A randomised placebo-controlled study to investigate GNbAC1 an anti-HERV-W-Env monoclonal antibody in patients with recent onset of type 1 diabetes: rationale and design

Running Title: Rationale and Design of GNbAC1 Study in Type 1 Diabetes

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ABSTRACT (251 words)

Aims

Human endogenous retroviruses (HERVs) elements, remnants of ancestral viral genomic insertions, are emerging targets in several autoimmune diseases. In type 1 diabetes (T1D) patients, the envelope protein of HERV-W (HERV-W-Env) is detected in 70% of sera and is found expressed by acinar cells in 75% of T1D pancreata. HERV-W-Env pathogenic properties include inhibition of insulin secretion by pancreatic beta cells, and hyperglycemia associated with decreased levels of insulin in a transgenic mouse model, suggesting the involvement of HERV-W-Env in T1D pathogenesis. GNbAC1, a humanised monoclonal antibody targeting specifically HERV-W-Env is tested for the first time in T1D patients.

Method/Design

This trial is a randomised placebo controlled 2-arm study with the objective of showing the safety and pharmacodynamics response of GNbAC1 in T1D patients. Sixty T1D patients are planned to be included. GNbAC1 will be tested versus placebo at the dose of 6 mg/kg administered intravenously; 6 drug administrations will be performed at 4-week intervals. The primary endpoint will record adverse events, physical examination and vital signs as well as clinical laboratory data. Secondary endpoints will be: glycated haemoglobin blood levels; C-peptide levels up to 2 hours after mixed meal tolerance test; fasting and postprandial blood glucose; change from baseline in percentage of subjects not requiring insulin; daily use of insulin. T1D and autoimmune related antibodies will be assessed.

Conclusions

This first safety and pharmacodynamics study of the monoclonal antibody GNbAC1 in T1D patients, if positive, may open the door for the development of an innovative non-immunomodulatory disease modifying drug for T1D.

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INTRODUCTION

Despite three decades of intense clinical research and development, there are currently no registered disease-modifying treatments for type 1 diabetes (T1D) [1]. These development efforts have mainly focused on immunosuppressors and immunomodulators with the objective of preserving the pancreatic β cells from complete destruction. Different immunomodulatory approaches have been tested in clinical development: blocking tumour necrosis factor alpha (TNF-α) by etanercept or blocking Interleukin-1 (IL-1) by canakinumab, inactivating IL-1β with gevokizumab, inhibiting B lymphocyte function with rituximab, blocking T-cells with abatacept or alefacept, modulating T-cell by anti-CD3 antibodies such as teplizumab or otelixisumab or enhancing Treg by low dose of Interleukin-2 (IL-2). However, encouraging results with these treatments in early clinical development were either not confirmed in late phase trials or significant safety issues related to immunomodulation were reported and therefore none of these treatments has yet reached the registration stage for T1D [2].

We describe here the design and rationale for the first clinical trial of an innovative therapeutic approach for T1D based on the identification of a new pathologic target, which may lead to a non-immunomodulatory disease modifying therapy. This new approach aims at neutralizing a protein called HERV-W-Env which is encoded by genes of endogenous retroviral origin [3]. Human endogenous retroviruses (HERV) are mobile genetic elements that have been incorporated into primate germline DNA, during the evolution and are currently accounting for approximately 8% of the total human genome [4]. Among tens of HERVs families described, some have been associated with autoimmune diseases such as Systemic Lupus Erythematous, Rheumatoid Arthritis, Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis and Sjögren's syndrome [5]. In particular, the HERV-W family has been involved in the pathogenesis of MS through its envelope protein HERV-W-Env, also known as MSRV-Env [6-8].

Emerging biomarker data associate HERV-W-Env with the pathophysiology of T1D. Indeed, HERV-W-Env was detected in human T1D patients by three different methods, and in three different types of human samples. Firstly, in an antigenaemia study, it was shown that 70% of T1D patients (21/30) were positive for HERV-W-Env by ELISA technique in serum; in comparison, 12% of non-T1D controls (11/93) displayed positivity. Secondly, HERV-W-Env RNA was detected in peripheral blood mononuclear cells (PBMC) of 57% of T1D patients

(13/23) while only 12% of controls were positive (3/26). Lastly, immunohistochemical analyses were performed on human pancreas biopsies and showed that HERV-W-Env protein was highly expressed in the pancreas of 75% of T1D patients (15/20), whereas 16% of controls were positive (3/19). Interestingly, HERV-W-Env expression is observed in T1D patients with short to long disease duration [9].

An extensive immuno-histological analysis of human T1D pancreata further revealed that HERV-W-Env is expressed by acinar cells surrounding Langerhans islets [9] and that this expression correlates with the presence of macrophage infiltrates within the exocrine pancreas. This observation was corroborated by an HERV-W-Env transgenic mouse model. Indeed, mice expressing HERV-W-Env displayed immune cells infiltrates in their exocrine pancreas, a feature associated with hyperglycemia and decreased levels of insulin [9].

HERV-W-Env pathogenic properties appeared to be mediated by the interaction with toll-like receptor 4 (TLR4), a receptor involved in the initiation of innate immune response against microbial infection [10-11]. HERV-W-Env induces immunopathogenic effects and was shown to promote monocyte maturation, dendritic cell differentiation and release of pro-inflammatory cytokines, such as TNFα, IL1β, IL12β and IL6 [10-12]. Apart from affecting the immune system, HERV-W-Env also exerts deleterious effects on non-immune cells expressing TLR4 receptor, in particular on pancreatic β cells, which are known to express TLR4 receptor [13-15]. Indeed, it has been demonstrated that HERV-W-Env directly inhibits insulin secretion in a dose-dependent manner in primary human Langerhans islets and in rat INS1E insulinoma cell line. This inhibition reached 50% at 100ng/mL of HERV-W-Env in human beta cells. This *in vitro* finding is relevant with immunohistological observations of human pancreas showing that HERV-W-Env is expressed by acinar cells [9].

The humanised, IgG4 monoclonal antibody, GNbAC1, specifically targets and binds to HERV-W-Env [16]. The mode of action of GNbAC1 is upstream of the pro-inflammatory cascade, representing a potential new and well tolerated therapeutic solution for the pathogenic process, which does not directly target molecular or cellular components of the immune system. *In vitro*, GNbAC1 is able to maintain insulin secretion by human pancreatic β cells despite high levels of HERV-W-Env [9]. In addition, the release of pro-inflammatory cytokines IL-6 and TNF-α induced by HERV-W-Env in C57BL/6 mice is inhibited by the administration

GNbAC1 [12], an important feature knowing the role of these cytokines in T1D pathogenesis [17].

In clinical development, GNbAC1 has been tested so far in more than 300 healthy subjects or patients suffering from MS with a favourable safety profile [18]. GNbAC1 was assessed for the first time in Humans in a Phase I trial in 33 healthy subjects up to a dose of 6mg/kg. The safety of GNbAC1 was good and a dose-linear pharmacokinetics was observed [19]. These findings were confirmed in another Phase I study where single doses of GNbAC1 up to 36 mg/kg were tested without any safety signals and with a confirmation of the pharmacokinetic data observed at lower dose [20]. GNbAC1 was also tested in 10 MS patients in a placebo-controlled single ascending dose Phase IIa study with an open-label one year extension at 2 and 6 mg/kg every 4 weeks. The safety of GNbAC1 appeared favorable in MS patients where only a few adverse drug reactions could be attributed to treatment [21-22]. The PK was confirmed to be dose-linear in patients with an accumulation factor of about two fold [22]. The pharmacodynamic markers related to MSRV declined during treatment [21] and TLR4 hyper-activity in peripheral monocytes was observed to be renormalised during the course of the study [23]. GNbAC1 is currently tested in a large Phase IIb study in more than 260 patients with MS up to a dose of 18 mg/kg every 4 weeks [24]. All these elements converge to support GNbAC1, as a safe HERV-W-Env antagonist treatment. We postulate that GNbAC1 by its neutralising action on HERV-W-Env with a potential pathogenic role in T1D, may preserve the insulin function and possibly stop the auto-immune process in early diabetic patients.

Here we report the study design of the first multicentre, double-blind, randomised, placebo-controlled phase IIa study testing GNbAC1 in patients with T1D. This study will test first the safety of repeated doses of 6 mg/kg of GNbAC1 in patients receiving their usual dose of insulin and, second, assess whether the insulin function and the autoimmune process may be positively modified.

Study objectives

The primary objective of the study is to assess the safety and tolerability of 6 consecutive 4-weekly doses of GNbAC1 in patients with recent onset of T1D. The secondary objective is to determine the

pharmacodynamic response to GNbAC1 on biomarkers of T1D, in particular biomarkers assessing the insulin function and biomarkers related to auto-immune processes.

Study design

This will be a multicentre, double-blind, randomised, parallel-group phase-IIa study in 60 T1D patients receiving GNbAC1 or placebo via 6 consecutive 4-weekly 1-hour i.v. infusion during 24 weeks. The patients will be randomised by an interactive response system (IRS) at a ratio 2:1 to 2 treatment groups: GNbAC1 6 mg/kg (40 patients) or placebo (20 patients) as an add-on treatment to their usual insulin treatment. The overall design of the study is shown in Figure 1.
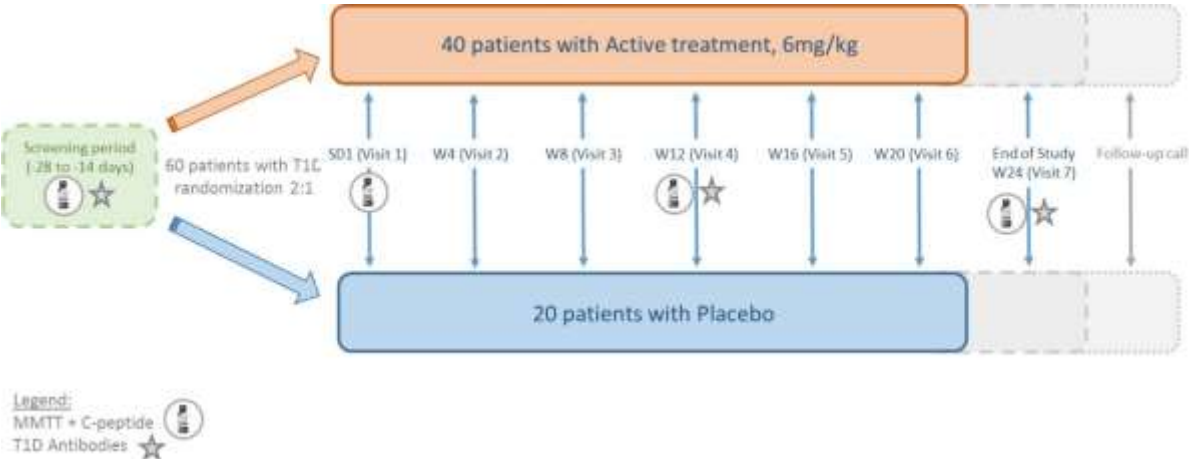

Figure 1. Design of the study with the timing of the main assessments

Setting

The study is planned to take place in 13 hospitals or diabetes centres in Australia.

Study population

The patient population will satisfy the following criteria: Male or female (if female: without childbearing potential or with a negative pregnancy test (serum or urine) and willing to use highly effective contraceptive methods throughout the study duration and until at least 5 months after the last study treatment) with a definite diagnosis of T1D diagnosed a maximum of 4 years prior to the signed informed consent, with a peak stimulated C-peptide of ≥0.2 nmol/L during a mixed meal tolerance test (MMTT) performed during the screening period, between 18 to 45 years of age (both inclusive), positive for at least one diabetes-associated auto-antibody (Anti-glutamic acid decarboxylase-65 (anti-GAD-65) antibody, anti-islet cell antibody, anti-insulin antibody, anti-zinc transporter 8 (ZnT8) antibody). Patients will be excluded if they have type 2 diabetes, abnormal liver function tests, positive serology for HIV and/or active viral hepatitis B or C, moderate to severe renal impairment, current or past (within the last 2 years) alcohol or drug abuse, history or presence of serious or acute heart disease, if they are using the following medications (β-cell stimulants, glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase-IV (DPP-IV) inhibitors, insulin sensitisers such as metformin, thiazolidinedione, immunosuppressive or immunomodulatory drugs without a sufficient washout period before starting the study.

Investigational Medicinal Product and Placebo

GNbAC1 is a recombinant humanised monoclonal antibody of the IgG4/kappa class targeting HERV-W-Env for i.v. administration [18]. The dose of 6 mg/kg GNbAC1 was established based on the early experience in MS where the 6 mg/kg dose was safe and associated with pharmacodynamic responses [21]. The placebo is the vehicle of GNbAC1.

Procedures

Adverse events will be reported by the patients or investigators at each visit. Vital signs and clinical safety laboratory including haematology blood chemistry, renal and liver functions and urinalysis will be performed at each visit. Cardiac safety will be assessed with 12-lead ECG at screening and at Day 169. Waist circumference will be measured at Days 0, 85 and 169. Total daily insulin use will be recorded during three days per week during the first week following the first drug administration and during the week preceding each following drug administration up to last visit using an e-diary. Hypoglycaemic episodes will be recorded throughout the study from Day 1 until the end of the study, and between visits, using an e-diary.

Concerning the pharmacodynamics assessments, the C-peptide will be measured at Screening, Days 1, 85 and 169, measurements will be taken at 0, 30, 60, 90 and 120 minutes after the MMTT. The auto-antibodies anti-GAD-65, anti-islet cell, anti-insulin, anti-ZnT8 and anti-IA-2 will be measured at screening, Days 85 and 169. HbA1c will be measured at all visits. Fasting blood glucose will be measured at all visits, except Screening. Postprandial blood glucose, triglycerides, adiponectin will be measured at Days 1, 85 and 169.

Human anti-GNbAC1 antibodies, anti-thyroglobulin and anti-TPO antibodies, anti-transglutaminase antibodies, anti-21-hydroxylase antibodies, total IgA as well as MSRV biomarkers will be measured at Days 1, 85 and 169.

Endpoints

The primary endpoints are related to safety: Serious Adverse Events (SAE), Adverse Events (AE), physical examination, vital signs and clinical laboratory values.

The secondary endpoints are pharmacodynamics endpoints 1) related to diabetes: glycated haemoglobin (HbA1c) blood levels; C-peptide levels as assessed by Area Under the concentration

Curve from 0 to 2hours (AUC_{0-2h}), maximum concentration (C_{max}) and concentration at 90 minutes (C_{90min}); fasting and postprandial (2 hours post-meal) blood glucose; change from baseline in percentage of subjects not requiring insulin; daily use of insulin (total units); Anti-glutamic acid decarboxylase-65 (anti-GAD-65) antibody, anti-islet cell antibody, anti-insulin antibody, anti-zinc transporter 8 (ZnT8) antibody; 2) related to other auto-immune or anti-drug processes: anti-tyrosine phosphatase-related antigen 2 (IA-2) antibody; anti-GNbAC1 antibodies.

The following exploratory endpoints will be assessed: MSRV biomarker (mRNA); triglycerides and adiponectin; anti-thyroglobulin, anti-thyroperoxidase (TPO) antibodies, anti-transglutaminase antibodies, total Immunoglobulin A (IgA) and anti-21-hydroxylase antibodies to assess an impact on auto-immune thyroid and coeliac disease which are known to be associated with type 1 diabetes [25-26].

Statistical analysis

The tolerability/safety and pharmacodynamics data will be evaluated descriptively. Exploratory analyses will be performed on pharmacodynamic endpoints to assess differences between treatment groups. Subgroups defined by baseline HERV-Env-W blood levels will be used to perform exploratory stratified analyses on the pharmacodynamics and safety endpoints to identify whether blood HERV-W-Env biomarkers may be predictive of responses with the objective of developing a potential companion diagnostic test [16].

Sample size calculation

The total sample size (N=60) is not based on a formal statistical assessment. This number of subjects is considered sufficient to achieve the primary safety objectives of the study.

Ethics Approval

The study has been approved by the central Human Research Ethics committee of St Vincent's Hospital, Melbourne, Victoria, Australia.

CONCLUSIONS

GNbAC1 is a new monoclonal antibody with an innovative mode of action in T1D: by targeting the HERV-W-Env protein expressed on acinar cells in the pancreas and on circulating lymphocytes and monocytes, it is expected that GNbAC1 could inhibit the inflammatory and toxic actions of HERV-W-Env in the T1D pathophysiology, and thereby open the door to an efficacious and truly disease-modifying treatment of T1D.

This Phase IIa study will be performed in T1D patients who have some preserved insulin function as assessed by C-peptide levels after MMTT. Although the primary objective is a safety objective, the pharmacodynamic responses in these patients will be of major significance. It is expected that any inhibitory effect of GNbAC1 on the pro-inflammatory and β-cell toxic effect induced by HERV-W-Env should be rapid, within weeks, and therefore it is expected that signs of a pharmacodynamic response will be observed already within a period of 6 months as it was observed with MSRV biomarker response in MS patients [21,23].

The usual regimen of insulin of the patients will be pursued during the trial. As GNbAC1 is a monoclonal antibody it is not expected to show any pharmacokinetic or pharmacodynamic interactions with the insulin treatment [27], however insulin consumption as well as blood glucose will be monitored during the trial.

This study once completed will provide the first results on an innovative approach for the treatment of T1D. If any evidence for improving the insulin function and/or reducing the auto-immune processes

is obtained during the trial, this will open the door to the development of the first non-immunomodulatory disease modifying drug for T1D.

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