

# Letters to the Editor

Blood Coagulation and Fibrinolysis 2021, 32:423–426

## Subcutaneous injection of mRNA vaccines against severe acute respiratory syndrome coronavirus 2: an option for severe bleeding disorders or anticoagulated patients?

Matthias Karer<sup>a</sup>, Karin Stiasny<sup>b</sup>, Markus Zeitlinger<sup>a</sup> and Bernd Jilma<sup>a</sup>

<sup>a</sup>Department of Clinical Pharmacology and <sup>b</sup>Center for Virology, Medical University of Vienna, Vienna, Austria

Correspondence to Bernd Jilma, MD, Department of Clinical Pharmacology, Medical University Vienna, Waehringerguertel 18-20, A-1090 Vienna, Austria  
Tel: +43 1 40400 29810; e-mail: bernd.jilma@meduniwien.ac.at

Received 20 April 2021 Accepted 30 April 2021

To the editor,

Up to now, mRNA-based vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with an emergency approval of the Food & Drug Administration (FDA) or conditional approval by the European Medicines Agency (EMA) are used intramuscularly, leading to safety concerns in patients on anticoagulants or bleeding disorders.

Current guidance of coronavirus disease 2019 (Covid-19) vaccination in patients with bleeding disorders recommends administration of specific factors, previous prothrombin time testing and/or adjustment of hemostatic therapies prior to intramuscular vaccination [1]. If these measures are not feasible, everything should be optimized to minimize risk of bleeding events, for example smallest gauge needle possible, applying pressure for at least 10 min and repeated self-inspection after injection. In addition, a recent statement of the International Society on Thrombosis and Haemostasis encouraged the application of Covid-19 vaccines intramuscularly in individuals taking direct anticoagulants, while attempting to reduce adverse events [2].

Although preclinical tests in nonhuman primates showed an equivalent immunological response of mRNA vaccines when administered intramuscularly or intradermally, companies only examined intramuscular administrations in their trials and therefore recommend this route of application [3,4]. In general, other vaccines are preferably given subcutaneously in patients with bleeding disorders, with no evidence of decreased efficacy [5]. Whether the mRNA-based Covid-19 vaccines provide a sufficient immunological response in patients with bleeding disorders when administered subcutaneously into fat rather than muscle tissue remains to be elucidated. Therefore, further insight into the efficacy and safety regarding the route of administration could potentially provide a safe alternative for patients with bleeding disorders.

Here, we compared data from one healthy investigator receiving a subcutaneous and two investigators receiving an intramuscular dose of 30 µg of BNT162b1 (Comirnaty; Pfizer, New York City, New York, USA) on day 1 and day 22. The subcutaneous application of BNT162b1 has not yet been approved by the FDA or EMA and was therefore used off-label. Informed consent was obtained from all participants prior to all study related activities. All participants were tested weekly using either a qPCR based test (April to November 2020) or a SARS-CoV-2 antigen test (Abbott Panbio, Lake Forest, Illinois, USA, November 2020–March 2021).

Adverse events were assessed according to the BNT162b1 Phase I/II study [4]. SARS-CoV-2 neutralization test was performed as described before from serum drawn at day 17 and day 36 [6]. To simulate a bleeding disorder one investigator anticoagulated himself deliberately with rivaroxaban 20 mg and self-injected the vaccine subcutaneously 2 h after the anticoagulation: this resulted in only mild local reactions after each injection and only minimal systemic adverse effects after the 2nd dose, while demonstrating a neutralizing antibody response of 120 (Table 1). This was comparable with an age-matched control receiving an intramuscular injection, who, however, experienced moderate adverse events including chills and fatigue. One younger investigator showed a high antibody response of 640 after the second intramuscular dose, while experiencing moderate adverse events including chills, headache and muscle pain.

This discrepancy in neutralization test titers in regard to age can be explained by data showing that part of the patients (24–54 years of age) receiving 30 µg BNT162b1 intramuscularly had a neutralizing antibody response below the limit of detection 22 days after initial vaccination [7].

Tolerability of mRNA-based vaccines is rather poor with higher rates of systemic and local reactions than what we are normally used to experience with other injections, but given the time-critical development process in this ongoing pandemic, the focus was mainly on achieving a robust immune response rather than a good tolerability.

A recent review on adjuvanted, live-virus and nonadjuvanted vaccines encourages an intramuscular administration of these vaccines in patients without bleeding disorders, due to a reduced likelihood of local adverse events [8]. Nevertheless, given the potential risks of an intramuscular injection in patients with a bleeding disorder and the high immunogenicity of mRNA vaccines, this does not outweigh the risks of a potential for severe bleeding events.

**Table 1 Severe acute respiratory syndrome coronavirus 2 neutralization titers after BNT162b1 administration**

Subject no.	Age (years)	Sex	Route of application	Adverse events after 2nd dose	NT titer <sup>a</sup> day 17	NT titer day 36
1	50	Male	Subcutaneous	Mild	<10	120
2	45	Male	Intramuscular	Moderate	<10	120
3	27	Male	Intramuscular	Moderate	60	640

NT, neutralization test; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. <sup>a</sup> NT titer is defined as the reciprocal of the serum dilution required for protection from SARS-CoV-2-induced cytopathic effects in a Vero E6 cell-based assay. (6) (Starting dilution 1 : 10).

Due to the extremely restricted access to vaccines for clinical trials in this ongoing pandemic, a prospective clinical trial with a sufficient sample size was not feasible, but boosting by natural infection was excluded by weekly SARS-CoV-2 testing in the current investigation for many months before and during vaccination.

The current case study is encouraging, providing first – although limited – data on a potentially sufficient humoral immune response when administering BNT162b1 subcutaneously, either deliberately in patients with a bleeding disorder or inadvertently in patients with obesity, while indicating a good tolerability. Nevertheless, prospective studies with a sufficient sample size are urgently needed to confirm the safety, immunogenicity and tolerability of subcutaneous or even intradermal injections for patients with bleeding disorders. The latter may be particularly attractive because lower doses have been shown to be equally immunogenic at least for influenza vaccines, particularly in individuals less than 60 years of age [9,10]. Such an approach could quickly increase available vaccine doses in a pandemic, in which vaccine supplies cannot meet world-wide vaccine demands.

### Acknowledgements

Author contributions: M.K., M.Z. and B.J. were involved in study design. M.K. and K.S. were responsible for data acquisition. All authors contributed to the interpretation of data, writing and revising the letter, as well as providing final approval of the version to be published.

Funding statement: This work was supported by the Austrian Science Funds grant #SFB54-P04.

### Conflicts of interest

M.K., K.S., M.Z. and B.J. declare they have no conflict of interest associated with the content of the current letter.

### References

- 1 European Association for Haemophilia and Allied Disorders. Brussels, Belgium (23 December 2020) EAHAD co-signs Covid-19 vaccination guidance. Available at: <https://eahad.org/covid-19-vaccination-guidance-for-people-with-bleeding-disorders/> [Accessed 23 February 2021]
- 2 International Society on Thrombosis and Haemostasis. Carrboro, USA (12 March 2021) ISTH statement on AstraZeneca COVID-19 vaccine and thrombosis. 2021; Available at: <https://www.isth.org/news/556057/ISTH-Statement-on-AstraZeneca-COVID-19-Vaccine-and-Thrombosis.htm>. [Accessed 19 March 2021]
- 3 Lindgren G, Ols S, Liang F, Thompson EA, Lin A, Hellgren F, et al. Induction of robust B cell responses after influenza mRNA vaccination is accompanied by circulating hemagglutinin-specific ICOS<sup>+</sup> PD-1<sup>+</sup> CXCR3<sup>+</sup> T follicular helper cells. *Front Immunol* 2017; **8**:1539.

- 4 Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. *Nature* 2020; **586**:589–593.
- 5 Santagostino E, Riva A, Cesaro S, Esposito S, Matino D, Mazzucchelli RI, et al., The HEVA Study Group. Consensus statements on vaccination in patients with haemophilia – results from the Italian haemophilia and vaccinations (HEVA) project. *Haemophilia* 2019; **25**:656–667.
- 6 Koblishcke M, Traugott MT, Medits I, Spitzer FS, Zoufaly A, Weseslindtner L, et al. Dynamics of CD4 T cell and antibody responses in COVID-19 patients with different disease severity. *Front Med* 2020; **7**:592629.
- 7 Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, et al. COVID-19 vaccine BNT162b1 elicits human antibody and T H 1 T cell responses. *Nature* 2020; **586**:594–599.
- 8 Cook IF. Subcutaneous vaccine administration – an outmoded practice. *Hum Vaccin Immunother* 2020; **17**:1329–1341.
- 9 Kenney RT, Frech SA, Muenz LR, Villar CP, Glenn GM. Dose sparing with intradermal injection of influenza vaccine. *N Engl J Med* 2004; **351**:2295–2301.
- 10 Belshe RB, Newman FK, Cannon J, Duane C, Treanor J, Van Hoeck C, et al. Serum antibody responses after intradermal vaccination against influenza. *N Engl J Med* 2004; **351**:2286–2294.

DOI:10.1097/MBC.0000000000001048

OPEN

### Identification of a recurrent missense mutation in the *FGA* gene likely causing a congenital fibrinogen disorder

Runguang Gao<sup>a</sup>, Meixia Bi<sup>b</sup>, Bei Li<sup>a</sup>, Xiaojing Yue<sup>a</sup>, Fang Yuan<sup>a</sup>, Xiaoke Zhang<sup>a</sup> and Xiong Wang<sup>c</sup>

<sup>a</sup>Department of Laboratory Medicine, Jiaozuo Women's and Children's Hospital, <sup>b</sup>Department of Laboratory Medicine, Jiaozuo Hospital of Traditional Chinese Medicine, Jiaozuo and <sup>c</sup>Department of Laboratory Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Correspondence to Xiong Wang, PhD, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology, Wuhan 430000, Hubei, China  
E-mail: wangxiong@tjh.tjmu.edu.cn

Received 15 November 2020 Revised 14 May 2021  
Accepted 25 May 2021

To the editor,

Heritable dysfibrinogenemia is an autosomal dominant disorder, characterized by the functional anomaly of circulating fibrinogen but with normal antigen level [1]. Most patients with heritable dysfibrinogenemia are

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.