Methotrexate eluting stents: to modify or cure?
A C Morton, J Gunn

Just as a single antibiotic cannot treat all infections, it may be that a variety of agents utilised in drug eluting stents will be necessary to treat restenosis.

With the introduction of drug eluting stents (DES) into routine percutaneous coronary intervention (PCI), many consider the battle against restenosis won. A more realistic viewpoint, perhaps, is that these are merely the early engagements in what will eventually turn out to be a longer war. The evidence base for sirolimus and paclitaxel eluting stents is impressive, with target vessel revascularisation < 5% at nine months in selected patients and lesions. One area of uncertainty is whether these two agents alone are sufficient to treat the wide variety of lesions found in day-to-day practice; just as a single antibiotic cannot treat all infections, it may be that a variety of agents will be necessary to treat restenosis. Another question is whether there will be room to further lower the restenosis rate (ideally to zero) in the “real world” where complex coronary artery lesions (long, diffuse, calcific, etc) are the norm rather than the exception. Is there room for more troops on the restenosis “field of battle”? In this issue of Heart, Huang and colleagues describe the effects of methotrexate contained in a new biological polymer coating (SAE) upon in-stent stenosis in a porcine model of coronary artery stent implantation.

METHOTREXATE

Methotrexate is a folate antagonist and is widely used in the treatment of proliferative diseases such as Crohn’s disease, cancer, rheumatoid arthritis, and psoriasis. Folates are essential for the synthesis of purine nucleotides and thymidylate that, in turn, are essential for DNA synthesis and cell division. In order to act as coenzymes, folates must be reduced to tetrahydrofolate. Methotrexate exerts its cytotoxic effects by inhibiting dihydrofolate reductase and depleting intracellular tetrahydrofolate, leading to inhibition of cell division. It also has some anti-inflammatory effects by virtue of its ability to inhibit the secretion of cytokines.

The strength of using a coated stent as the carrier for an anti-restenosis agent is the ability to achieve a high local concentration of potent therapeutic agent, exactly where it is required, while using a tiny total quantity, thereby avoiding systemic side effects. Methotrexate, for example, when given for resistant psoriasis in the dose range 10–25 mg, can cause myelosuppression, mucosis, and pneumonitis. In the present study, 150 µg of the drug was loaded onto the stent; a 100-fold lower total dose than the clinical systemic dose just quoted. No systemic toxicity would, therefore, be expected, although there might be a potential for local effects upon the vessel wall. Furthermore, polymers containing the drug applied to the stent surface can be formulated to allow elution over a prolonged time frame. In the case of the polymer described in the study of Huang and colleagues (SAE), this elution “window” was up to one month.

DRUG DELIVERY STRATEGIES

Local drug delivery to target restenosis is not a new concept. Huang and colleagues acknowledge the work of Cox and associates, 11 years ago, in which they delivered methotrexate from cellulose ester polymer coated stents. They found that local delivery of methotrexate had no effect on neointimal hyperplasia in stented porcine coronary arteries. The main difference between the two studies was the polymer used. One conclusion, therefore, might be that either the polymer in Cox’s study was inferior in terms of biocompatibility to the SAE used by Huang, or that methotrexate is not effective and Huang’s main findings are misleading.

Early drug delivery strategies using a “leaky” balloon were cumbersome, dangerous, wasteful, and ultimately unsuccessful; but they spawned the present “revolution” of DES in interventional cardiology. The polymer is the key to this new technology. To achieve local delivery, a drug must be loaded, retained, and released in a controlled fashion. The polymer must be inert and able to withstand the rigours of sterilisation and stent deployment. Several different agents have already been shown to fulfill these and other criteria, including phosphorylcholine (used for the elution of dexamethasone and ABT578) and chondroitin sulfate and gelatin (used for paclitaxel elution). In the paper by Huang and colleagues, SAE coated stents were deployed into normal pig coronary arteries at minimal oversize (1.1:1 stent-artery ratio) to test polymer biocompatibility. No significant difference in neointima, lumen, inflammatory response, or thrombus formation was seen. They also showed that SAE could elute methotrexate for one week in vitro. It is highly likely that this time frame is prolonged when surrounded by tissue in vivo.

See end of article for authors’ affiliations

Correspondence to:
Dr Julian Gunn,
Cardiovascular Research Group, Clinical Sciences Building, Northern General Hospital, Sheffield S5 7AU, UK;
J.Gunn@Sheffield.ac.uk

Abbreviations: DES, drug eluting stents; PCI, percutaneous coronary intervention

Heart 2004;90:121–122. doi: 10.1136/hrt.2003.019638
The authors, therefore, successfully confirmed that SAE possesses the requisite properties for successful local drug delivery.

ANIMAL MODELS

The key question surrounding a new combination of stent/polymer/drug is, of course, “does it work?”. This is not a simple question to answer on the basis of animal studies. The answer will only be definitive when an appropriate, randomised controlled trial is performed in human subjects. There are two schools of thought concerning animal models. One states that their purpose is simply to demonstrate safety and, because of their inevitable biological differences from man (normal arteries, juvenile development, inter-species differences, etc), are not expected to replicate chronic atherosclerosis. In favour of this argument is the clinical efficacy of several agents whose preclinical results were less than overwhelming (sirolimus and brachytherapy being two such examples).

The other school of thought asserts that a reduction in experimental neointima in the animal model (even if modest) is a prerequisite to clinical trials, because this forms a late stage in the hierarchy of screening of potentially useful drugs. Both schools of thought, however, require rigorous standards of conduct of the animal experiments.

In a recent consensus statement by experts in North America, a whole series of standards of conduct of animal models of coronary angioplasty and stenting were published. In that paper, one of the key requirements was that both the placebo and the treatment group (polymer only and polymer + methotrexate in the case of Huang and colleagues) should be deployed in such a way that the injury to the randomisation observer to the identity of the stents, and (ideally) study stents at the correct stent:artery ratio (intended to be known for over 10 years that the thickness of neointimal growth in animal models is related to the amount of injury sustained by the artery at the time of intervention—whether it be oversized balloon inflation or oversized stent implantation.

We have recently shown that this relation extends down to even mild stretch-type injury without deep laceration. It is critically important, therefore, to have matched injury in both groups. An excess of injury in the control group will give rise to a false positive result for the agent in question. This may be the case in the paper of Huang and colleagues. For the (key) efficacy study, the injury score in the control group was 0.41 (0.32) and in the methotrexate eluting group 0.20 (0.13) (p < 0.05). In addition, but, in our view, as a consequence of this disparity in injury, the inflammation score and subsequent measurements of neointimal growth were both reduced in the treatment group compared with control. The authors claim that methotrexate is responsible for all these differences. This is, in our view, an unreasonable assumption. It is more likely that the difference in injury was a consequence of differences in implanting the study stents at the correct stent:artery ratio (intended to be 1.2:1 in the efficacy study)—a task that requires precision, quantitative angiography of a high order, blinding the observer to the identity of the stents, and (ideally) randomisation.

LATE STENT THROMBOSIS

Late stent thrombosis remains an important long term concern with drug eluting stents. Although the “first-in-man” study has now provided us with short, medium, and three year safety data for the rapamycin eluting stent, the long term effects of cytotoxic agents are still unknown. “Late-late” thrombosis after intracoronary brachytherapy is now being described in sporadic cases and it is not far-fetched to speculate that a similar problem may emerge with DES, particularly if long stent lengths are used and endothelial regeneration is retarded. Vascular toxicity and incomplete healing have been seen with paclitaxel eluting stents. Methotrexate has also been shown to inhibit vascular endothelial cell proliferation in vitro. Reassuringly, in the study of Huang and colleagues, at four weeks the luminal surface of the methotrexate loaded stent was endothelialised. These results are encouraging for the long term safety of this device. Methotrexate is presumed to exert its cytotoxic effect by inhibiting smooth muscle cell proliferation. To address this issue, Huang and colleagues examined the effect of methotrexate upon smooth muscle cells and compared it with paclitaxel. Unlike paclitaxel, which showed a dose dependent reduction in smooth muscle cell proliferation and survival, methotrexate had no effect upon either variable.

We can conclude from the study of Huang and colleagues that methotrexate eluting polymer coated stents are safe in a mid term study using a porcine model, but that a question mark hangs over their efficacy. It is too early to say whether methotrexate eluting stents will be in the second or third wave of combatants in the war on restenosis.

Authors’ affiliations
A C Morton, J Gunn, Cardiovascular Research Group, University of Sheffield, Sheffield, UK

REFERENCES
1 Moses JW, Leon MB, Pappas JJ, et al. Sirolimus-eluting stents versus standard stents in patients with a stenosis in a native coronary artery. N Engl J Med 2003;349:315–23.
2 Stone G. TAXUS-IV: angiographic and IVUS results of the pivotal prospective, multicenter, randomized trial of polymer-based paclitaxel-eluting stents in patients with de novo lesions. Transcatheter Cardiovascular Therapeutics symposium: Washington DC, 19 September 2003 (oral presentation) www.tct.com/taxus.html.
3 Huang Y, Salu K, Liu X, et al. Methotrexate loaded SAE coated coronary stents reduce neointimal hyperplasia in a porcine coronary model. Heart 2004;90:195–9.
4 Cueto M, Sulli A, Pizzocini C, et al. Anti-inflammatory mechanisms of methotrexate in rheumatoid arthritis. Ann Rheum Dis 2001;60:729–35.
5 Cox DA, Anderson PG, Roubin GS, et al. Effect of local delivery of heparin and methotrexate on neointimal proliferation in stented porcine coronary arteries. Coronary Artery Dis 1992;3:237–48.
6 Malik N, Gunn J, Shepherd L, et al. Phosphorylcholine-coated stents in porcine coronary arteries: in vivo assessment of biocompatibility. J Invas Cardiol 2001;13:193–201.
7 Farb A, Heller PF, Shroff S, et al. Pathological analysis of local delivery of paclitaxel via a polymer coated stent. Circulation 2001;104:473–9.
8 Suzuki T, Kapia G, Hayashi S-I, et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. Circulation 2001;104:1188–93.
9 Reissman PK, Stella P, Vanbilloen H, et al. Intracoronary beta-radiation of de novo coronary lesions using a 108Re liquid-filled balloon system: 6 month results from a clinical feasibility study. Catheter Cardiovasc Intervent 2002;55:26–36.
10 Schwartz RS, Edelman ER, Carter A, et al. Drug-eluting stents in preclinical studies: recommended evaluation from a consensus group. Circulation 2002;106:1867–73.
11 Schwartz RS, Huber KC, Murphy JG, et al. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. J Am Coll Cardiol 1992;19:267–74.
12 Gunn J, Arnold ND, Chan KH, et al. Coronary artery stretch versus deep injury in the development of in-stent neointima. Heart 2002;84:447–51.
13 Abizaid A. Updates from the FIM experience: are the results durable? Transcatheter Cardiovascular Therapeutics symposium: Washington DC, 18 September 2003 (oral presentation).
14 Sianos G, Mollet N, Holma S, et al. Late-late occlusion after intracoronary brachytherapy. Circulation 2003;108:669–70.
15 Hirata S, Matsubara T, Saura R, et al. Inhibition of in vitro vascular endothelial cell proliferation and in vivo neovascularization by low-dose methotrexate. Arthritis Rheum 1989;32:1065–74.
16 Liang GC, Nemickas R, Madayag M. Multiple percutaneous transluminal angioplasties and low dose pulse methotrexate for Takayasu’s arteritis. J Rheumatol 1989;16:1370–3.