CHAPTER 14

CYCLOSPORIN-A

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The introduction of cyclosporine A (CsA) led to one of the major breakthroughs in medicine. The immunosuppressive drug CsA was discovered in the 1970s in the laboratories of Sandoz (now known as Novartis) in Basel. J. F. Borel and H. Stähelin have been regarded as the principal discoverers.[1]

CsA is a powerful immunosuppressant drug that has been extensively used for many years in the field of organ transplantation. The detection of the interesting biological profile of CsA (immunosuppression without cytotoxic activity) occurred in the very first experiment. CsA selectively inhibits transcription of interleukin (IL)-2 and several other cytokines, mainly in T-helper lymphocytes.

The immunosuppressive effect of CsA was confirmed in various experimental models, including skin and bone marrow transplantation studies in mice. Borel and Stähelin subsequently started transplantation experiments with CsA in animals and, impressed by the dramatic results. Then CsA was applied to the kidney, liver and pancreas transplant patients.[2] After these pioneer successes, European[3] and Canadian[4] multicenter trials showed the superiority of CsA-based regimens in graft and patient survival. Then, CsA-based protocols rapidly became standard therapy in kidney transplantation.

Structure and physical properties

Cyclosporine ($C_{62}H_{111}N_{11}O_{12}$) (Figure 1) was first isolated from *Tolypocladium inflatum* Gams. The drug has a molecular weight of 1200 kD and comprises 11 amino acids, one of which is unique, and most of which are hydrophobic (water solubility value: 0.00952). It is highly soluble in lipids and other organic solvents. Seven of its amino acids are N-methylated, which may explain its resistance to inactivation in the gastrointestinal tract.[5]

Formulations:

The drug exhibits very poor solubility in water, and, as a consequence, suspension and emulsion forms of the drug have been developed for oral administration and for injection. Oral, intravenous (i.v.), ophthalmic, topical, and aerosol formulations of CsA are available.

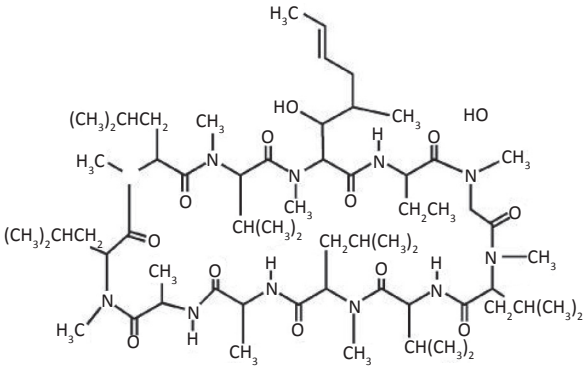


Figure 1. The chemical structure of cyclosporine [6].

The i.v. forms of the drug should only be used if enteral administration is not possible, because of the higher potential toxicity due to i.v. route. The microemulsion formulation of CsA, Neoral®, has significant benefits over the original CsA formulation (Sandimmune®) with a more predictable absorption profile and improved clinical outcomes.[7] Sandimmune® and Neoral® are not bioequivalent and cannot be used interchangeably. For patients unable to take oral cyclosporine, the i.v. dose should be equal to one-third of the oral dose and should be given twice daily.

The CsA capsules and oral solution are bioequivalent. A topical emulsion of CsA for the treatment of inflammation caused by dry eye syndrome has been marketed since 2002. The dose of medication and route of administration depend upon the specific condition being treated.

MECHANISM OF ACTION

Calcineurin-dependent mechanism

Early biological studies revealed that CsA inhibits T cell activation by blocking the transcription of cytokine genes, including those of IL-2 and IL-4. Upon entering T cells, CsA binds with high affinity to cyclophilins, especially to the cytosolic 17 kDa cyclophilin A which is the most abundant cyclophilin in T cells. The cyclophilin–CsA complex, but not cyclophilin alone, can bind to another cytosolic protein, calcineurin, which is a calcium and calmodulin dependent phosphatase.[8] This

chondrial $Ca2^{+}$. Decreasing intramitochondrial $Ca2^{+}$ allows for reversal of cardiac hypertrophy caused in the original cardiac response. Decreasing the release of cytochrome C caused decreased cell death during injury and disease.[46] MPTP opening contributes to the loss of mitochondrial function observed in the failing heart.[47] Some of the active or recruiting clinical trials are listed in table-3.

REFERENCES:

1. Heusler K, Pletscher A. The controversial early history of cyclosporin. Swiss Med Wkly. 2001; 131(21-22): 299.
2. Calne RY, White DJG, Thiru S, Evans DB, McMaster P, Dunn DC, Craddock GN, Pentlow BD, Rolles K. Cyclosporin A in patients receiving renal allografts from cadaver donors. The Lancet 1978/II: 1323.
3. Cyclosporin in cadaveric renal transplantation: one-year follow-up of a multicenter trial. Lancet 1983; 2: 986.
4. A randomized clinical trial of cyclosporine in cadaveric renal transplantation. N Engl J Med. 1983; 309(14): 809.
5. Kapturczak MH, Meier-Kriesche HU, Kaplan B. Pharmacology of Calcineurin Antagonists. Transplant Proc, 2004; 36 (Suppl 2S): 25S.
6. Wenger, R. M. Synthesis of cyclosporine and analogues: structural and conformational requirements for immunosuppressive activity. Progress in Allergy 1986; 38: 46.
7. Shah MB, Martin JE, Schroeder TJ, First MR. The evaluation of the safety and tolerability of two formulations of cyclosporine: Neoral and sandimmune. A meta-analysis. Transplantation 1999; 67: 1411.
8. Wiederrecht G, Lam E, Hung S, Martin M, Sigal N. The mechanism of action of FK-506 and cyclosporin A. Ann N Y Acad Sci 1993; 696: 9.
9. Timmerman LA, Clipstone NA, Ho SN, Northrop JP, Crabtree GR. Rapid shuttling of NF-AT in discrimination of Ca2+ signals and immunosuppression. Nature 1996; 383: 837.
10. Miroux, C., O. Morales, K. Ghazal, S. B. Othman, Y. de Launoit, V. Pancre´, F. Conti, and N. Delhem. 2012. In vitro effects of cyclosporine A and tacrolimus on regulatory T-cell proliferation and function. Transplantation 2012; 94: 123.
11. Azzi JR, Sayegh MH, Mallat SG. Calcineurin inhibitors: 40 years later, can't live without ...J Immunol. 2013; 191(12): 5785.
12. Karin M. The regulation of AP-1 activity by mitogen activated protein kinases. J Biol Chem 1995; 270:16483.
13. Copeland, Kenneth R. Immunosuppressive activity of cyclosporine metabolites compared and characterized by mass spectrometry and nuclear magnetic resonance. Clinical Chemistry 1990; 36(2): 225.
14. Lensmeyer GL, Wiebe DA, Carlson IH, Subramanian R. Concentrations of cyclosporin A and its metabolites in human tissues postmortem. J Anal Toxicol. 1991; 15(3): 110.
15. Kung L, Batiuk TD, Palomo-Pinon S, Noujaim J, Helms LM, Halloran PF. Tissue distribution of calcineurin and its sensitivity to inhibition by cyclosporine. Am J Transplant. 2001; 1(4): 325.
16. Small DS, Acheampong A, Reis B, Stern K, Stewart W, Berdy G, Epstein R, Foerster R, Forstot L, Tang-Liu DD. Blood concentrations of cyclosporin a during long-term treatment with cyclosporin a ophthalmic emulsions in patients with moderate to severe dry eye disease. J Ocul Pharmacol Ther 2002; 18(5): 411.
17. http://www.drugbank.ca/drugs/DB00091 (access date: March 28th, 2015).
18. Olshan AF, Mattison DR, Zwanenburg TS. International Commission for Protection Against Environmental Mutagens and Carcinogens. Cyclosporine A: review of genotoxicity and potential for adverse human reproductive and developmental effects. Report of a Working Group on the genotoxicity of cyclosporine A. Mutat Res 1994; 317: 163.
19. Kim H, Jeong JC, Yang J, Yang WS, Ahn C, Han DJ, Park JS, Park SK. The optimal therapy of calcineurin inhibitors for pregnancy in kidney transplantation. Clin Transplant. 2015; 29(2): 142.
20. Constantinescu S, Pai A, Coscia LA, Davison JM, Moritz MJ, Armenti VT. Breast-feeding after transplantation. Best Pract Res Clin Obstet Gynaecol. 2014; 28(8): 1163.
21. http://www.uptodate.com/contents/cyclosporine-systemic-drug-information (access date: March 28th, 2015)
22. Johnston A, David O, Cooney G. Pharmacokinetic validation of neural absorption profiling. Transplant Proc 2000; 32: 53S.
23. Knight SR, Morris PJ. The clinical benefits of cyclosporine C2-level monitoring: a systematic review. Transplantation. 2007; 83(12): 1525-35.
24. Saint-Marcoux F, Rousseau A, Le Meur Y, Estenne M, Knoop C, Debord J, Marquet P. Influence of sampling-time error on cyclosporine measurements nominally at 2 hours after administration. Clin Chem 2003; 49: 813.
25. Nashan B, Bock A, Bosmans JL, Budde K, Fijter H, Jaques B, Johnston A, Lück R, Midtvedt K, Pallardó LM, Ready A, Salamé E, Salizzoni M, Suarez F, Thervet E. Use of Neoral C monitoring: a European consensus. Transpl Int 2005; 18: 768.
26. Borel JF, Feurer C, H. U. Gubler, and H. Stahelin. Biological effects of cyclosporin A: a new antilymphocytic agent. Agents Actions 1976; 6: 468.
27. Calne, R. Y., D. J. White, K. Rolles, D. P. Smith, and B. M. Herbertson. Prolonged survival of pig orthotopic heart grafts treated with cyclosporin A. Lancet 1978; 1: 1183.
28. Green, C. J., and A. C. Allison. Extensive prolongation of rabbit kidney allograft survival after short-term cyclosporin-A treatment. Lancet 1978; 1: 1182.
29. Calne, R. Y., K. Rolles, D. J. White, S. Thiru, D. B. Evans, P. McMaster, D. C. Dunn, G. N. Craddock, R. G. Henderson, S. Aziz, and P. Lewis. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. Lancet 1979; 2: 1033.
30. Starzl TE, Klintmalm GB, Porter KA, Iwatsuki S and Schroter GP. Liver transplantation with use of cyclosporin a and prednisone. N Engl J Med 1981; 305: 266.
31. Reece, I. J., O. H. Frazier, A. Painvin, O. J. Okereke, L. B. Chandler, T. W. Krudewig, and D. A. Cooley. Early results of cardiac transplantation at the Texas Heart Institute. Thorax 1984; 39: 676.

32. Toronto Lung Transplant Group. Unilateral lung transplantation for pulmonary fibrosis. N Engl J Med 1986; 314: 1140.

33. Iacono AT, Corcoran TE, Griffith BP, Grgurich WF, Smith DA, Zeevi A, Smaldone GC, McCurry KR, Johnson BA, Dauber JH. Aerosol cyclosporin therapy in lung transplant recipients with bronchiolitis obliterans. Eur Respir J 2004; 23(3): 384.

34. Schmitt J, Rosumeck S, Thomaschewski G, Sporbeck B, Haufe E, Nast A. Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol. 2014; 170(2): 274.

35. Amor KT, Ryan C, Menter A. The use of cyclosporine in dermatology: part I. J Am Acad Dermatol. 2010; 63(6): 925.

36. Babalola O, Strober BE. Management of psoriasis in pregnancy. Dermatol Ther. 2013; 26(4):285.

37. Herrmann B, Mueller W. Therapy of rheumatoid arthritis with cyclosporin A, a new immunosuppressive drug. Aktuelle Rheumatol 1979; 4:173.

38. Kitahara K, Kawai S. Cyclosporine and tacrolimus for the treatment of rheumatoid arthritis. Curr Opin Rheumatol. 2007; 19(3): 238.

39. Meyrier A. Treatment of idiopathic nephrotic syndrome with cyclosporine. A J Nephrol 1997; 10: 14.

40. Lichtiger S, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, Michelassi F, Hanauer S. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Eng J Med 1994; 330: 1841.

41. Cattran DC, Alexopoulos E, Heering P, Hoyer PF, Johnston A, Meyrier A, Ponticelli C, Saito T, Choukroun G, Nachman P, Praga M, Yoshikawa N. Cyclosporin in idiopathic glomerular disease associated with the nephrotic syndrome : workshop recommendations. Kidney Int. 2007; 72(12): 1429.

42. Kwan LP, Mok MM, Ma MK, Lam MF. Acute drug toxicity related to drinking herbal tea in a kidney transplant recipient. Ren Fail. 2014; 36(2): 309.

43. Colombo D, Lunardon L, Bellia G. Cyclosporine and herbal supplement interactions. J Toxicol. 2014; 2014: 145325.

44. Sullivan PG, Thompson M, Scheff SW. Continuous infusion of cyclosporin A post-injury significantly ameliorates cortical damage following traumatic brain injury. Exp. Neurol. 2000; 161 (2): 631–7.

45. Elrod JW, Wong R, Mishra S, Vagnozzi RJ, Sakthievel B, Goonasekera SA, Karch J, Gabel S, Farber J, Force T, Brown JH, Murphy E, Molkentin JD. Cyclophilin D controls mitochondrial pore-dependent Ca2+ exchange, metabolic flexibility, and propensity for heart failure in mice. J. Clin. Invest. 2010; 120 (10): 3680.

46. Mott JL, Zhang D, Freeman JC, Mikolajczak P, Chang SW, Zassenhaus HP. Cardiac disease due to random mitochondrial DNA mutations is prevented by cyclosporin A. Biochem. Biophys. Res. Commun. 2004; 319 (4): 1210.

47. Sharov VG, Todor AV, Imai M, Sabbah HN. Inhibition of mitochondrial permeability transition pores by cyclosporine A improves cytochrome C oxidase function and increases rate of ATP synthesis in failing cardiomyocytes. Heart Fail Rev. 2005; 10(4): 305.

48. https://clinicaltrials.gov/ct2/results?term=cyclosporin (access time: March 28th, 2015).