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MINI-FOCUS ISSUE: HEART FAILURE

ADVANCED

CASE REPORT: CLINICAL CASE

Perioperative Management of Takayasu Arteritis for Cardiac Surgery in a Patient Treated With Tocilizumab

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ABSTRACT

We describe the case of a young woman with Takayasu arteritis with severe stenosis in the main trunk of the left coronary artery. After administration of prednisolone and tocilizumab to control disease activity, coronary artery bypass grafting was performed. Here, we report the successful perioperative management of this cardiac surgery. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2020;2:2363–7) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 23-year-old Japanese woman presented with a dry cough that she had had since the spring of 2018. She experienced chest pain, dizziness, and palpitations during exertion from January 2019 and consulted a practitioner in early April of that year. She was prescribed a bronchodilator for suspected cough-variant asthma. In May 2019, she was referred to our hospital (Japan Community Healthcare Organization Osaka Hospital, Osaka, Japan) because of worsening chest pain.

LEARNING OBJECTIVES

- To understand perioperative treatment of patients with TAK who are treated with TCZ.
- To review medical, surgical, and subsequent treatment methods from the onset of TKA.
- To understand changes in CRP, SAA, ESR, and IL-6 caused by TCZ administration.

PAST MEDICAL HISTORY

The patient had no history of cardiovascular disease or any family history of Takayasu arteritis (TAK).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included atherosclerosis, giant cell arteritis, and TAK.

INVESTIGATIONS

On arrival, her blood pressure was 106/57 mm Hg, and her heart rate was 86 beats/min. There was no difference in blood pressure between the bilateral brachial arteries. Electrocardiography revealed sinus rhythm with no abnormal findings. The chest radiograph did not reveal pulmonary edema or pleural

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CRP = C-reactive protein

CT = computed tomography

ESR = erythrocyte sedimentation rate

GC = glucocorticoid

IL = interleukin

LMCA = left main coronary artery

PSL = prednisolone

SAA = serum amyloid A

TAK = Takayasu arteritis

TCZ = tocilizumab

effusion. Echocardiography demonstrated mild aortic regurgitation and preserved cardiac contractility. Levels of C-reactive protein (CRP), serum amyloid A (SAA) proteins, and erythrocyte sedimentation rate (ESR) were elevated at 5.23 mg/dl, 224 μg/ml, and 113 mm/h, respectively. Laboratory investigations before treatment are summarized in Table 1. Computed tomography (CT) with angiography revealed severe stenosis in the ostia of the left main coronary artery (LMCA) (Figure 1). CT also revealed arterial wall thickening and delayed contrast enhancement in the ascending aorta to the aortic arch, left common carotid artery, left subclavian artery, and pulmonary artery. The right superficial femoral artery exhibited stenosis, and the right ankle-brachial index was decreased to 0.88 without intermittent claudication. She was diagnosed with TAK (1).

TABLE 1 Laboratory Investigations

Test	Value	Unit	Reference Range
White blood cells	6,300	/μl	3,300–8,600
Red blood cells	449	$\times 10^4$/μl	386–492
Hemoglobin	9.5	g/dl	11.6–14.8
Platelets	48.3	$\times 10^4$/μl	15.8–34.8
Sodium	139	mEq/l	138–145
Potassium	3.9	mEq/l	3.6–4.8
Chloride	103	mEq/l	101–108
Blood urea nitrogen	11	mg/dl	8–20
Creatinine	0.64	mg/dl	0.46–0.79
AST	12	IU/l	13–30
ALT	9	IU/l	7–23
LDH	117	IU/l	119–229
Albumin	3.6	g/dl	4.1–5.1
HDL	46	mg/dl	48–103
LDL	84	mg/dl	65–163
TG	42	mg/dl	30–117
HbA1c	5.6	%	4.6–6.2
Fasting blood glucose	76	mg/dl	60–109
NT-proBNP	42	pg/ml	<125
CK	85	IU/l	45–163
Troponin I	0.4	pg/ml	<26.2
C-reactive protein	5.23	mg/dl	<0.3
Serum amyloid A	224	μg/ml	<8
Erythrocyte sedimentation rate	113	mm/h	<15
Interleukin-6	2.3	pg/ml	0.221–4.62
HLA-B52 allele	Positive	–	–

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; HLA = human leukocyte antigen; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; NT-proBNP = N-terminal fragment of pro-B-type natriuretic peptide; TG = triglyceride.

MANAGEMENT

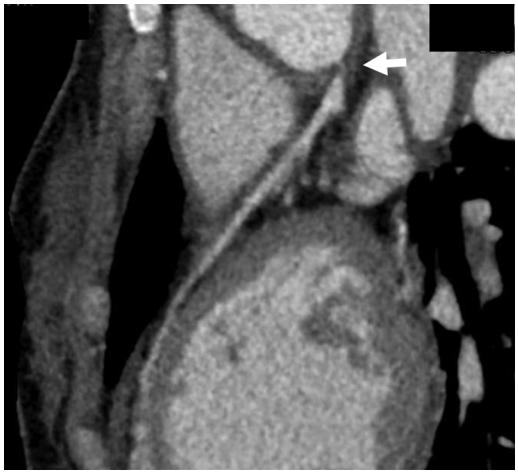
After hospitalization, she restricted her exercise to less than light exertion, and nitroglycerin and carvedilol were prescribed for effort angina. For TAK, prednisolone (PSL) was initiated at 45 mg (1 mg/kg/day). CRP, SAA, and ESR rapidly declined (Figure 2). After PSL administration for 2 weeks, the dose was gradually decreased by 5 mg every week. However, CRP, SAA, and ESR increased again when the dose was reduced to 30 mg. Tocilizumab (TCZ; 162 mg) was subcutaneously administered every week because of the TAK relapse. After TCZ administration, levels of CRP, SAA, and ESR decreased, and the interleukin (IL)-6 level increased (Figure 2). Thereafter, reduction in PSL was continued to a dose of 10 mg, and coronary angiography was performed. Stenosis of the ostia of the LMCA remained (Figure 3, Video 1), and good collateral flow was observed from the right coronary artery to the left circumflex artery (Video 2). TCZ was suspended for 5 weeks, and a minimally invasive coronary artery bypass graft (CABG) was performed. The left internal thoracic artery was connected to the left anterior descending artery. After surgery, there was a temporary increase in CRP, which was then normalized, but after 1 week or more post-operatively, a sharp increase was observed again (Figure 2). Because infections could be ruled out on the basis of chest CT and blood culture, TAK was thought to have recurred, and TCZ administration was restarted. After resumption of TCZ administration, left pleural effusion associated with delayed wound healing increased (Figure 4). It took up to 4 weeks after the operation for the effusion to resolve. She was discharged from the hospital on day 140, 23 days after surgery.

DISCUSSION

TAK is a type of chronic inflammatory vasculitis of unknown origin that affects large vessels (2,3). Although glucocorticoids (GCs) are the principal therapy for TAK, we reported the efficacy of TCZ for GC-refractory patients with TAK (4–6). The long-term outcomes of coronary artery revascularization for TAK have been reported. CABG is superior to percutaneous coronary intervention despite medical therapy in TAK patients with coronary artery involvement (7).

In patients receiving GCs, it is often difficult to suspend administration of these agents and perform surgical treatment because of the likelihood of TAK relapse. Other immunosuppressant agents are often discontinued for a certain period before surgical intervention. However, there is no clear standard regarding how and to what extent the GC dose should be reduced in combination with TCZ.

FIGURE 1 Cardiac Computed Tomography Angiography on Admission

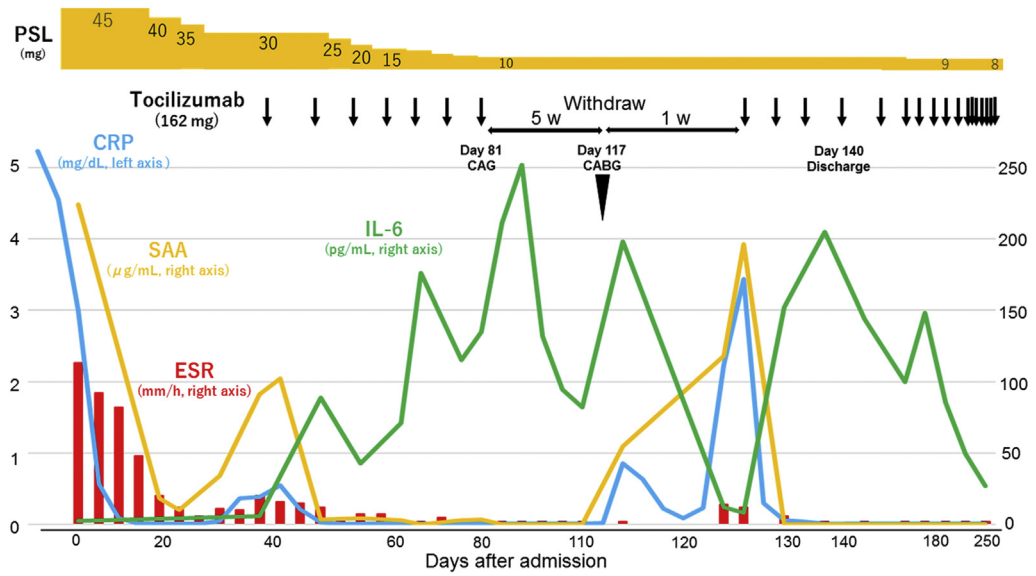


Severe stenosis is observed in the ostia of the left main coronary artery **(arrow).**

The GC dose should be as low as possible to prevent relapse of inflammation, considering the risk of post-operative infection. The rate of wound complications is 2- to 5-fold and is dose dependent in patients receiving long-term GC treatment (8). In our case, the dose of GCs could be reduced to 10 mg before surgery with the additional administration of TCZ. Moreover, several operative methods can be considered, such as conventional CABG or coronary ostial patch angioplasty (9). In our case, minimally invasive CABG was performed to reduce the extent of surgical wounds and risk of infection. As a result, post-operative infection did not occur in our patient.

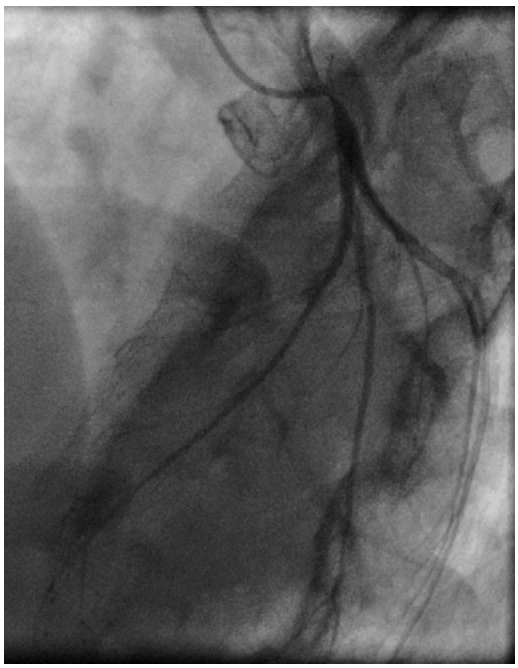
There are no guidelines or documents that clearly state the perioperative withdrawal period for patients undergoing TCZ administration with TAK. However, certain opinions have been reported for rheumatoid arthritis. According to the guidelines from the American College of Rheumatology, patients undergoing TCZ subcutaneous injection once a week for rheumatoid arthritis should have treatment withdrawn 2 weeks before surgery. TCZ can be resumed a minimum of 2 weeks after surgery in the absence of wound healing problems, surgical site infection, and systemic infection (10). In our case, because the preoperative withdrawal period was 5 weeks long, TCZ had to be resumed to treat TAK relapse before wound healing was complete. Therefore, wound healing was delayed by early resumption of TCZ. Given these results, our patient possibly could have had no wound

FIGURE 2 Treatment Progress Chart



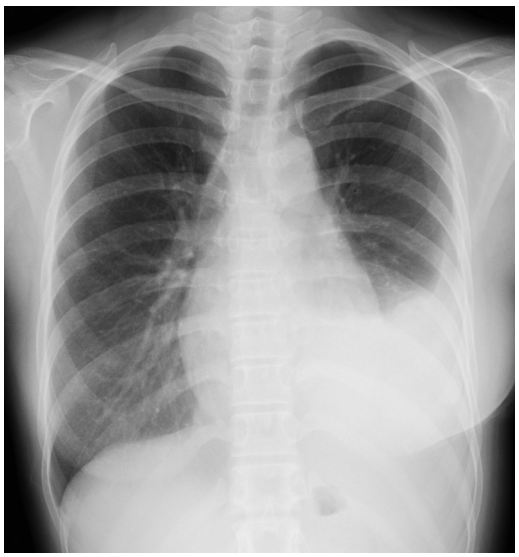
Tocilizumab was administered every week from admission day 39 because of relapse of Takayasu arteritis with prednisolone (PSL) treatment at a dose of 30 mg. Tocilizumab was suspended for 5 weeks before surgery. Tocilizumab was restarted 1 week after surgery because of Takayasu arteritis relapse. Please note that the number of days on the horizontal axis is not constant. CABG = coronary artery bypass graft; CAG = coronary angiography; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IL = interleukin; SAA = serum amyloid A protein.

FIGURE 3 Coronary Angiography Before Surgery



Coronary angiography demonstrates 99% stenosis of the ostia of the left main coronary artery before surgery (left anterior oblique cranial view).

FIGURE 4 Chest Radiograph 1 Week After Tocilizumab Readministration



The size of the left pleural effusion associated with delayed wound healing has increased.

healing delay if she had undergone a 2-week withdrawal period before CABG.

FOLLOW-UP

Coronary angiography was performed 5 months after minimally invasive CABG. The degree of stenosis of the LMCA remained unchanged, but the bypass graft was patent. The patient had no chest pain or heart failure. Serum IL-6 levels gradually decreased, and the dose of PSL could be reduced to 8 mg 10 months after starting TAK treatment (Figure 2).

CONCLUSIONS

TCZ is effective in patients with refractory TAK, even during the perioperative period for invasive surgery. The dose of GCs can be reduced by administering TCZ. Further research is warranted to understand optimal perioperative TCZ management to reduce the impact on wound healing.

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AUTHOR DISCLOSURES

Dr. Nakaoka has received grants and personal fees from Chugai as a consultant of the sponsor-initiated clinical trial using tocilizumab for Takayasu arteritis during the conduct of the study. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Isobe M, Amano K, Arimura Y, et al. JCS 2017 guideline on management of vasculitis syndrome-digest version. Circ J 2020;84:299–359.

2. Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. Ann Intern Med 1994;120:919–29.

3. Watanabe Y, Miyata T, Tanemoto K. Current clinical features of new patients with Takayasu arteritis observed from cross-country research in Japan: age and sex specificity. Circulation 2015; 132:1701–9.

4. Nakaoka Y, Higuchi K, Arita Y, et al. Tocilizumab for the treatment of patients with refractory Takayasu arteritis. Int Heart J 2013;54:405–11.

5. Nakaoka Y, Isobe M, Takei S, et al. Efficacy and safety of tocilizumab in patients with refractory

Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). Ann Rheum Dis 2018;77:348–54.

6. Nakaoka Y, Isobe M, Tanaka Y, et al. Long-term efficacy and safety of tocilizumab in refractory Takayasu arteritis: final results of the randomized controlled phase 3 TAKT study. Rheumatology (Oxford) 2020;59:2427–34.

7. Wang X, Dang A, Lv N, et al. Long-term outcomes of coronary artery bypass grafting versus percutaneous coronary intervention for Takayasu arteritis patients with coronary artery involvement. Semin Arthritis Rheum 2017;47:247–52.

8. Wang AS, Armstrong EJ, Armstrong AW. Corticosteroids and wound healing: clinical considerations in the perioperative period. Am J Surg 2013;206:410–7.

9. Oishi K, Arai H, Yoshida T, et al. Coronary ostial patch angioplasty with femoral artery in Takayasu arteritis. Ann Thorac Surg 2020;110:e427–30.

10. Goodman SM, Springer B, Guyatt G, et al. 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons guideline for the perioperative management of antirheumatic medication in patients with rheumatic diseases undergoing elective total hip or total knee arthroplasty. J Arthroplasty 2017;32:2628–38.

KEY WORDS disease activity, interleukin-6, perioperative management, Takayasu arteritis, tocilizumab

APPENDIX For supplemental videos, please see the online version of this article.