gingival overgrowth and prevent recurrence of the gingival lesions. This suggests that plaque-induced gingival inflammation may be important in the development and expression of CsA-induced gingival overgrowth. Most of this evidence, however, has been compiled from cross-sectional studies, and it is not clear whether the plaque is a contributory factor or a consequence of the gingival changes. This is evidenced by the fact that several well-controlled studies have failed to demonstrate a correlation among plaque, gingival inflammation, and CsA-induced gingival overgrowth. In addition, it has been shown that optimum plaque control and removal of local irritants do not prevent the development of CsA-induced gingival overgrowth.

Collectively, these studies suggest that plaque-induced gingival inflammation augments the severity of CsA-induced gingival overgrowth. It is therefore reasonable to assume that proper oral hygiene can be expected to minimize the severity of CsA-induced gingival enlargement by eliminating the inflammatory component of the lesion. However, it is unlikely that optimal plaque control measures could prevent the occurrence of such gingival lesions.

Another mechanism that may be involved in the pathogenesis of CsA-induced gingival overgrowth is the influence of the inducing drug on the sodium and calcium flux of gingival fibroblasts. Despite their pharmacologic diversity, all 3 types of drugs associated with gingival enlargement have a similar mechanism of action at the cellular level, where they inhibit intracellular calcium ion influx. It has been proposed that the production of collagenase is modulated by calcium influx and that, once collagenase production is altered, fibroblasts of affected patients produce an inactive form of collagenase or a smaller amount of collagenase. Either of these changes would limit collagen degradation and, thus, allow an unregulated increase in gingival connective tissue volume.

Therefore, the action of these various drugs on the sodium and calcium ion flux may prove to be the key to understanding why 3 dissimilar drugs have a common side effect on a secondary target issue, such as gingival connective tissue. Additionally, some studies have reported synergistic effects and an increased incidence and severity of gingival overgrowth when CsA is administered concurrently with calcium channel blockers, such as nifedipine.

**Cellular and molecular mechanisms involving growth factors**

In recent years, cellular and molecular biologic techniques have elucidated a variety of growth factors that control connective tissue homeostasis. Such growth factors are obvious targets for drugs, and their expression may be important in the pathogenesis of CsA-induced gingival overgrowth. Two growth factors known to be major elements in wound repair and connective tissue homeostasis are platelet-derived growth factor (PDGF) and transforming growth factor-β1 (TGF-β1).

Platelet-derived growth factor is a major mitogen and chemoattractant for fibroblasts, stimulating fibroblastic proliferation and synthesis of glycosaminoglycans, proteoglycans, fibronectin, and collagen. It also exerts influences on endothelial and vascular smooth muscle cells, facilitating angiogenesis.

Transforming growth factor-β1 selectively stimulates the synthesis of connective tissue matrix components, such as collagen, fibronectin, proteoglycans, and glycosaminoglycans. It may enhance these effects by reducing the synthesis of proteinases that are involved in connective tissue degradation, such as collagenase, plasminogen activator, and elastase. Transforming growth factor-β1 and PDGF often function together in tissue-turnover processes.

Recent attention has focused on the role of cytokines and growth factors in the pathogenesis of drug-induced gingival overgrowth. These investigations are based on the premise that cellular homeostasis in tissues is likely to be the result of a balance among complex interactions of antagonistic molecules, in which cytokines and growth factors play a major role. On a cellular and molecular level, the macrophage is now recognized as being instrumental in the regulation of cellular proliferation and growth as well as the regulation of production of the basic components of connective tissue turnover, such as extracellular matrix and collagen. It is believed that the macrophage mediates its key role in connective tissue turnover through the release of cytokines and growth factors. The cellular and molecular mechanisms of CsA-induced gingival overgrowth may be related to...
changes in macrophage phenotype. The investigation of macrophage phenotype has a unique application to the problems of gingival inflammation and drug-induced gingival overgrowth. The macrophage is long-lived and has tremendous potential for responding to the microenvironment and modifying it by secreting cytokines and growth factors that control the magnitude of the inflammatory and healing response. Thus, on a cellular and molecular level, the macrophage is now recognized as the major mediator of connective tissue turnover, maintenance, and repair.\textsuperscript{89-91}

For macrophages to perform their functions in the orchestration and execution of both the degradative and reparative aspects of tissue turnover, they must exhibit a specific phenotype at the appropriate time.\textsuperscript{92-96} Recently, it has been demonstrated that the differentiation and maturation of macrophages from monocytes results in multiple mature macrophage phenotypes.\textsuperscript{93,94} Each macrophage phenotype is characterized by expression of specific marker antigens and receptors as well as the ability to respond to substances in the local microenvironment via differential secretion of specific cytokines or growth factors.

Specifically, at sites of inflammation within connective tissues, an inflammatory macrophage phenotype has been identified that represents cells associated with production of catabolic pro-inflammatory cytokines (interleukin-1\(\beta\) [IL-1\(\beta\)], interleukin-6, and tumor necrosis factor-\(\alpha\)), recruitment and degranulation of neutrophils, and facilitation of immune-mediated inflammatory tissue destruction.\textsuperscript{95} During wound healing or during debridement and remodeling following infection, a reparative and proliferative macrophage phenotype has been identified that represents cells associated with production of essential anabolic polypeptide growth factors (PDGF, TGF-\(\beta\), and basic fibroblast growth factor) that stimulate fibroblastic proliferation, extracellular matrix production, and angiogenesis.\textsuperscript{95-98} Recent investigations have suggested that the destructive and reparative phases of tissue turnover may be determined by these specific macrophage subsets and that the maintenance process could be manipulated through control of macrophage phenotype.\textsuperscript{95}

Initial in vitro studies have demonstrated that phenytoin alters IL-1\(\beta\) production in macrophages,\textsuperscript{99} possibly leading to upregulation of PDGF gene expression.\textsuperscript{97} There has been recent interest in the pathogenesis of drug-induced gingival enlargement in relation to the expression of PDGF. It was demonstrated in vitro that phenytoin causes an increase in PDGF messenger RNA (mRNA) expression and PDGF secretion in cultured macrophages and monocytes.\textsuperscript{81} These findings suggest that drug-induced increases in PDGF secretion from macrophages could be an important factor in the expression of gingival overgrowth.

This hypothesis was further confirmed by in vivo studies of PDGF expression in CsA-induced gingival overgrowth. It was demonstrated that PDGF-B mRNA is significantly greater in overgrown tissues from CsA-treated patients than it is in normal controls and that the amount of PDGF-B mRNA upregulation resulting from inflammation alone is much less than the degree of upregulation produced by CsA treatment.\textsuperscript{95} In addition, PDGF-B-producing cells were identified as mature macrophages.\textsuperscript{85}

Recently, these results were confirmed, as the increase in PDGF-B gene expression was shown to result from an increased amount of PDGF-B mRNA production by macrophages rather than an increase in the number of PDGF-B-positive macrophages in the overgrown tissues.\textsuperscript{86} Additionally, it was demonstrated in vitro that cultured monocytes and macrophages exhibit a significant increase in PDGF secretion in response to CsA.\textsuperscript{86} These investigators also demonstrated a significant inflammation-independent increase in PDGF-B mRNA expression in vivo in overgrown tissues from phenytoin-treated patients as was previously demonstrated for CsA-treated patients.\textsuperscript{85}

With respect to other growth factors, an increased accumulation of TGF-\(\beta\), basic fibroblast growth factor, and their receptors has also been demonstrated in nifedipine and phenytoin-induced overgrown gingival tissues.\textsuperscript{97} These findings have been supported by studies investigating the pathogenesis of CsA-induced renal fibrosis, another significant adverse effect of CsA therapy. These studies have demonstrated that CsA enhances expression of PDGF and TGF-\(\beta\) in the renal tissues of experimental animals,\textsuperscript{101,102} in cell culture systems,\textsuperscript{103} and in the serum of CsA-treated patients.\textsuperscript{104}

**FUTURE DIRECTIONS**

There are presently large voids in the understanding of the mechanisms involved in the pathogenesis of CsA-induced gingival enlargement. The question arises as to why the gingiva is more commonly the site of drug-induced overgrowth than other organs. One possibility relates to the fact that even healthy gingiva is in a continuous state of repair (cell and tissue turnover) because of a constant environmental insult from bacterial plaque (pathologic wounding) and masticatory attrition.\textsuperscript{96} Polypeptide growth factors play an important role in this reparative or maintenance process. Consequently, one would expect to find one or more of the growth factors associated with tissue repair in normal gingiva. This assumption has been supported by studies that have demonstrated the presence of PDGF-positive mononuclear cells in healthy gingiva.\textsuperscript{85}
porting the concept that the gingiva is in a continuous state of wound repair. Similarly, one would also expect to find elevated levels of these growth factors in conditions that involve increased tissue volume, such as drug-induced gingival overgrowth.

The role of macrophage phenotype is very much related to the concept of disruptions in normal cytokine and growth factor homeostasis. As previously mentioned, the gingiva can be considered to be in a constant state of maintenance and repair because of a constant inflammatory insult and pathologic challenge via bacterial plaque. Within this scenario, host-mediated tissue destruction observed in chronic inflammatory diseases, such as periodontitis, may be related to an inflammatory macrophage phenotype expressing catabolic pro-inflammatory cytokines, and proliferative conditions, such as drug-induced gingival enlargement, may be related to a reparative and proliferative macrophage phenotype expressing anabolic polypeptide growth factors. Thus, macrophage phenotype may be the determinant of whether tissues enter into a state of inflammatory destruction or proliferation.

This assumption has been supported by studies that have reported an upregulation of the inflammatory macrophage subset in inflamed gingival tissues and by other studies that have demonstrated an upregulation of the reparative and proliferative macrophage subset in proliferative conditions, such as sarcoidosis. Furthermore, PDGF-producing macrophages in drug-induced overgrown gingival tissues have been identified as the reparative and proliferative macrophage subset and IL-1β-producing macrophages in inflamed gingival tissues as the inflammatory macrophage subset.

Although CsA-induced gingival overgrowth is considered to have a strong inflammatory component, periodontal destruction is not usually a characteristic of this proliferative condition. These observations suggest that the tissue-destructive component of the inflammatory response is masked or overwhelmed by the tissue-regenerative component. It is likely that the reparative and proliferative macrophage phenotype mediates the tissue response. This macrophage subset could be responsible for the lack of periodontal destruction as well as the enhanced expression of growth factors in these tissues. As the chief source of pro-inflammatory cytokines and polypeptide growth factors, macrophages are critical to the regulation of many pathologic processes, such as periodontitis, which involve chronic inflammation and host-mediated tissue injury. Perhaps in inflammatory diseases such as periodontitis, the temporal balance between the production of pro-inflammatory cytokines and essential growth factors is crucial in determining the degree of inflammatory tissue damage.

It should be pointed out, however, that other cell types, such as fibroblasts and endothelial cells, have also been shown to produce polypeptide growth factors at wound sites. Although the amount of growth factors produced by these cells is minor compared to that produced by macrophages, the possibility exists that these cells also contribute to the observed levels of growth factors in these tissues.

To date, all available data strongly suggest that the pathogenesis of gingival overgrowth elicited by drugs is more complex than simple direct action, likely involving an interplay among the various cytokines known to be present within the gingival milieu. Thus, although it would be simpler if the CsA-induced tissue response were specific in nature, it is likely that a complex interaction among several growth factors and cytokines contributes to the clinical presentation. A review of the various studies regarding the pathogenesis of drug-induced gingival overgrowth supports the hypothesis that the etiology of this condition is multifactorial. There appear to be 3 significant factors that are important in the expression of these gingival changes, notably the inducing drugs, plaque-induced inflammatory changes in the gingival tissues, and genetic factors. Nevertheless, the hypothesis of a drug-induced upregulation of essential polypeptide growth factors as the underlying mechanism of CsA-induced gingival overgrowth is promising and warrants further investigation.

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