The ILLUMENATE Clinical Program

Demonstrating the efficacy of the Stellarex™ drug-coated balloon.

BY HENRIK SCHRÖDER, MD

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Recently published data from the ILLUMENATE first-in-human (FIH) study[1] are promising, and more and equally robust clinical trials are well underway to assess the safety and effectiveness of the Stellarex™ drug-coated balloon (DCB; Spectranetics Corporation).

ILLUMENATE FIRST-IN-HUMAN STUDY

The purpose of the ILLUMENATE FIH study was to assess the safety and effectiveness of the Stellarex™ DCB to inhibit restenosis in the superficial femoral (SFA) and/or popliteal artery. ILLUMENATE FIH was a prospective, single-arm, multicenter study with independent adjudication by angiographic and duplex ultrasound core laboratories (VasCore). The study was composed of two sequentially enrolled patient cohorts. In the first 50-patient cohort, lesions were treated with traditional predilatation with an uncoated angioplasty balloon prior to inflation of the DCB. In the second 30-patient cohort, lesions were treated by direct DCB application without predilatation.

The primary efficacy endpoint was 6-month late lumen loss, as determined by the angiographic core laboratory. The major secondary endpoint was major adverse event rate at 6 months, which was defined as cardiovascular death, amputation, and/or clinically driven target lesion revascularization (TLR).

In the first cohort (the predilatation group, n = 58 lesions), the mean lesion length was 7.2 cm, and baseline stenosis was 75.1%. Calcification was present in 62.1% of lesions, and 12.1% were occluded. Both endpoints met their prespecified performance goals: At 6 months, the major adverse event rate was 4%, and the mean late lumen loss was 0.54 mm. The Kaplan-Meier estimate of primary patency, as determined by the duplex ultrasound core laboratory was 89.5%[i] at 12 months and 80.3% at 24 months, whereas freedom from clinically driven TLR was 90.0%[ii] at 12 months and 85.8% at 24 months. Additionally, there were no amputations or cardiovascular deaths reported through 24 months (Figure 1).

These promising results instill high confidence in this second-generation DCB technology, which is set to further advance the treatment options for patients with peripheral artery disease. When these results are reviewed in context with other multicenter DCB trials reporting primary patency rates by duplex core lab adjudication, ILLUMENATE FIH compares favorably.[2,3] These promising long-term findings suggest that the Stellarex™ coating is the right formulation that balances deliverability with durability and transfers an effective amount of the antirestenotic drug to the treatment site.

ECONOMIC IMPACT

The economic implications of durable results are at the forefront of everyone's minds as the prevalence of peripheral artery disease increases and medical costs rise.

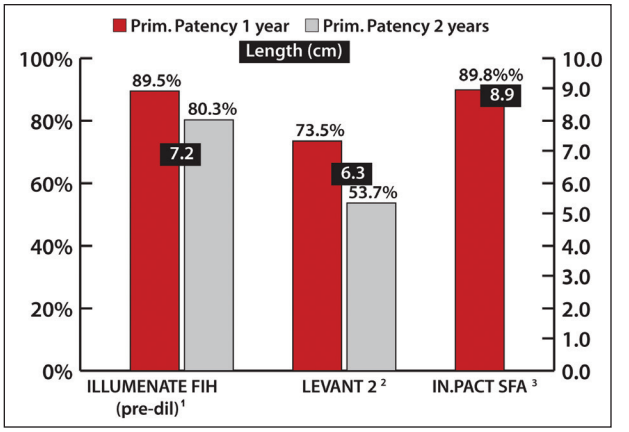

Figure 1. Primary patency rates at 1 and 2 years (when available) across three multicenter DCB studies with the same duplex ultrasound core lab and duplex-derived peak systolic velocity ratio threshold (≤ 2.5).

[i] The primary patency rate was 89.5% at day 365 and 87.7% at day 395, the upper end of the follow-up window. The primary patency rate was 80.3% throughout the 24-month follow-up window (at day 730 and day 760).
[ii] The freedom from clinically driven TLR was 90.0% at day 365 and 87.9% at day 395, the upper end of the follow-up window. The rate was 85.8% throughout the 24-month follow-up window (at day 730 and day 760).

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It doesn't surprise me that the 2-year patency rate of 80.3% compares favorably to other drug-coated balloon (DCB) data. This shows that the amount of paclitaxel that is on the surface of the balloon does not play such a major role, and that the outcome depends on what is imbedded in the vessel wall. We know that with a lot of products, up to 20% of the drug at maximum is getting to the vessel wall; most of the drug is either washed off or stays on the balloon. The total drug dosage on the balloon is not the major driver. The amount of drug that reaches the vessel wall is the ultimate driver of success. The delivery is more precise and better if you can decrease the amount of drug coating on the balloon compared to other balloons.

I think what is very important, and which might differentiate one DCB from another, is what the curve concerning target lesion revascularization and restenosis looks like compared to other products.

It is important to look at the long-term (12 month or 2 year) patency and target lesion revascularization rates in DCBs because, in a balloon that doesn't work as well, there might be good results in the short term but a falloff in the long term and no durable results. Therefore, it's very important to have that good long-term result and, if nothing happens between 12 and 24 months, that is really a good sign.

Data from the ILLUMENATE FIH and historical plain-old balloon angioplasty (POBA) data were used to construct a budget impact model through 2 years.[1,2,4,5] The model was based on the total cost of the baseline procedure plus revascularizations (determined by clinically driven TLR rates). Costs for the baseline procedure and clinically driven TLR were assigned to both groups using the 2013 German G-DRG reimbursement tariffs. The budget impact model demonstrated cost advantages for Stellarex™ through 24 months. At 12 months, a patient treated with Stellarex™ cost ~€450 less than with PTA (€3,575 vs €4,027); at 24 months, the difference increased to €741 (€3,668 vs €4,409). Extrapolated to 25,000 patients with peripheral artery disease, the use of Stellarex™ has the potential to save the health care system more than €11,000,000 at 12 months and more than €18,500,000 at 24 months. The number of patients treated with Stellarex™ (compared to PTA) to prevent one TLR was four at 12 months and three at 24 months.

An interesting element of the ILLUMENATE FIH study was the previously mentioned "direct cohort," in which lesions were treated without predilatation. Twenty-eight patients with 37 lesions were included in the direct DCB cohort analysis; two patients were excluded because they were predilatated. The mean lesion length was 6.4 cm, and calcification was present in 48.6% of lesions. At 6 months, the mean late lumen loss was 0.08 mm, indicating a good drug effect. However, the primary patency rate was 77.5% at 12 months,[iii] which was lower than the 89.5% observed in the predilatation cohort. The freedom from the clinically driven TLR rate, per Kaplan-Meier estimate, was 85.4% at 12 months.[iv] The lower patency and freedom from TLR rates in the direct cohort can partially be explained by two TLRs

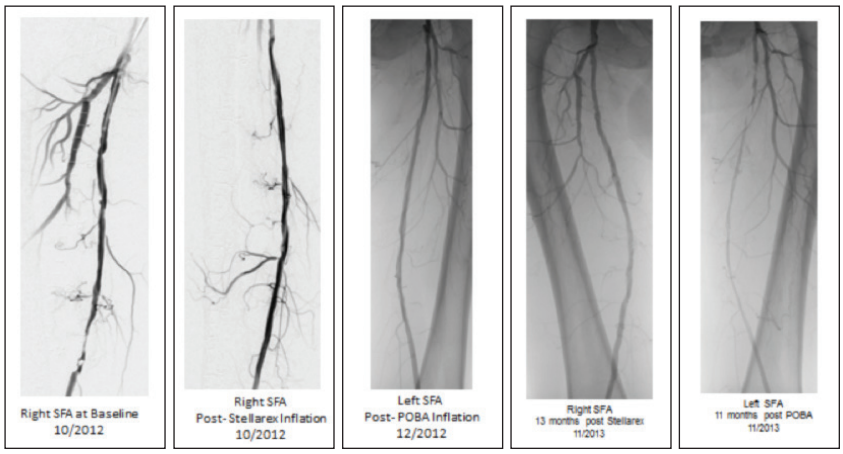

Figure 2. Angiograms of a 50-year-old male patient with claudication due to bilateral SFA disease. He had two lesions in the right SFA treated with the Stellarex™ DCB. The left SFA was subsequently treated with an uncoated angioplasty balloon. Approximately 1 year later, the lesions treated with Stellarex™ were patent, and the POBA-treated lesion was reoccluded.

[iii] The primary patency rate was 77.5% throughout the 12-month follow-up window (at day 365 and day 395).
[iv] The freedom from clinically driven TLR rate was 85.4% throughout the 12-month follow-up window (at day 365 and day 395).

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Regarding cost effectiveness of treatment using DCBs, it is essential to know that not every DCB performs the same. There are elementary differences in coating technologies, including drug dose and the presence or type of excipient that has an impact on the patients' clinical outcome in terms of freedom from target lesion revascularization. Thus, profound knowledge of the current literature is essential for the appropriate treatment choice.

From the payers' perspective, preserving the acute clinical benefit as long as possible reduces the overall health care costs of the individual patient. This cost effectiveness has been shown up to a 2-year period after the index procedure for the United States, Germany, Switzerland, and the United Kingdom. DCBs have been shown to be at least equally cost effective as drug-eluting stents for femoropopliteal TASC II A and B lesions and superior to bare-metal stents and plain-old balloon angioplasty. The gain in cost effectiveness is related to the reduced TLR rates but also to the more effective and less expensive treatment options in case of a reintervention.

From the providers' perspective, the situation is different: Cost effectiveness means sufficient reimbursement for the use of a given technology. In the case of DCBs, this means that the price difference between a DCB and a conventional balloon catheter must be covered by the payer; considering that this means that for an individual patient more than one single DCB might be necessary, and some lesions deserve up front predilatation. On the other hand, physicians are not responsible for reimbursement systems—that's a governmental, health care responsibility—but we are responsible for offering our patients the best possible care. Thus, the aim of the treating physician should be to use the best available technology, including the most effective DCB. Currently, this choice is difficult because no head-to-head comparisons yet exist. However, a valuable guide could be using only devices in clinical practice outside of study protocols that have solid published data or, at least, data from high-quality, multicenter, independently adjudicated trials.

The most relevant data for the payers is a stable clinical follow-up of the patient after the treatment of his or her underlying disease, in case of peripheral artery disease claudication or critical limb ischemia, without rehospitalization or target lesion revascularization. This is the main source of driving costs. Obviously, it would also be of interest if it could be shown that preserved vessel patency and ambulation would result in an extension of survival or a reduction of overall cardiovascular events, and if the patient benefits, in terms of quality of life and in the long term, could be improved.

that were thrombotic occlusions that occurred in two patients who were not compliant with their prescribed antiplatelet medications. It is noteworthy that the rates of postdilatation (35.1% vs 12.1%) and stent placement (8.1% vs 5.2%) were higher in the direct cohort versus the predilatation cohort. These findings suggest a role for predilatation in potentially improving outcomes and lowering the need for permanent implants, thus supporting the value proposition of DCBs.

ONGOING STUDIES

The ILLUMENATE FIH study is the first in a series of five robust studies that will evaluate the safety and effectiveness of the Stellarex™ DCB in a broader population.

ILLUMENATE EU-RCT

The ILLUMENATE European randomized, controlled study will enroll up to 360 patients at approximately 24 sites in the European Union. Subjects with symptoms of claudication or rest pain are being randomized to treatment with the Stellarex™ DCB or a bare PTA balloon catheter for de novo or restenotic lesions in the SFA and/or popliteal arteries. Patients will be followed for 5 years.

ILLUMENATE Pivotal

The ILLUMENATE Pivotal randomized clinical trial is being conducted at approximately 45 centers in the United States. It is a prospective, randomized, multicenter, single-blind study that will enroll up to 360 subjects with symptoms of claudication or rest pain, with follow-up through 5 years. The study is being led by Dr. Sean Lyden of the Cleveland Clinic in Cleveland, Ohio, and Dr. Prakash Krishnan of Mount Sinai Heart in New York City, New York.

ILLUMENATE Global

ILLUMENATE Global is a prospective, single-arm, multicenter study that is enrolling patients in Europe, Australia, New Zealand, Canada, and Colombia. All subjects enrolled will undergo treatment with the Stellarex™ DCB and will be followed for 3 years. Prof. Thomas Zeller from Herz-Zentrum Bad Krozingen in Germany is the Global Principal Investigator. The International Principal Investigators are Dr. Yann Goueffic from the Hopital Nord Laennec in France, Dr. Andrew Holden from the Auckland City Hospital in New Zealand, and Dr. Carlos Mena of Yale University in the United States.

ILLUMENATE PK

ILLUMENATE PK is a prospective, nonrandomized, single-arm, multicenter, pharmacokinetic study that is currently ongoing in New Zealand and is led by Dr. Andrew Holden. All subjects enrolled will undergo treatment with the Stellarex™ DCB and have periodic blood draws to measure the amount of paclitaxel in their blood. The study will enroll 25 subjects.

CASE REPORT

The angiograms in Figure 2 show an interesting case of a 50-year-old man with symptomatic (Rutherford class 3) bilateral SFA disease. Two lesions in the right SFA were treated with a direct DCB technique. The 7.9-cm lesion in the mid-SFA and the proximal 5.9-cm lesion were both treated with 5- X 80-mm Stellarex™ DCBs. The left SFA was treated with an uncoated angioplasty balloon. Approximately 1 year later, the artery treated with the Stellarex™ DCB is patent, whereas the artery treated with POBA is restenotic.

We are excited about the data published to date and clinical work that is currently underway. We have a dedicated group of physicians around the world participating in these trials, and we look forward the next wave of data. ■

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