Author's reply — Intravenous immunoglobulin treatment in women with four or more recurrent pregnancy losses: A double-blind, randomised, placebo-controlled trial

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eClinicalMedicine
2022;52: 101617
Published online xxx
https://doi.org/10.1016/j.eclinm.2022.101617

We thank Yamamoto and Suzuki for their comments on our recent paper that revealed a high dose of intravenous immunoglobulin (IVIG) in early pregnancy was effective for women with ≥4 recurrent pregnancy losses (RPLs) of unexplained aetiology.[1] As they pointed out, this double-blind randomised controlled trial is referred to as a phase III study in the clinical study protocol according to agreement with the Japan Pharmaceuticals and Medical Devices Agency, given the current lack of promising treatments for unexplained RPL.[2] However, the editor and reviewers of the journal indicated that this trial should be essentially called a pivotal Phase II study but not a Phase III study, considering the sample size and the number of inclusion/exclusion criteria. A phase II efficacy study establishes how well the treatment might work in a select group of patients rather than a phase III/IV effectiveness study (to estimate how well the treatment might work in an unselected, real-world population).

Second, the clinical study protocol describes that the primary outcome is ongoing pregnancy rate at 22 weeks of gestation in women who received the study drug excluding those who miscarried due to fetal chromosome abnormality (modified intention-to-treat [modified-ITT] population). However, this trial found that the ratio of miscarriage with abnormal chromosome karyotype in the IVIG group (3/50, 6·0%) was significantly lower than that in the placebo group (10/49, 20·4%, p=0·03). This is potentially a part of IVIG treatment effect, and the IVIG might have a preventative role in averting miscarriage with abnormal chromosome karyotype increasing the ratio of live birth. Similarly, in 2015 Greco et al. discovered that transferred embryos with abnormal chromosome karyotype have the ability to develop into healthy euploid newborns, one year after the start of this trial.[3] In addition, the ratio of miscarriage with unknown chromosome karyotype in the IVIG group (4/19, 21·1%) was higher than that in the placebo group (1/31, 3.2%, p=0·0622), but these miscarriages with unknown karyotype had been counted as miscarriages with normal chromosome karyotype for the statistical analyses in the modified-ITT population. These problems confound interpretations of results in the modified-ITT population. For that reason, the editor and reviewers of the journal directed that the ITT population, but not the modified-ITT should be set up to anticipate a treatment effect and, consequently, we mainly described and discussed results in all women who received the study drug (ITT population).

Contributors

HY, MD, SS, and TT contributed the contents of this reply and gave approval of the version to be published.

Declaration of interests

None.

DOI of original article: http://dx.doi.org/10.1016/j.eclinm.2022.101601

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