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Cyclosporin-induced gingival overgrowth in children

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Summary. Cyclosporin is a potent immunosuppressant drug commonly used to prevent organ transplant rejection. In recent years, there has been a widening of its therapeutic use and an increase in the number of patients undergoing transplantation. Gingival overgrowth is one of several oral side-effects of cyclosporin, with a quoted prevalence of between 8% and 100%. There is continued debate over the factors which modify the degree of overgrowth, including individual sensitivity, age, dose of drug, duration of drug therapy and the presence of dental plaque. The exact mechanism of gingival overgrowth is still being debated, but appears to be caused by a combination of the proliferation of fibroblasts within the gingival tissue, an increase in the deposition of collagen and extracellular matrix, and a decrease in phagocytosis with a net gain in gingival tissue mass. A number of treatment options are utilized in the treatment of gingival overgrowth, including CO_2 laser surgery, improved oral hygiene, the use of antibiotics such as metronidazole and azithromycin, and surgical intervention. In the clinical application of cyclosporin, there is little correlation between cyclosporin dose, serum trough levels and total exposure to the drug, making it difficult to achieve the desired therapeutic response. These problems were previously further complicated by the variability of absorption of the drug via the gastrointestinal tract. The original cyclosporin formulation, Sandimmune®, was replaced by a new formulation, Neoral®, which has a more reliable absorption, and gives a closer correlation between trough concentration levels and individual bioavailability. There is a conflict of opinion over whether or not the side-effect profile of Neoral varies from its precursor Sandimmune. It has yet to be seen whether the increased bioavailability of Neoral will result in an increased severity and prevalence of gingival overgrowth. An alternative immunosuppressant drug, tacrolimus, which is a macrolide antibiotic with a different side-effect profile, has emerged as a substitute for cyclosporin in organ transplantation. However, there have been conflicting reports of its side-effects and its capacity to cause gingival overgrowth.

Introduction

The aims of this paper are to review the applications of cyclosporin, to provide an update on its association with gingival overgrowth with regard to both the widening of its therapeutic applications and the alteration in its formulation, and to examine the evidence for the advantages of tacrolimus over cyclosporin.

The aims of the review will be considered under the following topics:

- cyclosporin uses and effects;
- mechanisms of gingival overgrowth;
- management of cyclosporin-induced gingival overgrowth;
- cyclosporin pharmacology;
- Neoral; and
- tacrolimus.

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Cyclosporin uses and effects

Cyclosporin is a potent immunosuppressant drug that is traditionally, but not exclusively, used to prevent rejection of organ and tissue transplants. Paediatric organ transplantation is becoming more prevalent. Indeed, cardiac and liver transplantation are now available to babies under one year of age. Moreover, survival following paediatric organ transplantation is also improving: the 2-year survival rates following cardiac and renal transplantation are 69% and 78%, respectively [1].

Furthermore, the therapeutic application of cyclosporin is widening to include treatments for such diseases as Behçet's disease, pemphigus vulgaris and rheumatoid arthritis, as shown in Table 1 [2–5]. Cyclosporin has a number of side-effects, most of which are a direct consequence of drug-induced immunosuppression. Many lesions resulting from cyclosporin therapy are orally related, and include gingival overgrowth, hairy leukoplakia, an increased propensity for both fungal and viral infections, and a high incidence of malignant change, especially lip cancer, but also including post-transplant lympho-proliferative disorders [6,7]. Gingival overgrowth is one of the most prevalent of these oral conditions and was first reported in the early 1980s [8–17]. The reported prevalence of cyclosporin-induced gingival overgrowth in transplant recipients is between 8% and 100% [17–24]. The prevalence of gingival over-growth that has been reported in children medicated with cyclosporin is summarized in Table 2. This variation could be attributed to differences in individual sensitivity, either related to the expression of human lymphocyte antigens, which are proteins found on the surface of most tissue cells which give an individual her or his unique tissue type, or between different fibroblast populations [10,25–27].

Table 1. Applications of cyclosporin.

Type 1 diabetes mellitus
Psoriasis
AIDS
Behçet's disease
Multiple sclerosis
Myasthenia gravis
Allergic encephalomyelitis
Pemphigus vulgaris
Mycosis fungoides
Systemic lupus erythematosus
Primary biliary cirrhosis
Schistosomiasis
Rheumatoid arthritis
Chronic active hepatitis

Cyclosporin-induced gingival overgrowth could also be related to the age of the patient. Daly *et al*. [26] reported that adolescents were at greatest risk of developing cyclosporin-induced gingival overgrowth, attributable to either the added effect of growth hormone on the fibroblast response, or to the greater mitotic and secretory capability of young fibroblasts. On the other hand, Kilpatrick *et al*. [28], examining heart–lung transplant recipients, concluded that cyclosporin-induced gingival overgrowth is more severe in younger children.

Cyclosporin-induced gingival overgrowth could also be related to therapy duration. Two clinical studies have reported that the severity of gingival overgrowth was inversely related to the duration of cyclosporin therapy [23,29]. It is clear that future clinical studies which examine the effect of cyclosporin may have to be more closely controlled with respect to age and therapy duration.

The effect of plaque on the prevalence and severity of gingival overgrowth has been much debated [28,30–32], but may be the reason for reports of gingival overgrowth during tooth exfoliation and eruption [33]. However, the evidence is scant and is primarily based on individual case reports rather than clinical trials.

Mechanisms of gingival overgrowth

As described by Chabria *et al*. [34], there is a disparity in opinion regarding the histopathogenesis of cyclosporin-induced gingival overgrowth. Some researchers have expressed the view that fibroblasts are acted upon by the drug to proliferate [35], whilst others believe that it is the increased production of the ground substance of collagen and extracellular matrix that is responsible [36]. It may be that a balance of the two hypotheses is the case, and Gagliano *et al*. [37], who looked *in vitro* at the effect of cyclosporin on human gingival fibroblast collagen turnover, suggested that gingival enlargement induced by cyclosporin mainly results in a disturbance in the connective tissue haemostasis, interfering with fibroblast proliferation and determining an increased volume of extracellular matrix. However, it is not only an increase in matrix production that results in gingival overgrowth, but also the decreased rate of phago-cytosis that occurs in fibroblasts affected by cyclo-sporin that will provide an overall increase in the mass of gingival tissue [38].

Table 2. Summary of literature reporting cyclosporin-induced gingival overgrowth in children.

	Study information				Oral findings	
Authors	Date	Number of subjects	Mean age in months (range)	Type of transplant	Prevalence of gingival overgrowth	Other comments
Svirsky	1989	1	37	Liver	100%	–
Zaia *et al*.	1993	1	84	Liver	100%	–
Funakoshi *et al*.	1992	5	53	Liver	100%	No relation between gingival overgrowth, and dose or therapy duration
Seow *et al*.	1991	7	39 (1–34)	Liver	86%	Gingival overgrowth worsened with therapy duration
Ross *et al*.	1989	21	100 (24–192)	Liver	Not reported	Increased plaque index in subjects, but no correlation between trough cyclosporin, therapy duration or concomitant nifedipine medication
Lowry *et al*.	1995	19	36 (36–195)	Cardiac	47% minor, 53% significant	Gingival overgrowth not related to the age of the patient, time post-transplant, cyclosporin dose, trough cyclosporin concentration or nifedipine medication
Karpinia *et al*.	1996	49	(70·8–223·2)	Renal	77·5%	Gingival overgrowth not related to dose per day. In young subjects, the duration of cyclosporin ingestion may be the most critical factor
Wilson *et al*.	1998	60	(36–216)	Renal	27%	Larger variation in gingival overgrowth in children compared to adults. Gingival overgrowth was related to cyclosporin, nifedipine and azathioprine concentration
Hosey *et al*.	1995	55	(8–194)	Liver	62%	There was a significant inverse relationship between gingival overgrowth severity and duration of cyclosporin No association was found with serum trough concentration or with nifedipine
Allman *et al*.	1994	26	104 (18–205)	Liver and renal	84%	No association found with age, graft type, gender, age at transplant, duration of cyclosporin therapy or serum trough concentration. Nifedipine did not influence occurrence or severity

Management of cyclosporin-induced gingival overgrowth

There have been various methods of reducing gingival overgrowth, ranging from CO_2 laser surgery [39], improved oral hygiene [33], and the use of antibiotics such as metronidazole [33,40] and azithromycin [40]. Oettinger-Barak *et al*. [41] described a case of cyclosporin-induced gingival overgrowth treated initially with oral hygiene instruction, scaling and root planning under local anaesthesia, which brought about a significant reduction in gingival enlargement, and subsequently, cessation of drug therapy combined with continued periodontal treatment to further improve the oral condition. However, surgical intervention is also common, and it has recently been suggested that a periodontal flap may give a more sustained reduction than gingivectomy [42]. Nevertheless, the impact of repeated surgery on the child has not been fully explored.

Cyclosporin pharmacology

The pharmacology of cyclosporin might hold some answers to the variation in gingival overgrowth prevalence, particularly in relation to dosage. Cyclosporin is insoluble, and in the early stages of its development, it was difficult to promote its absorption from the gastrointestinal tract. The rate of absorption was equally difficult to measure. The 'trough' cyclosporin serum concentration, the lowest level of drug concentration between doses, is the most commonly used way to measure dose in clinical practice, but it is a very poor guide to the therapeutic efficacy of the drug. It has been shown that there is little correlation between cyclosporin dose, serum trough levels and total exposure to the drug [29]. This could explain why clinical studies into paediatric organ recipients have frequently reported no association between the trough serum

concentration, and neither the prevalence nor the severity of gingival overgrowth [22,23,28,30].

Cyclosporin is highly lipophilic and is readily distributed across most biological membranes, and therefore, it is extensively distributed throughout the body and the body fluids, including saliva [43,44]. Its absorption from the gastrointestinal tract into the enterocytes occurs largely in the upper small intestine. This is dependent upon various factors, such as oil droplet size, bile, lipase, pH, surface area and gastrointestinal transit time. Absorption is also facilitated by either the sodium requiring transport systems for peptides or by uptake by the lymphatic system [45,46]. With children, the absorption is even more variable, since it is also related to the length of the small intestine, the time post-transplant, the type of organ failure or disease, food, race, age, diarrhoea, gastrointestinal motility, hepatic function, and bile flow [46–52]. This wide variation makes it difficult not only to achieve the desired therapeutic response in the growing child, but also leads to further complications in the relationship between dose, blood level and outcome.

Some researchers believe that there is a 'threshold dose', below which the biological effect of the drug or one of its metabolites on the gingival tissues is dispelled [10,17,53]. However, no human clinical studies support this as being the case. Moreover, available studies, in both paediatric and adult patients, oppose this view [20,23,28,29].

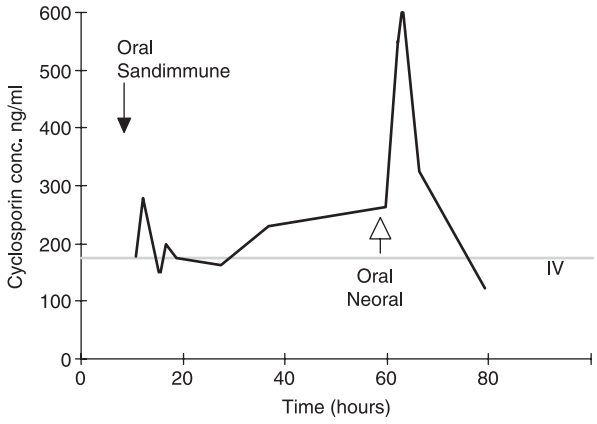

Fig. 1. Typical cyclosporin concentration time curve following oral Sandimmune (black arrow) and oral Neoral (white arrow) administration. Following administration of Neoral, maximum concentration and the area under the curve are greater, and the curve follows a more predictable pattern. The horizontal grey line indicates the steady-state concentration of cyclosporin on continuous intravenous infusion [52].

Neoral

Since its initial introduction, there has been a change in the formulation of cyclosporin. The purpose of this change has been to increase bioavailability and reduce the pharmacokinetic variation between patients. The original 'Sandimmune' formulation of cyclosporin was an oil-in-water macroemulsion in which the drug was suspended in olive or corn oil, and dispensed as a soft gelatin capsule or in solution. This has now been replaced by a new microemulsion formulation, 'Neoral'. Neoral has been demonstrated to have more consistent absorption and a closer correlation between blood trough values and total drug exposure in children [54]. Therefore, trough cyclosporin levels might be a more meaningful determinant of individual bioavailability in this new formulation [55]. A comparison between the cyclosporin concentration curves of both preparations is shown in Fig. 1, where the total drug exposure is seen as the area under the curve (AUC) and the maximum concentration is referred to as C_{max} [52].

Although the pharmacokinetic profile of Neoral has been found to be more consistent in size and shape, and C_{max} significantly higher, compared to Sandimmune, the trough levels in both preparations have been shown to be the same. Moreover, no significant difference was seen in the correlation between trough levels and AUCs in either formulation [56].

There have been conflicting reports in the medical literature as to whether Neoral has the same side-effects as the Sandimmune formulation. Numerous studies have reported that, despite the higher AUC and C_{max} of the Neoral preparation, there is no increased toxicity [55,57]. On the other hand, some authors have warned that the increased exposure to cyclosporin might increase drug-related adverse effects. Bennett *et al*. [58] reported nephrotoxicity, arteriopathy, microcalcification and fibrin thrombi in the glomeruli in renal graft recipients whose medication had been changed to Neoral. They suggested that the two cyclosporin preparations were not equivalent in terms of safety or efficacy.

A reduction in dosage of cyclosporin of between 6% and 20% has been recommended following transition to the Neoral preparation, but this has been shown to provide insufficient immunosuppression, especially in renal transplant recipients [55]. Dunn *et al*. [59] recommended that the initial dosage of

the microemulsion Neoral should be the same as that of the previously administered macroemulsion formulation, Sandimmune. Thereafter, the dose of cyclosporin microemulsion should be adjusted to produce a whole-blood trough cyclosporin concentration the same as that achieved previously with the oil-based formulation. The current *British National Formulary* recommends that conversion between brands should be undertaken under consultation with the drug manufacturers [60].

It is not yet clear whether or not there is likely to be an increased prevalence and severity of gingival overgrowth associated with the increased bioavailability of the Neoral preparation of cyclosporin. Furthermore, it is clear that, until a simple valid clinical means of measuring the cyclosporin level is developed, the true association between cyclosporin concentration and gingival overgrowth will continue to elude dental researchers.

Tacrolimus

Tacrolimus, a macrolide antibiotic isolated from *streptomyces tsukuboensis*, is a potent immunosuppressive drug that has different medical side-effects than cyclosporin. There is debate over whether or not tacrolimus causes gingival overgrowth. James *et al*. [61] and McKaig *et al*. [62] concluded that tacrolimus was not associated with gingival overgrowth, whilst the work of Busque *et al*. [63] and Ellis *et al*. [64] suggested otherwise. Ellis *et al*. described tacrolimus associated gingival overgrowth as less extensive than that seen with cyclosporin, and suggested that the overgrowth seen could not be entirely attributed to concomitant calcium channel blocker drug therapy [64]. Despite several studies observing the outcomes of immunosuppression with tacrolimus [64–72], there is little evidence of why the variation in the pathogenesis of tacrolimus in respect to gingival overgrowth occurs.

Psychological and behavioural problems in medically compromised children are often difficult to assess since these may be secondary to hospitalization, and to school and family problems. Despite this, Kemper *et al*. [73] showed that tacrolimus medication was associated with neuropsychological and behavioural side-effects such as anorexia nervosa-like symptoms with weight loss, amenorrhoea, depression, school problems, insomnia, and aggressive and anxious behaviour in some of the children in their study. Whilst no comparable information is available with respect to cyclosporin, the simple switch from tacrolimus to cyclosporin to reduce gingival overgrowth alone should be considered in this wider context. In addition, the side-effects of tacrolimus also include renal impairment, abnormalities in glucose metabolism and neurotoxicity, even though it is considered an important therapeutic option for tailoring immunosuppressive therapy to the transplant recipient [74].

Summary

Cyclosporin is being used in a greater number of therapeutic regimes for medical illness and in progressively younger patients. Gingival overgrowth is a widely reported side-effect of cyclosporin therapy. However, it does not affect all patients equally or indeed at all. The reason for this variation is not clear, but could possibly be related to individual genetic variation, age, duration of therapy and dose. The Neoral microemulsion preparation has now replaced Sandimmune, but the effect of the resultant increased bioavailability on gingival overgrowth has yet to be explored. The effect of tacrolimus on gingival overgrowth has also yet to be clarified.

What this paper adds

- The prevalence of cyclosporin-induced gingival overgrowth in children receiving organ transplants varies between 27–100%.
- The effects of changing formulation of cyclosporine from Sandimmun® to a new microemulsion Neoral®.

Why this paper is important for paediatric dentists

- The use of cyclosporin is more prevalent among children and adolescents due to increased survival rates after organ and tissue transplants and due to a widening range of indications.
- Management of gingival overgrowth ranges from oral hygiene, scaling, root planning to surgical intervention using periodontal flap.

Résumé. La cyclosporine est un immunodépresseur puissant utilise régulièrement pour prévenir les rejets de transplants. Elle a connu ces dernières années un élargissement de son utilisation thérapeutique et une augmentation dans le nombre de patients bénéficiant d'une transplantation. L'accroissement gingival est des effets indésirables de la ciclosporine avec une prévalence de 80 à 100%. Le débat est incessant sur les facteurs influençant le degré d'accroissement, incluant la sensibilité individuelle, l'âge, la dose, la

durée d'administration du médicament et la présence de plaque dentaire. Le mécanisme exact de l'accroissement est toujours discuté, mais ce dernier semble dû à une combinaison de prolifération des fibroblastes dans le tissu gingival, une augmentation du dépôt de collagène et de matrice extra-cellulaire et une diminution de la phagocytose avec une augmentation de la masse tissulaire gingivale. Plusieurs options de traitement sont possibles, incluant la chirurgie par laser CO2, l'amélioration de l'hygiène buccale, l'utilisation d'antibiotiques comme le métronidazole et l'azithromycine et l'intervention chirurgicale. D'un point de vue clinique, il y a peu de corrélation entre la dose de ciclosporine, les niveaux sériques et l'exposition totale au médicament, rendant difficile d'obtenir la réponse thérapeutique désirée. Ces problèmes sont compliqués en amont par la variabilité de l'absorption du médicament au niveau gastro-intertinal. La formule commercial initiale, Sandimmune®, a été remplacée par une nouvelle formulation, Neoral®, dont l'absorption est plus fiable et donne une corrélation plus proche entre les niveaux sériques et la biodisponibilité individuelle. Il existe un conflit d'opinion sur le fait que les effets indésirables de Neoral® diffèrent de ceux de Sandimmune®. Il n'a pas encore été établi si la biodisponibilité augmentée de Neoral® conduit à une prévalence et sévérité augmentée de l'accroissement gingival. Une alternative à la ciclosporine dans les transplantations d'organes, en tant qu'immunosuppresseur, est le tacrolimus, antibiotique macrolide dont les effets indésirables sont différents. Les rapports sont cependant contradictoires quant à ses effets indésirables et sa capacité à provoquer un accroissement gingival.

Zusammenfassung. Cycolosporin ist ein starkes Immunsuppressivum, das zur Prävention der Transplantatabstoßung eingesetzt wird. In den vergangenen Jahren wurde es breiter eingesetzt, außerdem nahm die Zahl der Transplantatpatienten zu. Gingivavergrößerung ist eine der beschriebenen unerwünschten Wirkungen von Cyclosporin im Mundbereich mit Angaben zur Prävalenz von 8% bis 100%. Es gibt eine anhaltende Diskussion dazu, welche Faktoren den Grad der Gingivavergrößerung bestimmen, darunter individuelle Disposition, Alter, Dosierung, Dauer der Therapie sowie die Anwesenheit von Plaque. Die exakten Mechanismen der Gingivavergrößerung sind immer noch in der Diskussion, es liegt aber wohl eine Kombination vor aus Fibroblasten proliferation und verstärkter Ablagerung von Kollagen und interzellulärer Matrix einerseits sowie einem verminderten Abbau durch Phagozytose andererseits, woraus eine Nettozunahme an Gingivamasse resultiert. Verschiedene Behandlungsoptionen kommen zum Einsatz, darunter CO2 Laserablation, Verbesserung der Mundhygiene, Antibiotika wie Metronidazol oder Azithromycin und operative Verfahren. Bei klinisher Anwendung von Cyclosporin gibt es nur geringe Korrelationen zwischen der Dosierung, Serumkonzentrationen oder Gesamtwirkstoffexposition, dies erschwert es, einen wünschenswerten therapeutischen Effekt zu erzielen. Früher wurde dies noch erschwert durch eine variable gastrointestinale Resorption. Das Originalpräparat, Sandimmun®, wurde durch ein neues Medikament, Neoral® ersetzt, mit einer wesentlich zuverlässigeren intestinalen Absorption des Wirkstoffs. Es ist umstritten, inwieweit das Nebenwirkungsprofil zwischen Neoral und seinem Vorläuferpräparat verschieden sind. Weiter muss sich erts nocvh zeigen, ob sich die erhöhte Bioverfügbarkeit in verstärkter Prävalenz und Schweregrad der Gingivavergrößerung äußert. Ein Alternativpräparat ist Tacrolimus, ein Makrolidantibioltikum mit einem unterschiedlichen Nebenwirkungsspektrum. Im Hinblick auf Gingivavergrößerung gibt es diesbezüglich jedoch widersprüchliche Angaben.

Resumen. La ciclosporina es un fármaco inmunosupresor usado comúnmente para prevenir el rechazo del trasplantes deróganos. En los años recientes se ha ampliado su uso terapéutico y ha aumentado la cantidad de pacientes sometidos a trasplante. El crecimiento excesivo de la encía es uno de los efectos severos en boca de la ciclosporina con una prevalencia citada entre el 8 y el 100%. Hay un debate continuo sobre los factores que modifican el grado de crecimiento excesivo, que incluyen la sensibilidad, la edad, la dosis del fármaco, la duración y la presencia de placa dental. El mecanismo exacto de crecimiento excesivo gingival está todavía en debate, pero parece ser debido a la combinación de la proliferación de fibroblastos del tejido gingival, un aumento en la deposición de colágeno y matriz extracelular y un descenso en la fagocitosis con una ganancia neta en la masa de tejido gingival. Se han utilizado una serie de opciones en el tratamiento del crecimiento gingival excesivo que incluyen la cirugía con láser, la mejora de la higiene bucal, el uso de antibióticos como el metronidazol y la azitromicina y la intervención

quirúrgica. En la aplicación clínica de ciclosporina hay poca correlación entre la dosis de ciclosporina, niveles bajos en suero y exposición total al fármaco, haciéndose difícil realizar la respuesta terapéutica deseada. Estos problemas previamente se complican por la variabilidad de la absorción gastrointestinal del fármaco. La fórmula original de la ciclosporina, Sandimmune®, se reemplazó por una nueva fórmula, Neoral®, que tiene una absorción más fiable y da una relación más cercana entre los niveles bajos de concentración y la biodisponibilidad individual. Hay divergencia de opiniones sobre si el efecto lateral del Neoral varía en relación con el precursor Sandimmune. Todavía no se ha visto si la mayor biodisponibilidad del Neoral redundará en un aumento de la severidad y prevalencia del crecimiento excesivo gingival. Ha surgido como sustituto de la ciclosporina en el trasplante de órganos, un fármaco tacrólimo, inmunosupresor alternativo, que es un antibiótico macrólido con un efecto lateral diferente. Sin embargo, hay informes contradictorios sobre sus efectos laterales y su capacidad para producir crecimiento gingival excesivo.

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