

Rapamune has recently been identified as a key treatment option for kidney-transplant patients following the early withdrawal of cyclosporine, and could represent a new era of long term treatment for these patients.

Transplanted kidney structure and function improved with sirolimus-based therapy

Recent reports from the Rapamune Maintenance Regimen (RMR) study have revealed that kidney-transplant patients who remain on sirolimus (Rapamune®, Wyeth)-based therapy following early withdrawal of cyclosporine demonstrate better kidney histology and function 3 years after transplantation than those who continue on the drug. The study, published in a recent issue of the *Am. J. Transplant.*, was carried out by Alfredo Mota's group at the Hospitais da Universidade de Coimbra, Portugal. It sheds new light on the long-term care and treatment of kidney-transplant recipients and could change the way such patients are treated.

Mota commented on the publication of his findings "Graft function and histology are seen as predictive of renal transplant survival. Despite their efficacy, calcineurin inhibitors are known to contribute to suboptimal renal graft half-life because they increase blood pressure, decrease glomerular filtration rates (GFR), and contribute to chronic allograft nephropathy."

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"From the Rapamune Maintenance Regimen study we already know that early cyclosporine elimination significantly improved renal function

and blood pressure. Now in the 3-year biopsy results of the same study we see an improvement in glomerular filtration rates, and, in the biopsies, a significant decrease in tubular atrophy. This reinforces the advantages of a sirolimus-based immunosuppressive regimen with early cyclosporine withdrawal over continuous combined sirolimus-cyclosporine maintenance therapy for management of renal transplant patients" he continued.

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The RMR study involved a total of 525 patients who were started on a combination of rapamune, cyclosporine and steroids. After 3 months of use, 430 of these patients were then randomized to have either cyclosporine withdrawn and continue on a once-a-day regimen of rapamune and steroids, or to continue with the original course of treatment.

Protocol biopsies were examined and each of the six components (diffuse or focal inflammation, tubular atrophy, intimal proliferation, glomerular sclerosis, mesangial matrix increase and interstitial fibrosis) were scored using the Chronic Allograft Damage Index (CADI).

Results of the trial at 36 months revealed that the CADI score and the mean tubular atrophy score was lower in the patients who had cyclosporine withdrawn than in those who chose to continue on cyclosporine. In addition, at this time renal function was also

significantly improved in patients who had a withdrawal of cyclosporine compared with those who continued on the drug.

In response to this result, Mota commented "Tubular changes are hallmarks of cyclosporine nephrotoxicity. Thus, these data suggest that sirolimus-based, cyclosporine-free therapy will reduce the incidence of tubular atrophy if cyclosporine is withdrawn early in the post-transplantation period."

Joseph Camardo, Senior Vice President of Global Medical Affairs at Wyeth Pharmaceuticals who manufacture rapamune commented on the study findings "These findings from the RMR study are important to physicians, patients, and the renal transplant community." He continued to add "Current immunosuppressive regimens involving the use of calcineurin inhibitors, such as cyclosporine, have long been associated with nephrotoxic effects. This new histology data strengthens evidence that Rapamune can be used to avoid the toxic effects of calcineurin inhibitors."

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It is now recommended that rapamune is used initially in a combination regimen with cyclosporine and corticosteroids. In patients at low to moderate immunologic risk, cyclosporine can then be withdrawn 2–4 months after transplantation and the dose of rapamune increased to reach recommended blood concentrations.

Priority Paper Alerts

Association between congestive heart failure and hospitalization in patients with Type 2 diabetes mellitus receiving treatment with insulin or pioglitazone: a retrospective data analysis.

Rajagopalan R, Rosenson RS, Fernandes AW, Khan M, Murray FT. *Clin. Ther.* 26(9), 1400–1410 (2004). As a result of recent concerns regarding the possibility of an association between the use of thiazolidinediones (TZDs) and an increased risk of congestive heart failure (CHF) in patients, this study sets out to examine the risk of CHF in patients with Type 2 diabetes and to compare any association with CHF in patients receiving the TZD pioglitazone with those receiving insulin alone. The retrospective analysis carried out in patients with Type 2 diabetes aged 18 years or over who had begun pioglitazone or insulin therapy between January 1999 and December 2001 concluded that pioglitazone therapy was associated with lower incidence rates of CHF compared with insulin therapy.

Use of sibutramine in overweight adult hispanic patients with Type 2 diabetes mellitus: a 12-month, randomized, double-blind, placebo-controlled clinical trial.

Sanchez-Reyes L, Fanghanel G, Yamamoto J, Martinez-Rivas L, Campos-Franco E, Berber A. *Clin. Ther.* 26(9), 1427–1435 (2004). Report of a 12-month, randomized, placebo controlled clinical trial examining the effect of sibutramine and glibenclamide on body weight and glycemic control in a cohort of obese Hispanic patients with Type 2 diabetes in accordance with a body mass index greater than 27 kg/m². Patients between the ages of 24 and 65 years with Type 2 diabetes who had previously been receiving glibenclamide monotherapy for at least 2 weeks and who currently presented with stable glucose concentrations were randomized to receive 10 mg sibutramine or placebo once daily and measurements of changes in body weight, waist circumference and glycosylated haemoglobin were recorded. Results from the sibutramine group showed a reduction in body weight from a mean of 73.9 kg at baseline to 69.8 kg at month 12, along with a decrease in body mass index from 29.9 to 28.2 kg/m². In addition, waist circumference and plasma fasting glucose concentrations were significantly reduced, demonstrating that in this population, the combination of sibutramine and glibenclamide therapy achieved weight loss for up to 12 months and was also associated with a better level of glycemic control than in the placebo group.

Tysabri[®] approved for treatment of multiple sclerosis

Tysabri[®] (natalizumab) has been recently approved by the Food and Drug Administration (FDA) for the treatment of multiple sclerosis (MS).

Elan Pharmaceuticals reported that 942 MS patients who took the drug for 1 year had a 66% reduction in relapses, compared with placebo. A second trial looked at MS patients who had one or more relapses with the drug Avonex[®]. Some received Tysabri or placebo along with Avonex. The Tysabri–Avonex treatment reduced relapse frequency by 54%, compared with placebo. The most frequent serious side effects were pneumonia, rash, fever, low blood pressure and chest pain.

The approval of the monoclonal antibody treatment Tysabri was the first time the government approved the targeted therapy to treat multiple sclerosis. The approval covers

intravenous delivery of the drug once a month in a doctor's office.

"It's exciting news for patients with MS," said David Ross from the FDA's Center for Drug Evaluation and Research. "There are no cures for MS, but it does reduce the frequency of relapses, a significant manifestation of the disease."

J Theodore Phillips from Baylor University Medical Center (TX, USA) said, "the relapses are devastating for patients who often were perfectly healthy before developing the chronic ailment. Without warning, a relapse can erase vision, turn a working arm or leg useless or numb feeling below the waist. That will last for several weeks followed by a slow improvement," said Phillips. "The best we have been able to do, up to this point, has been to reduce relapse frequency by about a third," he concluded.

Prialt[™] gains European recommendation for the intrathecal treatment of severe chronic pain

The European Committee for Medicinal Products for Human Use (CHMP) have recently recommended Elan Corp's ziconotide (Prialt[™]) for the intrathecal treatment of severe, chronic pain. The recommendation will now be proposed for the final stages of marketing authorization by the European Commission, a process that generally takes 3 months from CHMP approval.

The CHMP approval was partly based on the results of a Phase II clinical trial which was carried out in order to evaluate the efficacy and safety of intrathecal ziconotide in patients experiencing pain that was inadequately controlled by, or who

were intolerant to opioid analgesics. Lars Ekman, Executive Vice President, and President of Research and Development at Elan commented "We are encouraged by the Committee's positive recommendation and look forward to receiving final approval in the near future." He continued "Elan remains committed to making this unique orphan therapy available to those patients in Europe who are burdened by severe chronic pain, many of whom are currently without adequate relief."

Severe chronic pain is defined as pain that lasts longer than 6 months. It occurs most commonly as a result of a major trauma or failed back surgery.

Study results show dramatic decrease in reports of cardiovascular disease events in patients with diabetes

A recent examination of data from the Framingham Heart Study by researchers with the study group has reported that adults with diabetes have, in recent decades, experienced a 50% decrease in their incidence rate for cardiovascular disease (CVD) events. Caroline Fox, a researcher from the National Heart, Lung and Blood Institute, Framingham (MA, USA) and colleagues began their examination of the results of the study in an attempt to determine whether the declines in CVD events were experienced in adults with and without diabetes.

Examination of data from the Framingham Heart Study has been released recently indicating that there has been a notable 50% decrease in the incidence of cardiovascular disease in patients with diabetes in recent years.

Results from their examination suggest that “Adults with diabetes have experienced a 50 percent reduction in the rate of incident CVD, although persons with diabetes have remained at a consistent, approximate twofold excess for CVD events compared with those without diabetes. Adults without diabetes have had a smaller but statistically similar 35 percent reduction in CVD event rates.

Patients with diabetes have benefited in a similar manner to those without diabetes during the decline in CVD rates in the US population over the last few decades. Although gains have been made, substantial opportunity remains for additional progress to reduce the high absolute risk of CVD events in persons with diabetes.”

Results of the study can be found in the November 24th issue of *JAMA*.

Combunox™ receives approval for the treatment of short term acute, moderate-to-severe pain

Combunox™ (Forest Pharmaceuticals Inc.), the first fixed-dose combination analgesic of the opioid oxycodone (5 mg) and the nonsteroidal anti-inflammatory (NSAID) cyclooxygenase (COX) inhibitor ibuprofen (400 mg) for the short-term treatment of acute, moderate-to-severe pain has been approved by the US Food and Drug Administration (FDA). Speaking of the FDA approval, Howard Solomon, Chairman and CEO of Forest commented “The approval of Combunox provides physicians with a unique new option for managing the type of pain experienced by many patients each year following surgery or injury.” Combunox was approved by the FDA following a review of efficacy data from three double-blind, placebo controlled trials where the combination drug demonstrated significantly greater pain relief than oxycodone 5 mg alone, ibuprofen 400 mg alone or placebo. In addition, the drug was found to be safe and well tolerated with the most commonly reported side effects being nausea, vomiting, somnolence, dizziness and headache – common side effects associated with all opioid analgesics.

It is reported that up to 25 million Americans seek medical attention for acute pain annually. Combunox is expected to be released in March 2005.

Swedish approval granted for valsartan in the treatment of high-risk heart attack patients

The Medical Products Agency (MPA) of Sweden has granted valsartan (Diovan®, Novartis Pharma) its first European approval for the treatment of high-risk heart attack patients. Valsartan is marketed as a first-line high blood pressure agent and is the first in its class to achieve approval for such an indication. The approval was granted based in the results of an international trial which demonstrated that efficacy of the drug at preventing death in heart attack survivors. This approval of the drug in Sweden is a positive step towards full European licensure and Novartis Pharma are positive that Diovan will become a leader in its field.

Speaking of the results, Jörg Reinhardt, Head of Development, Novartis Pharma AG commented “Combined with Diovan's well

established double-digit blood pressure reduction efficacy and proven cardio-protective benefits, the approval in Sweden secures Diovan's place on the forefront of cardiovascular medicine.” He continued “We look forward to acquiring similar indications across the European Union to provide heart attack survivors a protective treatment that may be life-saving.”

Novartis are now pursuing applications in an additional 13 EU member states in accordance with MRP regulations which state that a EU member state is required to recognize the marketing authorization of another member state within 90 days. In addition, approval is being sought in Iceland, USA, Australia and in a number of Asian and Latin American countries.

Treatment-related risks of cancer therapy have dropped over the last 10 years

Based on an analysis of results from Phase I trials carried out between 1991 and 2002, the risks of treatment incurred by participating cancer patients have dropped over this 10-year period. Researchers from Massachusetts General Hospital (MA, USA) looked at studies evaluating single-agent therapy for advanced solid tumors. Agents already approved by the US Food and Drug Administration were excluded.

A total of 213 studies were identified. The overall toxic

New research suggests that risks associated with treatment for cancer, such as toxic death, have decreased over the last 10 years

death rate was 0.54% and the objective response rate was 3.8%. The toxic death rate fell during the study period. In the first 4 years, it was 1.1%, which fell to 0.06% in the last 4 years.

Subjects participating in the studies between 1999 and 2002 were 91% less likely to die from their experimental treatment than those treated between 1991 and 1994 ($p = 0.009$). However, the earlier results show a 54% less chance of experiencing an objective response than the latter group ($p = 0.001$).

Although treatment response rates also dropped during the study period, this trend was not consistent with the fall in toxic death rates, therefore, it is possible that the risk-benefit ratio has improved, explains lead author Thomas G Roberts.

The drop in toxic death rate is due, in part, to the decreased toxicity of newer agents and to an increased focus on safety issues in clinical research.

"Changes in the types of cancer drugs under study and in the clinical research environment have made participation in single-agent Phase I cancer trials safe, particularly with respect to the probability of experiencing a treatment-related death," Roberts's team conclude.

Possible link found between SSRI use and abnormal bleeding

A report in the November 22 issue of *Arch. Intern. Med.* has demonstrated a possible increased risk of abnormal bleeding in new users of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression. The suggested relationship, based on case reports and observational studies, may result from the role that serotonin is believed to play in blood clotting.

The study, carried out by researchers at the Utrecht Institute for Pharmaceutical Sciences, The Netherlands, have reported 196 cases of abnormal bleeding from a group of 64,000 new SSRI users from 1992 to 2000. Welmoed Meijer from the Utrecht Institute commented on the findings "We found a significant association between degree of serotonin reuptake inhibition by antidepressants and risk of hospital admission for abnormal bleeding."

"Antidepressants with a high degree of inhibition of serotonin reuptake were associated with a 2.6-fold increased risk of bleeding events compared with antidepressants with a low degree of serotonin reuptake inhibition" they concluded.

Tacrolimus most effective topical calcineurin inhibitor for eczema therapy

Results from a 12-year review of data examining topical calcineurin inhibitors (TCIs) in the treatment of atopic dermatitis (atopic eczema) have demonstrated that tacrolimus (Protopic[®], Fujisawa Healthcare Inc.) is significantly more effective in both adults and children compared with pimecrolimus (Elidel[®], Novartis Pharma) – the other most commercially available TCI. The study results were presented recently at the 13th Congress of the European Academy of Dermatology and Venereology (Italy) by Alan Fleischer Jr of Wake Forest University School of Medicine (NC, USA) where he commented "There are a number of myths concerning therapies for atopic dermatitis."

Tacrolimus offers a distinct advantage over topical steroid therapy which has been the cornerstone of eczema treatment of over 50 years in that it does not possess the associated side-effects of long term use including skin thinning, striae, dyspigmentation, rebound effects (flare of symptoms on stopping treatment) and tachyphylaxis.

"TCIs offer distinct advantages over conventional AD therapy and have a unique mode of action, which provides skin-selective treatment that relieves the signs and symptoms of AD. A major advantage is that they can be used for long-term treatment" continued Fleischer. The most common application-site side effects associated with both tacrolimus and pimecrolimus are burning sensations, erythema, pain and pruritus, the incidences of which are similar for both agents.

The studies carried out demonstrated that tacrolimus was more effective than pimecrolimus in the eczema area and severity index (EASI), itch, investigator's global assessment and percent affected body surface area. Fleischer concluded that "Extensive clinical experience developed over 12 years shows that tacrolimus is significantly more effective in both adults and children than pimecrolimus. This evidence is vital for dermatologists, pediatricians and general physicians across Europe who are committed to help alleviate the misery and hardship of many of their patients – young and old – living with eczema."