

## New immunosuppressive drugs and lung transplantation: last or least?

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Lung transplantation has become an accepted treatment modality for end stage lung disease.<sup>1</sup> Traditionally, immunosuppressive maintenance therapy consists of cyclosporin, azathioprine, and prednisolone in kidney and liver transplantation as well as in lung transplantation. Despite the use of these drugs, acute rejection occurs frequently, especially in the first weeks and months after lung transplantation. Although these periods are now almost never life threatening, they are associated with substantial morbidity. Prevalences of acute rejection ranging from 60% to 100% have been reported, depending on whether acute rejection is based on clinical or histological diagnosis.<sup>2-4</sup> The incidence of acute rejection is far higher after lung transplantation than after any other form of solid organ transplantation. This may be due to the fact that the donor lung contains a substantial amount of immunocompetent tissue and because the lungs are constantly exposed to environmental factors.<sup>5</sup>

Bronchiolitis obliterans syndrome (BOS) is the major cause of morbidity and mortality in long term survivors of lung transplantation.<sup>6,7</sup> It occurs in approximately 30-50% of recipients still alive one year after transplantation and is characterised by progressive airway obstruction, usually in the presence of histological evidence of obliterative bronchiolitis (OB).<sup>8</sup> Once established it is usually refractory to immunosuppressive treatment,<sup>9</sup> thus stressing the importance of preventing this long term complication. As the frequency and severity of periods of acute rejection are the main risk factors for development of BOS,<sup>8</sup> it follows that it is of utmost importance to prevent acute rejection. A substantial effort has therefore been made to develop and introduce new immunosuppressant drugs, not only to prevent and treat acute and chronic rejection, but also with the hope of fewer side effects. This review will focus on recently approved immunosuppressant drugs, some of their pharmacological properties, evidence of their effectiveness in organ transplantation in general, and reported results in lung transplantation in particular. Furthermore, promising immunosuppressive drugs under investigation and the inhalation of cyclosporin or corticosteroids will be considered briefly.

### Mycophenolate mofetil

In 1896 mycophenolic acid (MPA) was obtained from a species of *Penicillium* and its antifungal activity was noted.<sup>10</sup> Mycophenolate mofetil (MMF, Cellcept®) is the ester pro-drug and is rapidly hydrolysed in vivo to MPA, the active compound. MPA strongly inhibits the enzyme inosine monophosphate dehydro-

genase which is essential for the de novo purine synthesis in lymphocytes, thereby preventing lymphocyte proliferation. Bioavailability after oral administration of MMF is excellent, and it is renally excreted as an inactive salt after hepatic glucuronidation with a mean half life of approximately 18 hours.<sup>11</sup> The recommended daily oral dosage is 1 g twice daily. Specific side effects are mainly gastrointestinal symptoms including nausea, diarrhoea, and cramps. The incidence of side effects has been shown to subside with longer use.<sup>12</sup>

Its efficacy in reducing the incidence of rejection after cadaveric renal transplantation has been investigated in three multicentre, randomised, double blind studies in which MMF was compared with either placebo or azathioprine.<sup>13-15</sup> These large studies yielded comparable results. The incidence of rejection was about 50% lower in the groups treated with MMF than in the control groups. In a multicentre open label trial the efficacy and safety of MMF in combination with cyclosporin was compared with high dose steroids together with azathioprine and cyclosporin in patients with renal allograft rejection refractory to antilymphocyte globulin. Additional treatment with MMF resulted in a 45% reduction in graft loss and death six months after enrollment in the study.<sup>16</sup> Zuckermann *et al* compared MMF with azathioprine in a non-randomised open trial in 40 lung transplant recipients (data presented at the European Society of Organ Transplantation, Budapest 1997, abstract 109) and found the incidence of histologically proven acute rejection in the group treated with MMF to be significantly lower six months after transplantation (24% versus 87%). This study was hampered by a rather low survival rate at six months of 76% in the group treated with MMF and 65% in the azathioprine treated group. MMF has recently been compared with azathioprine in a non-randomised study in 22 lung transplant recipients.<sup>17</sup> A lower incidence of biopsy proven rejection during treatment with MMF was found during the first 12 months after transplantation and the prevalence of BOS at one year in the azathioprine treated group was twice as high (36%) as in the group treated with MMF (18%), although this difference was not statistically significant. A European multicentre phase III trial is currently being conducted in which MMF is being compared with azathioprine after lung transplantation, both in conjunction with cyclosporin and corticosteroids. The primary end point is the development of BOS, with acute rejection being a secondary end point.

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### Tacrolimus

Tacrolimus (FK506, Prograf®) is a macrolide antibiotic with a short history. It was isolated in 1986 from *Streptomyces tsukubaensis*.<sup>18</sup> Although structurally different from cyclosporin, tacrolimus has a similar mode of action. Both drugs bind to intracellular proteins and interfere with the signal transduction from T cell surface receptors to the nucleus in lymphocytes, preventing transcription of lymphokine genes involved in T cell activation.

Tacrolimus is a hydrophobic compound and bioavailability after oral administration is poor and variable. It is almost completely metabolised through the cytochrome P-450 pathway in the liver with a half life of about nine hours. Because of these pharmacokinetic properties and its narrow therapeutic index, drug level monitoring is essential.<sup>19</sup>

Both a large US study and a European multicentre trial have shown the superiority of tacrolimus based therapy over cyclosporin in reducing the incidence and severity of rejection up to one year after liver transplantation. No difference was found in terms of graft and patient survival. The tacrolimus based therapy was associated with more side effects, primarily nephrotoxicity and neurotoxicity.<sup>20 21</sup>

In a prospective randomised study the efficacy of tacrolimus was compared with that of cyclosporin in 74 lung transplant recipients. Acute rejection occurred less frequently in the tacrolimus group (89% versus 100% at six months), and fewer courses of methylprednisolone were given.<sup>4</sup> Keenan *et al* reported the long term results of this study and found a markedly reduced incidence of biopsy proven OB in the tacrolimus treated group (21.7% versus 38%) with a trend towards improved survival.<sup>22</sup> Tacrolimus has also been used as rescue therapy for BOS. In a non-randomised trial with 12 patients no improvement in lung function could be found although the rate of decline decreased.<sup>23</sup> In a similar study in 10 single-lung transplant recipients with histologically confirmed OB the lung function stabilised after treatment was changed from azathioprine and cyclosporin to tacrolimus.<sup>24</sup> Finally, in a retrospective study of 14 patients with recurrent or persistent acute rejection the incidence and severity of acute rejection declined significantly after maintenance immunosuppressive treatment was changed from cyclosporin to tacrolimus.<sup>25</sup>

### New drugs under investigation

Sirolimus (rapamycin) is very similar to tacrolimus in being a product of a *Streptomyces* species and these drugs are structurally related. It binds to the same intracellular protein as tacrolimus, the so called FK-binding protein, yet it fails to inhibit the calcineurin phosphatase activity. Its effect depends on interfering with the cell cycle progression and it inhibits calcium independent signalling pathways in T and B cells.<sup>26</sup> It appears that rapamycin not only inhibits the proliferation of lymphocytes, but of mesenchymal and endothelial cells also.<sup>27-29</sup> It has subsequently been shown in animal airway transplant

models that administration of rapamycin markedly inhibits the fibroproliferative response to transplantation.<sup>30 31</sup> As OB probably represents the result of this response to injury, it is hoped that the use of rapamycin in lung transplantation will lessen the impact of this devastating complication. Initial clinical experience from phase II trials in renal recipients suggests that the combination of rapamycin and cyclosporin is superior to cyclosporin alone in reducing the frequency of acute rejection episodes.<sup>32</sup> Preliminary data from phase III trials of rapamycin in renal transplant recipients seem to confirm its efficacy,<sup>33 34</sup> but a remarkably high number of withdrawals from the study due to side effects was noted. A randomised controlled multicentre trial comparing rapamycin or a rapamycin derivative with azathioprine in patients at risk for BOS is likely to be conducted soon.

Specific antilymphocyte antibodies such as the polyclonal antithymocyte globulin and the monoclonal OKT3 have been used for some time in induction regimens or for the treatment of steroid resistant rejection.<sup>35</sup> Their use is limited because of the increased risk of infection, troublesome side effects, and substantial costs. New blocking antibodies directed towards different cell receptors involved in the stimulation of alloreactive lymphocytes are currently being developed. From the results of two large randomised, placebo controlled trials it appears that the humanised anti-IL-2-receptor antibodies are effective in reducing the incidence of rejection after kidney transplantation.<sup>36 37</sup>

Mizoribine and brequinar sodium have much in common with MMF. They interfere with nucleotide biosynthesis, thereby inhibiting B and T cell proliferation. Mizoribine has been extensively used in Japan as a steroid sparing alternative to azathioprine. A European trial in kidney recipients showed that the incidence of rejection decreased with the use of mizoribine.<sup>38</sup> Brequinar sodium has not yet been used in human subjects.

### Inhalation of immunosuppressants

Inhaled medication is commonly used in patients with asthma or chronic obstructive pulmonary disease as this route of administration allows a high dose of the drug to reach the affected organ with fewer systemic complications. The transplanted lung is, of course, also accessible to inhaled therapy. A lower incidence of OB was reported in seven heart-lung recipients treated with 2 mg nebulised budesonide twice daily for acute rejection resistant to intravenous corticosteroids compared with a control group.<sup>39</sup> Speich *et al*<sup>40</sup> have described the effect of inhaled fluticasone in one patient with BOS grade II who was treated with ten treatment pairs of two weeks duration with either fluticasone (1000 µg twice a day) or placebo. Both subjective and objective improvement, as determined by lung function, occurred with high dose fluticasone. Iacono *et al* reported that seven out of nine patients with biopsy proven OB refractory to enhanced immunosuppression treated with aerosolised

cyclosporin A had histological improvement and a reduced rate of decline in forced expiratory volume in one second (FEV<sub>1</sub>) compared with pretreatment values and with nine untreated historical control recipients with OB.<sup>41</sup> The same group reported similar results in patients with refractory acute allograft rejection.<sup>42 43</sup>

### Conclusions

Many new treatment modalities have emerged with potentially more effective drugs, yet the side effects of these seem acceptable in most instances. In principle, immunosuppressive drugs are selected or designed purely to suppress lymphocyte function and inflammatory reactions, irrespective of the organ transplanted. However, in most countries drug regulatory agencies insist on controlled clinical trials for each type of transplantation separately before such a drug can be registered for use. This means that, in the case of lung transplantation, registration of these drugs comes last because of the smaller number of lung transplants performed. For example, in the Eurotransplant area of Germany, Austria, the Netherlands, Belgium and Luxembourg 3117 kidney transplants and over 1000 liver transplants were performed in 1997 compared with 158 (double or single) lung transplants.<sup>44</sup> Lung transplant recipients are far more frequently affected by rejection than patients with other organ transplants and are at greater risk for chronic transplant dysfunction and ultimately graft loss. It is clear that they are in even greater need of more potent immunosuppressant drugs than other organ recipients. Since there is no alternative, their lives depend on keeping the graft viable for as long as possible by any means.

Lung transplantation has reached its present status mainly by developments in surgery, patient selection, and the availability of potent first generation T cell immunosuppressive drugs. However, further developments in lung transplantation will depend on three levels of commitment. Firstly, lung transplant physicians, committed to providing the best medical care available, are inherently inclined to use new drugs initially in rescue situations. If newer immunosuppressive drugs that are not registered for use in lung transplantation are deemed necessary, these drugs should not be withheld. Whenever possible these drugs should be given as part of a multicentre trial to establish their efficacy. Secondly, it is obvious that, despite the smaller numbers of lung transplant recipients, the frequency of chronic transplant dysfunction considerably exceeds that of other major transplant activities. For this reason the involvement of pharmaceutical companies in conducting clinical trials in lung transplantation should be encouraged early after the introduction of a new drug. Lastly, drug regulatory authorities should grant temporary registration for the use in lung transplantation of those drugs that are of proven benefit in other forms of solid organ transplantation before clinical trials in lung transplantation have been formally finalised.

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