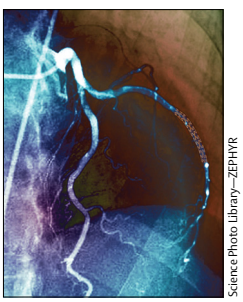
Magnesium stent scaffolds: DREAMS become reality



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Published Online
November 8, 2015
http://dx.doi.org/10.1016/S0140-6736(15)00804-1

Why are bioresorbable scaffolds so exciting? Simply because they fulfil the task of scaffolding the artery wall during the healing period, and thereafter vanish. In other words, their lifetime is adjusted to the healing process, thus avoiding any risk of causing a new disease (eg, late thrombosis, in-stent restenosis, or neoatherosclerosis) as can happen with permanent stents. Permanent stents do a perfect scaffolding job, but remain in place when they are no longer necessary, leading to a foreign body reaction with complications.[1] By contrast with conventional thinking, permanent scaffolding is unnecessary: do native arteries need scaffolding? We should listen more carefully to the common sense of patients who often ask: "Doctor, when do you intend to retrieve your stent from my coronary artery?" The response is that bioresorbable scaffolded vessels are uncaged thanks to the degradation process of bioresorbable scaffolds, allowing positive remodelling, which sometimes occurs after balloon angioplasty.[2,3] Nevertheless, the concept of bioresorbable scaffolds needed some time to emerge, because adequate materials needed to be developed, mainly made from polymers, but also from magnesium.

In *The Lancet*, Michael Haude and colleagues[4] present the third study on bioresorbable magnesium coronary scaffolds. In their first study (PROGRESS),[5] the bare scaffold showed its safety, without an increased risk of death or myocardial infarction at 1 year. However, clinically driven target lesion revascularisation was high at 4 months (23·8%), with 0·83 mm in-segment late lumen loss, rising to 26·7% at 1 year. Restenosis was due to both scaffold failure and neointimal growth. In the second study (BIOSOLVE I),[6] the mechanical properties of the DREAMS 1G drug-eluting absorbable metal scaffold were significantly improved and paclitaxel was added, resulting in a decreased but still suboptimum rate of in-segment late loss (0·52 mm), and reduced clinically driven target lesion revascularisation (5·0% at 1 year). Haude and colleagues' present study (BIOSOLVE-II)[4] assessed the second-generation drug-eluting absorbable metal scaffold (DREAMS 2G) in 123 patients. Prolonged scaffolding time due to improved manufacturing processes, optimised design, and a switch to sirolimus resulted in an encouraging reduction in mean in-segment late lumen loss (0·27 mm [SD 0·37]), and clinically driven target lesion revascularisation (2% [95% CI 0·2–5·9]), at 6 months. The DREAMS 2G device was not only refined with regard to the magnesium backbone design, but also in the introduction of a drug–polymer coating, with sirolimus in combination with a bioresorbable poly-L-lactide acid polymer, prolonging the stability of the magnesium backbone scaffolding.[7] Interestingly, the mean scaffold area at 6 months was no different to that post-procedure (6·21 mm^2 [SD 1·22] *vs* 6·24 mm^2 [1·15]).[4]

The investigators' perseverance has been fruitful, because their results now compete with data for the most commonly used polymer scaffold (the Absorb bioresorbable vascular scaffold system [ABSORB BVS]), with a similar rate of in-segment late lumen loss at 6 months (0·36 mm).[8] Notably, the mechanical properties of ABSORB BVS have likewise been improved through two prototypes, to decrease chronic shrinking.[8,9]

Haude and colleagues' findings[6] show that not only polymers, but also magnesium scaffolds, are able to provide solid scaffolding, and degrade safely, with no further late lumen loss related to neointimal growth. A huge effort was made to render the original scaffold more mechanically appropriate during the healing phase, with less neointimal growth.[7] The choice of sirolimus remains smart after 15 years, and we have to acknowledge Robert Falotico's vision.[10]

We do not wish to criticise drug-eluting stents, which remain the gold standard for the time being. For 20 years they have provided a solid alternative to bypass surgery:[11] almost 90% of coronary revascularisation procedures worldwide are done with stents. Nevertheless, we agree with John Ormiston who said that "In 10 years we will look back and laugh when we remember that we used to leave permanent pieces of metal in patients' coronary arteries" (Ormiston J; Mercy Angiography, Mount Eden, Auckland, New Zealand; personal communication). Technology still has to improve—namely, it is still uncertain when arteries should be uncaged, via scaffold dismantling, which is a necessary step for every scaffold to degrade before disappearing.

Comparisons between bioresorbable scaffolds and drug-eluting stents are important, but we know that 6 month late lumen loss is no longer the gold standard for assessment, because scaffolded arteries will undergo a late lumen gain after 1–2 years due to dismantling. Neointimal hyperplasia will not be a safety issue in

uncaged scaffolded arteries because it does not translate into lumen loss, but ensures coverage before complete bioresorption. The best we can ask from a bioresorbable scaffold is to inhibit constrictive remodelling, uncage the artery (ie, for the scaffold to dismantle itself) as soon as possible after healing, and totally disappear leaving no remnants. Which scaffold will disappear first: the magnesium or the polymer one? We are now awaiting a late (5 year) follow-up of the DREAMS 2G scaffold, which can be expected to show complete resorption of the magnesium scaffold, and safe clinical outcomes by comparison with a drug-eluting stent.

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AL is a co-founder of, and has received research funding from, Arterial Remodeling Technologies. YY declares no competing interests.

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Dupilumab: a milestone in the treatment of atopic dermatitis

Published Online October 8, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00389-X

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Atopic dermatitis is the most common chronic inflammatory, pruritic skin disease with a high prevalence, both in adults (2–10%) and children (15–30%).[1,2] From a scientific viewpoint, atopic dermatitis can be attributed to both a genetically mediated epidermal barrier dysfunction and Th2-driven inflammation.[3,4] Therefore, classic treatment regimens, such as emollients, topical steroids, and calcineurin inhibitors, are still regarded as viable.[5] For severe cases, systemic use of the immunosuppressant ciclosporin has been approved in many countries, a move that has reduced disease activity by up to 50%.[6] In view of recent insights into the Th2-driven inflammatory characteristic of atopic dermatitis, it seemed worthwhile to investigate the inhibition of Th2-related molecules, such as the cytokines interleukin (IL)-4 and IL-13, so as to achieve a greater reduction of inflammation. The anti-interleukin-4 receptor (IL-4R) α antibody dupilumab inhibits signalling via IL-4 and IL-13 by inhibiting both IL-4 type 1 and 2 receptors on various immune cells.[7] Results of four early phase studies (phases 1 and 2) in patients with atopic dermatitis have already shown promising results.[8]

In *The Lancet*, Diamant Thaçi and colleagues[9] present their novel results from a randomised, double-masked, placebo-controlled, dose-ranging phase 2b study of dupilumab use in adult patients with moderate-to-severe atopic dermatitis. 380 patients, randomly assigned, received 300 mg of dupilumab once a week (n=63), 300 mg every 2 weeks (n=64), 200 mg every 2 weeks (n=62), 300 mg every 4 weeks (n=65), 100 mg every 4 weeks (n=65), or a placebo (n=61). The efficacy data confirm the results from the four early phase studies, with a mean reduction in the Eczema Area and Severity Index (EASI), the trial's primary endpoint,