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Scientific Letter

Improving BNT162b2 mRNA Vaccine Tolerability without Efficacy Loss by Pidotimod Supplementation

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To the editor.

A new pandemic emerged last year for the healthcare community worldwide: Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-Cov2). Coronavirus disease 2019 (Covid-19) has affected hundreds of millions of people globally since it was declared.[1] Different studies on Covid-19 try to find an effective therapy for the virological phase[2,3] and the immunological phase.[4–8] Several vaccines have been developed to stop the spread of the virus and gain mass immunity. BNT162b2 mRNA vaccine is largely effective and is widely administered in high-risk populations.[9] However, despite the high effectiveness, vaccination can be associated with grade 1-2 local reactions (pain at the injection, injection-site redness, or swelling) and systemic reaction (fatigue, fever, headache).[10] These reactions discourage vaccination in some people. The use of drugs capable of rebalancing the activity of the immune system against infections, such as pidotimod, could reduce the adverse effects and get the immunological vaccine response.[5,11] Based on these premises, a study was designed to verify whether the use of pidotimod mediated the immune response linked to the second dose of Covid-19 vaccination, evaluating as an endpoint the adverse effects and immunological response associated with injection of the second dose of BNT162b2 mRNA vaccine into a healthy population in subjects taking Pidotimod versus a control group taking no therapy.

We designed a single-center cohort study to test this hypothesis by enrolling healthcare workers (nurses and doctors working at the Infectious Diseases Clinic, University' G. D'Annunzio', SS Annunziata Hospital of Chieti Italy), undergoing the BNT162b2 mRNA vaccination from January to February 2021. Clinical and demographical data were collected for each participant. All nurses and doctors working in the Infectious Diseases Clinic (Covid-19 unit) who had carried out the first dose of the BNT162b2 mRNA vaccine were proposed to participate, up to the enrollment of 30 participants (12 of which were male (40%), and all of them were of Caucasian ethnicity with a median age of 48 years), excluding all healthcare workers with a paste or present diagnosis of COVID-19. All the participants were negative for the SARS-CoV-2 molecular swab at the enrollment. All participants were randomized to receive Pidotimod or not. A total of 10 participants took Pidotimod 800 mg bid orally fasting from the fourth day before the second dose of the BNT162b2 mRNA vaccine for six days. The remaining 20 participants did not take any therapy. Demographic, clinical, and adverse event data were collected one week after the vaccination. The two groups of subjects, with and without supplementation with pidotimod, were homogeneous for age and sex.

All participants filled out a questionnaire investigating the following effects: pain, redness, swelling and pain in the injection site, headache, fatigue, musculoskeletal pain, fever, gastrointestinal symptoms, itching, lymphadenopathy, difficulty falling asleep/insomnia, agitation, skin rash, anaphylaxis, and others.

A plasma sample was collected in all participants five days before the second vaccination dose and seven days after the second dose to measure the SARS-CoV-2 IgM and IgG levels developed.

All participants vaccinated had no adverse events immediately (within an hour) after vaccine administration. No significant differences were found between the anti-SARS-Cov2 IgM and IgG levels before vaccination of the two groups. Likewise, we found no significant differences between the two groups comparing the anti-SARS-CoV2 IgM levels post-vaccination. All the components of the "pidotimod group" increased their IgM value versus the 65% of the control group ($p<0.05$). The SARS-Cov2 IgG levels were statistically increased after vaccination in both groups, but we have not found significant differences between the groups (**Table 1**).

Table 1. Parameters and adverse events in vaccinated with and without Pidotimid.

	Vaccinated without Pidotimod (20 pt)			Vaccinated with pidotimod (10 pt)			
Parameters (mead ± DS)	**media**		**ds**	**media**		**ds**	**t**
Age (years)	39,55	±	11,58	41,80	±	12,15	0,31
IgM before vaccine (UM)	2,57	±	4,00	1,34	±	1,70	0,18
IgM after vaccine (UM)	2,95	±	2,60	1,95	±	1,65	0,14
Increase in IgM	13/20			10/10			**0,02**
IgG after vaccine (UM)	2712,64	±	1683,03	2500,77	±	2029,88	0,38
IgG before vaccine (UM)	307,17	±	733,82	136,25	±	135,63	0,24
N° adverse events for each subject	3,30	±	1,89	2,20	±	1,55	0,06
N° adverse events without local pain for each subject	2,45	±	1,76	1,30	±	1,42	**0,04**
Adverse events N° (%)							
Pain, redness and swelling of injection site	5 (25)			4 (40)			0,70
Only pain of injection site	15 (75)			5 (50)			**0,03**
Headache	10 (50)			4 (40)			0,50
Fatigue	12 (60)			3 (30)			0,20
Skeletal-muscle pain	12 (60)			3 (30)			0,20
Fever	6 (30)			2 (20)			0,40
Gastrointestinal symptoms	4 (20)			1 (10)			0,70
Itch of injection site	1 (5)			0			//
Limphadenophaty	0			2 (10)			//
Difficulty falling asleep, agitation	3 (15)			1 (10)			**0,03**
Widespread skin rash	0			0			0
Anaphylaxix	0			0			0
Other	0			0			0

The number of total adverse events described in the control group (without supplementation) was higher than in the group with pidotimod supplementation, and the difference is significant ($p< 0.05$) if we compare the number of adverse events described, excluding the injection site pain that is the most common and expected event between the two groups (**Table 1**).

Analyzing the adverse events in detail, in the group of subjects supplemented with pidotimod, fewer cases of pain at the injection site of the vaccine are described, and fewer cases of difficulty falling asleep and agitation than in the control group (**Table 1**).

This study describes a strategy to reduce the adverse events without reducing the immunologic response to SARS-CoV-2 vaccination.

The study's main finding is the evidence of reduction of vaccination-related adverse events by using pidotimod.

BNT162b2 vaccine is a nucleoside-modified mRNA vaccine developed by Pfizer and BioNTech to prevent COVID-19. BNT162b2, like gene-based vaccines, carries genetic instructions for producing an antigen by the vaccine recipient cells; specifically, the target is the antigen of the surface spike protein, which is used by the virus to bind and fuse with host cells.[12,13] BNT162b2 administered as two 30 µg doses 21 days apart was generally well tolerated in the studies.[9] The registration study showed reactogenicity in 8183/21720 participants. BNT162b2 vaccine provoked local reactions, mainly mild-to-moderate pain at the injection site (more than 80%). A noticeably lower percentage of participants reported injection-site redness or swelling. Systemic events were reported more often in younger than the older population. Systemic reactions are often described more after the second dose than after the first. The most-reported systemic events were fatigue and headache (more than 50%). After the second dose, more than 15% of participants reported fever. Severe systemic events were reported in less than 2% of vaccine recipients.[9]

These reactions are linked to the immune response established in the patient.[14] These effects are often disabling, leading vaccinators to take time off work or the need to take medications. Therefore, it may discourage some candidates from vaccinating.

Therefore, it is useful to search for a substance that reduces adverse events without altering, but possibly improving, the immune response to the vaccine. The immunomodulating molecule pidotimod appeared an ideal candidate. Pidotimod is a dipeptide able to act on immune activities, as demonstrated in previous studies, by improving macrophages' function and increasing the secretion of certain cytokines.[15,16] The effect of Pidotimod was previously analyzed in the elderly, demonstrating its immunostimulatory effect, able to improve T cells proliferation;[17–19] this finding has recently also been demonstrated for the HIV positive population.[11]

From the clinical point of view, pidotimod in coadministration with influenza vaccination, in a chronic obstructive pulmonary disease adult study, showed a lower exacerbation in patients to the placebo.[20]

In a recent study in outpatient populations affected by SARS-CoV2 infection, pidotimod appeared to be a valid option to reduce the duration of symptoms in patients, as an earlier defervescence could prevent the indolent course of cytokine cascade activation.[5]

Starting from these assumptions, the data of our work in the healthy population has shown that it is possible to reduce the rate of events related to the reactogenicity of the vaccine.

An interesting remark is an increase in IgM levels in all the subjects of the pidotimod group, which could represent a booster effect on the subsequent immunological memory developed by the subjects.

On the other hand, there were no significant differences in IgG levels, probably due to a limited period of observation and the small size of the sample.

This work demonstrates how pidotimod improves tolerability, not interfering with the production of antibodies in subjects. The findings described in this paper could encourage more doctors and people to get vaccinated, allowing them to gain the mass immunity needed to end this pandemic first.

The study's main limitation is the small number of people and the limited observation time.

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Claudio Ucciferri[1, 2], Jacopo Vecchiet[1], Antonio Auricchio[1] and Katia Falasca[1].

[1] Clinic of Infectious Diseases – Department of Medicine and Science of Aging, University "G. d'Annunzio" Chieti-Pescara– Italy.
[2] Department of Medicine and Health Sciences, University of Molise – Campobasso – Italy.

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Correspondence to: Falasca Katia. Clinic of Infectious Diseases, Dept. of Medicine and Science of Aging, University "G. D'Annunzio" School of Medicine, Via dei Vestini, 66100 Chieti – Italy. Tel. +39-0871-358595. E-mail: k.falasca@unich.it

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