Comparison of Efficacy and Safety of Lower-Dose to Higher-Dose Oral *Prednisone* After Percutaneous Coronary Interventions (the IMPRESS-LD Study)

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This study assessed clinical and angiographic efficacies of oral treatment with prednisone at low-dose (LD) versus the previous high-dose (HD) immunosuppressive dosage used after percutaneous coronary interventions (PCIs) with bare metal stents in patients with multivessel coronary artery disease. Forty-three patients with multivessel disease successfully treated with multiple PCIs were matched to the previous HD IMPRESS-2/MVD study population. The 43 patients were treated for 103 coronary stenoses and received 30-day oral prednisone treatment (LD group 1 mg/kg for 5 days, 0.5 mg/kg for 10 days, 0.25 mg/kg for 15 days) and were compared retrospectively with the 43 patients in the HD IMPRESS-2/MVD study with 116 treated coronary lesions (HD group 1 mg/kg for 10 days, 0.5 mg/kg for 20 days, 0.25 mg/kg for 15 days). The primary clinical end point was 12-month event-free survival rate (defined as freedom from death, myocardial infarction, and need for target vessel revascularization). The secondary end point was angiographic restenosis at 8 months assessed by quantitative coronary angiography. Event-free survival rates were 74% and 93% in the LD and HD groups, respectively (relative risk 4.6, 95% confidence interval 1.18 to 17.8, $p = 0.019$). Restenosis was observed in 4 lesions (4%) in the HD group and in 20 lesions (22%) in the LD group ($p < 0.001$). Mean late lumen loss was 0.61 ± 0.35 mm, and the loss index was 31.3 ± 21.6% in the HD group compared with 0.87 ± 0.61 mm and 52.03 ± 25.1% in the LD group ($p = 0.03$ and 0.02, respectively). In conclusion, antirestenotic efficacy of oral treatment with prednisone after conventional PCI is dose sensitive. A 50% dose decrease in oral prednisone, as tested in this study, is less effective than the previously tested HD IMPRESS therapeutic scheme. **(Am J Cardiol 2007;99:1082–1086)**

High-dose (HD) prednisone given orally for a short period of 45 days after percutaneous coronary intervention (PCI) with implantation of bare metal stents significantly decreases the incidence of major cardiac events at 1 year in patients with multivessel disease (MVD) compared with controls (relative risk 0.34, 95% confidence interval [CI] 0.12 to 0.96, $p < 0.006$).[1] Similar treatment effects were obtained in patients treated with single-vessel intervention and HD prednisone (relative risk 0.18, 95% CI 0.05 to 0.61, $p = 0.0063$).[2] This study assessed clinical and angiographic efficacies and incidence of drug-related side effects of oral prednisone in patients with multivessel coronary artery disease treated with PCI followed by a low-dose (LD) prednisone protocol. The lower dose used in this study has anti-inflammatory effects but cannot be considered effectively immunosuppressive.[3] The population of this study was matched to and compared with patients included in the previous HD Immunosuppressive Therapy for the Prevention of Restenosis After Coronary Stent Implantation (IMPRESS-2)/MVD study.[1]

Methods

The IMPRESS-LD is a prospective, controlled registry of patients with multivessel coronary artery disease and clinical evidence of ischemia amenable to PCI and without contraindication to stent implantation and subsequent steroid treatment. Use of prednisone to prevent restenosis after PCI was approved by the ethical committee of our hospital, and all patients who enrolled gave their informed consent according to ethical regulations. Between January 2004 and March 2005, 43 patients were selected for inclusion in this study.

The IMPRRESS-LD is a matched 1:1 comparison of the efficacy of oral prednisone treatment given at a lower dose, with a similar population previously enrolled in the full-dose IMPRESS-2/MVD study.[1] Patients were matched on a case-control basis considering age, gender, coronary risk factors, and angiographic features, i.e., number and length of coronary stenoses. All patients had multivessel coronary artery disease and clinical evidence of myocardial ischemia and were treated with multiple PCIs. After PCI, all patients started a treatment with oral prednisone that was decreased in dosage and length by nearly 50% compared with previous

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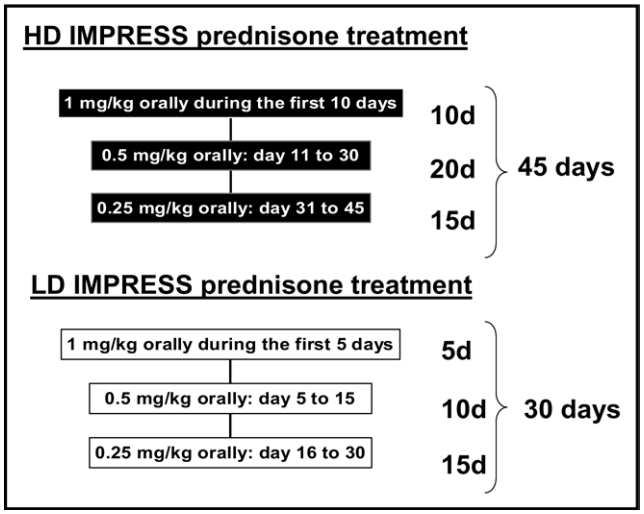

Figure 1. Therapeutic scheme of IMPRESS HD and LD studies.

IMPRESS studies, as shown in Figure 1. Oral prednisone was given at doses of 1 mg/kg for 5 days only, 0.5 mg/kg for 10 days, and 0.25 mg/kg for 15 days, whereas prednisone had been given orally at doses of 1 mg/kg for 10 days, 0.5 mg/kg for 20 days, and 0.25 mg/kg for 15 days in previous IMPRESS studies.[1,2]

All patients were pretreated with aspirin and a thienopyridine (ticlopidine 250 mg 2 times/day for 72 hours; clopidogrel 300-mg loading dose ≥6 hours before PCI); thienopyridine was continued for 1 month and aspirin indefinitely. Statins were recommended in all patients. After PCI, total creatine kinase and its MB isoform were measured at 6, 12 and 24 hours. Creatine kinase-MB increase >3 times the upper normal limit during follow-up was registered as myocardial infarction.

Patients without contraindications were prescribed oral prednisone at hospital discharge according to the LD protocol (Figure 1). Contraindications to enter the study were the same as those specified in previous studies: drug-eluting stent implantation, life expectancy <24 months, occurrence of any in-hospital complication related to the PCI procedure, contraindication to use of aspirin or thienopyridine, and contraindications to steroid use, including diabetes, recent myocardial infarction (<3 weeks), active peptic ulcer, active infectious disease, and uncontrolled severe hypertension. Potential undesirable metabolic effects that steroids could induce in diabetic subjects prevented the investigators from treating such patients. No restriction was used for clinical presentation of angina, angiographic characteristics of coronary lesions, and the PCI strategy, except use of drug-eluting stents.

All patients were controlled clinically 30 days after the procedure to assess correct and complete assumptions of steroid therapy and eventual occurrence of side effects. All patients underwent provocative stress testing within 6 months of PCI and subsequent outpatient clinic management. Angiographic follow-up was scheduled 8 months after PCI to assess occurrence of angiographic restenosis. Twelve months after the index procedure, all patients were managed in outpatient clinics by assigned independent clinicians to verify the incidence of any major adverse cardiac event included in the primary end point of the study, i.e., death (from any cause), myocardial infarction after discharge (defined as increase/decrease in creatine kinase-MB and new ischemic electrocardiographic changes), and recurrence of symptoms or ischemia requiring revascularization. Target vessel and nontarget vessel revascularizations were also assessed.

The secondary end point of the study was angiographic binary restenosis rate: diameter stenosis ≥50% at 8-month follow-up, inside the stent, within 5 mm of stent edges, or in segments treated with balloon angioplasty alone.

Interventions were performed through the femoral or radial approach. All patients had multivessel interventions. Unfractionated heparin was always used intravenously to maintain an activated clotting time >250 seconds during the procedure. As in the previous IMPRESS-2/MVD study, the "spot stenting" technique was preferred, whenever possible, to full coverage with stents in cases of diffuse coronary artery disease. PCIs were considered successful when a diameter stenosis ≤30% was achieved in each lesion treated and a Thrombolysis In Myocardial Infarction grade ≥2 flow was obtained in the vessel. Angiographic recordings for quantitative coronary analysis (QCA) were obtained in ≥2 orthogonal views of each coronary segment treated after administration of intracoronary nitroglycerin. At follow-up angiography, the same orthogonal views were obtained. Angiographic images were sent to an independent core laboratory for centralized QCA using the automated edge-detection system (Medis Medical Imaging Systems, Leiden, The Netherlands), as described elsewhere.[2] All lesions recorded at baseline, after PCI, and at follow-up were of adequate quality for QCA, and values of all lesions were used for statistical calculations.

Continuous data are expressed as mean ± SD, and discrete variables as absolute value and percentage. The study sample results from matched 1:1 comparison with patients with similar clinical, procedural, and angiographic characteristics as in the IMPRESS-2/MVD study. Only patients with MVD and multiple PCIs were enrolled to test the effects of the 2 treatments in a population at high risk of major adverse cardiac events in the absence of a beneficial additional treatment. Identical clinical and angiographic end points were applied in the 2 studies. Student's t test was used to compare differences between continuous variables. Chi-square statistic with Yates correction or Fisher's exact test, when appropriate, was used to test associations of categorical data. A logistic multivariate model was tested to assess the predictive value of factors related to occurrence of clinical events. Parameters of the model included HD or LD treatment with prednisone, left ventricular ejection fraction, clinical presentation, angiographic lesion type, length of stented lesion, and vessel diameters calculated by QCA before and after PCI. Event-free survival curves were obtained by Kaplan-Meier method and compared by log-rank test (Figure 2). A p value ≤0.05 was considered statistically significant.

Results

Forty-three patients were enrolled in the study. Patients were well matched with the 43 patients of the previous

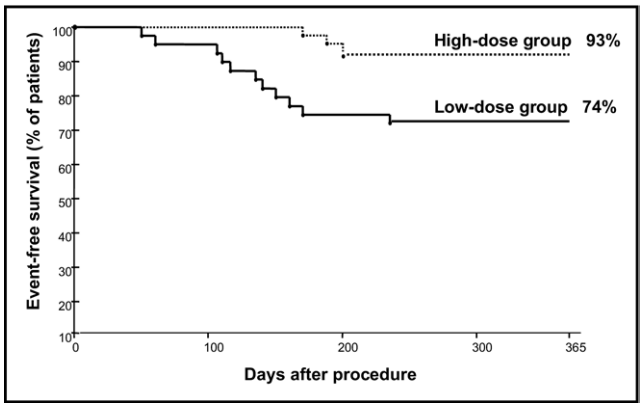

Figure 2. Event-free survival curves (death, nonfatal myocardial infarction, and repeat revascularization due to recurrence of ischemia) in 2 study groups at 12-month follow-up (log-rank test 6.97, p = 0.008).

Table 1
Baseline clinical data

Variable	Prednisone Dose		p Value
	High (n = 43)	Low (n = 43)	
Age (yrs)	61 ± 10	63 ± 9	0.3
Women	7 (16%)	8 (19%)	0.8
Systemic hypertension	36 (84%)	34 (79%)	0.6
Smokers	13 (30%)	9 (21%)	0.3
Hypercholesterolemia	30 (70%)	33 (77%)	0.5
Previous myocardial infarction	23 (54%)	18 (42%)	0.3
Peripheral artery disease	8 (19%)	6 (14%)	0.4
Previous coronary bypass	2 (5%)	3 (7%)	0.6
Acute coronary syndrome	12 (28%)	19 (44%)	0.1
Left ventricular ejection fraction (%)	54 ± 7	56 ± 7	0.4
Lesions treated/patient	115 (2.7)	103 (2.4)	0.2
Glycoprotein IIb/IIIa inhibitors	8 (19%)	9 (21%)	0.8
Statins	39 (91%)	38 (88%)	0.7
β Blockers	18 (42%)	22 (51%)	0.4
Calcium channel blockers	26 (61%)	26 (61%)	1
Angiotensin-converting enzyme inhibitors	29 (67%)	27 (63%)	0.7

IMPRESS-2/MVD population. Baseline clinical, angiographic, and procedural details of the IMPRESS-LD and the HD IMPRESS-2/MVD studies are presented in Tables 1 and 2.

Patients were treated for 103 coronary lesions; 12 lesions (11.7%) were treated with balloon angioplasty only and 119 stents were placed in the remaining 91 lesions. Rotational atherectomy was required in 2 cases of very calcified and diffuse left anterior descending lesions; directional atherectomy was used in a left anterior descending/first diagonal bifurcation lesion before stenting.

At 30-day follow-up, 5 patients (11.6%) reported side effects to prednisone therapy (gastric pain, hypertension, or fluid retention). Side effects did not require treatment withdrawal and responded always to medical therapy.

Clinical follow-up was obtained in all patients at 12 months. Two patients died suddenly (5%), and 2 developed Q-wave myocardial infarction (5%) due to occlusion of a nontarget vessel that had mild stenosis at the time of the PCI

Table 2
Baseline angiographic and procedural data

Variable	Prednisone Dose		p Value
	High (115 lesions)	Low (103 lesions)	
Complex lesions (B2 + C)	65 (56%)	49 (48%)	0.2
Thrombotic lesions	16 (14%)	12 (12%)	0.6
Long-term total occlusion	11 (10%)	8 (8%)	0.6
Only balloon angioplasty	13 (11%)	12 (12%)	0.9
Direct stenting	37 (32%)	29 (32%)	0.8
TIMI grade 3 flow before PCI	87 (76%)	88 (85%)	0.07
TIMI grade 3 flow after PCI	115 (100%)	103 (100%)	1
Vein graft	1 (1%)	1 (1%)	
Left main coronary artery	2 (2%)	1 (1%)	
Left anterior descending coronary artery	38 (33%)	37 (36%)	0.4
Right coronary artery	51 (44%)	35 (34%)	
Left circumflex artery	23 (20%)	29 (28%)	
Length of stented segments	17.0 ± 7.1	17.5 ± 9.4	0.4
Diameter of largest in-stent balloon	3.2 ± 0.5	3.18 ± 0.5	0.8
Length of balloon PCI segments	23.5 ± 8.2	23.2 ± 4.9	0.9
Diameter of balloon PCI segments	2.81 ± 0.4	2.7 ± 0.4	0.5

TIMI = Thrombolysis In Myocardial Infarction.

Table 3
Clinical outcome at follow-up

Clinical Events at 12 mos	Prednisone Dose		p Value
	High (n = 43)	Low (n = 43)	
Event-free survival	93%	74%	0.019
Death	—	2 (5%)	0.15
Nonfatal myocardial infarction	—	2 (5%)	0.15
Target vessel revascularization	3 (7%)	7 (16%)	0.2
Recurrence of ischemia or angina	2 (5%)	8 (19%)	0.04
Any event	3 (7%)	11 (26%)	0.019
Nontarget vessel revascularisation	0	2 (5%)	0.2
PCI	3 (7%)	9 (21%)	0.06
Coronary bypass	—	1 (2%)	0.3

in 1 patient and occlusion of the target vessel in the distal (nontreated) segment in the other. Recurrence of ischemia or angina occurred in 8 patients (19%). Repeat target vessel revascularization was performed in 7 of these 8 patients (16%), and the remaining patient was managed medically. Clinical outcome is presented and compared with previous outcome in the HD IMPRESS-2/MVD study in Table 3.

Comparison of occurrence of major cardiac adverse events in patients with MVD PCI treated with LD versus HD prednisone treatment showed a significantly higher incidence of clinical events in the LD group (26% vs 7%, relative risk 4.6, 95% CI 1.18 to 17.8, p = 0.019) and event-free survival rates at 12 months were 74% in the LD group and 93% in the HD IMPRESS-2/MVD study (log-rank test 6.97, p = 0.008; Figure 2). From multivariate regression analysis, treatment with LD prednisone was the only independent variable that correlated with occurrence of

Table 4
Quantitative coronary analysis at eight-month follow-up

QCA	Prednisone Dose		p Value
	High (n = 106 lesions)	Low (n = 91 lesions)	
Baseline			
Reference diameter (mm)	2.95 ± 0.99	2.86 ± 0.71	0.5
Minimum luminal diameter (mm)	0.98 ± 0.43	0.96 ± 0.51	0.7
Diameter stenosis (%)	66 ± 15%	67 ± 12%	0.4
After angioplasty			
Reference diameter (mm)	3.14 ± 0.47	3.06 ± 0.54	0.2
Minimum luminal diameter (mm)	2.95 ± 0.5	2.89 ± 0.5	0.4
Diameter stenosis (%)	6.5 ± 7	7 ± 5	0.6
Acute gain (mm)	1.97 ± 0.61	1.93 ± 0.57	0.7
Follow-up			
Reference diameter (mm)	2.99 ± 0.47	2.94 ± 0.51	0.4
Minimum luminal diameter (mm)	2.3 ± 0.57	2.03 ± 0.9	0.01
Diameter stenosis (%)	23 ± 16	32 ± 25	0.01
Late loss (mm)	0.61 ± 0.35	0.87 ± 0.61	0.03
Late-loss balloon angioplasty (mm)	0.41 ± 0.43	0.63 ± 0.52	0.04
Late loss within stents (mm)	0.65 ± 0.42	0.89 ± 0.56	0.03
Net gain (mm)	1.31 ± 0.7	1.05 ± 0.97	0.03
Loss index within stent (%)	31.3 ± 21.6	52.03 ± 25.1	0.02
Global restenosis rate (%)	4	22	0.0001

clinical events (relative risk 2.1, 95% CI 1.1 to 4.2, p = 0.03).

Thirty-nine of 43 patients underwent protocol angiographic follow-up (91%) at a mean of 280 ± 126 days. Two patients died before scheduled follow-up and 2 refused repeat angiography. QCA was performed on 91 of the 103 treated lesions. Angiographic end point of binary restenosis rate inside the stent, within 5 mm of stent edges, or in segments treated with balloon angioplasty was 22% (20 of 91 lesions). Mean late lumen loss per patient was 0.87 ± 0.61 mm, and the loss index was 52.03 ± 25.1%. Higher late loss values were observed in patients with LD treatment than in those with HD treatment. The different treatment effect was apparent despite stent implantation or balloon dilation alone. In the 2 patients who had Q-wave myocardial infarction during follow-up, target lesions were patent and without restenosis. QCA details are presented in Table 4 and compared with results from the HD IMPRESS-2/MVD study.

Discussion

Results of this prospective, nonrandomized, observational assessment of clinical and angiographic outcomes of patients who underwent multivessel PCI followed by LD oral therapy with prednisone showed that nearly 50% decreases in drug dosage and treatment length were ineffective in preventing occurrence of major adverse clinical events and angiographic restenosis compared with HD prednisone treatment.

In 2 previous studies, administration of oral HD prednisone prevented the occurrence of restenosis after bare metal stent implantation.[1,2] In particular, the IMPRESS-2/MVD study demonstrated the efficacy of this immunosuppressive therapy in a population with characteristics similar to those in the present study, i.e., patients with MVD and frequent complex coronary lesions, such as long-term total occlusions and diffuse and/or calcified or thrombotic lesions. Retrospective comparison of the 2 matched populations showed significantly worse clinical and angiographic outcomes when the dose of prednisone was decreased by nearly 50%, suggesting that the beneficial effects of systemic treatment with prednisone depends on the administered dose. Therefore, efforts should be made to gain patients' best compliance to the HD treatment protocol.

With the exception of the HD IMPRESS studies, previous experiences with steroids after PCI have been negative.[4–6] In particular, the randomized, placebo-controlled Multi-Hospital Eastern Atlantic Restenosis Trial (M-HEART) study[4] and a randomized study by Lee et al[5] showed that neither a single intravenous bolus administration of methylprednisolone given before PCI nor an intravenous bolus followed by 1-week oral administration of prednisone[6] decreases restenosis. Similarly, low doses of dexamethasone eluted from a phosphorylcholine-coated stent did not prevent restenosis in patients with acute coronary syndrome.[7] The low dosage and very short length of steroid treatment used in these studies are likely the main reasons for the lack of efficacy. A single LD approach, a short 1-week drug treatment, or brief dexamethasone stent elution are unlikely to achieve immunosuppressive effects and arrest tissue growth that ensues after vessel wall injury caused by PCI.[8,9] Steroids exert beneficial effects on platelet function, smooth muscle cell proliferation, collagen synthesis, and inflammatory cell migration and activation, thus interfering with several steps of the cascade leading to neointima formation and subsequent lumen loss.[10,11] The present report further defines the importance of treatment regimen to achieve clinically relevant results with steroids after conventional PCI. The efficacy of this treatment is related to systemic immunosuppressive effects[12] similar to those obtained with

the HD protocol investigated in our previous studies. Conversely, administration of prednisone at anti-inflammatory doses offers no therapeutic advantage in decreasing clinical events after PCI. Similar negative observations with low to moderate prednisone regimens, unable to suppress the immune-mediated inflammatory response, have been reported in the context of other diseases with inflammatory etiologic pathways.[13,14]

The study is limited by its nonrandomized, nonblinded nature and retrospective comparison with a previously reported series. However, although the 2 groups of patients compared in this study were well matched and presented similar baseline and procedural characteristics, the clinical outcome was significantly different according to treatment protocol. As in the 2 previous IMPRESS studies, exclusion of diabetic patients remains an important limitation of systemic treatment with prednisone.

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