EuroIntervention

Blowing against the wind?

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This editorial refers to "Immunosuppressive Oral Prednisone After Percutaneous Interventions in Patients with Multi-Vessel Coronary Artery Disease. The IMPRESS-2 / MVD Study" by Flavio Ribichini *et al.*, published in this issue of EuroIntervention.

Summary of findings in IMPRESS-2/MVD study

In this prospective registry[1], the authors are testing in 86 consecutive patients undergoing multivessel coronary angioplasty the safety and efficacy of high-dose oral prednisone in reducing angiographic and clinical restenosis. They applied the treatment scheme (prednisone 1 mg/kg for 10 days starting within 48 hours after the procedure, 0.5 mg/kg for 20 days, 0.25 mg/kg for 15 days) that was shown to be effective in the randomized IMPRESS I trial[2]. Compared to a "control" group, patients treated with oral prednisone had better event-free survival at one year, less target vessel revascularization and a low rate of angiographic restenosis. The authors conclude that "oral immunosuppression with prednisone effectively reduces clinical restenosis in patients undergoing complex, multivessel PCI."

Critique

A number of critical comments can be voiced. The study design is not randomized such that any comparison with a "control group" is inappropriate. The control group itself is heterogeneous and among others, it includes patients who cannot be considered for the prednisone therapy. Since drug-eluting stents were not available, the question arises why a number of control patients, who ended up receiving bare-metal stents, were denied the proven benefit of bypass surgery. Given the many contra-indications for therapy with high-dose steroids, the applicability of such treatment in daily practice can be questioned.

At the same time, most of these criticisms can easily be rebutted. Since the IMPRESS I randomized trial[2] was positive, the authors did not want to repeat a similar design but have rather attempted to verify the efficacy of short-term, high-dose, oral prednisone treatment in patients and lesions at much higher risk of restenosis. Indeed, the complexity of both the case load and the procedural technique would qualify the current study as being representative for "advanced angioplasty in real life conditions" much like was the case in other carefully conducted registries on drug-eluting stents such as RESEARCH[3], T-SEARCH[4] or ARTS II[5]. Of note, procedural technique was not restricted to stent implantation. In order to account for the diversity and complexity of these challenging lesions/patients, the authors did apply the full spectrum of available technologies, including stand-alone balloon angioplasty or ablative methods, as was felt most appropriate. In doing so, the authors show that

A. clinical outcome when using bare-metal stents and oral steroids is comparable to the one reported in the above mentioned drug-eluting stent registries;

B. the oral prednisone scheme could safely be applied in 37% of the overall mulivessel population that was selected for percutaneous treatment at the participating institutions. Considering that systematic repeat angiography was performed in the prednisone group only (which invariably results in a number of non clinically-justified reinterventions), patient outcome could possibly be even better in the real world when therapy is exclusively driven by clinical follow-up. Conversely, the outcome of those patients who did not qualify for prednisone treatment was unacceptably poor when treated with bare-metal stents. In those patients, alternative solutions have to be proposed, among which bypass surgery or angioplasty using drug-eluting stents.

Remaining and unresolved issues

Many open questions remain regarding the relation between inflammation and restenosis after percutaneous coronary interventions[6]. The current study does not indicate whether this drug regime would

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be equally effective in patients who do not show increased CRP levels, either prior to stented angioplasty or at 48 hours, as a consequence of the procedure. This raises interrogations about the mechanism of action of high-dose steroids, being either systemic or merely focal, at the treated sites. Of note, stents that are eluting dexamethasone locally are commercially available[7]. Diverging opinions prevail regarding their efficacy. In case the coronary effects obtained with high-dose systemic prednisone resulted merely from a local effect, then increasing the dose and/or altering the kinetics of elution of dexamethasone from a stent-polymer delivery platform would appear like a very valuable option to pursue.

Before advocating widespread use of this treatment protocol in patients who would qualify, additional safety data should be obtained in larger patient populations, even though the safety results of the combined IMPRESS trials are reassuring, in particular with respect to stent thrombosis. Although the authors suggest that the proposed approach would be less costly than the presently advocated systematic use of drug-eluting stents, a formal cost-effectiveness analysis would still need to be performed.

Implications

In addition to potential future clinical implications, especially in countries where drug-eluting stents are not yet universally available, the current data provide additional insights into the understanding of the relationship between clinical outcome and angiographic surrogate endpoints, such as late loss. This is yet another study showing that reduction of neointimal proliferation below a critical threshold may be sufficient to sustain a good clinical outcome, implying that abolition of tissue ingrowth is not indispensable to this end. Despite the higher propensity for in-stent neointimal proliferation in the present study as compared to IMPRESS-I, reducing late loss to 0.61±0.35 mm was sufficient to constrain the target vessel revascularization rate at 7%, identical to results only obtainable thus far in similar lesions/patients with the use of drug-eluting stents.

Where to go from here?

Further mechanistic insights from animal studies are needed in order to understand how such systemic immunosuppressive treatment modifies the biological interaction between the vascular wall and the stent implant. At the same time, these studies should address the healing response and its time course, both of which pertain to late side effects such as subacute and late stent thrombosis, especially with drug-eluting stents[8].

Several new hypotheses can now be tested in clinical studies. Obviously, this pharmacological approach could be proposed to patients in whom drug-eluting stents are not indicated because of planned surgery, intolerance or resistance to dual antiplatelet therapy. With additional safety data at hand, one could design a randomized trial in non-diabetics in order to test non-inferiority of this approach when compared to stenting using drug-eluting stents. One could also evaluate the incremental benefit of combining short-term high-dose steroid therapy with drug-eluting stents having limited antiproliferative power or the adjunctive value of oral steroids in patient/lesion subsets remaining at high-risk for recurrence despite the use of drug-eluting stents (with the exclusion again of patients with diabetes).

However, I am afraid that pursuing these interesting and potentially important avenues of research and securing the necessary funding will prove to be extremely difficult. Even the current study was difficult to fund, as stated on several occasions in the manuscript. In his cover letter to the Editor-in-Chief of EuroIntervention at the time of manuscript submission, Ribichini ironically made the following statement: "*... I just want to tell you that the present manuscript has undergone several revisions before reaching its present form. Indeed, I am proud to communicate that our article has been previously rejected from ALL major Journals of cardiology since its first submission in February 2004...*".

Apparently, the authors feel like they are blowing against the wind, and it is a strong one!

Blowing against the wind?

There appears to be resistance to accept the current findings and lack of interest to push the concept forward. Arguing that the scientific evidence is not strong enough seems unfair when the results of ARTS II[5], yet another registry, are readily endorsed by the community.

Obviously, the current approach is one that is diametrically opposed to what is now widely accepted as "the long awaited for" successful solution to the vexing problem of restenosis. It is hard to forget that for so many years, every attempt at preventing restenosis with a variety of orally given drugs has failed. Even previous trials that have used steroids[9-12] have failed, and the reasons why are being discussed by Ribichini *et al.*[1]. Nevertheless, one has to accept the growing evidence suggesting that the right drugs, when given orally at the right dose schedule, reaching for the appropriate targets, can be effective in controlling the process of clinical restenosis[1,13,14].

In conclusion, numerous reasons, some of which are listed above, can account for the prejudice expressed by many stakeholders (journal editors and reviewers, industrial partners, both from the pharmaceutical and the biomedical device industry) against the current approach. This type of work typically falls within the scope of "fundless clinical research", a problem that is growing, as recognized during an ESC Policy Conference in 2002[15], but remains so far without solution.

In any case, further to this publication in EuroIntervention, the relevance of the combined results of IMPRESS I and IMPRESS-2/MVD can no longer be ignored or simply dismissed!

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