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Abstract and Keywords: The second page should contain an abstract of about 150-200 words. It should state the purpose of the study, a brief description of the procedures employed, main findings and principal conclusions. Three to five keywords should also be listed below the Abstract.

Text: Wherever possible, the text should consist of an introduction, materials and method, results, discussion, conclusions, references and acknowledgements.

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iv) Agency publication:
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v) Journal article on the Internet:
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TOWARDS MORE RATIONAL PRESCRIBING

The articles in JUMMEC deal with a wide variety of issues; foremost amongst them, is the discussion on the rational use of drugs in treating many illnesses and medical conditions.

Certainly, drug therapy is critical for the treatment of many illnesses and conditions but in the present climate of rising cost of care and limited resources, we should ask ourselves if we are getting value for our money; in other words, there should be more rational use of drugs. Antibiotics are amongst one of the more frequently prescribed drugs. In fact, it had been reported to account for as much as 50% of some hospital pharmacy budgets. The widespread use of antibiotics had lead to the emergence and spread of microbes, that are resistant to cheap and effective "first-line" drugs.

Resistance to antimicrobials is a natural biological phenomenon – a case of survival if you like. Factors that contribute to this emergence of drug resistance include human practices ranging from poor prescribing, unnecessary or not indicated use, under-dosing or using for too short a duration, poor compliance on the part of the patient, as well as veterinary prescribing in animal husbandry.

As seen from the paper on antimicrobial susceptibility of *Pseudomonas aeruginosa,* susceptibility of this organism to the newer, more expensive antimicrobials has already been compromised. Fortunately, community-acquired *Pseudomonas aeruginosa* infections are still 100% susceptible. That being the case, every effort should be made to prevent further emergence of more drug-resistant organisms.

This problem of antimicrobial resistance has reached an alarming stage of global importance, that in September 2001, WHO launched the first global strategy to combat the problem of drug resistance. The University of Malaya Medical Centre should be commended for having developed an antibiotic guideline for use in the hospital – to enhance and encourage more rational antibiotic prescribing.

Besides drug resistance, drug cost is also a matter of huge concern in any health care organization. Here again, it is timely that efforts have been made to relook at the cost of drugs. An original article compared the use of risperidone with olanzapine in the treatment of schizophrenia.

Besides cost being the underlying principle in drug prescribing, efficacy and safety should be important considerations as well. While steroids would seem a less expensive choice as an agent for immunosuppression after renal transplantation, there are other alternatives, albeit more expensive, which would be safer, less toxic and more efficacious. In the review article, discussion was centred on the withdrawal or avoidance of use of steroids after renal transplantation.

Complementary medicine is currently in vogue although much of it has not been well understood nor has it been scientifically studied. Substances that are ingested, either supplements or remedies, have not been subjected to the same rigorous processes that new drugs have to undergo when seeking registration. The paper on cytoprotective effect of honey with extracts of *Chromolaena odorata* L. a herb, is certainly worth further reading. Obviously for such herbs to be deemed efficacious and of medicinal value would require well-designed, blinded randomized-control trials performed on humans.

Cardiovascular disease (CVD) is very prevalent in Malaysia. It is still the number one cause of medically certified deaths in our country. Interest in aetiological factors, one of which is obesity, is being extensively studied. It is interesting to note in the paper, "Body fat comparison between basketball and netball players in Malaysia" that even amongst national athletes, in particular, female basketball and netball players, their average percentage of body fat, is higher than the desired average for elite sportsmen.

Angina is one of the presenting symptoms of coronary heart disease. However, trying to reach a diagnosis of angina could be quite complicated and fraught with uncertainties. The use of simple neural network architecture to diagnose angina was discussed in some detail in this issue.

While CVD is the number one killer in Malaysia, deaths due to road traffic accidents (RTA) are not far behind. In fact, year after year, we read about the large number of RTA deaths. There could be many contributing factors to this, and poor visual acuity is certainly a possible cause. It would appear from the paper on visual defects amongst commercial vehicles drivers that indeed visual defects are under-diagnosed. Greater efforts should be made to detect visual defects, not only amongst commercial vehicle drivers but all drivers, too.

Finally, it is encouraging to note that maternal mortality in Malaysia had declined very significantly over the last 50 years. However, this is no reason to rest on our laurels. It had been discussed in "Measuring maternal mortality in Malaysia" that we should be looking at the lifetime risk of maternal mortality and not at maternal mortality ratio alone. More importantly, the question is, could maternal mortality be further reduced. And now, with more interest in maternal mortality and so many clinical trials being conducted that include a significant number of women, it can be said that the era of women, has finally arrived.

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STEROID WITHDRAWAL OR AVOIDANCE IN RENAL TRANSPLANT RECIPIENTS

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ABSTRACT: Steroids remain an important component of maintenance immunosuppression after renal transplantation. Their anti-inflammatory action is partly due to the sequestration of CD4+ lymphocytes in the reticuloendothelial system. Steroids bind to intracellular receptors and the resulting steroid-receptor complex alters the transcription of cytokines by binding to glucocorticoid response elements on DNA. Transcription factors whose actions are altered by glucocorticoids include activating protein-1 (AP-1) and nuclear factor-κB (NF-κB). The main cytokines whose production by antigen-presenting cells is inhibited by steroids are interleukin-1 (IL-1), required for helper T-cell activation, and IL-6, required for B-cell activation. Other pro-inflammatory cytokines such as interferon gamma and tumour necrosis factor are also inhibited. This multiplicity of immunosuppressive actions is not fully replicated by other immunosuppressants. However, there are concerns about the long-term side effects of steroids. This review will examine the attempts at steroid withdrawal or steroid avoidance in renal transplant patients. ***(JUMMEC 2006; 9(1): 2-6)***

KEYWORDS: steroid withdrawal, renal transplantation, immunosuppressants

Introduction

Steroids remain an important component of maintenance immunosuppression after renal transplantation. While still incompletely understood, recent discoveries have provided insights into their mechanisms of action (1). Their anti-inflammatory action is partly due to the sequestration of CD4+ lymphocytes in the reticuloendothelial system. Steroids bind to intracellular receptors and the resulting steroid-receptor complex alters the transcription of cytokines by binding to glucocorticoid response elements on DNA. Transcription factors whose actions are altered by glucocorticoids include activating protein-1 (AP-1) and nuclear factor-κB (NF-κB). The main cytokines whose production by antigen-presenting cells is inhibited by steroids are interleukin-1 (IL-1), required for helper T-cell activation, and IL-6, required for B-cell activation. Other pro-inflammatory cytokines such as interferon gamma and tumour necrosis factor are also inhibited. This multiplicity of immunosuppressive actions is not fully replicated by other immunosuppressants.

However, there are concerns about the long-term side effects of steroids. These include hyperglycaemia, dyslipidaemia, hypertension, truncal obesity, cushigoid features, osteoporosis, aseptic bone necrosis, growth disturbances in children and cataracts. The first four factors may contribute to cardiovascular disease, a leading cause of mortality and morbidity in transplant patients (2). The cost of steroid-related side effects in the US is estimated at $5,300 per patient (3).

This review will examine the attempts at steroid withdrawal or steroid avoidance in renal transplant patients. Concomitant maintenance immunosuppressants may include calcineurin inhibitors (cyclosporine, tacrolimus), antimetabolites (azathioprine, mycophenolate mofetil) or sirolimus, which inhibits the mammalian target of rapamycin (mTOR). During the initial, high-risk post-transplant period, patients may also receive induction therapy with OKT3 (an anti-CD3 monoclonal antibody), antithymocyte (ATG) or antilymphocyte (ALG) globulins, or the IL2-receptor antagonists, basiliximab or daclizumab.

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Cyclosporine/azathioprine-based regimes

Cyclosporine gained widespread usage in renal transplantation after it was shown to improve short term graft survival compared to azathioprine (4,5,6). Steroid withdrawal in the early (6-12 days) post-transplant period was abandoned after it was found to increase the rate of acute rejection (AR) (7). A meta-analysis of randomized controlled trials (RCT's) of late steroid withdrawal with this regime examined nine studies with a total of 1,461 patients (8). The authors found a 14 per cent increase in AR and a 40% increase in graft failure in the steroid withdrawal group. Steroid withdrawal from patients with stable graft function at 1-6 years post-transplant (9). While there were no documented AR episodes, serum creatinine at 1-year post-withdrawal was significantly higher than in the control steroid maintenance group. In the largest RCT, worse 5-year graft survival in the steroid withdrawal group was found, although this effect was not detected on shorter follow-up (10). These two studies suggest that apart from precipitating AR, steroid withdrawal may also impair graft function, possibly by increasing chronic rejection. The study (10) also emphasizes the importance of long-term follow-up in these studies. Because of these results, enthusiasm for steroid withdrawal in patients on this regime has waned.

However, a recent trial studied the possibility of steroid withdrawal with the addition of an anti-IL2 receptor antibody. One hundred fifty-seven patients on cyclosporine and azathioprine were randomized to receive induction with basiliximab or placebo. Steroids were withdrawn five months post-transplant. Patients in the basiliximab group had higher success in steroid withdrawal, fewer AR's (25.3% at 1 year) and fewer graft losses (11).

Cyclosporine/mycophenolate mofetil-based regimes

Mycophenolate mofetil (MMF) is an antimetabolite which is superior to azathioprine in preventing AR (12,13,14). Two major studies have looked at steroid withdrawal in cyclosporine/MMF-based regimes. The European trial (15) randomized 500 patients to standard therapy or to steroid withdrawal after 12 weeks of half-dose prednisolone (low/stop group). They found a higher AR rate at 12 months follow-up in the low/stop group. Interestingly, there was no difference between the groups among patients who received induction therapy with OKT3 or antithymocyte globulin. The US trial (16) recruited primary transplant patients with no early AR and randomized them to standard therapy or steroid withdrawal at three months post-transplant. The study was terminated prematurely when the steroid withdrawal group was found to have a much higher 1-year AR rate (30.8% vs 9.8%). This difference was especially pronounced among the African-American subjects. However, several recent smaller RCTs have found no increase in AR after steroid withdrawal (17,18,19).

Tacrolimus-based regimes

Tacrolimus is a calcineurin inhibitor which is superior to cyclosporine in preventing AR (20,21,22) and preserving graft function (23). There have been no large RCTs of steroid withdrawal in patients on tacrolimus-based regime. A retrospective analysis by the Pittsburgh group of 795 patients on tacrolimus and azathioprine or MMF found better graft survival in patients in whom steroids were withdrawn (24). However, there may be bias as these patients had lower immunologic risks compared to those in whom steroids were continued. A small RCT (25) involving patients with low immunologic risks found no AR and 100 per cent graft survival in both steroid withdrawal and maintenance group at 24-months' follow-up. However, four out of 48 patients developed rising creatinine after steroid withdrawal, which recovered after steroids were restarted.

Steroid sparing and avoidance protocols

A significant disadvantage of late steroid withdrawal is that some steroid side effects, such as osteopaenia, have their greatest effects during the early post-transplant period, when high doses of steroids are used. In addition, steroids may affect the development of tolerance by inhibiting T-cell apoptosis (26). The development of powerful induction immunosuppressive agents has stimulated interest in the use of steroids for only a limited period (i.e., a few days) or not at all.

Since the mid-nineties, a Danish centre has been using a steroid-free protocol consisting of ATG for ten days together with maintenance cyclosporine and MMF. A review of 100 consecutive transplant recipients showed a 1- and 4-year graft survival of 97% and 82% respectively (27). There were only 13 episodes of AR, mostly in the first three months, and all were successfully reversed. A steroid-free regime is also possible with Campath 1H, a lymphocyte-depleting, humanized anti-CD52 monoclonal antibody. With two doses of Campath 1H and low dose maintenance cyclosporine, the Cambridge group was able to achieve graft survival of 29/31 at a mean follow-up of 21 months, with six episodes of AR (28).

Several studies have looked at regimes with anti-IL2 receptor antibody induction. With tacrolimus/MMF/anti-IL2 receptor antibody immunosuppression, steroid-free patients had a higher AR rate at six months post-transplant, but the difference disappeared by 12 months. However, it is unclear whether the patients

were randomized, and the mean follow-up period was short (29).

A case series of patients receiving daclizumab induction and maintained on cyclosporine and MMF was published (30). The 1-year graft survival was 89 per cent with an AR rate of 25 per cent, most of which were steroid-responsive and the majority of which occurred in the first month. However, by the end of the first year, a third of the patients required maintenance steroids. Further follow-up at three years post-transplant showed good graft survival and graft function, and few late rejections (31). A prospective RCT is in progress comparing daclizumab induction and two days of steroids with no daclizumab and 16 weeks of steroids. Maintenace immunosuppression is with tacrolimus and MMF. An interim analysis at a mean follow-up of 11 months found no difference in AR rates between the two groups (32).

Initial experience with basiliximab has been similarly positive. A comparative study was done on a 4-day steroid regime with steroid maintenance, with concomitant cyclosporine, MMF and basiliximab induction (33). At six months' follow-up, there was no difference in AR rate and serum creatinine between the two groups. A randomized study of 27 patients receiving basiliximab/cyclosporine/MMF to maintenance steroids or no steroids was carried out (34). The no steroids group also received two extra doses of basiliximab at 60 and 64 days post-transplant. There were no differences in AR and creatinine clearance after follow-up for one year.

Sirolimus-based regimes

Sirolimus is a relatively new immunosuppressant with a unique target (mTOR). There has not yet been RCTs of steroid withdrawal using a sirolimus-based regime. In an uncontrolled observational study, 75.4 per cent of 156 patients on cyclosporine and sirolimus had their steroids successfully withdrawn at one week to two years post-transplant. At three years, the AR rate was 6.4 per cent, the chronic rejection rate was 5.1 per cent and graft loss occurred in 7.7 per cent (35).

Metabolic benefits of steroid withdrawal

The main reason for steroid withdrawal is the purported metabolic benefits. This assumption was recently challenged by the findings of a retrospective review (36). After a mean follow-up of 7.6 years, the authors found no further metabolic benefits of prednisolone reduction to below 10 mg every other day. In addition, most of the early metabolic benefits of steroid withdrawal were not sustained over longer periods.

Identifying patients suitable for steroid withdrawal/avoidance

The RCTs of steroid withdrawal cannot give us clear-cut answers as to who can undergo steroid withdrawal or be started on a steroid-free protocol. The studies vary greatly in the patients' characteristic, concomitant immunosuppression, timing and rate of steroid withdrawal, duration of follow-up and study end-points. Thus, the consideration of the risk:benefit ratio should be individualized, based on the patients' immunologic profile, transplant history and concomitant medications, the severity of steroid-related side effects, coexisting cardiovascular risk factors, and the opportunity for a retransplant should the current graft fail.

Thus, prime candidates for steroid withdrawal or avoidance would be a non-sensitised recipient of a well-matched graft from a living donor, without delayed graft function or acute rejections, and who has good, stable graft function. Steroid withdrawal or avoidance should also be considered in patients who already suffer from significant steroid-related side effects (such as osteopaenia, or growth retardation in children) or who have significant coexisting cardiovascular risk factors, especially diabetes mellitus, dyslipidaemias, hypertension or a strong family history of cardiovascular disease. Few patients are likely to meet all these criteria, so the eventual decision should be made after careful consideration by the clinician and the patient.

Conclusion

In conclusion, newer, more powerful immunosuppressants have reduced the risk of steroid withdrawal or avoidance. Many of the studies on these agents are small, short and have not been published in peer-reviewed journals. In addition, the metabolic benefits of steroid withdrawal may not be sustained nor superior to low dose maintenance steroids. Therefore, the overall risk:benefit ratio should be individualized for each patient.

References

1. Hricik DE. Steroid-free immunosuppression in kidney transplantation: An editorial review. Am J Transplant 2002; 2: 19-24.
2. United States Renal Data System. USRDS 1998 Annual Data Report. The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, MD, 1997.

3. Veenstra DL, Best JH, Hornberger J, Sullivan SD, *et al*. The incidence and long-term cost of steroid-related side-effects after renal transplantation. Am J Kidney Dis 1999; 33: 829-839.

4. Canadian Multicentre Trial Group. A randomized clinical trial of cyclosporine in cadaveric renal transplantation. N Engl J Med 1983; 309: 809-815.

5. Canadian Multicentre Trial Group. A randomized clinical trial of cyclosporine in cadaveric renal transplantation. Analysis at three years. N Engl J Med 198; 314: 1219-1225.

6. European Multicentre Trial Group. Cyclosporine in cadaveric renal transplantation: one-year follow-up of a multicentre trial. Lancet 1983; 2: 986-989.

7. Schulak JA, Mayes JT, Moritz CE, *et al*. A prospective randomized trial of prednisone versus no prednisone maintenance therapy in cyclosporine-treated and azathioprine-treated renal transplant patients. Transplantaion 1990; 49: 327-332.

8. Kasiske BL, Chakkera HA, Louis TA, *et al*. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. J Am Soc Nephrol 2000; 11: 1910-1917.

9. Ratcliffe PJ, Dudley CRK, Higgins RM, *et al*. Randomized controlled trial of steroid withdrawal in renal transplant recipients receiving triple immunosuppression. Lancet 1996; 348: 643-648.

10. The Canadian Multicentre Transplant Study Group. Low dose steroid therapy in cyclosporine-treated renal transplant recipients with well-functioning grafts. Can Med Assoc J 1992; 147: 645-656.

11. Sandrini S, Rizzo G, Valente U, *et al*. Basiliximab facilitates steroid withdrawal after renal transplantation: Results of an Italian multicentre, placebo-controlled study (SWISS study) (abstract). Am J Transplant 2002; 2 (S3): 172.

12. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and steroids for prevention of acute rejection. Lancet 1995; 345: 1321-1325.

13. US Renal Transplant Mycophenolate Mofetil Study Group. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. Transplantation 1995; 60: 225-232.

14. The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, randomized clinical trial of mucophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. Transplantation 1996; 1: 1029-1037.

15. The Steroid Dosing Study Group. Double-blind comparison of two corticosteroid regimen plus mycophenolate mofetil and cyclosporine for the prevention of acute renal allograft rejection. Transplantation 2000; 70: 1352-1359.

16. Steroid Withdrawal Study Group. Prednisone withdrawal in kidney transplant recipients on cyclosporine and mycophenolate mofetil – A prospective randomized study. Transplantation 1999; 68: 1865-1874.

17, Francos GC, Frankel CJ, Dunn SR, *et al*. Double-blind, placebo-controlled, three year study of steroid withdrawal using a Neoral and mycophenolate mofetil (MMF)-based immunosuppressive regimen in primary renal transplant recipients (abstract). Am J Transplant; 2(S3): 172.

18. Budde K, Fritsche L, Geissler S, *et al*. Steroid withdrawal in long-term cyclosporine A treated patients using mycophenolate mofetil: A prospective randomized pilot study. Transplant Proc 2001; 33: 3250-3252.

19. Boletis JN, Konstadinidou I, Chelioti H, *et al*. Successful withdrawal of steroids after renal transplantation. Transplant Proc 2001; 33: 1231-1233.

20. Pirsch JD, Miller J, Deierhoi MH, *et al*. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression after cadaveric renal transplantation. FK506 Kidney Transplant Study Group. Transplantation 1997; 63: 977-983.

21. European Tacrolimus Multicenter Renal Study Group. Multicentre randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection: a report of the European Tacrolimus Multicenter Renal Study Group. Transplantation 1997; 64: 436-443.

22. European Tacrolimus *vs* Ciclosporin Microemulsion Renal Transplantation Study Group. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomized multicentre study. Lancet 2002; 359: 741-46.

23. Vincenti F, Jensik SC, Filo RS, *et al*. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years. Transplantation 2002; 73: 1370.

24. Chakrabarti P, Wong HY, Toyofuku A, *et al*. Outcome after steroid withdrawal in adult renal transplant patients receiving tacrolimus-based immunosuppression. Transplant Proc 2001. 33: 1235-1236.

25. Critterio F, Rigotti P, Scata MC, *et al*. Steroid withdrawal in renal transplant patients immunosuppressed with tacrolimus (abstract). Am J Transplant 2002; 2 (S3): 172.

26. Smiley ST, Csizmadia V, Gao W, *et al*. Differential effects of cyclosporine A, methylprednisolone, mycophenolate mofetil and rapamycin on CD154 induction and requirement for NF-κB: implications for tolerance. Transplantation 2000; 70: 415-421.

27. Birkeland SA. Steroid-free immunosuppression in renal transplantation. Transplantation 2001; 71: 1089-1090.

28. Calne R, Moffatt SD, Friend PJ, *et al*. Campath 1H allows low-dose cyclosporine monotherapy in 31 cadaveric renal allograft recipients. Transplantation 1999; 68: 1613-1616.

29. Kaufman B, Leventhal JR, Fryer JP, *et al*. Kidney transplantation without prednisone (abstract) Transplantation 2000; 69 (supp) S133.

30. Cole E, Landsberg D, Russell D, *et al*. A pilot study of steroid-free immunosuppression in the prevention of acute rejection in renal allograft recipients. Transplantation 2001; 72: 845-850.

31. Zaltzman J, Cole E, Halloran P, Russell D, *et al*. Long-term follow-up of a steroid-free renal transplant cohort (abstract). Am J Transplant 2002; 2 (S3): 172.

32. van Riemsdijk I, Termeulen RG, Christiaans MH, *et al*. Anti-CD25 prophylaxis allows steroid-free renal transplantation in tacrolimus-based immunosuppression (abstract). Am J Transplant 2 (S3): 171.

33. Vincenti F, Monaco A, Grinyo J, *et al*. Rapid steroid withdrawal versus standard steroid treatment in patients treated with Simulect, Neoral, and Cellcept for the prevention of acute rejection in renal transplantation: A multicentre, randomized trial (abstract). Transplantation 69 (supp) S133.

34. Kumar MSA, Fa K, Fyfe B, *et al*. Steroid avoidance in kidney transplant recipients treated with Simulect, Neoral and Cellcept – A randomized prospective controlled clinical trial (abstract). Am J Transplant 2002; 2(S3): 393.

35. Mahalati K, Kahan BD. A Pilot study of steroid withdrawal from kidney transplant recipients on sirolimus-cyclosporine A combination therapy. Transplant Proc 2001; 33: 3232-3233.

36. Sivaraman P, Nussbaumer G, *et al*. Lack of long-term benefits of steroid withdrawal in renal transplant recipients. Am J Kidney Dis 2001; 37: 1162-1169.