New Immunosuppressive Agents in Chronic Progressive Glomerulopathies: an Update

Bloudíčková S., Viklický O.
Department of Nephrology, Transplant Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

Received May 17, 2004, Accepted September 14, 2004

Abstract: The etiology of chronic glomerulopathies is not yet clear, however the impairment of immune system is supposed to play a decisive role. Thus, immunosuppressants are often used to slow the activity and/or progression of the disease. Usually the patients are treated either by corticosteroids alone or by the combination of corticosteroids with other immunosuppressive agents. Recently, immunosuppressants successfully applied in the transplantation medicine have been also tested in the therapy of chronic glomerulopathies. Cyclosporine A, a potent calcineurin inhibitor, has been used as a second line therapy. The place of CsA in lupus nephritis and especially in IgA nephropathy is not defined so well as it is in idiopathic nephrotic syndrome. The newer calcineurin inhibitor tacrolimus is already widely used in the transplantation medicine while its effectiveness in clinical nephrology has to be tested.
Mycophenolate mofetil in monotherapy or with concomitant low-dose steroids can be regarded as an alternative therapeutical approach in case of standard regimens' failure. Sirolimus just entered clinical transplant medicine and its role in slowing the progression of chronic glomerulopathies is not yet clear.

Key words: Immunosuppression – Chronic nephropathy – Glomerulonephritis

Mailing Address: Ondřej Viklický, MD., Department of Nephrology, Transplant Centre, Institute for Clinical and Experimental Medicine, Vídeňská 1958/9, 140 21 Prague 4 – Krč, Czech Republic, Phone/Fax: +420 261 366 070, e-mail: ondrej.viklicky@medicon.cz

Introduction

The end stage renal failure (ESRF) represents an important medical, psychosocial and economical problem. Chronic glomerulopathies that often progress into ESRF embody a heterogeneous group of diseases with alternating relapses and remissions. The exact etiology of chronic glomerular nephropathies remains unknown. Thus its therapy is not etiological and in many patients with chronic glomerulopathies it progresses into ESRF.

Since the immune system deviation is hypothesized to play a main role in the pathogenesis, the first therapeutical approach might be the administration of immunosuppressants with the aim to reduce the pathological activity of immune system.

The potency of immunosuppressants differs in both the type of glomerulonephritis and in its stage. The corticosteroids remain the basis of therapy management for decades. As monotherapy, corticosteroids are often used in some glomerular diseases.

The alcylating agents like cyclophosphamide, azathioprine and chlorambucil have been administered in combination with corticosteroids or rarely alone. Since the use of corticosteroids and older immunosuppressives was extensively reviewed elsewhere [1–5], herein we focus on new immunosuppressants, that are recently successfully used in organ transplantation. However, their use in chronic glomerulonephritis remains to be fully elucidated (Tab. 1).

Table 1 – A possible role of new immunosuppressants in the therapy of chronic glomerulopathies in humans

Agent	Tested in	Reference
Cyclosporine A	Minimal change disease	6
	Focal and segmental glomerulopathy	2, 7–14
	Membranous nephropathy	15, 16
	IgA – nephropathy	5, 17–19
	Lupus nephritis	2, 20–26
Tacrolimus	Focal and segmental glomerulopathy	27
	Membranous nephropathy	28, 29
Mycophenolate mofetil	Minimal change disease	1, 32–36
	FSGS	37, 38
	Membranous nephropathy	37, 39
	IgA nephropathy	37, 40, 41
	Lupus nephritis	42–46
	Vasculitis	47
Rapamycin	Tested in clinical trials	48–52
		www.clinicaltrials.gov

Cyclosporine A (CsA)

CsA is a potent calcineurin inhibitor, which has been used for 20 years in organ transplantation. The treatment with CsA was shown to induce remission in 85% of steroid-sensitive patients suffering from minimal change disease. Recent opinion is to prolong the initial therapy to 6 months with trough blood concentration of 50–125 ng/mL. If there is no response, the therapy should be abrupt. If a remission is achieved, the therapy should continue for next 1–2 years at the lowest levels, at which the remission can be preserved. Unfortunately, in some patients (up to 40%) a total discontinuation of steroids is not possible and long-term low-dose therapy is inevitable [6].

Cyclosporine A seems to be an alternative for corticosteroids in the therapy of focal and segmental glomerulosclerosis (FSGS) [7]. Although FSGS is primary considered to be steroid-sensitive, the responsiveness to variant steroid –regimens varies only between 20–30% [2, 8–10]. In steroid -sensitive patients, a response to CsA within the first month of therapy is observed and as much as 77% of them achieve the remission till the 6th months. However, after CsA withdrawal, even 40–75% relapses occur within the first two months [11]. The combined therapy of CsA in the dose of 3.5 mg/kg/day and tapered prednisone for 6 months had induced a complete remission in 58% (in untreated control only in 2%) and 30% maintained it after 2 years follow-up. The potency of CsA is preserved even when low blood levels were used. CsA in a dose of 5 mg/kg/day with trough blood levels less than 50 ng/mL had brought a remission in 76% (52% complete remissions, 24% partial remissions) within 3 months [12]. In steroid resistant patients, there are just some randomized trials on the efficacy of CsA. CsA seems to have a potency to induce remission in 50–70% patients in a case that the duration of the therapy is less than 12 months with maximal daily dose to 5 mg/kg [13].

Interestingly, potentionally toxic intravenous CsA regimen (target trough blood levels 150–200 ng/mL) seems to be efficacious enough to induce and preserve a remission of recurring FSGS in pediatric kidney transplants [14].

In membranous nephropathy, CsA was effective in progressive form and recently represents the second line therapy in a case when standard regimen had failed. The therapeutical success can be expected within 6 months. CsA can be used in monotherapy, or better, with low-dose steroids. A dose of 3.5 mg/kg/day with trough blood levels 125–225 mg/L seems to be sufficient to induce a complete remission in 75% of the treated patients after 26 weeks. Despite high percentage of relapses after CsA discontinuation, after 1.5 years, 40% of patients had remission without deterioration of renal function [15, 16]. The efficacy of CsA in therapy of IgA nephropathy was proved just in patients with heavy proteinuria (>3 g/day) and/or certain impairment of renal function with serum creatinine varying between 140–150 μmol/L and/or diffuse mesangial proliferation in renal biopsy [5, 17].

The explanation of limited papers on the CsA effect in IgA nephropathy might be due to a negative communication by Lai et al. [18]. They observed just short-term effect in the CsA-treated patients as compared with the control group. Conversely, the CsA-treated patients revealed clear CsA toxicity. In other study, the immunomodulation by CsA does affect neither IgA- nor IgG-circulating immune complexes [19].

Recently, many studies proved favorable effect of CsA in the therapy of lupus nephritis of WHO classes IV and V. As a maintenance therapy of membranous lupus nephritis, CsA has an obvious efficacy in reducing of proteinuria and improving of immunological parameters of SLE [20, 21]. Concerning the proliferative lupus nephritis, CsA may be helpful if standard therapeutical regimen has failed in both adults and children. Its use resulted in an improvement of proteinuria and morphological injury as well as with the decrease of SLE activity [22, 23, 24]. The potency of CsA in inducing remission was proved to be preserved and safe also in crescent form of the disease with high titters of autoantibodies [25].

Despite indubitable efficacy of CsA, the long-term CsA therapy carries a potential for an increased morbidity and is associated with mild increasing renal interstitial fibrosis, tubular atrophy, vascular changes and renal function impairment [2]. The initial sensitivity to the CsA exposure may predict the renal dysfunction development [26].

Tacrolimus

Tacrolimus, another calcineurin inhibitor has been recently extensively used in kidney and liver transplantation. Unfortunately, there is just limited knowledge of its use in non-transplant indications. Similarly to cyclosporine, tacrolimus therapy may achieve remission of FSGS when administered with low-dose steroids in a dose similar to one used in transplantation (5–12 ng/mL). Tacrolimus was shown to reduce a high percentage of relapses (76%) observed in the case of tacrolimus withdrawal [27].

The 6 months tacrolimus treatment of membranous nephropathy resistant to conventional regimens resulted in complete remission [28]. The effect of tacrolimus was also examined in the experimental model of membranous nephropathy in the rat. In this model, the proteinuria was decreased and structural changes were ameliorated in the case of tacrolimus therapy [29].

There are no available data about the effectiveness of tacrolimus in IgA nephropathy. Most papers just dealt with its application in recurrent IgA nephropathy in renal transplant recipients [30]. Recipients with primary IgA nephropathy tend to relapse frequently after transplantation in CsA based immunosuppression. Tacrolimus ameliorated the graft and patients long-term survival rates, however had no influence on formation of IgA mesangial deposits [31]. Indubitable, more recent studies about the use of tacrolimus in the therapy of chronic glomerulopathies are warranted.

Mycophenolate mofetil (MMF)

MMF acts as a non-competitive reversible inhibitor of inosinmonophosphate-dehydrogenase (IMPDH), a key enzyme of the *de novo* synthesis of guanosine nucleotides. It has been broadly used in solid organ transplantation as an adjunctive agent.

Recent studies have demonstrated a potency of MMF in remission induction in steroid – and/or CsA-resistant or -dependent patients suffering from multiple relapses of idiopathic nephrotic syndrome [32, 33, 34]. Its efficacy seems to be preserved also in case of failure of the therapy with alcylating agents (CFA), which may induce a remission in steroid-resistant patients in 25–30% in oral form and in 50% in intravenous form [1, 35]. To reduce the risk of relapse after discontinuing of MMF therapy, a more prolonged (about 12 months) course can contribute, with average doses varying from 0.5 to 1 g twice daily. The MMF regimen decreases the exposure to CsA and corticosteroids and may lead to the subsequent withdrawal of these drugs [36].

MMF was used in the treatment of FSGS. A six months therapy (0.5–1 g/day) induced remission in 50% adults with already preexisting renal insufficiency simultaneously with discontinuation of concomitant administered corticosteroids. MMF significantly decreased proteinuria and ameliorated serum proteins and lipid parameters [37]. Analogous outcomes with MMF at 250–500 mg/m^2 and angiotensin blockers were also reported in children who have failed to conventional treatment [38].

In the treatment of membranous nephropathy, MMF preserves its potency even in CsA- and/or steroid-resistant patients or in patients frequently relapsing after CsA withdrawal. A monotherapy at doses 0.5–1 g twice daily or a combination with low-dose steroids should be sufficient enough for induction of remission and abruption of concomitant administered corticosteroids. Most patients have experienced markedly clinical improvement, but in some cases MMF dependency or relapse after withdrawal of corticosteroids may manifest despite continuation of MMF therapy [37, 39]. The duration of therapy and target blood levels have not been yet clearly defined.

Similarly to the treatment of FSGS and membranous nephropathy, MMF was shown to be effective in some patients suffering from IgA nephropathy who were resistant to previous therapy [40, 37]. Anecdotically, MMF was shown to be useful in treatment of recurrent IgA nephropathy in renal transplantation [41].

Recently some reports showed MMF to be an effective tool to ameliorate lupus nephritis resistant to previous therapeutical approaches. The clinical and laboratory improvement has been usually observed after 4–6 months of the therapy. MMF monotherapy (or with low-dose corticosteroids) results in the induction of remission, reduction of both relapses and side effects, when compared to the regimen of 6-months cyclophosphamide and methylprednisolone, followed by azathioprine [42]. The evaluation of

3 maintenance regimens (AZA, CFA, MMF) has confirmed the comparable efficacy of all three, however AZA and MMF were better tolerated [43]. A complete remission in 81% cases was noted in 12-months therapy (0.5–2.5 g/day in adults, 60 mg/m^2 in children). MMF ameliorated the clinical signs of SLE including proteinuria, renal functions and significantly decreases the SLE activity [44, 45, 46]. Simultaneously the doses of corticosteroids could be subsequently reduced in 80% of patients [47]. The observed side effects were dose-depend.

The combination of MMF and low-dose corticosteroids was shown to be effective even in pauci-immune necrotizing glomerulonephritis [48]. In this study, patients received MMF in dose 2g/day for 15 months after the completion of the induction therapy. This led to further decrease of grumbling disease activity and remaining proteinuria.

Sirolimus (Rapamycine)

Sirolimus as a mTOR inhibitor is a non-nephrotoxic agent, which has been recently administered in kidney transplant recipients with proved calcineurin drug nephrotoxicity or chronic allograft nephropathy [49].

Sirolimus has been recently tested in the therapy of FSGS, membranous nephropathy and in lupus nephritis (www.clinicaltrials.gov), however the first results are not yet available.

Similarly, rapamycine derivate (everolimus) was proved to be effective in the preventing of allograft vasculopathy and in preserving of allograft function [50, 51, 52]. Recently, everolimus was shown to be effective in the experimental model of puromycine-induced glomerulonephritis. In the case of pretreatment with everolimus, animals had significantly reduced proteinuria with lower glomerular invasion of monocytes/macrophages [53]. However, it is important to note that data from humans are still missing.

Conclusion

It is probable that modern immunosuppressants, because of their efficacy and low toxicity, will be broadly used in the therapy of chronic glomerular nephropathies. However, new data are necessary to set guidelines for the use of these immunosuppressants in special cases of glomerulopathy.

References

1. EDDY A. A., SYMONS J. M.: Nephrotic syndrome in childhood. *Lancet* 362: p. 629–39, 2003.
2. CAMERON J. S.: Focal and segmental glomerulosclerosis in adults. *Nephrol. Dial. Transplant.* 18: Suppl. 6, p. 45– 51, 2003.
3. PONTICELLI C., PASSERINI P.: Treatment of membranous nephropathy. *Nephrol. Dial. Transplant.* 16: Suppl. 5, p. 8–10, 2001.
4. SCHIELE J., NOWACK R., JULIAN B. A., VAN DER WOUDE F. J.: Treatment of immunoglobulin A nephropathy. *Ann. Med. Interne* 150: p. 127–136, 1999.

5. GOUMENOS D. S., DAVLOUROS P., EL NAHAS A. M., AHUJA M., SHORTLAND J. R., VLACHOJANNIS J. G., BROWN C. B.: Prednisolone and azathioprine in IgA nephropathy. *Nephron. Clin. Pract.* 93: p. 58–68, 2003.
6. SINGH A., TEJANI C., TEJANI A: One-center experience with CsA in refractory NS in children. *Pediatr. Nephrol.* 13: p. 26–32, 1999.
7. NEWSTEAD C. G.: Reccurent disease in renal transplants. *Nephrol. Dial. Transplant*. 18: Suppl 6, p. 68–74, 2003.
8. PONTICELLI C., PASSERINI P.: Alternative treatments for focal and segmental glomerular sclerosis. *Clin. Nephrol.* 55/5: p. 345–348, 2001.
9. PONTICELLI C., VILLA M., BANFI G., CESANA B., POZZI C., PANI A., PASSERINI P., FARINA M., GRASSI C., BAROLI A.: Can prolonged treatment improve the prognosis in adults with focal segmental glomerulosclerosis? *Am. J. Kidney Dis.* 34/4: p. 618–625, 1999.
10. PASSERINI P., PONTICELLI P.: Treatment of focal segmental glomerulosclerosis. *Curr. Opin. Nephrol. Hypertens* 10: p. 189–193, 2001.
11. KVEDER R.: Therapy-resistant focal and segmental glomerulosclerosis. *Nephrol. Dial. Transplant*. 18: p. 34–37, 2003.
12. CHISHTI A. S., SOROF J. M., BREWER E. D., KALE A. S.: Long-term treatment of focal segmental glomerulosclerosis in children with cyclosporine given as a single daily dose. *Am. J. Kidney Dis.* 38/4: p. 754–760, 2001.
13. CATTRAN D. C.: Cyclosporine in the treatment of idiopathic focal segmental glomerulosclerosis. *Semin. Nephrol.* 23/2: p. 234–41, 2003.
14. SALOMON R., GAGNADOUX M. F., NIAUDET. P.: Intravenous cyslosporine therapy in recurrent nephrotic syndrome after renal transplantation in children. *Transplantation* 75/6: p. 810–814, 2003.
15. CATTRAN C. D., APPEL G. B., HERBERT L. A., HUNSICKER L. G., POHL M. A., HOY W. E., MAXWELL D. R., KUNIS C. L.: Cyclosporine in patients with steroid-resistant membranous nephropathy: A randomized trial. *Kidney Int.* 59: p.1484–1490, 2001.
16. CATTRAN D. C., GREENWOOD C., RITCHIE S, BERNSTEIN K., CHURCHILL D. N., CLARK W. F., MORRIN P. A., LAVOIE S.: A controlled trial of cyclosporine in patients with progressive membranous nephropathy. *Kidney Int.* 47: p. 1130–1135, 1995.
17. YOSHIKAWA N., ITO H., SAKAI T., TAKEKOSHI Y., HONDA M., AWAZU M., ITO K., IITAKA K., KOITABASHI Y., YAMAOKA K., NAKAGAWA K., NAKAMURA H., MATSUYAMA S., SEINO Y., TAKEDA N., HATTORI S., NINOMIYA M.: A controlled trial of combined therapy for newly diagnosed severe childhood IgA nephropathy. *J. Am. Soc. Nephrol.* 10: p. 101–109, 1999.
18. LAI K. N., LAI MAC-MOUNE F., VALLANCE-OWEN: A short-term controlled trial of cyclosporine A in IgA nephropathy. *Transplant. Proc.,* 20/3: Suppl. 4, p. 297–303, 1988.
19. LAI K. N., LAM C. W., CHENG I. K., TAM J. S., LAI F. M.:Effect of cyclosporine A on circulating immune complexes in IgA nephropathy. *Int. Urol. Nephrol*., 23/3: p. 265–74, 1991.
20. WALLACE D. J.: Advances in the management of systemic lupus erythematosus. *Bulletin on the rheumatic diseases* 52/11: 2003.
21. ILLEI G. G., CZIRJÁK L.: Novel approaches in the treatment of lupus nephritis. *Expert Opin. Invest. Drugs* 10/6: p. 1117–1130, 2001.
22. BOGDANOVIC R., NIKOLIC V., PASIC S., DIMITRIJEVIC J., LIPKOVSKA-MARKOVIC J., ERIC-MARINKOVIC J., OGNJANOVIC M., MINIC A., STAJIC N.: Lupus nephritis in childhood: a review of 53 patients followed at a single center. *Pediatr. Nephrol.* 19: p. 36–44, 2004.

23. TAM L. S., LI E. K., LEUNG C. B., WONG K. C., LAI F. M. M., WANG A., SZETO C. C., LUI S. F.: Long-term treatment of lupus nephritis with cyclosporin A. *Q. J. Med.* 91: p. 573–580, 1998.
24. KUIPER-GEERTSMA D. G., DERKSEN R. H. W. M.: Newer drugs for the treatment of lupus nephritis. *Drugs* 63/2: p. 167–180, 2003.
25. DOSTÁL C., TESAŘ V., RYCHLÍK I., ŽABKA J., VENCOVSKÝ J., BARTŮŇKOVÁ J., STEJSKALOVÁ A., TEGZOVÁ D.: Effect of 1 year cyclosporine A treatment on the activity and renal involvement of systemic lupus erythematosus: a pilot study. *Lupus* 7: p. 29–36, 1998.
26. VÍTKO Š., VIKLICKÝ O.: Cyclosporine renal dysfunction. *Transplant. Proc.* 36: p. 243S–247S, 2004.
27. SEGARRA A., VILA J., POU L., MAJÓ J, ARBÓS A., QUILES T., PIERA L. L.: Combined therapy of tacrolimus and corticosteroids in cyclosporin-resistant or –dependent idiopathic focal glomerulosclerosis: a preliminary uncontrolled study with prospective follow-up. *Nephrol. Dial. Transplant.* 17: p. 655–662, 2002.
28. SZETO C. C., LEUNG C. B., LAI F. M. M., LI P. K. T.: Tacrolimus in resistant primary membranous nephropathy-a report of 3 cases. *Clin. Nephrol.* 59/4: 2003.
29. KOBAYASHI M., MURO K., YOH K., KONDOH M., IWABUCHI S., HIRAYAMA K., ISCHIZU T., KIKUCHI S., YAMAGUCHI N., KOYAMA A.: Effects of FK 506 on experimental membranous nephropathy induced by cationized bovine serum albumin in rats. *Nephrol. Dial. Transplant.* 13: p. 2501–2508, 1998.
30. BENABDALLAH L., REROLLE J.-P., PERALDI M.-N., NOEL L.-H., BRUNEEL M.-F., CARRON P.-L., MORELON E., KREIS H.: An unusual recurrence of crescentic nephritis after renal transplantation for IgA nephropathy. *Am. J. Kidney Dis.* 40/6: p. E20, 2002.
31. SUZUKI K., TANABE K., TOKUMOTO T., SHIMIZU T., ISHIKAWA N., YAGISAWA T., HONDA K., NIHEI H., TOMA H.: Effect of tacrolimus in renal transplant recipients with Immunoglobulin-A nephropathy. *Transplant. Proc.* 32: p. 1730–1732, 2000.
32. DAY C. J., COCKWELL P., LIPKIN G. W., SAVAGE C. O. S., HOWIE A. J., ADU D.: Mycophenolate mofetil in the treatment of resistant idiopathic nephrotic syndrome. *Nephrol. Dial. Transplant.* 17: p. 2011–2013, 2002.
33. FILLER G.: Treatment of nephrotic syndrome in children and controlled trials. *Nephrol. Dial. Transplant.* 18: Suppl 6, p. 75–78, 2003.
34. LANDE M. B., GUILLON C., HOGG R. J., GAUTHIER B., SHAH B., LEONARD M. B., BONILLA-FELIX M., NASH M., ROY III. S., STRIFE C. F., ARBUS G.: Long versus standard initial steroid therapy for children with the nephrotic syndrome. *Pediatr. Nephrol.* 18**:** p. 342–346, 2003.
35. BAJPAI A., BAGGA A., HARI P., DINDA A., SRIVASTAV R. J.: Intravenous cyclophosphamide in steroid-resistant nephrotic syndrome. *Pediatr. Nephrol.* 18**:** p. 351–356, 2003.
36. BARLETTA G. M., SMOYER W. E., BUNCHMAN T. E., FLYNN J. T., KERSHAW D. B.: Use of mycophenolate mofetil in steroid-dependent and –resistant nephrotic syndrome. *Pediatr. Nephrol.* 18: p. 833–837, 2003.
37. CHOI M. J., EUSTACE J. A., GIMENEZ L. F., ATTA M. G., SCHEEL P. J., SOTHINATHAN R., BRIGGS W. A.: Mycophenolate mofetil treatment for primary glomerular diseases. *Kidney Int.* 61: p. 1098–1114, 2002.
38. MONTANÉ B., ABITBOL C., CHANDAR J., STRAUSS J., ZILLERUELO G.: Novel therapy of focal glomerulosclerosis with mycophenolate and angiotensin blockade. *Pediatr. Nephrol.* 18: p. 772–777, 2003.
39. BRIGGS W. A., CHOI M. J., SCHEEL P. J.: Successful mycophenolate mofetil treatment of glomerular disease. *Am. J. Kidney Dis.* 31/2: p. 213–217, 1998.

40. BADID C., DESMOULIERE A., LAVILLE M.: Mycophenolate mofetil: implications for the treatment of glomerular disease. *Nephrol. Dial. Transplant.* 16: p. 1752–1756, 2001.
41. HARZALLAH K., BADID C., FOUQUE D., LEFRANCOIS N., TOURAINE J.-L., LAVILLE: Efficacy of mycophenolate mofetil on recurrent glomerulonephritis after renal transplantation. *Clin. Nephrol.* 59/3: p. 212–216, 2003.
42. ADU D.: The evidence base for the treatment of lupus nephritis in the new millennium. *Nephrol. Dial. Transplant.* 16: p. 1536–1538, 2003.
43. CONTRERAS G., ROTH D., PARDO V., STRIKER L. G., SCHULTZ D. R.: Lupus nephritis: a clinical review for practicing nephrologists. *Clin. Nephrol.* 57/2: p. 95–107, 2002.
44. FU Y. F., LIU G. L.: Mycophenolate mofetil therapy for children with lupus nephritis refractory to both intravenous cyclophosphamide and cyclosporine. *Clin. Nephrol.* 55/4: p. 318–321, 2001.
45. DOOLEY M. A., COSIO F. G., NACHMAN P. H., FALKENHAIN M. E., HOGAN S. L., FALK R. J., HERBERT L. A.: Mycophenolate mofetil therapy in lupus nephritis: Clinical observations. *J. Am. Soc. Nephrol.* 10: p. 833–839, 1999.
46. GAUBITZ M., SCHORAT A., SCHOTTE H., KERN P., DOMSCHKE W.: Mycophenolate mofetil for the treatment of systemic lupus erythematosus: an open pilot trial. *Lupus* 8: p. 731–736, 1999.
47. MOK C. C., LAI K. N.: Mycophenolate mofetil in lupus glomerulonephritis. *Am. J. Kidney Dis.* 40/3: p. 447–457, 2002.
48. NOWACK R., GOBEL U., KLOOKER P., HERGESSEL O., ANDRASSY K., VAN DER WOUDE F. J.: Mycophenolate mofetil for maintenance therapy of Wegener's granulomatosis and microscopic polyangiitis: a pilot study in 11 patients with renal involvement. *J. Am. Soc. Nephrol.* 10/9: p.1965–71, 1999.
49. KAHAN B. D.: Sirolimus: A ten-year perspective. *Transplant Proc* 36: p. 71–75, 2004.
50. AUGUSTINE J. J., HRICIK D. E.: Experience with everolimus. *Transplant. Proc.* 36: p. 500S–503S, 2004.
51. KOVARIK J. M.: Everolimus: A proliferation signal inhibitor targeting primary causes of allograft dysfunction. *Drugs Today* 40/2: p. 101–9, 2004.
52. VIKLICKY O., ZOU H., MULLER V., LACHA J., SZABO A., HEEMANN U.: SDZ-RAD prevents manifestation of chronic rejection in rat renal allografts. *Transplantation* 69/4: p. 497–502, 2000.
53. DANIEL C., ZISWILER R., FREY B., PFISTER M., MARTI H. P.: Proinflammatory effects in experimental mesangial proliferative glomerulonephritis of the immunosuppressive agent SDZ RAD, a rapamycine derivate. *Exp. Nephrol.* 8/1: p. 52–62, 2000.