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A Comparative Evaluation of Tacrolimus and Cyclosporine for the Treatment of Chronic Kidney Disease (CKD)

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Abstract

This review aims to compare and evaluate the therapeutic effect and safety of tacrolimus and cyclosporine, which are two effective immunosuppressive drugs treating chronic kidney disease. By reviewing other studies, the therapeutic mechanisms and side effect profiles of tacrolimus and cyclosporine are explored and compared in order to further comparison their effectiveness and safety. As their mechanisms are found to be similar, which is to block the signal transduction pathway leading to T-cell activation, more studies showed that tacrolimus appeared to be the better immunosuppressive agent compared to cyclosporine after conducting comparative experiments. Moreover, differences in their side effect profiles indicate that the dose and therapy conversion should be considered when tacrolimus and cyclosporine are used in clinical therapeutics of CKD. More research should be conducted to explore their pharmacokinetics, pharmacodynamics, and safety profiles so that getting a clearer understanding in their therapeutic mechanisms and a more advantageous reference for further clinical therapy selection

Keywords

Tacrolimus; cyclosporine; chronic kidney disease; CKD; immunosuppressive drugs.

1. Introduction

The kidney plays an indispensable role in the human body. The main obligation of the kidney is to excrete metabolites in the process of metabolism, so as to maintain the stability of the internal environment. To be more specific, the kidney has three main functions: 1) Urine production. The daily intake of water through the body circulation reaches the kidney, carrying some metabolites. Waste from the metabolic process is excreted from the kidney with urine, which is the first and most important function of the kidney. 2) The acid-base balance regulation and electrolyte stability. Through glomerular filtration, renal tubular reabsorption and secretion function, the kidney can discharge excess water in the body and regulate the acid-base balance and electrolyte stability in the body. 3) Endocrine function. The kidney can secrete renin, prostaglandin and kinin. Blood pressure is regulated by renin angiotensin aldosterone system and kinin bradykinin prostaglandin system, etc.

The definition of chronic kidney disease (CKD) mainly refers to the structural damage and dysfunction of the kidney caused by various reasons (the history of renal damage is more than 3 months). The diseases causing chronic kidney disease include primary and secondary glomerulonephritis, renal tubular injury, and renal vascular lesions, etc. The main risk factors for chronic kidney disease are age (e.g., old age), family history of CKD (including hereditary and non-hereditary nephropathy), diabetes mellitus, hypertension, obesity-metabolic syndrome, high protein diet, hyperlipidemia, hyperuricemia, autoimmune diseases, urinary tract infection or systemic infection, etc. Chronic kidney disease has five stages (Tab. 1), patients will develop kidney failure in

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stage 5. Glomerular filtration rate (GFR), an indicator of overall kidney function, refers to as the total amount of fluid filtered through all the functioning nephrons per unit of time [1].

Table 1. Stages of chronic kidney disease.

Stage	Description	eGFR (mL/min)	Potential complications of reduced GFR (in alphabetical order)
1	Kidney damage with normal or ↑GFR	≥90	❿ Anemia, including functional iron deficiency ❿ Blood pressure increases ❿ Calcium absorption decreases ❿ Dyslipidemia/heart failure/volume overload ❿ Hyperkalemia ❿ Hyperparathyroidism ❿ Hyperphosphatemia ❿ Left ventricular hypertrophy ❿ Metabolic acidosis ❿ Malnutrition potential (late)
2	Kidney damage with mild ↓GFR	60-89	
3	Moderate ↓GFR	30-59	
4	Severe ↓GFR	15-29	
5	Kidney failure	<15 or dialysis	

Source: Adapted from Identification, Evaluation and Management of Chronic Kidney Disease (www.health.gov.bc.ca/gpac/pdf/ckd.pdf)

Nevertheless, as a worldwide clinical disease, chronic kidney disease has increased the incidence rate and mortality rate in recent years. At present, immunosuppressants for the treatment of chronic kidney disease are effective, but most of them cause adverse reactions. Therefore, it is significant to find an immunosuppressant with high safety and stable therapeutic effect for the clinical treatment of chronic kidney disease. The research direction of this topic is to compare and evaluate the therapeutic effect and safety of two immunosuppressive drugs that treating chronic kidney disease – tacrolimus and cyclosporine.

2. Discussion

2.1 Glomerulonephritis causing ckd

As one of the diseases that causing CKD, glomerulonephritis is an autoimmune nephropathy induced when autoantibodies, immune complexes, and cells of the innate and the adaptive immune system invade and accumulate in the kidney [2]. T cells play a critical role in autoimmunity in terms of B-cell differentiation, antibody production, and promoting inflammation and cytotoxicity. As T cells are activated by autoantigens, they might secret inflammatory cytokines and expand locally in kidney. Immunosuppressive therapy is considered to be an effective method for the treatment of autoimmunity disease by inhibiting T cell activation.

2.2 Overview and comparison of therapeutic mechanisms

Cyclosporine was discovered in 1970s and categorized as immunosuppressants in early 1980s, while tacrolimus was approved as an effective immunosuppressant as cyclosporine [3]. To date, both of them are widely accepted immunosuppressive agents in prevention and treatment of allograft rejection in organ transplant recipients [3]. As data presented by Ferro et al., the symptoms of patients with CKD could be improved by reduction of arterial stiffness and improvement of blood pressure control after long-term use of immunosuppressive medication [4]. Referring to Table. 1, patients with CKD may have increasing blood pressure as a potential complication of reduced GFR.

Chemically speaking, cyclosporine is a cyclic endecapeptide, whereas tacrolimus is a macrocyclic lactone [3]. Although tacrolimus and cyclosporine are structurally unrelated, they are classified broadly as calcineurin inhibitors [5,6]. Both tacrolimus and cyclosporine bind immunophilins, a family of highly conserved proteins, to exert their effects. Differently, as tacrolimus binds to FK-binding proteins, cyclosporine binds to cyclophilin A [3,5]. After binding to immunophilins, the

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phosphatase action of calcineurin is inhibited by the resulting complexes. As a result, inhibition of calcineurin suppresses the transcription of early T-cell-activation genes and prevents the activation of the nuclear factor of activated T-cells (NFAT) family, so that affecting the transcription of cytokines. To some extent, the failure of T-cell activation can prevent the disease that inducing CKD such as glomerulonephritis. Seemingly, tacrolimus and cyclosporine are similar in therapeutic mechanism, as both of them inhibit calcineurin-pathway. However, compared to cyclosporine, tacrolimus is more potent (i.e., exerting similar effect at concentrations 100 times lower) with lower renal toxicity [6]. For the effectiveness, several reviews demonstrated that tacrolimus is more advantageous than cyclosporine as an immunosuppressive therapy. Ravanshad et al. found that tacrolimus, as an immunosuppressive drug, performed better than cyclosporine in patients with steroid-resistant nephrotic syndrome (SRNS) in terms of the lack of response to therapy, nephrotoxicity, and hypertrichosis [6]. Furthermore, the conclusion drawn by Lucey et al. also indicated that tacrolimus therapy is more beneficial than cyclosporine in liver transplantation with better renal function, lipid profile and blood pressure [7]. Similarly, as investigated by Przybylowski et al., tacrolimus was considered as a better immunosuppressive therapy leading to better kidney function in prevention of the CKD prevalence in heart transplantation, after being compared to the eGFR of patients receiving cyclosporine (tacrolimus was observed a higher eGFR) [8].

2.3 Comparison of side effects

As the therapeutic mechanisms of tacrolimus and cyclosporine therapy is similar, it is significant to consider the safety profile in terms of side effects. The side effects associated with tacrolimus therapy in solid-organ transplantation include neurologic complications, renal impairment, cardiovascular events, disturbance in glucose metabolism, neurologic disorders, and gastrointestinal events [5,9]. On the other hand, the side effects associated with cyclosporine therapy in transplantation are hypercholesterolemia and hypertension. By referring the symptoms of patients, therapy selections should consider the dose and therapy conversion. As immunosuppressive therapies, the side effects appeared in tacrolimus and cyclosporine therapy of solid-organ transplantation are meaningful for the treatment of CKD as reference.

3. Conclusion

In conclusion, tacrolimus and cyclosporine are alternatives as immunosuppressive agents, as their therapeutic mechanisms are similar, which is to block the signal transduction pathway leading to T-cell activation. As many studies indicated, tacrolimus appeared to be the better immunosuppressive agent compared to cyclosporine. However, their safety profiles are also different. For this reason, the dose and therapy conversion should be considered when tacrolimus and cyclosporine are used in clinical therapeutics of CKD. Furthermore, more research should be conducted to explore their pharmacokinetics, pharmacodynamics, and safety profiles so that getting a clearer understanding in their therapeutic mechanisms and a more advantageous reference for further clinical therapy selection.

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