quantitative review (CAPTIM,\(^1\) the Grines study,\(^2\) DANAMI-2,\(^3\) C-Port\(^4\)) were terminated early because of physician unwillingness to randomise patients to thrombolysis when primary PTCA was available. Although the CAPTIM trial was stopped early, there was a 24% decrease in the primary, combined endpoint in patients treated with primary PTCA.\(^3\) This result would probably have favoured primary PTCA even more, had CAPTIM reached targeted enrolment. Furthermore, the correspondents ignore the many limitations of prehospital thrombolysis: 26% of the patients given thrombolysis in CAPTIM required emergent rescue PTCA, a procedure associated with substantial risks. W. Weaver and colleagues\(^5\) found that only 4% of ambulance calls about chest pain are for patients with ST-segment elevation AMI who are eligible for thrombolysis, and half of all patients with ST-segment elevation AMI drive to hospital. Moreover, all ambulances responding to chest pain calls must be staffed by physicians.\(^5\) For these reasons, prehospital thrombolysis has not been instituted in many communities, and is less available than primary PTCA.

Melandri and Massel question our inclusion of the SHOCK trial. As we explained in our methods section, all of our analyses were done with and without the SHOCK data. Since trials of primary PTCA investigate emergent cardiac catheterisation, we contend that inclusion of the SHOCK trial is appropriate and necessary, especially since it addresses an important group of high-risk patients. Melass questions the inclusion of trials that used stents. Stents have never been shown to affect the rate of death, reinfarction, or disabling stroke, and their use reflects standard of care in current practice. There is, therefore, no justification to exclude these trials. We are mystified by Massel’s criticism of “jumping trials together”, since meta-analyses, by definition, pool data.

We agree with Melandi that large randomised controlled trials are preferable to meta-analyses. In order to definitively compare primary PTCA with thrombolysis, a randomised controlled trial would need 4400 patients (2200 in each group) to show a 2% mortality difference with 80% certainty with a p value less than 0.05. The largest such trial, DANAMI-2,\(^2\) enrolled 1572 patients and was stopped early because physicians were unwilling to randomise patients to thrombolysis. Furthermore, the conclusion of our study that “primary PTCA is better than thrombolytic therapy at reducing short-term major adverse cardiac events, including death in individuals with ST-segment elevation AMI. Furthermore, these favourable results are sustained long-term follow-up.”\(^*\) Ellen C Keeley, Judith A Boura, Cindy L Grines

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**Dipyrrone and agranulocytosis: what is the risk?**

Sir—In reviewing the Swedish study of agranulocytosis,\(^1\) Jayne Edwards and Henry McQuay (Nov 9, p 1438)\(^2\) emphasise the small number of cases, and conclude that the risk of agranulocytosis with dipyrrone is unquantifiable and likely to remain so. We disagree, and believe that they overlooked important earlier publications.

Sweden and other industrialised countries banned dipyrrone because of blood dyscrasias around 1974. The incidence of blood dyscrasias was estimated at one in 3000 users. In 1981, the German Bundesgesundheitsamt (BGA) calculated the risk of agranulocytosis with dipyrrone as one in 20 000 users per year, restricting the indications for its use, and banned all combinations.

In 1986, the International Agranulocytosis and Aplastic Anemia Study (IIAAS)\(^3\) reported the incidence of dipyrrone-induced agranulocytosis as one case in 1 100 000 user-weeks. The authors of that study calculated the incidence of agranulocytosis as new cases per year, dividing this figure by 52 (weeks) to obtain the denominator “user-week”, so converting an estimated incidence of one in 20 000, based on the annual number of cases and users, into the widely cited one per million users.

The IIAAS was criticised: centres were lost (Israel, Budapest), cases were too few (Milan, Sofia), a reference population was exaggerated (Ulma), and the user-week denominator was seemingly used to lower the incidence of dipyrrone-induced agranulocytosis.\(^4\)

Both the IIAAS and the BGA calculated the incidence from cases of agranulocytosis identified by the spontaneous reporting system. Such systems detect at best only 5% of the adverse reactions that occur.\(^5\) An incidence of one in 20 000 so calculated might thus represent a true incidence of about one in 1000, as the Swedish study found.

Offerhaus pointed out that limiting the discussion of risk of dipyrrone to agranulocytosis leads to an underestimation of the dangers of the drug.\(^6\) In 1983, the hospital-based adverse drug reaction (ADR) monitoring system in Berne had reported serious hypotension with dipyrrone in one person per 3000 patients. In 1999, the hospital-based ADR monitoring system in Bremen reported other serious immune reactions to dipyrrone, such as anaphylaxis, asthma, serum sickness, hypersensitivity vasculitis, alveolitis, pneumonitis, hepatitis, or haemolytic-uraemic syndrome about four times more often than agranulocytosis.

The Cochrane reviews by McQuay’s team confirm that one dose of dipyrrone is effective for postoperative pain and acute renal colic pain. Such treatment causes few adverse reactions, since it takes about 2 weeks to trigger immune reactions in patients new to the drug and to manifest infection due to dipyrrone-induced agranulocytosis. Therefore short-term studies miss the drug’s dangerous effects.

The frequency of serious ADRs, not lack of efficacy, makes dipyrrone unacceptable for therapeutic use.

A full version of this letter appears at http://image.thelancet.com/extras/02cco12094web.pdf

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Kidney transplantation with rabbit antithymocyte globulin and sirolimus monotherapy

Sir—S John Swanson and colleagues (Nov 23, p 1662)1 report the successful renal transplantation of 12 patients treated with an 8–10 days induction of rabbit antithymocyte globulin (RATG) followed by monotherapy with sirolimus. We have some questions and concerns about this approach.

Of the 12 patients, six received cadaveric grafts. According to the protocol, these patients also received RATG for 8 to 10 days before transplantation. How was this process organised in practice? Were these patients on an urgent waiting list and did they all undergo transplantation immediately after the end of the induction period with RATG?

The investigators emphasise the benefits of immunosuppressive monotherapy. Indeed, monotherapy will favour patients’ compliance and keep drug-related side-effects to a minimum. However, intercurrent diseases, such as gastrointestinal disease, may interfere with the absorption, metabolism, or both of the immunosuppressive drug. Such interference may result in temporary under-immunosuppression. Even after transplantation, our patients have not tolerated the allograft, and the risk of acute rejection. By contrast, when a patient is on a (low dose) multidrug regimen, risk of rejection will be much lower. Thus, monotherapy may not be the best immunosuppressive regimen.

Swanson and co-workers enthusiastically conclude that the reported regimen offers an alternative approach to promote allograft tolerance. In our opinion, the results of this small study do not support this enthusiasm, but rather the opposite. The investigators emphasise that the success of their regimen depends on the maintenance of high enough trough concentrations of sirolimus. They report three episodes of late rejections 3 and 6 months after transplantation. The concentration of one drug determines success or failure of this kind of regimen.

Before the introduction of ciclosporin in 1983, our standard immuno-suppressive protocol consisted of induction with high doses of antithymocytic globulin/antithymocyte globulin, azathioprine, and high-dose steroids. More than 20 years later, several of these patients still have a good functioning kidney with a minimum of immunosuppression with azathioprine and low-dose steroids. Although T-cell counts were heavily depleted immediately after transplantation, our patients have not tolerated the allograft, since when these patients stop taking immunosuppressive therapy, they reject their kidney.

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Authors’ reply

Sir—Yves Vanrenterghem, and colleagues raise some excellent questions. Induction therapy with polyclonal rabbit antithymocyte globulin (RATG) was initiated at transplantation before reperfusion and continued for 8–10 days thereafter. We should have described the timing of the regimen more clearly in our Research letter. Although it is more convenient, we believe that depletional induction after reperfusion is a suboptimum approach. It is important to start induction with RATG before allograft reperfusion to take maximum advantage of its potential anti-adhesion effects.1

Vanrenterghem and co-workers are right to question reliance on a single maintenance agent. We agree that such monotherapy is a cause for concern and underlined it in our study. Our findings are not intended to establish a new standard of care based on monotherapy immunosuppression; rather, our goal was to investigate this approach as a path toward investigations of allograft tolerance.

Vanrenterghem and colleagues point out that RATG followed by monotherapy with sirolimus does not lead to allograft tolerance. We agree, and did not make claims to the contrary. Nevertheless, we believe it is important to consider this approach because of its implications for investigational immune treatments aimed at transplant tolerance. Aggressive use of calcineurin inhibitors, steroids, or both can antagonise several methods of specific T-cell anergy and deletion in preclinical models. Specifically, studies show that these agents limit activation-induced cell death, prevent the function or expression of co-stimulation molecules, or prevent the T-cell receptor engagement and antigen recognition required for antigen-specific deletion.1,4

Since essentially all immunosuppressive regimens use steroids, calcineurin inhibitors, or both, the search to find and test potentially tolerogenic regimens has been hindered.1 Asking patients to forgo proven standard therapies because of interactions that may lead to rejection raises ethical quandaries. Investigators face the vexing problem of how to assess new approaches when preclinical data do not support drug combinations mandated by the existing standard of care. Furthermore, immunosuppression suffers from diminishing returns in that additional immunosuppression only minimally improves already good graft survival, yet substantially increases the morbidity associated with standard regimens. Thus, it is no longer appropriate to add investigational immunomodulatory agents to standard triple immunosuppression for phase 1 and 2 evaluation. Moreover, testing new compounds is difficult when combined with multimodal immunosuppression, since drug interactions and adverse events are difficult to ascribe to any one agent.

Investigations of new treatments are likely to be simplified by addition to a single maintenance agent. Unlike steroids and calcineurin inhibitors, sirolimus is mechanistically compatible with most pro-tolerant pathways.2–4 We believe that this approach offers a mechanistically sound and sufficiently protective immunosuppressive foundation upon which future manipulations that promote allograft tolerance can be added.

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