PROTOCOL for the Study for prevention of autoimmune non-insulin-dependent diabetes mellitus with sitagliptin (SPAN-S)

1 STUDY BACKGROUND

Slowly progressive insulin-dependent diabetes mellitus (SPIDDM) or LADA is characterized by non-insulin state at onset and later progress to insulin-dependency and positive for islet specific autoantibodies: GAD autoantibodies. We have conducted intervention study for slowly progressive beta cell failure using insulin instead of sulfonylureas (SU) (Tokyo Study) (Maruyama T, Tanaka S et al., J Clin Endocrinol Metab 2008, 93: 2115-21). We have reported preferable beta cell preservative effect of insulin therapy rather than SU in SPIDDM. However, complete prevention could not be attained in the Tokyo study. In order to clarify the possible intervention effect of sitagliptin, DPP-4 inhibitor and potentially have immunomodulatory effect, multiple randomized clinical trial, SPAN-S study is planned.

2 SCIENTIFIC RATIONALE AND RESEARCH AIMS

2-1 Rationale

Sitagliptin has immunomodulatory effect including chemokine/cytokine suppression through Treg stimulation and beta cell growing effect through activation of regenerating mechanisms in rodent models.

2-2 Research aims

The aim of SPAN-S trial is to establish the safety and usefulness for preventing progressive beta cell failure using sitagliptin in SPIDDM.

4 SUBJECTS RECRUITMENT

4-1 Inclusion criteria

(1) HbA1c: 6.9-8.4%

(2) GAD Ab positive

(3) fasting serum C-peptide: 1.0ng/ml or higher

(4) age: 20-79 years

(5) medication for diabetes: none or biguanide (metformin) only for at least 2 month

(6) no history of insulin or GLP-1 receptor antagonist treatment

Deviation: Duration (6 months to 5 years) was excluded because the onset of SPIDDM is gradual and the real duration is considered to be longer than clinically defined duration by several years.

4-2 Exclusion criteria

(1) women who were pregnant or planning on becoming pregnant

(2) renal dysfunction with serum creatinine ≥ 1.5 mg/dl for males and ≥ 1.3 mg/dl for females, or

creatinine clearance ≤ 50 ml/min

(3) patients who were deemed inappropriate to participate by their attending physician due to associated disease, complications or any other reasons

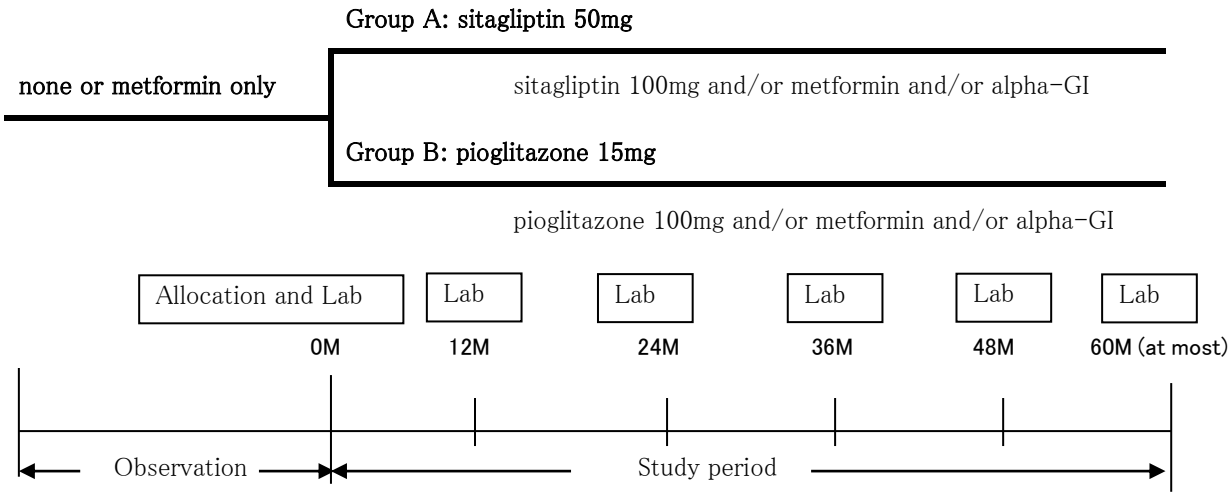
4-3 Randomisation

After obtaining written consent, each patient is randomized based on minimization adjusting for age, sex, HbA1c level, GAD Ab titer and metformin use before entry using a central web response system.

5 STUDY DESIGN

This study is a multicentre, open-label, prospective, randomised, controlled trial of intervention for progressive beta cell failure using sitagliptin and pioglitazone. Patients were scheduled for visits at 2-month intervals for up to 80 months (at least 12 months) of follow-up.

6 STUDY OUTLINE



6-1 Intervention group (sitagliptin group)

Sitagliptin is started at 50 mg once per day with the previous diabetes treatment. If glycemic control is not achieved during each visit, the regimens were intensified by either (1) increasing the dosage of sitagliptin to 100 mg, and/or (2) adding metformin (or increasing the dosage) at 250–2250 mg and/or an alpha-glucosidase inhibitor (acarbose, voglibose or miglitol). Target HbA1c is below 7.0%.

6-2 Control group (pioglitazone group)

Pioglitazone is started at 15 mg once per day with the previous diabetes treatment. If glycemic control is not achieved during each visit, the regimens were intensified by either (1) increasing the dosage of

pioglitazone to 30 mg, and/or (2) adding metformin (or increasing the dosage) at 250–2250 mg and/or an alpha-glucosidase inhibitor (acarbose, voglibose or miglitol). Target HbA1c is below 7.0%.

6-3 Concomitant medication

Any hypoglycemic agent other than described above is prohibited to be used during the study period. The patients in both groups are switched to an insulin injection regimen when HbA1c levels became ≥9.4% despite the above protocol of medication.

7 OUTCOMES

7-1 Primary outcome

HbA1c values, the proportion of patients whose HbA1c values increased to ≥ 9.4%, and the period from enrollment in which their HbA1c values increased to ≥ 9.4%

7-2 Secondary outcomes

(1) Glucose and C-peptide values in annual 75g oral glucose tolerance test (OGTT)
(2) Body weight
(3) Blood pressure
(4) Islet autoantibodies (GADAb, IA-2Ab, IAA, ZnT8Ab)
(5) Fasting glucose values

7-3 Safety assessments

Any adverse events in relation to the medications used in this study were evaluated and treated properly by physicians. Hypoglycemia was defined as a blood glucose level < 70 mg/dl (3.9 mmol/l), irrespective of hypoglycemic symptoms.

8 DISCONTINUATION CRITERIA

(1) Serious violation of the protocol
(2) Withdrawal of the consent
(3) The attending physician judges to stop the intervention due to adverse event
(4) Death of the participant
(5) Lost to follow-up
(6) Anytime the attending physician judges to stop the intervention

9 SAMPLE CALCULATION

A total 40 participants will be sufficient because the inclusion criterion that fasting serum C-peptide of 1.0 ng/ml or higher at registration is more stringent than the previous intervention trial (Maruyam T, Tanaka S et al., JCEM 2008, 93: 2115-21), in which preserved serum C-peptide levels showed more

evident deleterious progression of beta cell function. Taking into consideration of dropout, N = 40 in each group was initially planned.

10 FOLLOW-UP

2010/9-2020/12 (enrollment -2015/12)

Deviation: Follow-up period was shortened to 2017/2 because the principal investigator (TA) moved from Saitama Medical University to International University of Health and Welfare Hospital on 2015/4.