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<Invited Review Article>

Overview of Gingival Overgrowth in Transplant Patients

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· Abstract

Patients with gingival overgrowth are easily seen in dental clinics. Cyclosporin-A (CsA), a widely prescribed immunosuppressant induces gingival overgrowth in up to 35% of patients with medical history of organ transplantation. The immunosuppressant CsA can transform genetic expression of gingival fibroblasts, resulting in gingival overgrowth. Meticulous plaque control is recommended for treatment of gingival overgrowth. Substitution of the drug or surgical procedures such as gingivectomy and periodontal flaps should be considered after re-evaluation. Azithromycin is often recommended as a supplementary drug to reduce this side effect. Recent studies show that tacrolimus can be a more economic, efficient and safe substitute for CsA.

• Key words : Cyclosporine, Gingival overgrowth, Organ transplantation, Tacrolimus

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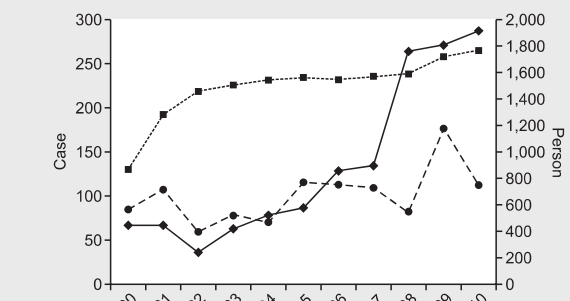
Introduction

Organ transplantation is a medical procedure performed to replace damaged or absent organs. Organs that can be transplanted are hearts, kidneys, livers, lungs, pancreas, intestines and thymuses. Incidence of organ transplantation has increased continuously (Fig. 1)[1]. It is not difficult to meet organ transplantation patients in daily practice. A number of these patients will have side effects induced by some drugs frequently and inevitably prescribed tothem.

Gingival overgrowth is a common oral side-effect in transplant patients which is often induced after taking immunosuppressants. These drugs are generally used to prevent rejection of transplanted organs and increase success rate of organ transplantation surgeries. The introduction of cyclosporin-A (CsA) as a immunosuppressive agent in 1978, marked the beginning of a new stage in the history of immunotherapy for transplant patients. Postoperative survival rate was greater and the quality of life was improved to a significant level as well[2,3]. CsA is a widely used immunosuppressive drug, and the prevalence of gingival overgrowth induced by CsA ranges from 20% to 35%[4-6]. But previous studies investigated the prevalence of gingival overgrowth as a side effect of certain drugs reported a very wide range (25~50%). This variability is due to discordance of parameters used in the studies[7]. Furthermore, these immunosuppressive drugs are often used concomitantly with calcium channel blockers, nifedipine or other dihydropyridines to reduce high blood pressure or nephrotoxicity, respectively[8]. Unfortunately this combination leads to an increase in the severity of gingival overgrowth[5].

We intend to review the prevalence, mechanism, treatment and the relationship between drugs known to cause this post-transplantation side effect.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	
◆ Brain death	52	52	36	68	86	91	141	148	256	261	268	
● Post mortem	74	104	61	69	84	133	129	122	98	193	126	
	944	1,386	1,462	1,464	1,553	1,433	1,505	1,463	1,532	1,688	1,782	■ Alive

Figure 1. Increasing tendency of transplantation in Korea from 2000~2010 (Korean Network for Organ Sharing).

Immunosuppressants and Calcium Channel Blockers as Inducers of Gingival Overgrowth

Various medications can cause overgrowth of gingiva. These drugs can be categorized broadly into 3 categories: anticonvulsants, immunosuppressants and calcium channel blockers. Immunosuppressants and calcium channel blockers are increasingly prescribed as the organ transplantation cases increases. Marshall et al.[9] reported in 1993 that as a worldwide trend, the use of cyclosporins continues to increase. It has been estimated that 10^9 patients worldwide will be medicated with cyclosporin within the next decade[10].

Cyclosporin induced gingival overgrowth was described in dental literature in 1983 for the first time[11,12]. Clinical appearance of gingival overgrowth does not differ between each inducing drugs (Fig. 2). The overgrowth normally begins at the interdental papillae, is more common in the anterior segments of the mouth and on the labial surfaces of the teeth. Overgrowth is usually confined to the attached

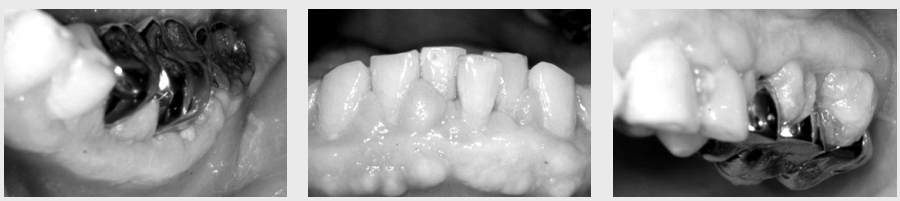


Figure 2. Clinical photographs of gingival overgrowth.

gingiva but may extend coronally and interfere with the occlusion, mastication and speech. The prevalence of this side effect differs according to the conditions of each individual.

Various calcium channel blockers are concomitantly prescribed since immunosuppressants cause hypertension as a side-effect of nephrotoxicity. Use of calcium channel blockers, together with cyclosporin raises the prevalence of gingival overgrowth.

Mechanism of Drug-induced Alterations in Gingival Tissues

The essential feature of all drug-induced gingival overgrowth is an increase in the connective tissue matrix[13]. Although many factors are involved, it all leads to a change in genetic expression of gingival fibroblasts leading to a collagen breakdown, collagen synthesis or production of non-collagenous matrix (Fig. 3)[14-16].

Cyclosporin Pharmacokinetics

CsA inhibits collagenase gene expression via activator protein-1 and c-Jun N-terminal kinase[17], and reduces collagen degradation by lowering phagocytosis[18] and the activities of lysosomal enzymes cathepsin-B and -L in gingival fibroblasts[19].

Biofilm (Bacterial Plaque)

Evidence shows that gingival overgrowth is a multi-factorial phenomenon and no single factor (either cellular or molecular) can be regarded fundamental in the expression of gingival overgrowth. The role of plaque accumulation to gingival overgrowth being contributory or consequential still remains uncertain. However, it is prudent to perform meticulous plaque control, and re-evaluation under appropriate oral hygiene level is recommended before any surgical treatment is decided upon. Studies show that when inflammatory reaction is triggered, cyclosporin induces fibroblasts to behave differently[20,21]. Any drug-induced gingival enlargement will distort gingival contours and impede mechanical plaque control measures significantly. Thus, reports on positive relationship between overgrowth and both plaque scores and inflammation are not surprising[22]. Plaque induces many changes in the gingival tissues, and hence modulates fibroblast-drug interactions[13].

Predisposing Factors: Age, Hereditary Conditions

Any effect of predisposing factors, such as age, sex and genetic conditions were evaluated. Studies suggest that children and adolescents are more susceptible with the prevalence of 70~97% while 25~50% in adults[23]. Higher incidence of gingival overgrowth is observed in the younger population. But the significance of contribution of age is diminished once transitive effect through cyclosporin concentration is statistically eliminated. Therefore, it is suggested that the basic factor influencing gingival overgrowth is cyclosporin blood concentration followed by plaque/gingivitis level[24].

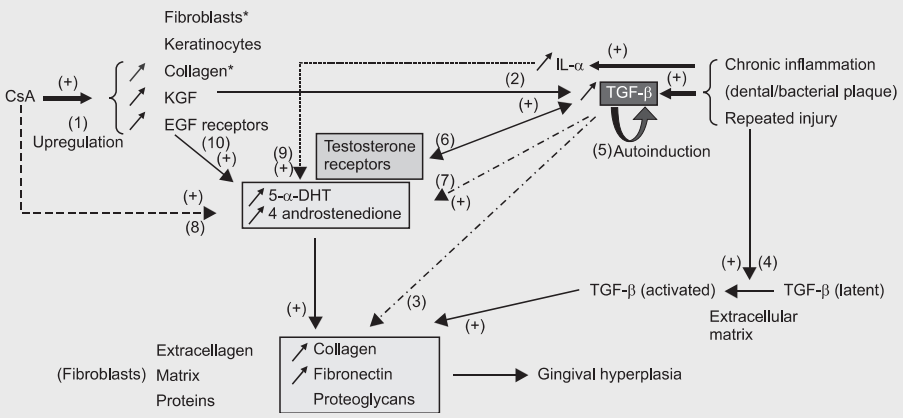


Figure 3. Mechanism of cyclosporin induced gingival hyperplasia. CsA: cyclosporin A, KGF: keratocyte growth factor, EGF: epidermal growth factor, 5-α-DHT: 5-a-di-hydro-testosterone, TGF: transforming growth factor.

Clinical studies by Hefti et al.[25] confirmed that effect of hormones in fibroblast metabolism vitro by many cellular experiments. It is speculated that certain drugs up-regulate androgen metabolites[26,27], which target gingival fibroblasts and cause genetic changes in collagen metabolism. Some genetic traits are more susceptible to drug-induced gingival overgrowth. Studies show that these genes could influence functional heterogeneity of gingival fibroblasts, collagenolytic activity, drug receptor binding, drug metabolism, collagen synthesis and many more factors[13].

Treatment of Gingival Overgrowth

While pathogenesis of drug-induced gingival overgrowth is controversial depending on the drug, clinical features observed are similar. Examination of clinical cases reveals that the enlarged tissues have two components: a drug induced fibrotic tissue and an inflamed tissue mostly due to bacterial plaque. As mentioned before, role of bacterial plaque as a contributing or a consequential factor is controversial[28], nevertheless it does not change the treatment plan. All patients with gingival overgrowth should be under a thorough plaque control before other treatment options are considered.

Treatment options can be divided into nonsurgical and surgical (Fig. 4). When considering nonsurgical treatment, the possibility of discontinuing or changing the drug should be taken into account. Since CsA has been reported as a high inducing factor of gingival overgrowth, tacrolimus (Tcr) is considered as an effective substitute. The antibiotic azithromycin has been suggested to aid in decreasing the gingival overgrowth[29] and it is to be looked into later in this review. When following a non-surgical treatment option and attempting drug substitution, at least 6~12 months should be given for the resolution of gingival enlargement before decision for surgical treatment is made[30]. During the non-surgical treatment phase, meticulous plaque control is mandatory for reduction of the symptoms.

Drug substitution does not always resolve gingival overgrowth. In these cases, periodontal surgery such as gingivectomy or periodontal flap can be attempted following re-evaluation. Gingivectomy has the virtue of simplicity and quickness but nevertheless osseous contouring cannot be achieved and sacrifice of keratinized tissue is made. Also the surgery site undergoes healing by secondary intention causing excessive discomfort and post-operative bleeding. Each surgical procedure should be chosen after considering the extent of the area to be excised, presence of periodontitis, the presence of osseous defects combined with the gingival enlargement lesions and the position of the bases of the pockets in relation to the existing mucogingival junctions[31].

Gingival overgrowth has a reputation for frequent relapses. Therefore, maintenance care is emphasized. Meticulous home care, use of chlorhexidine gluconate rinses and professional cleaning is recommended for prevention. A hard, natural rubber, fitted bite guard worn at night may also assist in the control of recurrence[32]. Recurrence occurs in 40% of patients within 18 months and as early as 3~6 months.

Azithromycin: For Decreasing Gingival Growth

Gingival overgrowth is treated by oral hygiene measures for plaque control, surgical treatment and drug substitution. Additionally, various case reports have described the efficacy and safety of azithromycin for the partial or complete

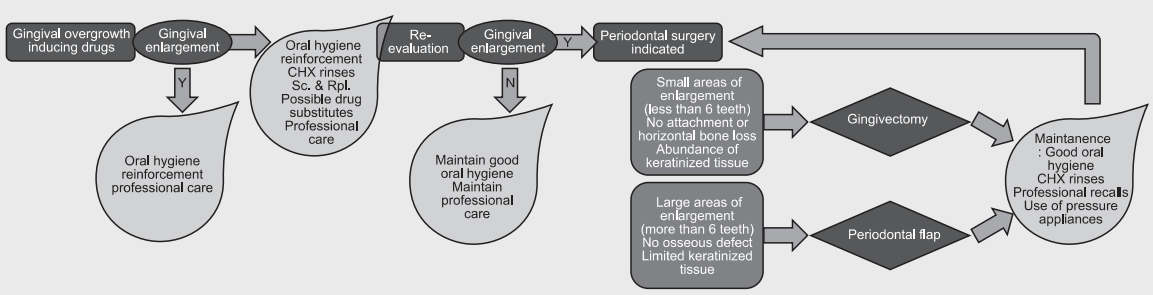


Figure 4. Treatment tree for gingival hyperplasia.

remission of drug-induced gingival overgrowth[33-35].

In vitro experiments with fibroblasts treated with CsA and azithromycin showed that the azithromycin inhibits the proliferation of cells, when CsA induced collagen accumulation and the mRNA level of type I collagen[36]. Azithromycin also increases the matrix metalloproteinase-2 (MMP-2) mRNA and activates MMP-2 which is known as a cell-surface associated type I collagen degrading metalloproteinase[37], a key player in extracellular matrix (ECM) remodelling[38].

A clinical experiment by Citterio et al.[34] showed that 5-day course of azithromycin was effective in 86% of patients. Five hundred mg per os, orally on day 1 and 250 mg from day 2 to day 5 was suggested as a highly effective and safe treatment for CsA-induced gingival hyperplasia. Furthermore, to prevent recurrent gingival hyperplasia and to increase success rate of graft, 5 day course of azithromycin protocol, every 8 to 12 months is recommended[34].

Tacrolimus: A New Age of Immunosuppressants

Tcr was introduced in 1987 as an immunosuppressive agent[39]. Although structurally different in formulation, the pharmacodynamics of Tcr are very similar to CsA while gingival overgrowth appears less frequently or less severely than subjects taking CsA[30,40,41]. A case report by James et al.[40] quantified the short term effect of the conversion from CsA to Tcr in 4 renal transplant patients with clinically significant gingival overgrowth. The result showed a mean overgrowth score decrease ranging from 24.9% to as high as 82.3% (returned to normal)[40]. Another case report showed that a treatment protocol including very thorough oral hygiene, scaling and root planing, chlorhexidine gluconate rinses (0.12%) and substituting CsA with Tcr resulted in almost complete reversion of gingival enlargement[30]. A study using regression analysis to assess the prevalence, severity and risk variables associated with gingival overgrowth was conducted. According to this study, significant risk variables are azathioprine dosage, papillary bleeding index and concomitant use of calcium channel blockers in both CsA and Tcr taking groups. Thus, although substitution to Tcr significantly reduces the prevalence and severity of gingival growth, simultaneous use of calcium channel blockers remains the major risk factor[41]. The reason why gingival overgrowth is more frequent and severe among patients who use CsA compared to patients who use Tcr is still not clear[42].

Microemulsified cyclosporin (cyclosporine ME) and Tcr is a newly recommended immunosuppressor due to their better bioavailability and clinical efficacy profile. A 10 years protocol model estimated that long-term costs are higher for Tcr, (considering the additional price related to rejection and graft loss) the cost effectiveness of treatment with Tcr tended to be better than that of cyclosporine ME[43].

Conclusion

Many transplant patients need periodontal treatment, primarily due to frequent occurrence of gingival overgrowth. Intraoral immune reactions and plaque-induced inflammation are thought to play a fundamental role in the unknown pathogenesis of this effect. Even accepting the lowest reported prevalence figures, it can be assumed that most dentists will have a number of patients in their care who will suffer from gingival overgrowth[9]. As plaque and gingivitis level is a predisposing factor, oral hygiene program prior to the surgery is a recommended preventive measure for patients scheduled for organ transplantation[24].

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