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Original Article

Trastuzumab Induces an Immediate, Transient Volume Increase in Humans: A Randomised Placebo-Controlled Trial

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ABSTRACT

Background: The exact extent of and the mechanism by which trastuzumab causes cardiac side effects are not completely unravelled. We investigated the (cardiotoxic) side effects of trastuzumab in a relatively large homogeneous population.

Methods: Healthy male volunteers ($n = 54$) with a left ventricle ejection fraction (LVEF) >55% were administered 6 mg/kg trastuzumab ($n = 46$) IV in 90 min in a placebo-controlled, parallel study. Placebo consisted of 0 · 9% NaCl ($n = 8$). Assessments included body weight, routine and cardiac laboratory markers and serial echocardiographic examinations (8 placebo and 9 trastuzumab treated participants) up to 63 days after dosing. Statistical analysis was done using repeated measurements of variance.

Findings: Following trastuzumab infusion, fluid retention was observed: mean body weight increased over the first 4 days post-administration with 0 · 4 kg (95%-confidence interval: −0 · 2, 0 · 9, $p = 0 · 2261$) compared to placebo, mean haemoglobin concentration decreased with 0 · 3 mM (−0 · 6, −0 · 1; $p = 0 · 0043$), as did haematocrit (−0 · 013 L/L [−0 · 024, −0 · 002], $p = 0 · 0216$), and protein (−2 g/L [−4, −0], $p = 0 · 0443$) and albumin (−2 g/L [−3, −1], $p < 0 · 0001$) concentrations. Elevations in NT-proBNP levels, parallel to the weight increase, were observed in individual cases, but not on a group level. Troponin-T concentrations did not increase.
The only echocardiographic parameter that changed significantly at all studied dose levels was E/A-ratio, a load-dependent parameter: from 1 · 81 (SD 0 · 42) to 1 · 98 (0 · 31) 3–5 days after administration, contrast to placebo of 0 · 57 (90%-CI: 0 · 21–0 · 93, $p = 0 · 0034$). Ejection fraction and pulsed-wave Doppler recorded parameters remained unchanged.

Interpretation: Single dose administration of trastuzumab in humans is associated with an immediate, transient extracellular volume increase, either as a primary or secondary (compensatory) response, which can be detected easily using routine clinical assessments. Echocardiographic changes, both short and long term, could not be found after single dose administration to drug-naive patients.

1. Introduction

Trastuzumab (Herceptin®) is widely and successfully used in the treatment of patients with solid tumours overexpressing the human epidermal growth factor receptor-2 (HER2, also known as ErbB2) most notably with mamma carcinoma or metastatic gastric cancer. Notwithstanding its widespread use in oncology, trastuzumab is feared for its association with cardiotoxic side effects, occurring in 1–7% of treated patients, depending on the concomitant and previous chemotherapeutic regimens (Garcia-Alvarez et al., 2010; Seidman et al., 2002).

The exact mechanism by which trastuzumab causes cardiac side effects is not completely unravelled. Existing evidence suggests that interaction with the HER2-signalling pathway by trastuzumab in cardiomyocytes, induces apoptosis, and interferes with cell survival mechanisms (Fuller et al., 2008; Gordon et al., 2009; Riccio et al., 2009). Compatible with these in vitro findings, electron microscopy evaluation of endocardial biopsies from patients who developed trastuzumab-associated cardiomyopathy showed ultrastructural changes in the mitochondria (Guarneri et al., 2006). It is, however, unknown how these findings translate into clinical practice. The main reason for this uncertainty is that trastuzumab is often administered in an adjuvant setting, in combination with or after previous use of radiation therapy or cytostatics with untoward cardiac effects, such as anthracyclines. Furthermore, trastuzumab is used in a heterogeneous population regarding gender, age, and co-morbidities. Seemingly, therefore, exploring trastuzumab in a homogenous population of healthy subjects could be of value to further delineate its cardiac effects and its time.

We recently performed a bio-equivalence trial in which the currently approved formulation of trastuzumab (Herceptin®) was compared with a trastuzumab drug product under development, code-named

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FTMB (Wisman et al., 2014). Aside from establishing bio-equivalence, serial assessments of echocardiographic measurements, body weight and laboratory parameters such as the N-terminal pro-peptide of B-type natriuretic peptide (NT-proBNP) were included in the trial design, both to safeguard the participant's well-being and to investigate the (cardiotoxic) side effects of trastuzumab. The aim of the analysis presented in this article was to compare the registered form of trastuzumab (Herceptin®) with placebo in healthy volunteers, in terms of the assessments of cardiac function, and thus to cardiotoxicity.

2. Methods

2.1. Study Design and Population

The trial was a single-centre study of parallel design that consisted of a placebo-controlled double-blind dose escalation scheme (Fig. 1, groups 1–4), and an open-label single-dose bio-equivalence part (Fig. 1, group 5) (Wisman et al., 2014). In total, 118 male volunteers, aged 18–45 years inclusive, who were deemed healthy after a full medical screening, were enrolled sequentially in one of five groups. All had a left ventricle ejection fraction (LVEF) >55%, measured with echocardiography. The study was approved by an accredited local (BEBO, Assen, The Netherlands) and national independent medical ethics committee (CCMO, The Hague, The Netherlands), and registered under NL37452·056·11/EudraCT 2011-002972-17. Each participant provided written informed consent.

Participants randomly received either placebo (250 mL 0 · 9% NaCl) or trastuzumab in 250 mL 0 · 9% NaCl, administered intravenously in 90 min. Two trastuzumab drug products were investigated: the registered form (Herceptin®) at a dose of 6 mg/kg ($n = 46$), and a biosimilar form, codenamed FTMB, in escalating doses of 0 · 5–6 mg/kg ($n = 64$). For the purpose of assessing the cardiac effects of trastuzumab, only participants who received the registered form of trastuzumab (Herceptin®, hereafter referred to as "trastuzumab") or placebo were analysed.

2.2. Randomisation and Masking

All participants were assigned a unique number. Study medication was dispensed by a pharmacist according to a pre-established computer generated sequence, prepared using SAS® (v9·1·3, SAS Institute Inc., Cary, NC, USA) by a statistician, both of whom were not involved in the clinical conduct of the study. Concealment of treatment allocation was thus implemented. Placebo and trastuzumab treatment looked alike.

2.3. Laboratory Assessments and Body Weight

At baseline and at 1, 2, 4, 8 and 63 ± 7 days post-treatment, body weight was determined on a calibrated scale and samples for routine clinical chemistry and haematology were collected. An additional sample for troponin-T and NT-proBNP only was taken at 8 h post-dose. Samples were analysed by the clinical laboratories of the Leiden University Medical Center (LUMC). The measured laboratory parameters included electrolytes, liver panel, urea, creatinine, albumin, total protein, lipid spectrum, complete blood count and leukocyte differential, troponin-T, and NT-proBNP (N-terminal pro-peptide of B-type natriuretic peptide).

Measurement of body weight in the follow-up period and laboratory assessments at 8 h and at 1, 2, and 8 days post-administration were incorporated in the clinical trial protocol with an amendment after the

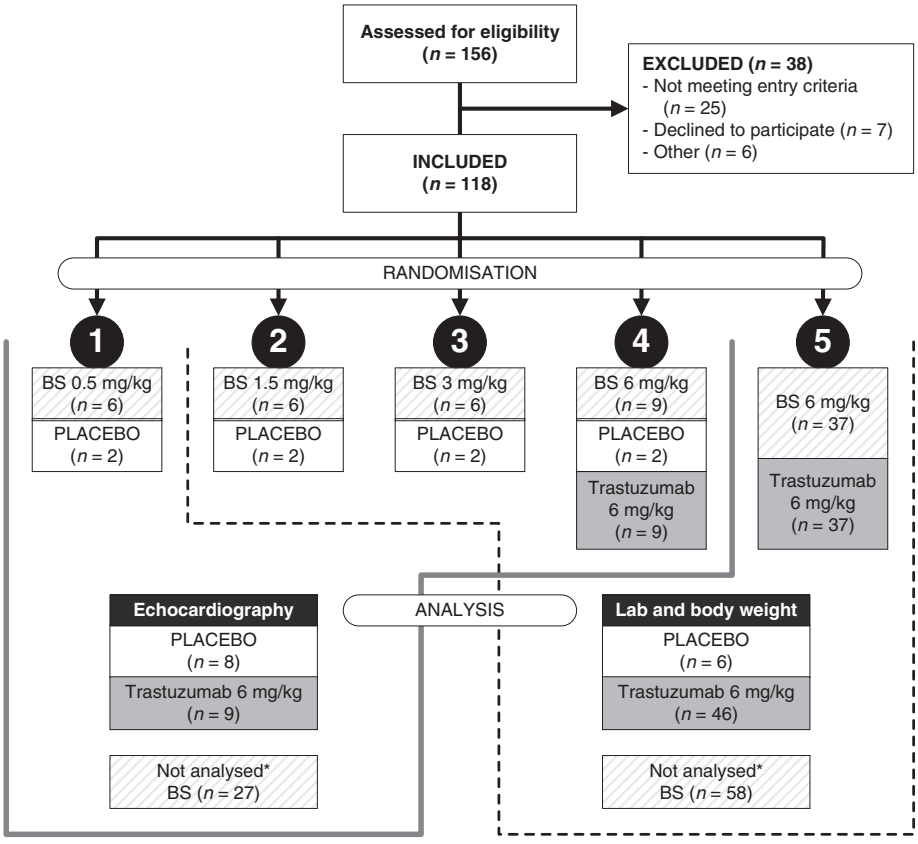

Fig. 1. Participant flow diagram. Flow of participants: enrolment was sequential in one of five groups (see main body); echocardiographic examinations were available for groups 1–4, laboratory results and body weight data were available for groups 2–5. Cohorts marked with an asterisk were not analysed, although baseline effects were included in the secondary analysis on the extended dataset (see main body). BS biosimilar product of trastuzumab.