Effect of Immunosuppressive Therapy on Clinical Outcomes for Patients With Aortic Stenosis Following Transcatheter Aortic Valve Implantation

Toshiki Kaihara, MD, PhD; Masaki Izumo, MD, PhD; Haruka Kameshima, MD; Yukio Sato, MD, PhD; Shingo Kuwata, MD, PhD; Masashi Koga, MD; Mika Watanabe, MD; Kazuaki Okuyama, MD; Ryo Kamijima, MD, PhD; Yuki Ishibashi, MD, PhD; Yasuhiro Tanabe, MD, PhD; Takumi Higuma, MD, PhD; Tomoo Harada, MD, PhD; Yoshihiro J. Akashi, MD, PhD

Background: Transcatheter aortic valve implantation (TAVI) is an established treatment for symptomatic patients with severe aortic stenosis (AS). Sometimes patients with severe AS taking immunosuppressants are encountered. The effect of immunosuppressive therapy on clinical outcomes in patients with AS following TAVI were investigated.

Methods and Results: In total, 282 consecutive patients with severe AS who underwent transfemoral TAVI from January 2016 to December 2018 at St. Marianna University School of Medicine were reviewed. They were divided into 2 groups: the immunosuppressants group (IM group) in which patients continually used immunosuppressive drugs (n=22) and the non-immunosuppressants group (non-IM group) (n=260). The composite endpoints of a major adverse cardiovascular and cerebrovascular event (MACCE) defined as non-lethal myocardial infarction, unstable angina pectoris, heart failure requiring hospitalization, stroke, and cardiovascular death were evaluated. There were no differences in the incidence of vascular access complications (32% vs. 20%, P=0.143) and the rate of procedure success (100% vs. 93%, P=0.377) between the IM and non-IM groups. During the median follow-up period of 567 (16–1,312) days after the TAVI procedure, there were no significant differences between the IM and non-IM groups in the incidence of infectious complications (14% vs. 9%, P=0.442) or MACCE (18% vs. 20%, respectively; P=0.845).

Conclusions: The use of IM after TAVI is not associated with increased vascular access complications or mid-term MACCE in patients with severe AS treated with TAVI.

Key Words: Immunosuppressants; Transcatheter aortic valve implantation; Vascular access complications
Effect of Immunosuppressors on Patients After TAVI

Methods

Study Population and Study Design
This study included 297 consecutive patients with AS who underwent TAVI at St. Marianna University Hospital from January 2016 to December 2018. Fifteen patients who underwent TAVI via an alternative approach were excluded from the study. Finally, the cases of the included 282 patients with AS who underwent TAVI with the transfemoral approach were retrospectively analyzed (Figure 1).

Immunosuppressive therapy was defined as taking an oral immunosuppressant drug (including steroids) within 24 h before or after the TAVI procedure. This definition does not include topical steroid applications, one-time systemic therapy, and inhaled steroid therapy. In this study, 20 of the 282 patients (7%) used immunosuppressants. We divided them into 2 groups: the immunosuppressants group (IM group, n=20) and the non-immunosuppressants group (non-IM group, n=262).

TAVI Parameters and Procedure
The left ventricular ejection fraction (LVEF), aortic valve pressure gradient (AVPG), and aortic valve area (AVA) were assessed with transthoracic echocardiography (TTE). The LVEF was determined by the biplane modified Simpson’s method. The AVPG was measured by continuous-wave Doppler echocardiography using multiple acoustic windows to determine the highest velocity. The AVA was calculated using the continuity equation. All TTE parameters of the severe AS patients were determined according to the guidelines of the American Society of Echocardiography.6,7 Therefore, the diagnosis of AS was made based on findings obtained by using TTE. Before the TAVI procedure, we generally added on antiplatelet therapy (100 mg of aspirin or 75 mg of clopidogrel) or anticoagulant therapy (warfarin or direct oral anticoagulants) for all patients. Procedural anticoagulation was achieved by using heparinization. The target-activated clotting time is 250–300 s.

We used two TAVI systems: the Medtronic CoreValve™ or Evolut R™/PRO™ (Medtronic, Minneapolis, MN, USA) and the Edwards SAPIEN XT™ or SAPIEN 3™ (Edwards Lifesciences, Irvine, CA, USA). We performed transfemoral TAVI (TF-TAVI) procedures by surgical cut-down or the direct puncture method. We performed the direct puncture method with a Perclose ProGlide™ Suture-Mediated Closure System (Abbott Vascular Devices, Redwood City, CA, USA). The selection of the method used depended on the conferred decision made by the heart team at our institution. The TAVI procedure time was defined as the time from the puncture (or surgical skin incision) of the access route to the end of the pressure hemostasis after the removal of the femoral sheaths.

Definitions of Comorbidities
Hypertension was defined as office systolic blood pressure ≥140 mmHg, office diastolic blood pressure ≥90 mmHg, or

Table 1. Underlying Diseases of Patients in the IM Group

<table>
<thead>
<tr>
<th>Diseases</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>7</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>4</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td>3</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>2</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>2</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>2</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>10</td>
</tr>
</tbody>
</table>

IM, immunosuppressants.

Table 2. Details of IM Drugs Taken by Patients in the IM Group

<table>
<thead>
<tr>
<th>Drugs</th>
<th>n</th>
<th>Daily mean dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>16</td>
<td>6.3</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Non-steroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2</td>
<td>4†</td>
</tr>
<tr>
<td>Tacrolimus hydrate</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Combined therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Tacrolimus hydrate</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

†Weekly mean dosage. IM, immunosuppressants.
receiving medical treatment for hypertension before admission. Dyslipidemia was defined as total cholesterol ≥220mg/dL, low-density lipoprotein cholesterol ≥140mg/dL, high-density lipoprotein cholesterol <40mg/dL, triglyceride ≥150mg/dL, or receiving medical treatment for dyslipidemia before admission. Diabetes mellitus was defined as a fasting plasma glucose level ≥126mg/dL, a 2-h plasma glucose level after 75g glucose loading ≥200mg/dL, casual plasma glucose level ≥200mg/dL, hemoglobin A1C ≥6.5% (national glycol-hemoglobin standardization program value), or medical treatment for diabetes before admission. Arteriosclerosis obliterans was defined as decreased arterial perfusion in the lower extremities (below the iliac arteries) in a patient whose ankle-brachial index was <0.90.
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Outcomes
The primary outcomes were the major adverse cardiovascular and cerebrovascular events (MACCE) defined as non-lethal myocardial infarction, unstable angina pectoris, heart failure requiring hospitalization, stroke, or cardiovascular death. The secondary outcome was all-cause mortality. Endpoints and procedural complications were evaluated by the Valve Academic Research Consortium-2 (VARC-2) criteria. Vascular access complications were defined as the complications of the access route indicated by a medical examination which a TAVI sheath actually passed through (iliofemoral arteries and abdominal aorta).

Statistical Analyses
All statistical analyses were carried out by using SPSS/Windows, ver. 19.0 (SPSS, Chicago, IL, USA). Data are presented as the mean (±SD) or frequencies (percentages). We used the unpaired t-test, Mann-Whitney U-test, and the chi-squared test to examine differences between groups, and a Kaplan-Meier analysis to examine changes over time to the endpoints. The multivariate Cox regression analysis assessed whether treatment with immunosuppressants was independently associated with the study endpoints. A 2-tailed P value <0.05 was considered significant.

Results
The underlying diseases and details of the immunosuppressive drugs used in the IM group are described in Table 1 and Table 2. The total number of drugs used to treat rheumatoid arthritis is the highest in the IM group. Prednisolone accounted for 80% of the immunosuppressive drugs used.

The baseline characteristics of the patients are summarized in Table 3. The IM group tended to be younger than the non-IM group, but these differences were not significant. Although the prevalence of hypertension and dyslipidemia in the IM group was significantly lower than in the non-IM group, there was no significant difference in Society of Thoracic Surgeons (STS) score between the 2 groups. The prevalence of peripheral artery diseases below iliac arteries and the severity of AS did not differ significantly between the IM and non-IM groups.

Regarding the MDCT parameters, the aortic annulus area (369 [342–413] mm² vs. 394 [347–447] mm², P=0.289) and the minimum lumen diameter of the femoral access (6.1±1.3 mm vs. 6.1±1.1 mm, respectively; P=0.678) were not significantly different between the IM and non-IM groups. LVEF was preserved in both groups, but was significantly higher in the IM group than in the non-IM group. The rate of the direct puncture was not significantly different between the IM and non-IM groups (73% vs. 66%, P=0.507). The rate of the use of new-generation devices (SAPIEN 3™ or Evolut R™/PRO™) reached 92%.

The procedure success rate of TAVI based on the VARC-2 criteria, defined as correct positioning of the prosthetic heart valve with the absence of MACCE during hospitalization in the IM and non-IM groups, was 100% and 93%, respectively, without significant difference (P=0.377). During the median follow-up duration of 567 (16–1,312) days, 57 patients had a vascular access complication, 55 patients had a MACCE, and 26 patients had an infectious complication requiring hospitalization, the details of which are shown as Table 4.

Although the rate of all infectious complications requiring hospitalization tended to be greater in the IM group than the non-IM group, the difference was not significant (14% vs. 9%, P=0.442, Figure 2). The incidence of vascular access complications (32% vs. 20%, P=0.143, Figure 3) and that of MACCE (18% vs. 20%, P=0.845, respectively; Figure 4) did not differ between the IM and non-IM groups. All-cause mortality did not differ between the IM and non-IM groups, either (P=0.879).

We performed a multivariate Cox regression analysis and included the STS score, the indexed AVA, and the minimum lumen diameter of the access route as covariates affecting the outcomes. The results of the analysis showed that immunosuppressant treatment was not an independent predictor of all infectious complications requiring hospitalization (HR 2.73, 95% CI: 0.92–8.06, P=0.069), vascular access complications (HR 0.80, 95% CI: 0.10–6.20, P=0.834), MACCE (HR 0.72, 95% CI: 0.25–2.08, P=0.547), or all-cause mortality (HR 0.76, 95% CI: 0.21–2.68, P=0.664).
As a result, the relatively low rate of surgical cut-down may have contributed to the low rate of vascular access complications.

Second, we analyzed the cases of patients who used not only steroids but also immunosuppressants including methotrexate, tacrolimus hydrate, azathioprine in this study. Although both steroids and immunosuppressants can cause a compromised situation, their precise advantages and disadvantages remain to be established. A previous study about TAVI showed the data for immunosuppressants except steroids, but it just compared the prognosis between TAVI and surgical aortic valve replacement.16 There have been no previous studies that consider the vascular complications of TF-TAVI patients with comorbid disorders treated by using immunosuppressants other than steroids. This difference may have influenced our findings.

Third, the steroid regimens, dosages, and administration routes were not integrated in the past studies. We excluded inhaled steroids in this study, and the average steroid dose was 6.1 mg/day of prednisolone, which is not very high. It may have affected the results of this study.

Technological innovations for TAVI continue to advance. The latest generation of the balloon-expandable SAPIEN 3 UltraTM system is said to achieve a lower profile of a sheath.17 Our present findings indicate that the use of immunosuppressants (including steroids) may be relatively safe for patients with AS, as the TAVI procedure is non-invasive.

**Study Limitations**

This study has some limitations. It was a single-center study, and the sample size was relatively small (n=282); however, the unification of the TAVI procedure and a reliable follow up of the patients could help counteract these limits. In addition, this was a retrospective analysis, and there thus
may have been selection bias. Although we minimized the risk of selection bias by using multivariate analysis, there is a possibility of inconclusive results. Finally, we excluded the patients with severe AS who underwent TAVI by using an alternative study approach; however, their prognosis is also important and presents a future topic of discussion.

Conclusions

The use of immunosuppressants was not associated with increased vascular access complications or mid-term MACCE in patients with AS who underwent TAVI.

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None.

Disclosures

Y.J.A. is a member of the Circulation Journal Editorial Team.

IRB Information

This study was granted an exemption from obtaining ethics approval from the St. Marianna University School of Medicine Ethics Committee because this study was a retrospective observational study.

References


Supplementary Files

Please find supplementary file(s):