Non tutti i pazienti fragili hanno una risposta immunologica soddisfacente. Lo confermano i risultati da uno studio nazionale finanziato dal Ministero della Salute e condotto in 13 centri di eccellenza italiani

In Italia sono circa 400 mila i pazienti fragili a maggior rischio per infezione da SARS-CoV-2, di questi 160 mila sono malati onco-ematologici. Nonostante il razionale per vaccinare precocemente i pazienti fragili fosse forte, poco sapevamo sulla qualità della loro risposta immunitaria, nonché sugli eventuali effetti collaterali della vaccinazione. Per rispondere a questi quesiti, importanti dal punto di vista scientifico, ma di immediato interesse per la sanità pubblica, è stato finanziato dal Ministero della Salute un progetto speciale denominato VAX4FRAIL.

VAX4FRAIL include 13 prestigiosi centri di ricerca italiani (IRCCS), ha arruolato in poco più di 5 mesi oltre 600 pazienti affetti da neoplasie onco-ematologiche e solide, malattie immuno-reumatologiche e neurologiche che sono stati inseriti in un database specifico.

In sintesi, i risultati di questi studi, che sostanzialmente confermano alcune esperienze da altri gruppi di altri paesi, suggeriscono che:

- la maggior parte delle persone fragili e clinicamente vulnerabili al COVID-19 riceve alti livelli di protezione già dopo 2 dosi di vaccino con un buon profilo di tollerabilità;
- per alcune categorie di pazienti, quali quelli con malattie immuno-reumatologiche la dose booster potenzia notevolmente sia la risposta anticorpale che quella cellulo-mediata;
- un tallone d'Achille rimane l'immunizzazione dei pazienti onco-ematologici sottoposti a trattamenti ad elevato impatto sul sistema immunitario, dove il connubio tra vaccinazione e prevenzione dell'infezione rappresentano sicuramente ad oggi la migliore strategia per ridurre le infezioni e complicanze da Sars-CoV2.

I due studi appena pubblicati su MedRxiv, in corso di revisione da due riviste scientifiche

1. Paolo Corradini, Chiara Agrati, Giovanni Apolone, Alberto Mantovani, Diana Giannarelli, Vincenzo Marasco, Veronica Bordoni, Alessandra Sacchi, Giulia Matusali, Carlo Salvarani, Pier Luigi Zinzani, Renato Mantegazza, Fabrizio Tagliavini, Maria Teresa Lupo-Stanghellini, Fabio Ciceri, Silvia Damian, Antonio Uccelli, Daniela Fenoglio, Nicola Silvestris, Fausto Baldanti, Giulia Piaggio, Gennaro Ciliberto, Aldo Morrone, Franco Locatelli, Valentina Sinno, Maria Rescigno, Massimo Costantini. **Humoral and T-cell immune response after three doses of mRNA SARS-COV-2 vaccines in fragile patients: the Italian VAX4FRAIL study.**

Abstract

Background Patients with solid or hematological tumors, neurological and immune-inflammatory disorders represent potentially fragile subjects with increased risk to experience severe COVID-19 and inadequate response to SARS-CoV2 vaccination.

Methods We designed a prospective Italian multicentric study to assess humoral and T-cell response to SARS-CoV2 vaccination in patients (n=378) with solid tumors (ST), hematological malignancies (HM), neurological (ND) and immuno-rheumatological diseases (ID). The immunogenicity of primary vaccination schedule and of the booster dose were analyzed.

Results Overall, patient seroconversion rate after two doses was 62.1%. A significant lower rate was observed in HM (52.4%) and ID (51.9%) patients compared to ST (95.6%) and ND (70.7%); a lower median level of antibodies was detected in HM and ID versus the others ($p<0.0001$). A similar rate of patients with a positive SARS-CoV2 T-cell response was observed in all disease groups, with a higher level observed in the ND group. The booster dose improved humoral responses in all disease groups, although with a lower response in HM patients, while the T-cell response increased similarly in all groups. In the multivariable logistic model, the independent predictors for seroconversion were disease subgroups, type of therapies and age. Notably, the ongoing treatment known to affect the immune system was associated with the worst humoral response to vaccination ($p<0.0001$), but had no effects on the T-cell responses.

Conclusions Immunosuppressive treatment more than disease type per se is a risk factor for low humoral response after vaccination. The booster dose can improve both humoral and T-cell response.

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2. Maria Teresa Lupo Stanghellini, Serena Di Cosimo, Massimo Costantini. Sara Monti, Renato Mantegazza, Alberto Mantovani, Carlo Salvarani, Pier Luigi Zinzani, Matilde Inglese, Fabio Ciceri, Giovanni Apolone, Gennaro Ciliberto, Fausto Baldanti, Aldo Morrone, Valentina Sinno, Franco Locatelli, Stefania Notari, Elena Turola2. Diana Giannarelli. Nicola Silvestris, on behalf of the VAX4FRAIL Study Group. **m-RNA-COVID19 vaccination can be considered safe and tolerable for frail patients. An analysis from the Italian, multicentric, observational, prospective trial VAX4FRAIL study.**

Abstract

Background Frail patients are considered at relevant risk of complications due to COVID-19 infection and, for this reason, are prioritized candidates for vaccination. As these patients were originally not included in the registration trials, fear related to vaccine side-effects and disease worsening was one of the reasons for vaccine hesitancy. Herein we report the safety profile of the prospective, multicenter, national VAX4FRAIL study (NCT04848493) to evaluate vaccines in a large trans-disease cohort of patients with solid or hematological malignancies, neurological and rheumatological diseases.

Methods Between March 3rd and September 2nd, 2021, 566 patients were evaluable for safety endpoint: 105 received the mRNA-1273 vaccine and 461 the BNT162b2 vaccine. Frail patients were defined per protocol as patients under treatment with hematological malignancies (131), solid tumors (191), immune-rheumatological diseases (86), and neurological diseases (158), including multiple sclerosis and generalized myasthenia. The impact of the vaccination on the health status of patients was assessed through a questionnaire focused on the first week after each vaccine dose.

Results The most frequently reported moderate-severe adverse events were pain at the injection site (60.3% after the first dose, 55.4% after the second), fatigue (30.1% - 41.7%), bone pain (27.4% - 27.2%) and headache (11.8% - 18.9%). Risk factors associated with the occurrence of severe symptoms after vaccine administration were identified through a multivariate logistic regression analysis: age was associated with severe fever presentation (younger patients vs. middle-aged vs. older ones), females presented a higher probability of severe pain at the injection site, fatigue, headache, and bone pain; the mRNA-1237 vaccine was associated with a higher probability of severe pain at the injection site and fever. After the first dose, patients presenting a severe symptom were at a relevant risk of recurrence of the same severe symptom after the second one. Overall, 11 patients (1.9%) after the first dose and 7 (1.2%) after the second one required to postpone or suspend the disease-specific treatment. Finally, 2 fatal events occurred among our 566 patients. These two events were considered unrelated to the vaccine.

Conclusions Our study reports that mRNA-COVID-19 vaccination is safe also in frail patients as expected side effects were manageable and had a minimum impact on patient care path.

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