Trends-in-Medicine

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SUMMARY

Cook has taken the lead in the drug-eluting stent rate, filing for European approval of its paclitaxel-eluting stent. However, Johnson & Johnson is not far behind, and, with 0% restenosis, sources still believe this will be the "best" in the class. Meanwhile, Boston Scientific has had a setback; the FDA refused to approve the company's plan for a Phase III trial of its paclitaxel-eluting stent.

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Drug-Eluting Stent Update

The race to develop drug-eluting stents to prevent restenosis is heating up.

COOKE has beaten J&J to the punch and announced on January 18, 2002, that it was the first company to submit a drug eluting stent for regulatory approval. Cook filed for a CE mark for its V-Flex Plus PTX, which elutes Angiotech's paclitaxel, based on the results of the ELUTES trial, which showed a restenosis rate of 3.1%.

JOHNSON & JOHNSON'S sirolimus(rapamycin)-coated Cypher stent continues to report positive news, and rumors are circulating that the trial will be stopped early (at the six-month point) because the results are so positive.

BOSTON SCIENTIFIC'S efforts to get a Phase III trial of a paclitaxel-eluting Express stent have stalled. The FDA denied the company's IDE request, and Boston Scientific now must revise that IDE substantially. A source said, "I just can't believe it. I'm very surprised the FDA turned Boston down. I think the Boston approach with paclitaxel is better than the Cook approach (Cook is dipping the stents, not imbedding a coating with the drug), but Boston may not have done its homework. The results on safety done in Europe looked very good. The restenosis rate was 4%, which was not a statistically significant difference from control, but that was not the purpose of the study, which was just to show safety. So, to me, unless there was more MACE, I can't see why Boston didn't get approved. It could be that the number of humans (in Phase II) is not enough, but there also could be some toxic effects – most likely related to MACE (thrombus related) – that the agency knows about but we don't. Paclitaxel is not as safe as rapamycin, and that is well-known. I know paclitaxel will work, but the question is whether it is as effective as rapamycin. I think it will be – both will have the same effect – but new intima will be slower coming back with rapamycin. Rapamycin is a better drug, but we don't want one company to have a monopoly."

The problem appears to be with a lack of data on the moderate-dose formulation. Boston Scientific reportedly is trying to decide now whether to go ahead with the less-effective low-dose, slow release formulation, for which there appears to be sufficient data, or do additional patients or an additional trial before proceeding with the moderate-dose formulation. A source said, "The problem with the moderate-dose is that there is no animal data to show safety when stents overlap. When low dose stents overlap, it

is equivalent to a moderate dose, and that is okay, but if moderate-dose stents overlap, we don't know the results. That is the problem."

Several concerns have been raised about the safety of paclitaxel, and most experts agree that there is a narrow therapeutic window for paclitaxel. A researcher explained, "One concern is that there is inflammation. Another is excessive thrombosis formation, which persists. And there may be medial necrosis, depending on the dose. These issues have been resolved in the sense that we know they occur in animals, but they don't seem to produce untoward effects. In animals, high doses of paclitaxel have a problem, but low doses don't – and humans may be different."

GUIDANT continues its two-pronged approach to drug-eluting stents – actinomycin on the MultiLink and a collaboration with Cook for paclitaxel-coated eluting Penta stents. A researcher said, "Actinomycin is the most dangerous of the three (rapamycin, paclitaxel and actinomycin)."

MEDTRONIC continues to try various compounds unsuccessfully, and the company's commitment to drug-eluting stents is unclear, given its rapid exchange stent problems.

BIOCOMPATIBLES is testing batimastat on its BiodivYsio stents. Abbott reportedly is considering buying Biocompatibles, and that sale could be dependent on the success of Biocompatibles drug-eluting stent technology.

JOMED has licensed Fujisawa's tacrolimus and is testing it with its FlexMaster stents with a nanoporous ceramic coating. At the European Society of Cardiology and Transcatheter Cardiovascular Therapeutics meetings in September 2001, experts indicated that tacrolimus did not work to prevent restenosis. They explained that tacrolimus works in a different way from sirolimus and, therefore, had no impact on restenosis. However, this theory obviously is being re-thought. An expert said, "Tacrolimus works on immunosuppression and not smooth muscle. It binds to the same protein, but when it binds it goes to a different receptor. It may work." Another expert said, "It's possible it won't work. Tacrolimus is anti-inflammatory as well as anti-proliferative, but the dose required is much higher than for rapamycin."

Two clinical trials of tacrolimus-eluting stents have gotten underway, both run by Dr. Eberhard Grube in Germany. PRESENT (PREliminary Safety Evaluation of Nanoporous Tacrolimus eluting stents) is a two-armed safety study in coronary angioplasty, and EVIDENT (Endo-Vascular Investigation Determining the Safety of a New Tacrolimus Eluting Stent Graft) is in saphenous vein grafts (SVGs).

Previously, Jomed was collaborating with Oxigene to use Oxigene's vascular targeting agents (VTAs) on its stents and reported, "Initial results from our preliminary work (with VTAs)…are very promising. In cell culture studies, we have seen a very strong inhibition of smooth muscle proliferation, which was even superior to traditional anti-tumor compounds. We expect to be able to release data from animal trials during early 2002." Apparently, that did not pan out. ♦