REVIEW ARTICLE

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Review of two immunosuppressants: tacrolimus and cyclosporine

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Abstract (J Korean Assoc Oral Maxillofac Surg 2023;49:311-323)

Immunosuppressants are vital in organ transplantation including facial transplantation (FT) but are associated with persistent side effects. This review article was prepared to compare the two most used immunosuppressants, cyclosporine and tacrolimus, in terms of mechanism of action, efficacy, and safety and to assess recent trials to mitigate their side effects. PubMed and Google Scholar queries were conducted using combinations of the following search terms: "transplantation immunosuppressant," "cyclosporine," "tacrolimus," "calcineurin inhibitor (CNI)," "efficacy," "safety," "induction therapy," "maintenance therapy," and "conversion therapy." Both immunosuppressants inhibit calcineurin and effectively down-regulate cytokines. Tacrolimus may be more advantageous since it lowers the likelihood of acute rejection, has the ability to reverse allograft rejection following cyclosporine treatment, and has the potential to reinnervate nerves. Meanwhile, graft survival rates seem to be comparable for the CNIs. To avoid nephrotoxicity, various immunosuppressants other than CNIs have been studied. Despite averting nephrotoxicity, these medications show increases in acute rejection or other types of adverse effects compared to CNIs. FT has been a topic of interest for oral and maxillofacial surgeons, and the postoperative usage of immunosuppressants is crucial for the long-term prognosis of FT. As contemporary transplantation regimens incorporate novel medications along with CNIs, further research is required.

Key words: Calcineurin inhibitors, Tacrolimus, Cyclosporine, Facial transplantation, Immunosuppressant

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I. Introduction

Since the introduction of immunosuppressants, outcomes of organ transplantation have improved drastically through the prevention or treatment of graft rejection. Ranging from single-organ transplantation procedures like kidney transplantation to heterogenic composite tissue allograft transplantation procedures like facial transplantation (FT), use of immunosuppressants has become common.

Types of immunosuppressants with their brand names are specified in Table 1. Immunosuppression regimens can be divided broadly into three categories of induction, maintenance, and rejection treatments, each with a specific application. Induction of immunosuppression using CD3 monoclonal antibody, anti-thymocyte globulin (ATG), basiliximab, and alemtuzumab is a strong prophylactic treatment regimen administered at the time of transplantation. However, prolonged use of an induction regimen is not recommended due to toxicity, which requires a relatively quick replacement with a maintenance regimen[1]. Among the drugs used for maintenance regimes, calcineurin inhibitors (CNIs) are the most common. Cyclosporine and tacrolimus are well-used CNIs, and their effects arise from inhibition of calcineurin. These two drugs bind to cyclophilin and FK506 binding protein 12 (FKBP-12) to form respective cyclosporine–cyclophilin and tacrolimus–FKBP-12 complexes[2]. These complexes competitively bind to calcineurin and inhibit its phosphatase activity, leading to dephosphorylation and regulation of the nuclear translocation of nuclear factor of activated T-cells (NFAT). This regulation leads to suppression of both interleukin (IL)-2 and IL-4 (principal T-cell growth factors) transcription, hindering T-cell activation[3,4].

Despite their immunosuppressive properties, CNIs also exhibit nephrotoxicity. The standard recommended doses of cyclosporine result in long-term renal dysfunction. While tacrolimus offers greater immunosuppressive efficacy than cyclosporine, it is also known to cause nephrotoxicity along

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with hyperlipidemia, thrombocytopenia, and diarrhea[5]. Reduction of CNI dosages has been achieved through co-administration of other drugs[5,6].

The aim of the present study was to review two well-known CNI maintenance regimen drugs—cyclosporine and tacrolimus—for their mechanisms of action, efficacy, and safety, along with recent attempts to overcome their deleterious side effects.

II. Methods

1. Focus question

"What is the general overview of the two widely used immunosuppressants tacrolimus and cyclosporine with regard to efficacy and safety, and what alternatives can be considered?"

2. Literature search

This review includes data collected through online literature searches in PubMed and Google Scholar using combinations of the following search terms: "transplantation immunosuppressant," "cyclosporine," "tacrolimus," "calcineurin inhibitor," "efficacy," "safety," "induction therapy," "maintenance therapy," "conversion therapy," and "nerve regeneration." A total of 1,442 articles was identified.

3. Inclusion criteria

The articles on cyclosporine and tacrolimus were sorted into the following five categories: "pharmacological profile," "mechanism of drug action," "efficacy and safety," "nerve regeneration," and "alternative drugs." Prescribing information

Table 1. Classification of immunosuppressants

Class	Medication	Brand name
CNIs	Cyclosporine	Sandimmune (Novartis)
		Neoral (Novartis)
	Tacrolimus	Prograf (twice daily) (Astellas Pharma)
		Advagraf (Astellas Pharma)
		Astagraf XL (Astellas Pharma)
		Graceptor (Astellas Pharma)
		Prograf XL (Astellas Pharma)
		Envarsus XR (once daily) (Veloxis Pharmaceuticals)
mTORis	Sirolimus	Rapamune (Pfizer)
	Everolimus	Certican (Novartis)
Antimetabolites	MPA, MMF	CellCept (Genentech)
		Myfortic (Novartis)
	Azathioprine	Imuran (Prometheus Laboratories)
Polyclonal antibodies	Anti-thymocyte globulin	
Monoclonal antibodies	OKT3, alemtuzumab, rituximab daclizumab, basiliximab, belatacept	
Others	Glucocorticoids	

(CNIs: calcineurin inhibitors, mTORis: mammalian target of rapamycin inhibitors, MPA: mycophenolate acid, MMF: mycophenolate mofetil)

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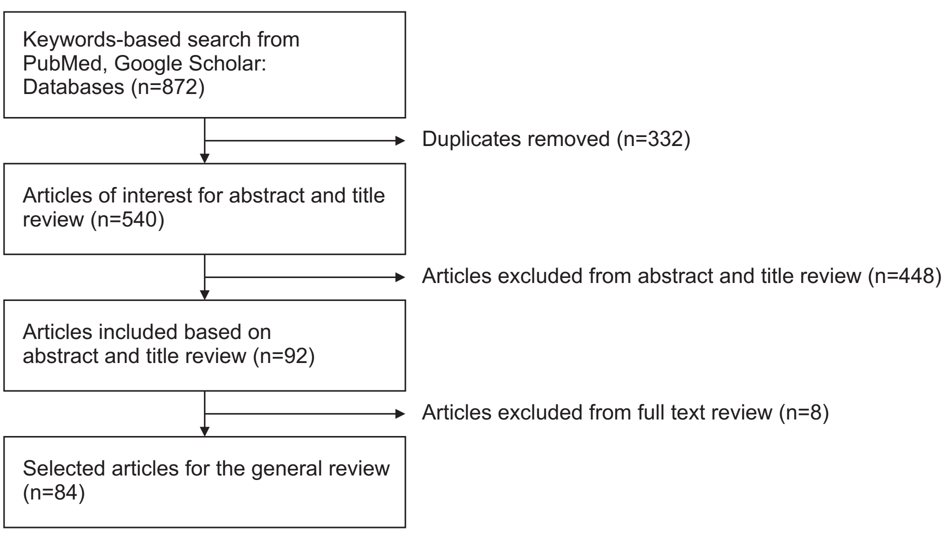

Fig. 1. Diagram of data selection flow showing the number of articles included and excluded in a stepwise process. A total of 84 articles was included in this general review.

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of Sandimmune (Novartis), Astagraf XL (Astellas Pharma), Prograf (Astellas Pharma), ENVARSUS XR (Veloxis Pharmaceuticals), and Nulojix (Bristol-Myers Squibb) was included as well.

4. Exclusion criteria

Exclusion criteria were non-English publications; duplicate articles; pediatric studies; animal studies; publications not related to organ transplantation (e.g., usage of immunosuppressants as anti-rheumatic or atopic dermatitis treatment); and publications such as editorials, case reports, and letters.

5. Screening

Articles published from January 1991 to May 2023 were collected based on specific keywords of "the pharmacological profile of cyclosporine and tacrolimus," "cyclosporine and tacrolimus" OR "CNI mechanism of action," "cyclosporine and tacrolimus" OR "CNI efficacy and safety," "cyclosporine and tacrolimus nerve regeneration," "cyclosporine and tacrolimus" OR "CNI alternative drugs." A total of 872 articles was identified and screened by title and abstract based on the criteria listed above. After excluding 332 duplicate articles, 540 were screened based on title and abstract; after a full-text review, 84 articles were included for analysis.(Fig. 1)

6. Data extraction

Based on the selected data, articles were summarized and organized into one of the following five categories: "pharmacological profile," "mechanism of drug action," "efficacy and safety," "nerve regeneration," and "alternative drugs."

III. Results

1. Cyclosporine and tacrolimus: pharmacological profile

Cyclosporine is a cyclic undecapeptide (Fig. 2. A) derived from a fungus, *Tolypocladium inflatum*, and is used broadly for its antifungal, anti-inflammatory, anti-parasitic, and immunosuppressive properties[7,8]. Due to its lipophilic characteristic, it shows very poor water solubility, and suspension or emulsion forms of oral or intravenous delivery systems have been developed[9]. The first cyclosporine formulation was released in 1983 by Sandoz (presently Novartis), under the brand name Sandimmune (Novartis)[10]. However, the original Sandimmune oral solution had a bitter taste, leading to low compliance among patients, which led to the development of a soft gel capsule version of the medication[9,10]. This drug was a crude oil-in-water emulsion preconcentrate with a bile-dependent absorption property with which a fat-rich meal intake was recommended to enhance bile flow[9,11]. To overcome the variations in bioavailability and bile-dependent absorption, a microemulsion formulation, Neoral (Novartis), was developed in July 1995. Neoral has a self-emulsifying property, which spontaneously forms a microemulsion with a particle size <0.15 μm in gastrointestinal fluids[12]. An intravenous cyclosporine formulation was also developed under the Sandimmune brand (Novartis) as a mixture of cyclosporine, polyoxyethylated castor oil, and alcohol. This intravenous formulation should be used with caution due to side effects caused by polyoxyethylated castor oil, such as hyperlipidemia, anaphylactic reaction, and peripheral neuropathy[13]. A recent formulation using Intralipid, an intravenous lipid calorie nutritional supplement, instead of polyoxyethylated castor oil was developed under the name NeuroSTAT (Abliva Co.)[14].

Tacrolimus, also known as FK506, is a 23-membered macrolide lactone (Fig. 2. B) first isolated from the soil fungus *Streptomyces tsukubaensis* No. 9993 in 1984[15]. In 1992, FK506 was officially named "tacrolimus," and, in 1993, Fujisawa Pharmaceutical Co. (presently Astellas Pharma) released Prograf as an immediate-release oral immunosuppressant[16]. While the conventional immediate-release formulation had to be taken twice daily, a more recently designed extended-release formulation showed a slower absorption rate

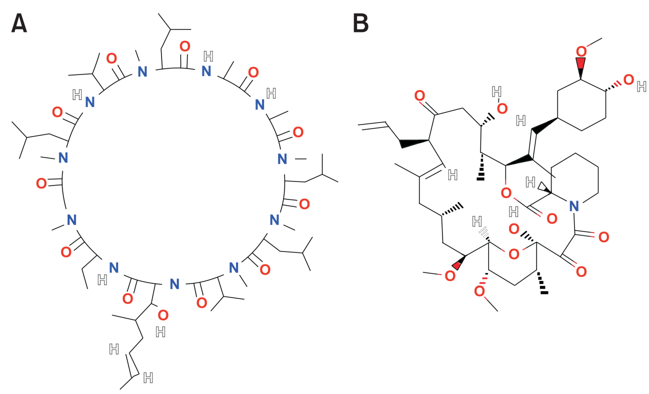

Fig. 2. Chemical structures of cyclosporine with a cyclic undecapeptide, neutral, lipophilic molecule with low water solubility (A) and of tacrolimus with a macrolide lactam with a 23-membered lactone ring with poor water solubility (B).
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and equivalent pharmacology to once-daily administration. Currently, various formulations of tacrolimus are available on the market, known by the following brand names: Prograf (twice-daily) (Astellas Pharma), Advagraf (Astellas Pharma), Astagraf XL (Astellas Pharma), Graceptor (Astellas Pharma), Prograf XL (Astellas Pharma), and Envarsus XR (once-daily) (Veloxis Pharmaceuticals)[17,18].

Tacrolimus can be administered by oral, sublingual, topical, or intravenous routes. Although oral intake is a standard route of administration, tacrolimus shows poor water solubility (4-12 μg/mL) and poor oral bioavailability together with high variability (4%-89%; average, 25%)[19]. Similar to cyclosporine, to overcome low solubility and low oral bioavailability, tacrolimus may be delivered by a self-emulsifying or micro-emulsifying drug delivery system that combines oil with lipophilic surfactants and co-surfactants, surpassing the hepatic first-pass metabolism through increased lymphatic transport[17,19]. When adopting the intravenous route, similar to the cyclosporine formulation, tacrolimus should be administered with caution, as anaphylaxis has been reported[20,21]. These hypersensitive reactions are side effects of organic solvents, such as castor oil derivatives; thus, alternative formulations have been released, such as nanosomal tacrolimus, which do not contain polyoxyl 60 hydrogenated castor oil[22]. For those patients in whom oral or intravenous routes are unavailable, a sublingual delivery system can be considered. Here, contents of the capsule are placed under the patient's tongue and allowed to dissolve completely; this delivery system requires only 50% of the oral dosage to achieve therapeutic trough level in kidney or liver transplant patients[23,24].

The bioavailability of both cyclosporine and tacrolimus depends on the cytochrome P450 (CYP) first-pass metabolism and drug efflux by p-glycoprotein (P-gp). The first-pass metabolism of tacrolimus mainly depends on CYP, especially CYP3A enzymes—30% of which are present in the liver and 70% in the small intestine[25,26]. While CYP3A4 in the liver and small intestine supports the majority of the metabolism of both cyclosporine and tacrolimus, CYP3A5 also contributes to cyclosporine metabolism[27]. P-gp is an ATP-driven efflux pump that limits the absorption and retention times

Table 2. Therapeutic dosages of cyclosporine and tacrolimus

Cyclosporine	Ref.	Tacrolimus	Ref.
Oral (Sandimmune and Neoral are not interchangeable) Sandimmune (Novartis) • 4 to 12 hours pre-transplant: 14 to 18 mg/kg by mouth for one dose • Initial single daily dose continued 1-2 weeks post-transplant • Reduce the dose by 5% per week to maintenance dose of 5 to 10 mg/kg per day by mouth divided twice per day.	33,34	Liver transplant: with corticosteroids only • Oral: IR: 0.1 to 0.15 mg/kg/day in two divided doses, every 12 hours ER: Extended release formulation is not FDA approved for liver transplantation due to increased mortality in female liver transplant patients. • IV: 0.01-0.05 mg/kg as a continuous infusion	35-37
Neoral (Novartis) • 12 hours pre-transplant: 10 to 15 mg/kg in two divided doses by mouth (12 hours apart) • Initial dosage maintained for 1-2 weeks post-transplant • Reduce the maintenance dose by 2-6 mg/kg per day in two divided doses by mouth.		Heart transplant: use in combination with azathioprine or MMF • Oral: IR: 0.075 mg/kg/day in two divided doses, every 12 hours • IV: initially 0.01-0.02 mg/kg/day as a continuous infusion	31,38
IV (maximum concentration 2.5 mg/dL) • 4 to 12 hours pre-transplant IV: 5 to 6 mg/kg IV for one dose over 2 to 6 hours • Post-transplant until the patient can tolerate oral therapy: 3 to 5 mg/kg IV once per day. • Adjust dosage according to trough levels		Lung transplant: use in combination with azathioprine or MMF • Oral: IR: 0.075 mg/kg/day in two divided doses, every 12 hours • IV: initial 0.3 mg twice daily (<50 kg) or 0.5 mg (>50 kg) twice daily as a continuous infusion	31,39
		Kidney transplant: use in combination with azathioprine or MMF • Oral: IR: initially, 0.2 mg/kg/day (with azathioprine) or 0.1 mg/kg/day (with mycophenolate mofetil) XL: 0.15 to 0.2 mg/kg/day with basiliximab induction; 0.2 mg/kg/day without basiliximab induction XR: initially 0.14 mg/kg/day (with antibody induction) • IV: 0.03 mg/kg/day as a continuous infusion	31,32,40,41

(IV: intravenous, Ref.: reference, IR: immediate-release, ER: extended-release, FDA: U.S. Food and Drug Administration, MMF: mycophenolate mofetil, XL: extra-long, XR: extended-release)

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of tacrolimus by extruding it back to the intestinal lumen[19]. Both CYP3A and P-gp are involved in the metabolism of various drugs other than tacrolimus, and both can be induced by rifampicin, isoniazid, or certain anti-convulsive drugs but inhibited by macrolide antibiotics, azole antimycotics, certain human immunodeficiency virus-protease inhibitors, statins, or calcium channel blockers[28].

Both cyclosporine and tacrolimus are primarily eliminated via the bile route. As much as 99% of cyclosporine is metabolized by CYP, and about 95% of it is excreted in the bile[29]. In a study tracking the deposition of ^{14}C-labeled tacrolimus in healthy human subjects, 77.8% (intravenous injection) to 94.9% (oral administration) of an administered dose was excreted in the feces and urine, with that in urine alone accounting for <3%[30].

The dosages of the two drugs necessary to prevent post-organ transplant rejection are summarized in Table 2[31-41].

2. Cyclosporine and tacrolimus: mechanisms of action

Cyclosporine shows immunosuppression through two pathways, the calcineurin/NFAT pathway and the JNK and p38 signaling pathway. For calcineurin/NFAT pathway inhibition (Fig. 3), after entering a T-cell, cyclosporine binds to cyclophilin with high affinity and forms a cyclophilin–cyclosporine complex that associates with calcineurin, a cytosolic protein serine/threonine phosphatase[3]. When T-cells are activated via engagement of T-cell receptors with their cognate ligands, the intracellular calcium level increases and activates calmodulin[3]. Calmodulin then interacts with the catalytic subunit of calcineurin, calcineurin A, activating the phosphatase activity of calcineurin. Calcineurin dephosphorylates NFAT family members (NFAT1, NFAT2, and NFAT4), which then translocate into the cell nucleus and become involved in transcriptional activation of genes that encode cytokines (e.g., IL-2, IL-4, CD40L)[3]. The cyclophilin–cyclosporine complex directly binds to calcineurin A and prevents calcineurin-mediated dephosphorylation, which leads to inhibition of the nuclear translocation of NFAT family members and subsequent gene expression in activated T-cells[3].

The other pathway involves inhibition of the mitogen-activated protein kinase (MAPK) pathway, which has significant roles in cellular activities such as proliferation, stress reactions, apoptosis, and immunological defense[42]. There are

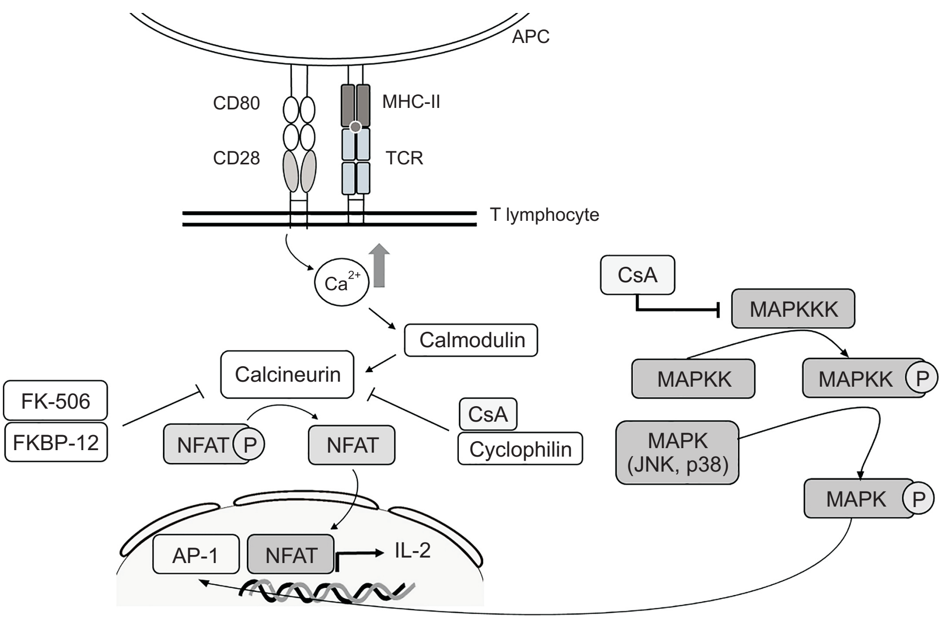

Fig. 3. Schematic drawings of calcineurin inhibitor pathways in which a phosphatase dephosphorylates NFAT family members that then are transported into the nucleus and bind to the nuclear promotor of the IL-2 gene. Production of IL-2 will lead to full T-cell activation. Cyclosporine and tacrolimus show immunosuppression by directly interacting with calcineurin to inhibit its phosphatase action. While tacrolimus (FK506) binds to FK-binding protein (FKBP) to form an FK506-FKBP complex, cyclosporine (CsA) binds with cyclophilin to form a cyclophilin-cyclosporine complex. Both complexes directly inhibit calcineurin activity, leading to immunosuppression. Cyclosporine immunosuppression can be achieved by inhibition of MAPK. When MAPKs are activated by signal cascades, they translocate into the nucleus and phosphorylate activator protein 1 (AP-1), which is crucial for transcription of IL-2. Thus, blocking upstream of the MAPKKK cascade by cyclosporine leads to inhibition of MAPK activation and to immunosuppression. (NFAT: nuclear factor of activated T cell, IL-2: interleukin-2, JNK: Jun N-terminal kinase, MAPK: mitogen-activated protein kinase, MAPKK: MAPK kinase, MAPKKK: MAPK kinase kinase)
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three types of MAPK pathways: extracellular signal-regulated kinase (ERK), Jun N-terminal kinase (JNK or MAPK8), and p38 (MAPK14)[42,43]. These MAPKs are activated through signal cascades: MAPK kinase kinase (MAPKKK) phosphorylates MAPK kinase (MAPKK), which then activates MAPK through phosphorylation[43]. Meanwhile, the JNK and p38 pathways are activated when a T-cell response is initiated by TCR and the CD28 co-stimulatory receptor, leading to translocation of activated MAPKs into cell nuclei to phosphorylate transcription factors such as activator protein 1 (AP-1)[3,42]. Activated AP-1 components along with NFAT transcription factor control the activation of important molecules such as the IL-2 gene, promoting the transcription of IL-2[44]. Cyclosporine places a block upstream of the MAPKKK cascade (e.g., MEKK1/MLK3/TAK1), leading to blockade of the p38 and JNK pathways but having no effect on ERK pathway activation[3,43].

The immunosuppression pathway of tacrolimus is similar to that of cyclosporine and targets calcineurin. Tacrolimus binds to immunophilins (FK-binding proteins) and forms a tacrolimus–FK-binding protein complex, which inhibits the phosphatase action of calcineurin, leading to suppression of IL-2 transcription[26]. Furthermore, tacrolimus inhibits the transcription of early T-cell-activation genes, which are involved in the production of IL-3, IL-4, IL-5, interferon-γ, granulocyte-macrophage stimulating factor, and tumor necrosis factor-α, as well as the production of proto-oncogenes such as c-myc and c-rel[26]. Although tacrolimus primarily participates in the cellular immune response, it can also block the activation of B-cells and the generation of antibodies. In an *in vitro* study, generation of T follicular helper cells, which are important mediators of the B-cell-mediated humoral immune response, was inhibited by 90%-95% by tacrolimus at therapeutic or subtherapeutic dosages[45]. The typical starting tacrolimus dosage for transplantation depends on the transplanted organ.(Table 2)

3. Cyclosporine and tacrolimus: efficacy and safety

Though the two immunosuppressants target the same pathway, tacrolimus showed qualitative effects similar to those of cyclosporine at 20- to 100-fold lower concentrations in both *in vivo* and *in vitro* experiments and at 20- to 50-fold lower concentrations at clinical doses (e.g., 5 mg twice daily of tacrolimus vs 150 mg twice daily of cyclosporine to achieve stable renal transplantation)[32]. Considering its efficacy for both renal and liver transplantation, tacrolimus-based immunosuppressive therapy was associated with a significant reduction in both the incidence and severity of acute rejection compared to cyclosporine-based therapy, while there were no significant differences in 1- and 2-year patient survival and graft survival rates between the two treatments[46]. In renal transplant recipients, the tacrolimus-treated group showed significantly higher long-term rates of graft survival (3-year graft survival rates of 88% vs 79% [$P<0.01$]; 5-year graft survival rates of 84% vs 70% [$P<0.01$])[47]. In a study comparing tacrolimus with cyclosporine microemulsion, neither treatment showed significant difference in patient survival, graft survival, nor incidence of acute rejection in renal and liver transplant patients[46], whereas Krämer et al.[48] showed significantly less frequent acute rejection over the first 6 months in the tacrolimus-treated group compared to the cyclosporine microemulsion-treated group (19.6% vs 37.3%, $P<0.0001$).

Tacrolimus has also been widely used for refractory rejection rescue therapy. Tacrolimus rescue therapy is frequently used following rejection of cyclosporine therapy, rejection of steroid treatment, or humoral rejection[49]. According to a Scandinavian multicenter retrospective analysis performed in 1997, among 32 renal allograft recipients, 21 were converted from cyclosporine-based therapy to tacrolimus due to acute refractory rejection and achieved a 52% (11 patients) graft survival rate at a mean follow-up of 46 weeks[49,50]. In an animal study, unlike those treated with cyclosporine, the tacrolimus-treated group showed suppression of IL-10 messenger RNA expression and serum IL-10 production along with significantly longer survival, which might account for the ability of tacrolimus to reverse allograft rejection during cyclosporine treatment[51].

In terms of safety, cyclosporine and tacrolimus both lead to nephrotoxicity, including both acute and chronic cases. Acute nephrotoxicity of CNIs usually accompanies acute arteriolopathy induced by increased vasoconstriction effects, toxic tubulopathy, and thrombotic microangiopathy, together with functional alterations such as that of intrarenal hemodynamics and a reduced glomerular filtration rate, which are reversible after dose reduction[2,52,53]. Chronic nephrotoxicity leads to progressive, irreversible damage of kidney structures such as the arteriolar hyalinosis of vessels, tubular atrophy and interstitial fibrosis, and fibrosis of Bowman's capsule or glomerular sclerosis[2,52,53]. It is not clear which of the two drug agents carries a greater risk for nephrotoxicity. Though older studies indicate that tacrolimus leads to a higher risk of nephrotoxicity, this result was attributed to the intravenous administration route[46]. According to the European Tacrolimus Multicenter

Renal Study Group[54], dialysis requirements for patients receiving tacrolimus and cyclosporine were comparable, at 44.9% (136/303) for tacrolimus versus 42.1% (61/145) for cyclosporine. Some studies suggest that tacrolimus is less nephrotoxic due to its weaker vasoconstrictive effect than cyclosporine together with lower serum creatinine level and higher glomerular filtration rates (GFRs)[2].

Neurotoxicity is another primary concern when using CNIs. Calcineurin, a crucial protein regulator involved in synaptic transmission and neuronal excitability, can be found in the cerebral cortex, striatum, substantia nigra, cerebellum, and hippocampus, among other areas of the brain[55]. CNI-associated endothelin, a potent vasoconstrictor, increases and may impact the vasoconstriction and vasospasm of cerebral vascular smooth muscle, resulting in local ischemia and white matter edema[2,55]. The major symptoms of neurotoxicity include posterior reversible leukoencephalopathy syndrome, akinetic mutism, toxic encephalopathy, and seizures, while minor symptoms include insomnia, visual symptoms, headache, tremor, paresthesia, and mood changes[55]. Comparing tacrolimus and cyclosporine, tacrolimus leads to higher incidence rates of neurologic complications like tremor, paresthesia, and insomnia, especially in liver transplant recipients[46]. Most of these neurotoxic effects can be resolved by significantly lowering the immunosuppressant dosage or stopping these medications, but some patients have experienced fatal or irreversible brain damage[56].

Other than nephrotoxicity and neurotoxicity, though tacrolimus leads to higher incidence rates of gastrointestinal disturbances (e.g., diarrhea, nausea, vomiting) and more frequent diabetogenic effects than cyclosporine (diabetes prevalence of 20% vs 4%), cyclosporine has been associated with greater incidence rates of hyperlipidemia, hypercholesterolemia, hirsutism, gingivitis, and gum hyperplasia[46,57].

4. Nerve regenerative property: tacrolimus vs cyclosporine

As previously discussed, CNIs, especially tacrolimus, show central nervous system-related neurotoxic effects (e.g., tremor, confusion, generalized spasm, speech disorder, and paresthesia) in liver transplant recipients[46,58]. However, through various animal studies, tacrolimus has been shown to exhibit neurotrophic and nerve-protective properties, leading to an increased number of axons and thicker myelin sheathing, quicker nerve regeneration, blood-nerve barrier restoration, and motor function recovery[59-63]. Meanwhile, cyclosporine does not show peripheral nerve-regenerative properties. In animal studies, cyclosporine could not induce motor recovery and facilitated a significantly reduced degree of axonal regeneration of sensory neurons. Instead, cyclosporine actually adversely affected the regeneration of peripheral nerves, reducing numbers of myelinated axons, myelin sheath thickness, and axon diameters[61,64].

Although cyclosporine and tacrolimus both target calcineurin, the results above suggest that tacrolimus has a distinct calcineurin-independent pathway that may be the cause of its capacity for nerve regeneration. Although the mechanism of action of tacrolimus on nerve regeneration is not completely understood, there are a few suggestions. As one example, tacrolimus binds to FKBP-12, which functions as a TGF-β1 receptor inhibitor, to activate the TGF-β1 pathway, stimulating NGF (nerve growth factor) synthesis in glial cells to regenerate nerves[61]. Also, calcineurin inhibition prevents the inactivation of growth-associated protein 43 and its key role in growth cone formation and axonal elongation[58,63]. Other than FKBP-12, the immunophilin FKBP-52 is another candidate mechanism of nerve-regenerative action, as FKBP-52 mediated *in vitro* neurotrophic activities in a study of FKBP-12 knockout mice[65].

As such, tacrolimus could be useful in situations where an autologous nerve graft might not be available. Especially for allograft cases such as hand or face allotransplant patients who receive the regimen of tacrolimus, mycophenolate mofetil (MMF), and a steroid, the nerve-regeneration property of tacrolimus might explain the recovery of sensation and motor function. In cases involving sensory nerves, the return of function was reported to occur independent of nerve repair. Though bilateral anastomoses of infraorbital and mental sensitive nerves (in the first face transplantation case) led to sensation recovery in the 14th postoperative week, the approximation of submental nerves near the mental foramen without suture (in the third face transplantation case) showed reinnervation of grafted skin 3 months after surgery[66,67].

5. Alternative immunosuppressants for maintenance

Although CNIs have been used as the gold standard for maintenance immunosuppression for organ transplant, many trials have sought to minimize the adverse effect of CNIs by converting patients to new drugs, such as MMF, sirolimus, everolimus, and belatacept.

1) MMF

MMF, currently available under the brand names CellCept (Genentech) and Myfortic (Novartis), is an immunosuppressant that emerged in the early 1990s with a mechanism that differs from that of cyclosporine and tacrolimus. It was based on the idea that deficiency of adenosine deaminase, an enzyme for de novo purine synthesis, leads to immunodeficiency. Mycophenolic acid (MPA) was selected for its ability to inhibit de novo synthesis of purine and was consequently developed into the morpholinoethyl ester of MPA under the name MMF[68]. MMF has high bioavailability and is hydrolyzed to MPA after oral administration to prevent T- and B-cell proliferation by inhibiting inosine monophosphate dehydrogenase, which controls de novo biosynthesis of purine[68,69].

MMF was initially used to prevent and treat acute rejection when using CNIs[70]. In renal transplant studies, MMF showed effectiveness in acute rejection rescue therapy, and combination administration of cyclosporine and MMF significantly reduced acute allograft rejection compared to placebo or azathioprine, another antagonist of purine metabolism[68]. In liver transplant studies, conversion from CNI to MMF monotherapy led to significant improvements in the serum creatinine level and calculated GFR[69]. Based on the most recent retrospective study of MMF monotherapy enrolling 94 liver transplant patients, the regimen was feasible without a high risk of acute rejection (4.2%, 4/94), and the estimated GFR was significantly increased by 6.3% for up to 5 years[71].

MMF is generally well tolerated but can cause dose-dependent adverse effects such as mild gastrointestinal side effects (nausea, vomiting, diarrhea); rare severe symptoms (cholestasis, hemorrhagic gastritis, pancreatitis, large bowl perforation); or myelosuppressive effects such as leukopenia, thrombocytopenia, and anemia[68].

2) mTOR inhibitors (sirolimus and everolimus)

Among immunosuppressants developed to avoid nephrotoxicity and other adverse effects, sirolimus and everolimus are part of the group of mammalian target of rapamycin inhibitors (mTORis). Although both bind to FKBP-12, instead of inhibiting calcineurin, they bind to mTOR to inhibit serine-threonine kinase and, ultimately, T-cell and B-cell proliferation and differentiation[72,73]. Sirolimus, available on the market under the brand name Rapamune (Pfizer), is a macrocyclic lactone antibiotic derived from *Streptomyces hygroscopicus*, and it was approved by the U.S. Food and Drug Administration (FDA) in 1999. Everolimus, or Certican (Novartis), is a derivative of sirolimus and was approved by the FDA in 2010[72,74]. Regardless of similar mechanisms of action, everolimus shows better bioavailability and lower target blood trough concentrations (3-8 ng/mL vs 4-20 ng/mL) than sirolimus, although no studies have shown a significant efficacy difference between these two medications[75].

For kidney transplantation, according to the most recent systemic review, mTORi conversion from CNI leads to significant GFR improvement but carries a greater risk for acute rejection (risk ratio, 1.72; P=0.330)[76]. Meanwhile, there were no significant differences in mortality and graft loss rate between an mTORi conversion group and a CNI group[74,76].

While mTORis show less frequent nephrotoxicity and a lower risk of cytomegalovirus infection than CNIs, their possible adverse effects include anemia, leukopenia, thrombocytopenia, hyperlipidemia, hypercholesterolemia, aphthous stomatitis, diarrhea, and rare non-infectious pneumonitis, with an incidence rate of 1%-12%[73].

3) Belatacept

Belatacept is an immunosuppressant (selective T-cell co-stimulation blocker) for intravenous injection in kidney transplant recipients approved by the FDA in 2011 under the brand name Nulojix (Bristol-Myers Squibb)[74,77]. As a fusion protein of the extracellular region of cytotoxic T-lymphocyte antigen-4 (CTLA-4) along with the Fc domain of human IgG1, belatacept binds to CD80/86 ligands of antigen-presenting cells, leading to an interaction of CTLA-4 and CD80/86, inhibiting co-stimulatory CD28-mediated T lymphocyte activation[77,78]. Although some recent studies suggest dosage reduction to 5 mg/kg on postoperative days 1, 15, 29, 43, and 57 along with 5 mg/kg administration every 4 weeks, the manufacturer-suggested dosage is 10 mg/kg on postoperative days 1 and 5 and weeks 2, 4, 8, and 12, together with 5 mg/kg every 4 weeks for maintenance[79,80].

Recent studies showed a significant improvement in eGFR following conversion to belatacept from CNI therapy[81,82]. A recent randomized study with 446 renal transplant recipients (n=223 conversion group, n=223 CNI-continuation group) recorded higher eGFR values from the belatacept conversion group (55.5 vs 48.5 mL/min/1.73 m^2) but also showed a higher rate of biopsy-proven acute rejection (8% vs 4%) with similar rates of 2-year survival with graft function[82].

Belatacept monotherapy (depleting induction with rabbit ATG preceded) in patients avoiding CNIs showed a higher rate of biopsy-proven rejection (34.5% vs 3%), a higher rate of delayed renal graft function (31% vs 21%), and higher eGFR values (161.9 vs 58.4 mL/min/1.73 m^2) than the tacrolimus monotreatment (depleting induction with rabbit ATG) group[83].

There are no reported statistical differences between belatacept and CNI groups in terms of serious adverse events, serious infection, and malignancies, although one study reported that the belatacept-treated group had higher incidence rates of viral infections (influenza, herpes, cytomegalovirus) and fungal infections (onychomycosis and tinea versicolor) than the CNI-treated group[81,84]. Belatacept maintenance is not recommended for liver transplant patients as it led to higher rates of graft loss and death compared to rates in the tacrolimus control group[74].

Thus, belatacept treatment in post-kidney transplant maintenance immunosuppression is a potential alternative to CNI therapy for improvement of renal function, but there are greater risks for acute rejection and an increased incidence of post-immunosuppressive viral or fungal infections.

6. CNIs for facial allotransplantation

Between cyclosporine and tacrolimus, tacrolimus is the key component of immunosuppressant regimen for facial allotransplantation. The combination of tacrolimus, MMF, and corticosteroid was the first immunosuppression regimen for successful vascularized composite allotransplantation, based on which the first human hand transplant was performed in France in 1998[85,86]. The first human face transplant was performed in France in November 2005[86]. As of 2020, 48 patients in the world have undergone FT[87].

In the current established facial transplant immunosuppression protocol, lymphocyte-depleting agents such as ATG or monoclonal alemtuzumab are commonly used[88]. Induction therapy is followed by a triple drug (tacrolimus, MMF, and

Table 3. Comparison of cyclosporine and tacrolimus

Medication	Cyclosporine	Tacrolimus
Brand name	Sandimmune (Novartis) Neoral (Novartis)	Prograf (twice daily) (Astellas Pharma) Advagraf (Astellas Pharma) Astagraf XL (Astellas Pharma) Graceptor (Astellas Pharma) Prograf XL (Astellas Pharma) Envarsus XR (once daily) (Veloxis Pharmaceuticals)
Pharmacologic profile	Poor oral bioavailability with poor water solubility[9,19] Metabolism: CYP3A4, CYPA5, P-glycoprotein[19,25-27] Excretion mainly through the biliary route[29]	
Route of administration	Oral: oral solution, soft gel capsule, microemulsion IV: administer with caution due to anaphylactic reaction[13] Topical delivery (e.g., eye, skin)	Oral: IR, ER, XL Sublingual: 50% of oral dosage[23] IV: Administer with caution due to anaphylactic reaction[20,21] Topical delivery (e.g., skin)
Mechanism of action	Calcineurin/NFAT pathway inhibition: cyclosporin–cyclophilin complex inhibits calcineurin, leading to inhibition of nuclear translocation of NFAT family members[3] JNK & p38 pathway inhibition: cyclosporine inhibits the upper stream of MAPKKK, leading to inhibition of p38 (MAPK14) and JNK (MAPK8) pathways[43,44]	Calcineurin/NFAT pathway inhibition: tacrolimus-FKBP12 complex inhibits calcineurin[26] Inhibition of activation of B-cells and antibody generation[45]
Efficacy	Compared to cyclosporine, tacrolimus shows similar qualitative effect at 20- to 50-fold lower concentration in clinical doses[32]	
Acute rejection	Acute rejection: lower for tacrolimus group[46]	
Graft-survival	1-year/2-year patient survival, graft survival: comparable[46] 3-year/5-year patient survival, graft survival: higher for tacrolimus group[47]	
Adverse effects	Nephrotoxicity (comparable with tacrolimus)[2,52,53] Neurotoxicity[55] Hyperlipidemia Hypercholesterolemia Hirsutism Gingivitis/gingival hyperplasia[57]	Nephrotoxicity (IV route may have a higher risk)[46] Neurotoxicity (higher rates shown in liver transplant patients)[46] Gastrointestinal disturbance Post-transplantation diabetes (higher than cyclosporine)[46]
Nerve regeneration	Lack of peripheral nerve regenerative property[61,64]	FKBP-12, FKBP-52 may mediate peripheral axon, and myelin sheath regeneration[61,65]

(XL: extra-long, XR: extended-release, IV: intravenous, IR: immediate-release, ER: extended-release, NFAT: nuclear factor of activated T cell, JNK: Jun N-terminal kinase, MAPK: mitogen-activated protein kinase, MAPKKK: MAPK kinase kinase, FKBP: FK506 binding protein)

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corticosteroid) maintenance protocol[88]. Although cyclosporine has not been included in the current regimen, it may be used for induction of donor-specific tolerance[89]. Also, cyclosporine administration may act as a safety switch to deter adverse effects from tacrolimus-resistant T cell activity[90].

IV. Conclusion

Both tacrolimus and cyclosporine function as immunosuppressants by inhibiting calcineurin, which downregulates IL-2 and other cytokine gene translations, and the two show similar graft survival rates. Tacrolimus is observed to reduce acute rejection, can rescue allograft rejection from cyclosporine treatment, and may have a latent ability for nerve reinnervation or regeneration. The overall comparisons of two drugs are summarized in the Table 3. To avoid CNI nephrotoxicity, alternatives like MMF, sirolimus, everolimus, and belatacept have been explored, leading to better GFR values, albeit with drawbacks such as higher acute rejection rates. Further comprehensive studies are needed as recent transplantation protocols increasingly recommend co-administration of various novel agents, rather than relying on cyclosporine or tacrolimus alone.

Furthermore, it is important that oral and maxillofacial surgeons understand the two most canonical CNI drugs and the changes in immunosuppressant trends as transplantation is no longer limited to single organs, and allotransplantation efforts, such as total FT trials, are ongoing. It is our responsibility as scientists and oral and maxillofacial surgeons to understand and utilize immunosuppressants and to develop related surgical technology for patients suffering major orofacial deformities.

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H.J.L. wrote the preliminary manuscript. H.M. revised and helped edit the manuscript. S.M.K. designed and coordinated the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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