

CLINICAL RESEARCH

Interventional Cardiology

Colchicine Treatment for the Prevention of Bare-Metal Stent Restenosis in Diabetic Patients

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Objectives	This study sought to test the hypothesis that colchicine treatment after percutaneous coronary intervention (PCI) can lead to a decrease in in-stent restenosis (ISR).
Background	ISR rates are particularly high in certain patient subsets, including diabetic patients, especially when a bare-metal stent (BMS) is used. Pharmacological interventions to decrease ISR could be of clinical relevance.
Methods	Diabetic patients with contraindication to a drug-eluting stent, undergoing PCI with a BMS, were randomized to receive colchicine 0.5 mg twice daily or placebo for 6 months. Restenosis and neointima formation were studied with angiography and intravascular ultrasound 6 months after the index PCI.
Results	A total of 196 patients (63.6 ± 7.0 years of age, 128 male) were available for analysis. The angiographic ISR rate was 16% in the colchicine group and 33% in the control group ($p = 0.007$; odds ratio: 0.38, 95% confidence interval: 0.18 to 0.79). The number needed to treat to avoid 1 case of angiographic ISR was 6 (95% confidence interval: 3.4 to 18.7). The results were similar for IVUS-defined ISR (odds ratio: 0.42; 95% confidence interval: 0.22 to 0.81; number needed to treat = 5). Lumen area loss was 1.6 mm^2 (interquartile range: 1.0 to 2.9 mm^2) in colchicine-treated patients and 2.9 mm^2 (interquartile range: 1.4 to 4.8 mm^2) in the control group ($p = 0.002$). Treatment-related adverse events were largely limited to gastrointestinal symptoms.
Conclusions	Colchicine is associated with less neointimal hyperplasia and a decreased ISR rate when administered to diabetic patients after PCI with a BMS. This observation may prove useful in patients undergoing PCI in whom implantation of a drug-eluting stent is contraindicated or undesirable. (J Am Coll Cardiol 2013;61:1679–85) © 2013 by the American College of Cardiology Foundation

Implantation of coronary stents after angioplasty has led to significant decreases in clinical events compared with plain balloon angioplasty (1,2). However, restenosis has been a considerable problem with bare-metal stents (BMS), which prompted the advent of drug-eluting stents. Their principal function is to inhibit in-stent neointima formation, thus decreasing restenosis rates (3).

The problem of restenosis appears to be more severe in certain subsets of coronary artery disease patients, including

those with diabetes, in whom some of the first BMS trials restenosis rates exceeded 50% (4). As a result, drug-eluting stents are particularly beneficial in these patients, in terms of angiographic outcomes and target lesion revascularization (5). However, there are diabetic patients undergoing percutaneous coronary intervention (PCI) who have important contraindications to implantation of drug-eluting stents, including patients with planned necessary surgery as well as those who need anticoagulation treatment, in whom triple antithrombotic therapy (double antiplatelet and 1 anticoagulant) is associated with a high risk of bleeding and should be as short term as possible (6).

See page 1686

Colchicine is an old drug with known anti-inflammatory and antiproliferative actions. Both of these effects could conceivably interfere with the formation of neointima in coronary stents, thus reducing the rate of in-stent restenosis

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Abbreviations and Acronyms

angio-ISR = angiographic in-stent restenosis

BMS = bare-metal stent(s)

CI = confidence interval

ISR = in-stent restenosis

IVUS = intravascular ultrasound

IVUS-ISR = intravascular ultrasound-defined in-stent restenosis rate

MLA = minimum lumen area

PCI = percutaneous coronary intervention

(ISR). In addition, it has been shown to be safe in different subsets of patients with cardiovascular disease (7,8). The aim of the present study was to study the effect of 6 months of treatment with oral colchicine on neointima formation and restenosis in diabetic patients undergoing PCI with BMS implantation.

Methods

Population. This was a double-blind, prospective, placebo-controlled study. Eligible patients were diabetic, 40 to 80 years of age, undergoing PCI in a coronary artery with

a diameter of at least 2.5 mm with a BMS. Acceptable reasons for not implanting a drug-eluting stent were: contraindication to long-term dual antiplatelet treatment, need for triple antithrombotic therapy, planned or high probability of necessary surgery in the following 12 months, or the patient's expressed wish in the context of the PCI informed consent procedure. Only 1 lesion per patient was included in the study. (If PCI was performed in >1 coronary site in a patient, the site with the greater artery diameter was included.) Diabetes mellitus had to be previously diagnosed by a specialist, with the patient treated with either oral medication or insulin. Exclusion criteria were left main artery disease (>30% in angiography); PCI performed as primary treatment for ST-segment elevation myocardial infarction, hepatic impairment (Child-Pugh class B or C); target vessel segment presenting particular technical challenges for intravascular ultrasound (IVUS) (e.g., marked tortuosity, vessel with steep take-off angle); severe or end-stage renal failure (estimated glomerular filtration rate ≤ 20 ml/min/1.73 m² or requiring dialysis); history of intolerance to colchicine, myopathy, and statin hepatotoxicity or myotoxicity; women with child-bearing potential; and inability or unwillingness to adhere to standard treatment or to provide consent. The protocol was approved by the institutional review boards. All patients provided informed consent.

Procedures. Patients underwent baseline coronary angiography and PCI, with IVUS evaluation of the implanted BMS. All stents were post-dilated with an appropriately sized noncompliant balloon. All stents were evaluated immediately after implantation with IVUS to obtain baseline measurements. Immediate post-implantation IVUS images were also used to optimize stent expansion and apposition and to identify significant edge dissections or significant residual plaque burden at stent edges, whereupon complementary corrective action was undertaken (e.g., further post-dilation or additional stenting), if deemed appropriate by the operator. (It was determined by the review board who

approved of the study protocol that it would not be ethical to disregard IVUS findings, although routine post-PCI IVUS-guided stent evaluation does not reflect current clinical practice.) Angiographic and IVUS follow-up was performed 6 months after the index PCI.

Angiographic vessel and lesion parameters were measured using quantitative coronary angiography software (Xcelera, Philips Healthcare, Eindhoven, the Netherlands). Late lumen loss was defined as the difference between the baseline in-stent minimum luminal diameter and the minimum luminal diameter on follow-up angiography. Angiographic ISR (angio-ISR) was defined as presence of >50% in-stent stenosis at the 6-month follow-up.

IVUS was performed after intracoronary administration of 0.3 to 0.5 mg of nitroglycerin. A digital IVUS catheter (Eagle Eye Gold, Volcano Corp., Rancho Cordova, California) was introduced into the target vessel and a pull back was performed through the implanted stent, with a motorized automatic pull back system (Track Back II, Volcano Corp.) at a constant speed of 0.5 mm/s. Additional pull backs were performed to ensure adequate quality of captured images. Captured IVUS data, identified only by a serial number, were analyzed offline. Each recorded pull back loop was inspected by formally trained IVUS operators who made manual corrections to the automated border delineation applied by the system software. Volumetric data were then automatically calculated. Neointima volume was calculated as stent minus lumen volume and divided by the stent length in millimeters to account for different stent lengths (normalized neointima volume). The percentage of neointimal volume was defined as in-stent neointimal volume divided by stent volume. In-stent minimum lumen area (MLA) was measured and recorded. IVUS-defined ISR (IVUS-ISR) was defined as in-stent MLA of <4 mm² at follow-up (a cutoff used in past studies [9]). In-stent lumen area loss was calculated as post-PCI MLA minus the MLA at follow-up. A subset of the pull backs (~20%) were analyzed twice, unbeknown to the reviewers. The intraobserver correlation index was 0.93 for lumen measurements and 0.91 for volumes. All IVUS pull backs were analyzed at a core laboratory.

Study treatments and adverse event monitoring. Patients were randomized to receive colchicine or placebo for 6 months. Colchicine was administered from the day of the index PCI (within 24 h) at a dose of 0.5 mg twice daily. Patients were followed with clinic visits until follow-up angiography at 6 months. Monitoring of adverse events focused on gastrointestinal manifestations, hepatotoxicity, myelotoxicity/hematotoxicity, myotoxicity, and alopecia. Complete blood counts and standard biochemical analyses (glucose, urea, creatinine, liver enzymes, creatine kinase, lactate dehydrogenase) were performed at 2, 4, 8, 16, and 24 weeks after the index PCI.

Outcome measures. The main outcome measures were angio-ISR and IVUS-ISR. Secondary outcome measures were angiographic and IVUS parameters of lumen loss and

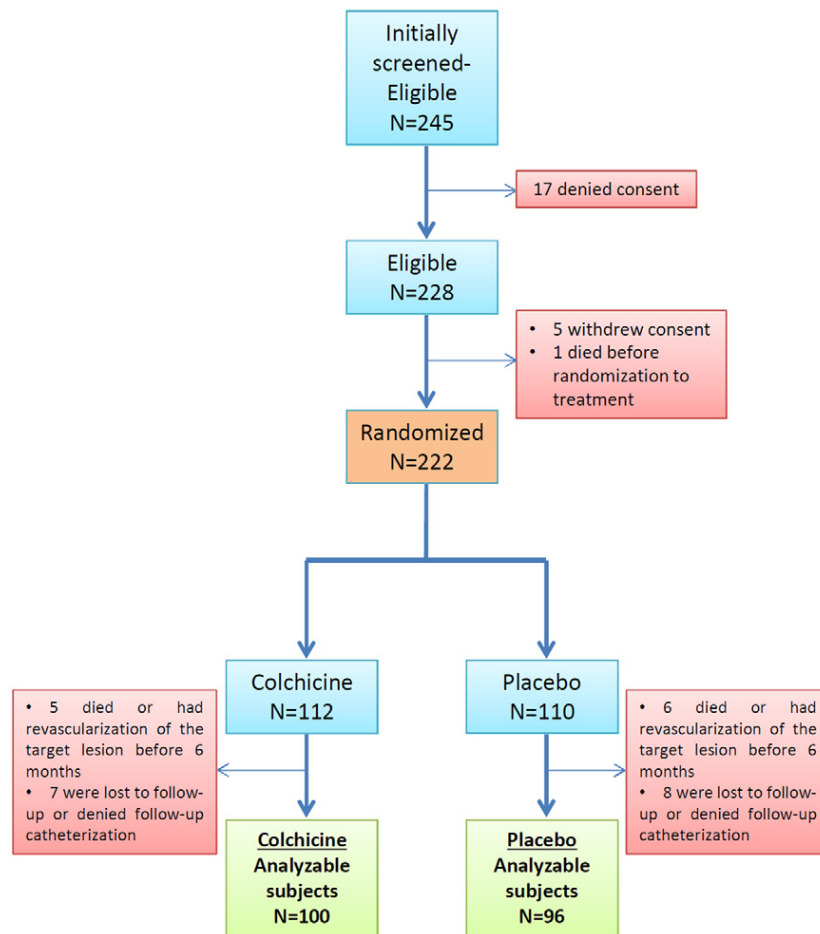


Figure 1 Study Flow Chart

Of 222 randomized patients, 196 were available for analysis.

in-stent neointimal hyperplasia, including late lumen loss (angiography), lumen area loss, percentage of neointima volume, and normalized neointima volume (IVUS).

Statistical analysis. Assuming a 40% rate of ISR in the control group, a sample size of 81 per group (in a 1:1 allocation ratio) would be required to have a probability of 80% to detect a 50% reduction in ISR, at an alpha level of 0.05. All patients who received at least 1 dose of study treatment were included in the analysis. Continuous variables were expressed as mean $\pm$ SD and compared using the Student *t* test, if their distribution did not deviate significantly from the normal distribution (tested with the Kolmogorov-Smirnov test). If a significant deviation from the normal distribution was found, continuous variables were expressed as median (interquartile range) and compared using nonparametric tests (Mann-Whitney *U* and Wilcoxon for unpaired and paired comparisons, respectively; all variables summarized as median and interquartile range were analyzed with nonparametric methods). Categorical variables were expressed as percentages and counts and compared using the chi-square test or

Fisher exact test if the produced matrices contained cells with an expected value <5 . Odds ratios were calculated using the Mantel-Haenszel procedure. SPSS software package version 17 was used (SPSS Inc., Chicago, Illinois). Values of $p < 0.05$ (2 sided) were considered indicative of statistical significance, with the exception of the 2 coprimary endpoints: to adjust for using 2 primary null hypotheses, we used the Sidak-Bonferroni formula to correct the expected type I error. The adjusted alpha level was thus calculated to be 0.025, and p values < 0.025 were considered statistically significant in the case of the two main outcome measures (angio-IVUS and IVUS-ISR).

Results

Study flow and population characteristics. Of 222 eligible patients who consented to take part in the study, 26 were not available for follow-up catheterization. As a result, 196 (100 in the colchicine and 96 in the placebo group) completed the study procedures and were available for analysis (Fig. 1). The 2 treatment arms were well

Table 1 Patient Characteristics

Feature	Overall (N = 196)	Colchicine Group (n = 100)	Placebo Group (n = 96)	p Value
Epidemiological background				
Age, yrs	63.6 ± 7.0	63.7 ± 6.9	63.5 ± 7.2	0.78
Male	128 (65)	63 (63)	65 (68)	0.49
BMI, kg/m ²	27.4 ± 3.9	27.4 ± 3.6	27.5 ± 4.3	0.59
Smoking	74 (38)	36 (36)	38 (40)	0.61
Hypertension	95 (49)	48 (48)	47 (49)	0.89
Diabetes	196 (100)	100 (100)	96 (100)	1.00
Insulin-treated	53 (27)	29 (29)	24 (25)	0.53
Family history of CAD	81 (41)	44 (44)	37 (39)	0.44
Renal dysfunction	65 (33)	36 (36)	29 (30)	0.39
LVEF, %	55.6 ± 6.8	55.3 ± 7.4	55.9 ± 6.2	0.51
Clinical presentation				
Stable CAD	135 (69)	72 (72)	63 (66)	0.34
ACS	61 (31)	28 (28)	33 (34)	
Procedure-related parameters				
Lesion site				
LAD	106 (54)	54 (54)	52 (54)	0.83
LCx	38 (19)	18 (18)	20 (21)	
RCA	52 (27)	28 (28)	24 (25)	
No. of stents	1 (1–2)	1 (1–2)	1 (1–2)	0.82
Total stent length, mm	24 (18–32)	24 (18–34)	20 (18–28)	0.81
Stent diameter, mm	3.0 (3.0–3.5)	3.0 (3.0–3.5)	3.0 (3.0–3.5)	0.46
CTOs	24 (12)	12 (12)	12 (13)	0.92

Values are mean ± SD, count (%), or median (interquartile range).

ACS = acute coronary syndrome; BMI = body mass index; CAD = coronary artery disease; CTO = chronic total occlusion; LAD = left anterior descending; LCx = left circumflex; LVEF = left ventricular ejection fraction; RCA = right coronary artery.

balanced with similar epidemiological and clinical background (Table 1).

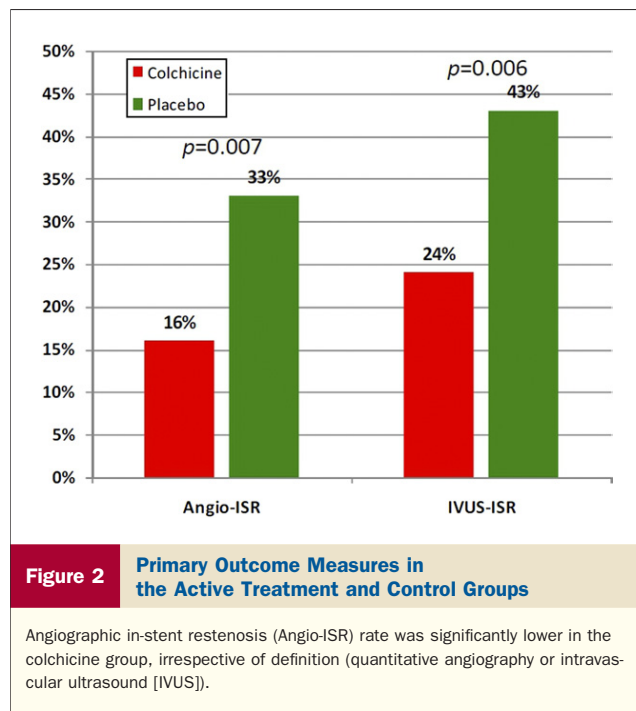
Outcome measures. The rate of angio-ISR in the total of 196 patients was 24% at 6 months (the severity of angiographic restenosis was overall moderate in the whole cohort, with the majority of patients with restenosis falling in the 50% to 70% stenosis severity range) (Table 2), with a significant difference between the 2 treatment arms: the angio-ISR rate was 52% lower in the colchicine group compared with the control group (Fig. 2). The odds ratio for colchicine-treated patients to have ISR on follow-up was 0.38 (95% confidence interval [CI]: 0.18 to 0.79). The number needed to treat with colchicine to avoid 1 case of angio-ISR was 6 (95% CI: 3.4 to 18.7).

The results in terms of IVUS-defined restenosis were similar (Fig. 2). The IVUS-ISR rate was 33%, with colchicine-treated patients having a 44% lower probability of IVUS-ISR at follow-up (odds ratio: 0.42; 95% CI: 0.22 to 0.81). Five patients had to be treated with colchicine to avoid 1 case of IVUS-ISR (95% CI: 3.2 to 18.1).

Both angiographic and IVUS descriptors of neointima formation indicated attenuation of neointimal hyperplasia in the colchicine group compared with the control group (Table 3). In terms of angiographic follow-up, late lumen loss in the control group was more than double that in the active treatment group, resulting in a significantly lower MLD at follow-up (Fig. 3). IVUS area and volume measurements were along the same lines. In-stent lumen area

Table 2 Grades of Stenosis Severity and In-Stent Minimum Lumen Diameter on Follow-Up Coronary Angiography in Patients With Restenosis (N = 48)

	Total (n = 48)			Controls (n = 32)			Colchicine (n = 16)		
	N	%	Cum. %	n	%	Cum. %	n	%	Cum. %
In-stent stenosis severity, %									
50–59	17	35.4	35.4	11	34.4	34.4	6	37.5	37.5
60–69	15	31.3	66.7	12	37.5	71.9	3	18.8	56.3
70–79	12	25.0	91.7	6	18.8	90.7	6	37.5	93.8
≥80	4	8.3	100.0	3	9.4	100.0	1	6.3	100.0
Minimum lumen diameter, mm									
>1.5	2	4.2	4.2	1	3.1	3.1	1	6.3	6.3
1.0–1.5	33	68.8	72.9	23	71.9	75.0	10	62.5	68.8
<1.0	13	27.1	100.0	8	25.0	100.0	5	31.3	100.0



loss was 1.6 mm² (interquartile range: 1.0 to 2.9 mm²) in colchicine-treated patients compared with 2.9 mm² (interquartile range: 1.4 to 4.8 mm²) in control subjects ($p = 0.002$). In accordance, the percentages of neointima volume and normalized neointima volume were 63% and 70% higher in the control group, respectively (Table 3).

In terms of clinical events, 1 patient in the control group and 1 in the active treatment group died during follow-up

(causes of death were recorded as acute pulmonary edema and stroke, respectively). Nine patients (4 of 112 patients [3.6%] in the colchicine group and 5 of 110 [4.5%] in the control group) underwent reintervention (defined in the present study as PCI of the target lesion or bypass grafting of the target vessel).

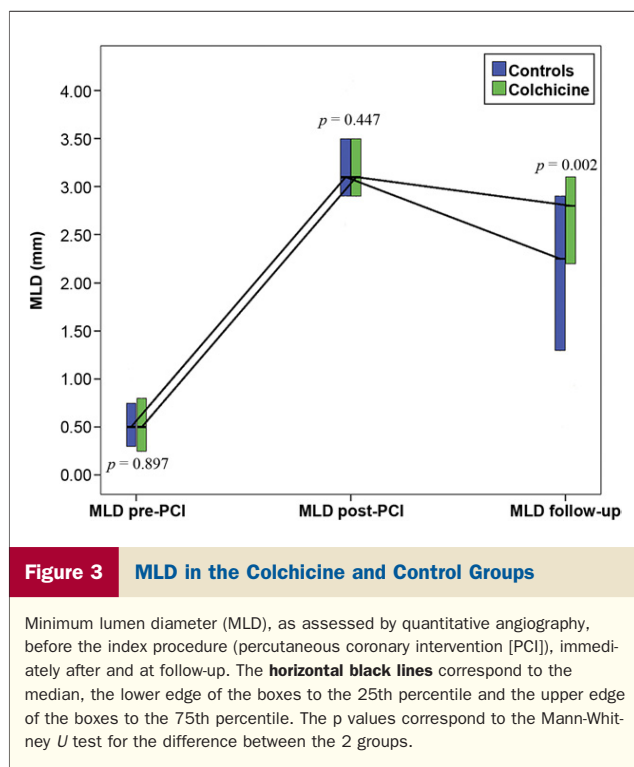
Adverse events and treatment discontinuation. Gastrointestinal symptoms (diarrhea and nausea) were the most common adverse events in the colchicine group. Of the colchicine-treated patients, 16% reported having diarrhea or nausea versus 7% of those taking placebo ($p = 0.058$). Myalgia and muscle cramps were reported by 15% and 10% of colchicine-treated patients and the control group, respectively ($p = 0.336$). In one of them, creatine kinase levels rose higher than 5 times the upper reference limit, returning to normal after discontinuation of a statin and colchicine. This patient had no signs or laboratory findings of rhabdomyolysis. No cases of hepatotoxicity or hematotoxicity were recorded. Two patients (1 from each treatment arm) reported accelerated hair loss.

Overall, 17 patients in the colchicine group (17%) and 9 patients in the control group (9%) discontinued their study medication before completing 180 days of treatment ($p = 0.116$). Colchicine-treated patients discontinued treatment earlier than the control group (mean duration of treatment among those who withdrew was 26 days in the colchicine group and 47 days in the control group; $p = 0.03$). Late lumen loss was 0.8 mm² (interquartile range: 0.3 to 1.5 mm²) in patients in the colchicine group who discontinued treatment and 0.3 mm² (interquartile range: 0.2 to 0.6 mm²) in those who completed treatment ($p = 0.025$). There was a non-

Table 3 Angiographic and IVUS Measurements at Baseline and Follow-Up				
Parameter	Overall (N = 196)	Colchicine (n = 100)	Placebo (n = 96)	p Value
Quantitative angiography				
Baseline stenosis, %	84 (75–91)	84 (75–92)	85 (75–90)	0.94
Lesion length, mm	21.3 (15.6–28.4)	21.5 (15.6–30.9)	17.9 (15.6–25.6)	0.89
Proximal reference diameter, mm	3.2 (3.0–3.6)	3.2 (3.0–3.6)	3.2 (3.0–3.6)	0.61
Distal reference diameter, mm	3.0 (2.8–3.4)	3.0 (2.8–3.4)	3.0 (2.8–3.5)	0.76
MLD pre-dilation, mm	0.5 (0.3–0.8)	0.5 (0.3–0.8)	0.5 (0.3–0.8)	0.90
MLD post-stenting, mm	3.1 (2.9–3.5)	3.1 (2.9–3.5)	3.1 (2.9–3.5)	0.45
MLD follow-up, mm	2.6 (1.6–3.0)	2.8 (2.2–3.1)	2.3 (1.3–2.9)	<0.01
Late lumen loss, mm	0.6 (0.3–1.4)	0.4 (0.2–0.8)	0.9 (0.5–1.8)	<0.01
IVUS				
Surface area measurements				
Baseline proximal reference MLA, mm ² *	8.1 (7.1–9.5)	8.1 (7.1–9.7)	8.1 (7.1–9.4)	0.47
Baseline distal reference MLA, mm ² *	7.5 (6.6–9.0)	7.8 (6.8–9.2)	7.3 (6.4–8.7)	0.11
Baseline in-stent MLA, mm ²	7.1 (6.1–9.0)	7.3 (6.2–9.1)	6.8 (6.1–8.7)	0.14
Follow-up proximal reference MLA, mm ² *	7.3 (6.4–8.7)	7.5 (6.6–9.1)	7.2 (6.2–8.2)	0.04
Follow-up distal reference MLA, mm ² *	6.7 (5.7–8.1)	7.0 (5.8–8.3)	6.3 (5.5–7.4)	0.02
Follow-up in-stent MLA, mm ²	4.9 (2.4–6.9)	5.5 (4.0–7.2)	4.2 (1.7–6.3)	<0.01
Volumetric parameters				
Stent volume, mm ³	164 (118–230)	169 (125–252)	158 (111–220)	0.20
In-stent neointima volume, %	25.0 (14.0–52.8)	20.5 (12.0–35.8)	33.5 (16.8–60.2)	<0.01
In-stent normalized neointima volume, mm ³ /mm	1.99 (1.12–3.71)	1.64 (0.95–2.99)	2.79 (1.36–3.96)	<0.01

Values are median (interquartile range). *The proximal and distal reference segments were 10-mm segments proximal and distal to the stent edges.

IVUS = intravascular ultrasound; MLA = minimum lumen area; MLD = minimum lumen diameter



significant trend toward a higher binary angio-ISR rate in those who discontinued (5 of 17; 29.4%) versus the rest of the colchicine group (11 of 72; 13.3%) ($p = 0.141$). Among patients who stayed on treatment until completion of the study, compliance was high, as indicated by pill counts (95.6% of doses were taken by the patients).

Patients lost to follow-up. To account for patients who were lost to follow-up or refused to undergo follow-up angiography, we performed an alternative analysis, with the assumption that all 7 patients of the colchicine group had ISR, whereas those 8 of the control group who did not present for follow-up angiography had an ISR rate similar to that of the rest of the control group. The difference in angio-ISR rate between the 2 arms remained significant in this analysis ($p = 0.048$), with an odds ratio of 0.54 (95% CI: 0.29 to 0.99).

Discussion

Colchicine was shown in the present study to be associated with a significant decrease in ISR at 6 months, when administered at a daily dose of 1 mg for 6 months to diabetic patients undergoing PCI with implantation of a BMS. Neointimal hyperplasia, as indicated by IVUS-derived area and volumetric parameters, was markedly attenuated in patients receiving colchicine. The population included in the present study is a clinically relevant subset of coronary artery disease patients undergoing PCI because the problem of ISR is especially important for diabetic patients and the use of drug-eluting stents is not always desirable or feasible.

Colchicine disrupts the mitotic spindle by inhibiting the self-assembly of microtubules (10). It has a potent anti-inflammatory effect and acts on several cellular components of the immune process, including neutrophils and macrophages, and affects the expression of cytokines (10–12). It has unique features compared with other available anti-inflammatory agents, including corticosteroids and non-steroidal anti-inflammatory drugs (namely, its antimitotic effect and the absence of detrimental effects on the cardiovascular system). Inflammatory processes play a prominent part in the molecular mechanisms of restenosis (13–16), and the centrality of their role remains valid despite modifications in the cascade model of restenosis proposed by Libby et al. (13) in 1992.

Colchicine has an antimitotic effect, obviously useful for preventing a process characterized by cellular hyperplasia, as well as an anti-inflammatory effect, which should inhibit the very important contribution of inflammation to in-stent neointima formation, and, on top of that, does not seem to share the undesirable properties of other classes of anti-inflammatory agents that render them unsafe for use in patients with cardiovascular disease. It appears that colchicine should, in all probability, be beneficial in preventing restenosis. However, it has been shown that this is not the case, at least as far as plain balloon angioplasty is concerned, as implied by experimental and clinical studies (17–19). O’Keefe et al. (18) studied 197 patients who received either colchicine 1.2 mg/day or placebo for 6 months after balloon angioplasty (without stenting) and found no difference in the angiographic restenosis rate. However, the mechanism of restenosis after balloon angioplasty differs in a substantial way from the mechanism of ISR. Elastic recoil and arterial vessel remodeling play an important role, in addition to neointimal hyperplasia, in restenosis after plain angioplasty, whereas in the case of stenting, lumen loss is almost exclusively due to neointima formation (20–22). As a consequence, because colchicine is unlikely to affect vascular elastic recoil or remodeling in any perceivable way, it could be expected to be ineffective in preventing restenosis after plain balloon angioplasty, while being effective in attenuating neointimal hyperplasia and, thus, decreasing ISR after stent implantation.

The revascularization rate of the target lesion was markedly lower than the observed rate of angiographic (or IVUS-defined) restenosis (the revascularization rate in the whole cohort was almost 4% in 6 months compared with a 24% rate of angio-ISR). This is explained by the fact that a large proportion of patients with ISR were asymptomatic. There are 3 main reasons for that: 1) patients were receiving carefully observed optimized medical treatment; 2) patients were diabetic (in whom silent ischemia is common [23,24]); and 3) a considerable percentage (66.7%) of the patients with ISR had an angiographic restenosis severity <70%.

The tolerability profile of colchicine was good in the present study, without serious adverse events related to treatment. This is most probably due to the relatively low

dose used (0.5 mg twice daily). This is consistent with the study by O’Keefe et al. (18), as well as other studies in different populations of patients with cardiovascular disease (7,8), in which daily doses of up to 2 mg have been used for periods ranging from 1 to 6 months.

Study limitations. The endpoints of the present study were not clinical. More powered studies with longer follow-up would be needed to demonstrate a clinical benefit for colchicine use in this setting. As a result, no firm clinical recommendation can be made on the basis of these findings.

Conclusions

Colchicine is associated with less neointimal hyperplasia and a reduced ISR rate when administered to diabetic patients after BMS placement. This observation may prove to be useful in patients undergoing PCI in whom implantation of a drug-eluting stent is contraindicated or undesirable.

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Key Words: bare-metal stent(s) ■ diabetes ■ hyperplasia ■ in-stent restenosis ■ intravascular ultrasound ■ neointima.