

Another coronary reperfusion regimen

See page 329

The INJECT trial reported in this issue compares a standard infusion of streptokinase with a new regimen of reteplase, given as two bolus injections 30 min apart. Clinical outcome was similar (equivalence) for these two regimens: mortality after 35 days was 9.53% in the streptokinase group and 9.02% after reteplase, and stroke rates were 1.00% and 1.23%, respectively.

Reteplase is a variant of tissue plasminogen activator that has a long plasma half-life, allowing bolus administration. Its advantages over streptokinase include better early coronary artery patency,¹ less hypotension (7.2% vs 8.8% in INJECT, $p < 0.005$), and a lower rate of allergic reactions (1.1% vs 1.8%, $p < 0.05$). Because of this more favourable adverse-effect profile, reteplase might be preferred provided the clinical outcome is similar to that achieved with streptokinase and provided the drug does not cost too much. Clinical equivalence is supported by the INJECT findings. The authors should be complimented on this design of an equivalence study although it is a pity that no data were collected that might explain the clinical findings.

In INJECT, equivalence was defined as a less than 1% absolute difference in 35-day survival between the two treatment groups. The survival advantage for reteplase over streptokinase was 0.53% (90% CI) (-0.71% to 1.76%). Stroke rates were higher with reteplase, but as in other studies^{2,3} almost half of the stroke patients died. The numbers of patients with either death or stroke remained lower for reteplase (9.59%) than for streptokinase (10.11%). Also, death or disabling stroke was less frequent in the reteplase group. Indeed, one can conclude that reteplase will not be worse than streptokinase by more than 0.71%. In addition, patients receiving reteplase had lower rates of heart failure, cardiogenic shock, and atrial fibrillation; this result suggests that infarct size was somewhat smaller than with streptokinase. However, infarct size was not measured directly.

Although the INJECT investigators were looking for equivalence, there were indications that the double-bolus reteplase regimen might be better than standard streptokinase. Coronary patency with this regimen in the phase II study was 85% (TIMI 2 and 3) with 60% TIMI 3 flow. These figures were similar to those achieved with accelerated alteplase in GUSTO (81% and 54%, respectively).⁴ Since early coronary patency is the major determinant of clinical outcome, one might have expected a 1% survival advantage for reteplase (double bolus) over streptokinase, similar to the higher survival rates with accelerated alteplase.³ This did not happen. Possible explanations include the width of the confidence interval of the survival difference in INJECT, this being compatible with a greater survival advantage. Twice as many patients would be needed to achieve a more precise estimate of this survival difference. Moreover, treatment delays were longer in INJECT than in GUSTO, and the later achievement of patency would result in less myocardial salvage. A third possibility is that the patency rates achieved in INJECT might have been lower than in the pilot study—or that reocclusion rates were higher. The importance of these issues emerged when GISSI-2 and ISIS-3 found no advantage of alteplase over

streptokinase, despite better patency rates with alteplase in the angiographic pilot studies.⁵⁻⁸ GUSTO helped to resolve the questions raised after these two megatrials by combining a large mortality study with angiographic^{3,4} and other substudies to analyse the pathophysiology of the treatment regimens.

The design of INJECT as an equivalence study might suggest that the current reperfusion strategies are not likely to be improved. However, such complacency is not warranted. Reperfusion by angioplasty has yielded superior early coronary patency rates, smaller infarct sizes, better residual left-ventricular function, and improved clinical outcome results—lower mortality and fewer strokes.⁹⁻¹¹ At the American College of Cardiology meeting earlier this year, Califf presented a pilot study showing that the combination of alteplase and integrilin (a platelet fibrinogen receptor blocker) yielded excellent patency rates: in 60 consecutive patients, all infarct vessels appeared patent at 90 min and 83% showed normal (TIMI-3) flow. This combination of drugs given intravenously may prove to yield clinical effects similar to those of angioplasty. These new developments must be tested in large clinical trials, and it would be a major scientific achievement if future trials were able to follow the GUSTO example of combining mechanistic studies and pathophysiology with clinical outcome.

Reteplase is likely to be introduced in clinical practice. INJECT shows reteplase (double bolus) to be at least equivalent to streptokinase, while it confers additional advantages. My current ranking of reperfusion strategies is direct angioplasty, then accelerated alteplase, followed by double-bolus reteplase, and lastly standard streptokinase. The choice in individual patients will depend not only on differences in clinical outcome but also on the costs and on the complexity of these treatment strategies in different hospital settings.¹²

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Hair-cell regeneration: cure for deafness?

Regeneration of sensory hair cells in the cochlea is an attractive proposition as a cure for deafness: find the right growth factor, apply it to the deaf inner ear, and wait for those hair cells to develop anew. Research towards this aim is underway, but will it be as simple as that? There are many problems to be solved.

The mammalian cochlea has evolved a uniquely complex arrangement of sensory hair cells and surrounding support cells, presumably because of some functional advantage of this arrangement, but the price has been the loss of the ability to regenerate sensory cells. hair-cell regeneration can be demonstrated in simpler auditory neuroepithelia, notably in birds and fishes,^{1,2} as well as in the mammalian vestibular neuroepithelia³⁻⁵ and in the cochlea at very immature stages.^{6,7} However, no-one has succeeded in stimulating regeneration in the mature mammalian cochlea.

The task to be achieved is to trigger a sensory epithelium that has long since degenerated and dedifferentiated into the renewed production not only of sensory hair cells but also of their innervation and the various specialised supporting cells required for auditory function. Much research is directed at learning how to trigger and recognise hair-cell regeneration (as opposed to repair) in a recently damaged cochlea, in which extensive dedifferentiation has not had time to occur. This is a useful first step. Further work is aimed at understanding (a) the cascade of gene action that defines and directs the normal development of a sensory hair-cell from an undifferentiated neuroepithelium,^{8,9} and (b) the molecular basis of the hair-cell regeneration that occurs spontaneously in the inner ears of non-mammalian vertebrates. These latter research areas are likely to provide the foundation for development of specific drug interventions. However, the ultimate test will be whether the residual dedifferentiated cells in the cochlea of a profoundly or severely hearing-impaired person can act as stem cells for the regeneration of a functional organ of Corti.

Who might be a good candidate for treatment to stimulate regeneration? Accurate diagnosis will be essential; there is little point in regenerating hair cells that cannot function because of a genetic defect. People who have recently sustained acute damage to their ears might be suitable for treatment to limit the progress of damage and stimulate hair-cell repair; this treatment may well be different to one devised to trigger regeneration, and could include use of growth factors to promote hair-cell

survival. Specificity of any treatment will likewise be vital. Growth factors are attractive candidates as regenerative stimulants and are the subject of intense investigation,¹⁰ but the disadvantage of using naturally occurring growth factors is that they have been adopted by the body for diverse functions. Consequently, they may have unpredictable and undesirable effects, even if the delivery is direct to the inner ear. Delivery of any peptide as a drug is fraught with difficulties, which is another reason to seek alternatives.

A possible route to devising a treatment to foster hair-cell regeneration would be as follows. First, the molecular events that set in train the process of hair-cell differentiation during normal development need to be defined. In particular, the mechanism of transcriptional control of key genes acting early in hair-cell differentiation needs to be understood. Transcription of a key hair-cell-specific gene acting very early in development can then be established as an in-vitro screen, by linking the gene's promoter to a convenient marker of transcription such as green fluorescent protein. High-throughput screening of many tens of thousands of potential stimulatory compounds, probably generated by combinatorial chemistry and probably including large numbers of steroid-like compounds, can then be achieved in a reasonable time. Leading contenders discovered by this means can be tested for specificity, and conventional (rational) drug design approaches can be used to modify the most promising compounds to enhance specificity. Specificity would be tested by use of cultured epithelial cells and ultimately in previously deafened animals.

Before this train of events can be set in motion we need to establish the essential early steps in initiating the development of a hair-cell. A genetic approach, by use of saturation mutagenesis, has been remarkably successful in providing the tools (mutations) to identify genes involved in determination of cell fate—eg, in the eye of *Drosophila*—and ongoing mutagenesis programmes in zebra fish will provide valuable clues to the genes involved in pattern formation in a vertebrate inner ear. This knowledge should be readily extendable to the mammalian organ of Corti.

So, what about growth factors? They may well play an important part in later stages of hair-cell development, and in repair or survival of damaged hair cells, but will they be sufficient to initiate new hair-cell formation? Although this seems unlikely, stranger ideas have worked. For example, it seemed unlikely at one time that the cochlear implant, remarkable in its simplicity compared with a normal functioning cochlea, could be so successful in aiding many deaf people.

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