Title: Prospective Analysis of Immunosuppressive Therapy in Cardiac Sarcoidosis With Fluorodeoxyglucose Myocardial Accumulation - PRESTIGE Study

Key Points

- This is the first prospective, randomized trial for cardiac sarcoidosis who failed to respond to prednisolone
- The 6 months standard protocol of prednisolone significantly reduced FDG accumulation and was effective in >80% of cases when the cutoff was defined by a 70% reduction in CMA from the baseline value.
- In patients with residual abnormal FDG accumulation in the heart after the standard protocol of prednisolone, methotrexate as an alternative therapy is not superior to repeat-prednisolone administration.

Summary:

The estimated prevalence of cardiac sarcoidosis (CS) in Japan is 7-9 per 100,000, with an incidence rate of approximately 1 per 100,000 per year. In this study, among more than 500 patients including suspected CS, patients with active cardiac sarcoidosis (n=59) with abnormal FDG accumulation in the heart after ^{18}F-FDG-PET*1 imaging were enrolled and treated with prednisolone (PSL), and the efficacy of methotrexate (MTX) as an alternative for patients refractory to PSL was also evaluated. The extent of active inflammatory cardiac metabolic activity (CMA)*2 was calculated using analysis software (GI-PET), and defined responders (R- group) as patients with a CMA reduction rate >70% after immunosuppression therapy in this study; otherwise, they were considered poor responders (P-R group). At 12 months' follow-up, patients were considered as recurrent if FDG accumulation decreased but exceeded 30% of the initial CMA value. During the 3.3-year follow-up period, 7 patients had cardiac events (sudden death: SCD, n=1, sustained ventricular tachycardia: SVT, n=3, heart failure hospitalization: HF, n=3), and although there was no significant difference between the 2 groups when SCD, SVT, and HF were included as composite cardiac events (P = 0.319), the P-R group had more subsequent SCD and HF events than the R-group (log-rank, P=0.048). To evaluate the efficacy of MTX as a PSL-sparing alternative, a total of 11 patients in the P-R group (n=9) and the recurrent group (n=2) were randomly assigned to the MTX group (n=5) or the repeat-PSL administration group (n=6). Although CMA levels tended to

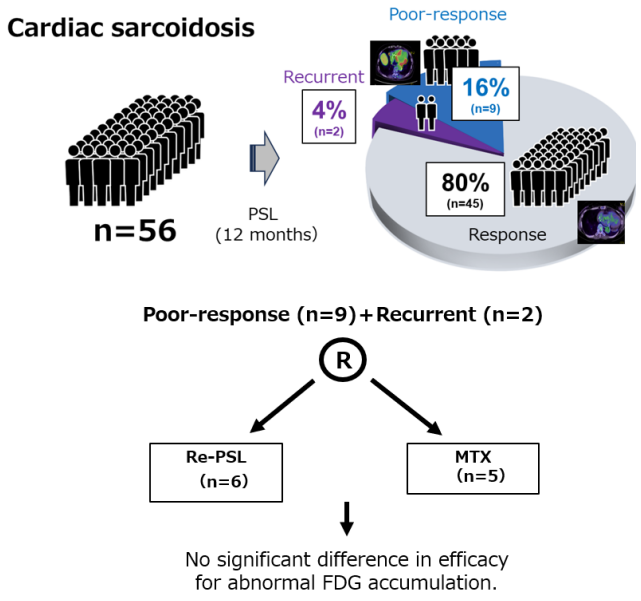
decrease in both groups, MTX had no advantage over repeat-PSL for patients refractory to initial PSL therapy. The results of this study were published online in the American scientific journal "JACC: Cardiovascular Imaging" on July 12, 2023.

1. Background

Sarcoidosis is a granulomatous disease of unknown cause that is regarded to cause damage to multiple organs, and especially cardiac complications have a significant impact on prognosis. For CS, bradycardia caused by intramyocardial conduction defects such as complete atrioventricular block and progressive loss of ventricular contractility, is recommended to be treated with PSL, but side effects such as abnormal glucose tolerance, hyperlipidemia, obesity and osteoporosis due to prolonged use of PSL lead a clinical problem. Furthermore, there are currently no established treatment guidelines for cases of inadequate response after PSL therapy. Although there have been case reports and a limited number of retrospective observational studies on the efficacy of MTX, there have been no prospective studies focusing on intervention methods and efficacy. In Japan, ^{18}F-FDG-PET has been covered by insurance since April 2012 as a method to evaluate the activity of sarcoidosis, and its effectiveness is clearly stated in the 2014 guidelines. In this study, we sought to evaluate the efficacy of PSL in patients with CS and active myocardial inflammation using ^{18}F-FDG-PET. In addition, because MTX is frequently used as a PSL-sparing alternative, we investigated the efficacy of MTX in patients refractory to PSL therapy.

2. RESULTS:

The mean age of the 59 CS patients was 63 years; 44 (75%) were female. After 6 months of initial PSL treatment, CMA was markedly reduced (203.3 ⇒ 1.0, p<0.001), as ACE and sIL-2R levels (ACE: 13.7 ⇒ 10.4 U/L, p=0.001, sIL-2R: 513 ⇒ 312 .5 U/mL, p<0.001), no significant changes were observed in BNP and TnT levels (BNP: 58.4 ⇒ 58.1 pg/mL, p=0.688, TnT 0.012 ⇒ 0.010



ng/mL, p=0.365). Of the 56 patients, 47 patients (84%) were classified into the R- group and 9 patients (16%) into the P-R group, and of the 47 patients in the R- group, 2 patients had an increase in CMA range after 6 months of PSL (5 mg/day) treatment. A total of 11 patients (9 in the P-R group and 2 in the recurrent group) were randomly assigned to the MTX group (n=5) or the PSL re-administration group (n=6) for an additional 6 months of intervention, and MTX had no advantage over re-PSL for patients refractory to initial PSL therapy.

3. Future Perspective

The current study found high efficacy of PSL and reconfirmed that it is a first-line drug of choice in the treatment of CS with active inflammation in the heart. Because the value was favorably correlated to and could predict future clinical events, CMA (SUV × accumulation area) is recommended to be used for evaluating cardiac inflammation in patients with sarcoidosis. MTX is expected to be a complementary and alternative drug to PSL; however, the current study could not show the superiority of MTX with low-dose PLS compared with high-dose PSL alone in patients refractory to initial PSL therapy. This study was a single-center, enrolled only Japanese (Asian) patients. Future multicenter studies involving a larger number of cases are needed to further evaluate the efficacy of MTX.

Terminology:

∗1 ^{18}F-FDG-PET-

^{18}F-FDG is a glucose tracer for PET examinations, and FDG accumulation is thought to reflect inflammatory cell infiltration, such as activated macrophages, in the lesion. Abnormal accumulation in the heart on ^{18}F-FDG-PET has been identified as one of the major criteria in the diagnosis of cardiac sarcoidosis, and is considered an important imaging modality.

∗2 Cardiac metabolic activity: CMA-

Cardiac metabolic activity defined as the multiplication of SUV by accumulation area, was automatically calculated by using semi-quantitative metrics. FDG accumulation in the liver was used as an internal control, and a spherical volume of interest, 3 cm in diameter, was set in the liver. When the SUV within the myocardium was higher than the mean SUV + 1.5 SD of the volume of interest in the liver, the regions were considered as positive for active sarcoidosis, whereas

those regions lower than the value were considered as negative.

Publication:
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JACC: Cardiovascular Imaging (electronic version dated on July 12)

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DOI: 10.1016/j.jcmg.2023.05.017

Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/JAC_230914.pdf