Suboptimal immune response to SARS-CoV-2 mRNA vaccination in myeloma is associated with anti-CD38 and BCMA-targeted treatment

Oliver Van Oekelen
Parekh Lab, Icahn School of Medicine at Mount Sinai

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Disclosure

I have no financial disclosure or conflicts of interest with the presented material in this presentation.
Study design and cohort

**MARS study** (Myeloma Antibody Response Study): opened early after vaccine approval
- Collaboration with Personalized Virology Initiative and SERONET

- **Goal:** characterize humoral and cellular immune response to SARS-CoV-2 in MM patients
  - 225 patients enrolled (09/2021)
  - Longitudinal collection of blood/saliva
  - Detailed clinical annotation
  - High-dimensional immune phenotyping

- Retrospective data collected on MM patients treated at MSH for which anti-spike IgG available

- **Cohort presented here:**
  - 320 MM patients in total, of 23 SMM patients
  - 260 (81%) with available anti-spike IgG >10 days after second dose of mRNA vaccine
  - 70.3% BNT162b2 (Pfizer) vaccine
  - T cell data in subset of 45 MM patients
Variable anti-spike IgG in myeloma patients following 2 doses of mRNA vaccine


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@ovanoekelen – oliver.vanoekelen@icahn.mssm.edu
Variable anti-spike IgG in myeloma patients following 2 doses of mRNA vaccine

1. Who are the non-responders?
   – Can we predict who will not respond?
   – Clinical/disease-related associations?

2. Does response persist?
   – Vaccine vs COVID-19 infection?
   – Effect of treatment?

3. Does it matter?
   – Do these patients develop infections?
   – Are they protected via cellular immunity?

4. How do we treat non-responders?
   – Counseling?
   – Myeloma treatment modification?
   – Boosters and passive immunization?

Lower anti-spike IgG levels / non-response in myeloma patients on anti-CD38 mAb and BCMA-targeted treatment

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>OR</th>
<th>95% C.I.</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>1.023</td>
<td>[0.980 - 1.070]</td>
<td>0.303</td>
</tr>
<tr>
<td>Male gender (0/1)</td>
<td>1.538</td>
<td>[0.693 - 3.568]</td>
<td>0.299</td>
</tr>
<tr>
<td>Vaccine type Moderna (0/1)</td>
<td>0.640</td>
<td>[0.243 - 1.553]</td>
<td>0.341</td>
</tr>
<tr>
<td>Lines of treatment (n)</td>
<td>1.152</td>
<td>[0.968 - 1.376]</td>
<td>0.109</td>
</tr>
<tr>
<td>Time since MM diagnosis (mo)</td>
<td>0.997</td>
<td>[0.986 - 1.006]</td>
<td>0.506</td>
</tr>
<tr>
<td>Response status (s)CR (0/1)</td>
<td>0.389</td>
<td>[0.152 - 0.917]</td>
<td>0.037</td>
</tr>
<tr>
<td>Lymphopenia ≥ Grade 3 (0/1)</td>
<td>2.463</td>
<td>[0.884 - 6.623]</td>
<td>0.076</td>
</tr>
<tr>
<td>Current regimen contains:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCMA-targeted treatment (0/1)</td>
<td>10.269</td>
<td>[2.898 - 40.405]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>anti-CD38 monoclonal antibody (0/1)</td>
<td>4.258</td>
<td>[1.660 - 12.694]</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Anti-spike IgG persists longer after COVID-19 infection
Anti-CD38 mAb and BCMA bispecific impact durability

- Patients on treatment with anti-CD38 mAb lose detectable IgG faster than other MM patients
- Patients on BCMA bispecific Ab (N = 10) rarely develop detectable IgG in our cohort
- Clinical significance unclear; collecting more (longitudinal) data
T cell responses are diminished in IgG non-responders

SARS-CoV-2 Specific CD4 T Cell Responses

% CD154+ Cytokine producing CD4 T Cells

*** ns *** ns ***

- IFNγ
- TNFα
- IL-2

Healthy Controls with detectable anti-Spike IgG Antibodies n=12
MM patients with detectable anti-Spike IgG Antibodies n=27
MM patients with undetectable anti-Spike IgG Antibodies n=18

Manuscript Submitted.
Third dose mRNA vaccine anecdotally effective in myeloma

43-year-old female
- Active treatment: daratumumab + carfilzomib + venetoclax + dexamethasone
- Persistent negative anti-spike IgG levels after 2 doses of BNT162b2 mRNA vaccine

64-year-old male
- SMM, no active treatment
- Negative anti-spike IgG levels after 2 doses of BNT162b2 mRNA vaccine

Data collection in larger MM cohort currently ongoing:
- Efficacy?
- Mixing vaccines vs. same product?
- Timing?
How can we best **identify** vulnerable patients?
- Clinical characteristics?
- Serology?
- T cell assays?

How do we properly **counsel** vulnerable patients?
- Longitudinal serological testing?
- Continuation of physical distancing and non-pharmacological interventions?
- Encourage vaccination of social contacts

How do we **adapt clinical practice**?
- Adapt anti-myeloma treatment?
- Timing of vaccination: hold myeloma treatment? Timing post transplantation?

How do we **boost the immune response** in vulnerable patients?
- Additional doses of vaccination?
- Passive immunization strategies?
Conclusions

- **SARS-CoV-2 anti-spike IgG response** is suboptimal and highly variable in MM patients after mRNA vaccination
- **Significant fraction (15%)** does not develop any detectable anti-spike IgG (non-responders)
- **Durability** of response is more limited in MM patients compared to healthy controls
- Treatment impacts durability: anti-CD38 mAb, BCMA bispecific, …
- Lack of IgG response associated with weaker SARS-CoV-2-specific T cell response
- **Third dose effect** currently being studied, anecdotally effective
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Thank you to all patients!
Thank you for your attention. Happy to answer any questions!