Educational Workshop

EW15: Vaccination of immunocompromised and allergic patients - are we missing the obvious?

Arranged with EVASG, ESGICH, TAE

Convenors: Ron Dagan, Beer Sheva, IL
Chrysanthi Skevaki, Athens, GR

Faculty: Per Ljungman, Huddinge, SE
Oriol Manuel, Lausanne, CH
Susanna Esposito, Milan, IT

Marked in red = no handouts available
Ljungman - Update on vaccination of oncology patients

Update on vaccination of oncology patients

Per Ljungman, MD, PhD
Karolinska University Hospital, Karolinska Institutet
Stockholm, Sweden

Conflicts of interest

Advisory board/consultant for Vical / Astellas regarding planning of and European PI for the ongoing phase III study

Advisory board for Merck regarding inactivated VZV vaccine and Swedish PI for the ongoing phase III study.
Research support Merck for antifungal studies

Swedish PI for Wyeth/Pfizer phase IV study of Prevenar 13.

Why / why not vaccinate?

+ -
Risk for infection Side effects
Risk for severe disease Cost
Loss of herd immunity
What determines immune status in cancer patients

- Previous vaccination and infection history
- Given anti-cancer therapy
  - Type
  - Intensity
- Autologous SCT recipients
  - Persistence of existing recipient immunity
- Allogeneic SCT recipients
  - Transfer of immunity from the donor
  - Persistence of existing recipient immunity

Measles, influence of previous antigen challenge; HSCT

Donor / recipient combinations

Ljungman et al Blood 1994
Why is the immunity lost?

- No. of antigen specific cells in the patient
- Eradication of patient memory B-cells by therapy
  - Graft-vs-host (lymphocyte) reaction?
  - Cytotoxic chemo-radiotherapy?
  - Anti-B-cell therapy
- No. of antigen specific cells in the donor graft

When should vaccinations be performed?

- When is the patient at risk for infection?
- What is the likelihood for an adequate immune response after therapy?
- Can we vaccinate before initiation of therapy?
- If not, when is it safe and effective?

Important "early" infections possibly preventable by vaccination

- Pneumococci
- Influenza
- CMV
- HBV
- Varicella – primary, reactivated
Important "late" infections possibly preventable by vaccination

- Pneumococci
- Influenza
- HBV – seroreversion
- Varicella – primary, reactivated
- HIB
- Papillomavirus
- Pertussis (?)

Other infections

- Diphtheria
- Tetanus
- Measles
- Rubella
- Meningococci
- Polio
- TBE
- Tuberculosis

"Travel vaccines"

What are the possible pre-therapy strategies?

- Complete routine schedules
- Immunize seronegative patients
- Boost existing pre-transplant immunity
- Immunize the donors (HSCT)
**Pretherapy vaccination - cancer patients**

It is unlikely that patients needing intensive therapy can wait for vaccinations before start of therapy.

Patients who can wait are unlikely to become very immunosuppressed.

Possible exceptions:
- low malignant lymphomas or CLL given anti-B cell antibodies
- patients requiring splenectomy
- myeloma patients early in the stage of the disease

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**Pre-transplant vaccinations - HSCT**

Usually undergo cytotoxic chemotherapy limiting the possibilities to perform pre tx vaccinations.

Vaccination efficacy during chemotherapy usually poor.

Pre-transplant immunity is frequently lost.

However in patients not receiving chemotherapy, pre-transplant vaccination can be considered for example against varicella.

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**Donor vaccination**

It has been shown to improve recipient immunity for:

Donor vaccination should be combined with early posttransplant vaccination.

Question:
- For which vaccines would it be of clinical importance?
- How do you get to the donors?
  - Ethics - unrelated donors / children
  - Time frame - the window of opportunity is narrow.
Patient vaccination: Caveat!

No true efficacy data does exist

Toxicity data quite robust for many vaccines

"All" efficacy data is on surrogate endpoints e.g immune responses!

but

Absence of Evidence is not Evidence of Absence

Risks with inactivated vaccines

No evident major risks for direct side effects

Local side effects
  Systemic side effects

Is there a risk for immune activation complications (rejection, GVHD, autoimmune phenomena)?

Existing data suggest the risks are very low

Increased risk with adjuvanted vaccines?

Risks with live vaccines

Possibility for vaccine induced disease especially in patients with suppressed T-cell immunity

Local or disseminated side effects

Risks for immune activation complications (rejection, GVHD, autoimmune phenomena)?

Existing data suggest that the risks are low
Responsibility for vaccination

WE NEED
YOU !!!

IDSA GUIDELINES

2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host

Ljungman - Update on vaccination of oncology patients
Ljungman - Update on vaccination of oncology patients

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Recommendation</th>
<th>Strength</th>
<th>Evidence Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (inactivated influenza vaccine)</td>
<td>U</td>
<td>Strong, very low</td>
<td></td>
</tr>
<tr>
<td>Repetis A</td>
<td>U</td>
<td>Strong, very low</td>
<td></td>
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Are recommendations followed?

663 HSCT recipients reviewed between December 2010 through February 2013 revealed that:

252 (38%) patients received the first series of recommended vaccinations by 6 months
398 (60%) received them by 1 year after HSCT

Ariza-Heredia EJ et al, ECCMID 2014

Influenza

Will vaccination prevent infection?
If not, can vaccination decrease the severity of disease?
When after therapy is it meaningful to vaccinate?
Are there any risks?
How to analyze immune response?
Influenza vaccinations to health care workers caring for leukemia patients and/or allogeneic/autologous HSCT recipients

• Seasonal influenza vaccination is strongly recommended annually for all health care workers (HCWs) of HSCT recipients and non-transplant leukemic patients. (A-II)

<table>
<thead>
<tr>
<th></th>
<th>Allo &lt; 12 m</th>
<th>Allo &gt; 12 m</th>
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</thead>
<tbody>
<tr>
<td>A1</td>
<td>9/35 (26%)</td>
<td>6/15 (40%)</td>
</tr>
<tr>
<td>A3</td>
<td>13/35 (37%)</td>
<td>8/15 (53%)</td>
</tr>
<tr>
<td>B</td>
<td>5/35 (14%)</td>
<td>6/15 (40%)</td>
</tr>
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</table>

<table>
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<tr>
<th></th>
<th>Auto &lt; 12 m</th>
<th>Auto &gt; 12 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>15/47 (32%)</td>
<td>9/19 (47%)</td>
</tr>
<tr>
<td>A3</td>
<td>21/47 (45%)</td>
<td>8/19 (42%)</td>
</tr>
<tr>
<td>B</td>
<td>8/47 (17%)</td>
<td>7/19 (37%)</td>
</tr>
</tbody>
</table>

Pauksen et al CID 2000
Influenza Vaccination for Immunocompromised Patients: Systematic Review and Meta-analysis by Etiology

Clinical efficacy of vaccination - SCT recipients

Risk factors for influenza during an epidemic in Brazil

177 patients were analyzed

Vaccination recommended at 6 months

Compliance 44%

Among vaccinated patients, the protection rate was 80%

Machado et al 2005
Median time from end of therapy: 29 months (7-65)

Fludarabine therapy was the strongest negative factor for vaccination response (all had received rituximab)
**Doses, intervals, and vaccine types**

- How should we use existing vaccines (conjugate; polysaccharide)?
- When can we start?
- Number of doses?
- Intervals between doses?

**What do the recommendations say?**

Children should receive age appropriate vaccinations

What about adults?
- What vaccine should be used?
- What schedule should be used?
- When should vaccines be given?

**IDSA**

- PCV13 should be administered to newly diagnosed adults with hematological (strong, very low) or solid malignancies (strong, very low) and children with malignancies (strong, very low) as described in recommendations 27a-c.
- PPSV23 should be administered to adults and children aged ≥2 years (strong, low) at least 8 weeks after the indicated dose(s) of PCV13.
Very few studies have looked at PCV in hemat malignancies. One randomized study in which one dose of PCV7 was compared to one dose of PPSV23 in patients with Hodgkin lymphoma. One dose of PCV7 gave lower antibody level increases than one dose of PPSV23.

Molrine et al, Ann Intern Med 1996

A subgroup of the PCV7 patients received 12 months later a PPSV23 dose and responded with higher antibody levels than the patients in the original study that got only PPSV23.

Chan et al, JID 1996

One dose of conjugate vaccine, CLL

Sinisalo et al, Vaccine 1997

78. Three doses of PCV13 should be administered to adults and children starting at age 3–6 months after HSCT (strong, low). At 12 months after HSCT, 1 dose of PPSV23 should be given provided the patient does not have chronic GVHD (strong, low). For patients with chronic GVHD, a fourth dose of PCV13 can be given at 12 months after HSCT (weak, very low).
Uncontrolled studies show that only one dose PCV gives quite poor response also in HSCT recipients.

Donor vaccination might improve the results

No controlled study have compared one vs. three doses of PCV

No controlled study has investigated the efficacy of the prime – boost strategy with 1 dose PCV followed by 1 dose PPSV23

Influence of Immunization Timing on the Response to Conjugate-Pneumococcal Vaccine after Allogeneic Stem Cell Transplantation; the IDPW01 trial
CID 2009

C Cordonnier, M Labopin, Y Chesnel, P Ribaud, R da la Camara, R Martino, A Ulmann, T Parkkali, A Locasciulli, K Yakouben, K Pauksen, D Niederwieser, J Apperley, E Bonnet, H Einsele, P Ljungman,
for the EBMT Infectious Diseases Working Party
Percentage of responders at the cut-off of ≥ 0.5µg/mL for all the 7 antigens of Prevnar®

<table>
<thead>
<tr>
<th></th>
<th>EARLY GROUP</th>
<th>LATE GROUP</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1 (before)</td>
<td>8% (6/74)</td>
<td>2% (1/64)</td>
<td>.08</td>
</tr>
<tr>
<td>S3 (1 mo after 3 doses)</td>
<td>56% (12/21)</td>
<td>34% (7/21)</td>
<td>.64</td>
</tr>
<tr>
<td>S6 (24 mo)</td>
<td>34% (15/44)</td>
<td>55% (23/42)</td>
<td>.06</td>
</tr>
</tbody>
</table>

S1 and S6: no difference
S3 (test of non-inferiority): we are 95% sure that the results in the early arm are not more than 13.5% worse than the results in the late arm.

Response to PPSV23 given at 12 or 18 months after HSCT

<table>
<thead>
<tr>
<th></th>
<th>Time</th>
<th>Early group</th>
<th>Late group</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>S4</td>
<td>4/51 (8%)</td>
<td>1/52 (2%)</td>
<td>.16</td>
<td></td>
</tr>
<tr>
<td>S5</td>
<td>21/50 (42%)</td>
<td>28/47 (60%)</td>
<td>.08</td>
<td></td>
</tr>
<tr>
<td>S6</td>
<td>17/44 (39%)</td>
<td>21/42 (50%)</td>
<td>.29</td>
<td></td>
</tr>
</tbody>
</table>

41% of non-responders to PCV7 responded.
The serotype coverage was extended.

Cordonnier et al, Vaccine 2010

Long-term immunity in the IDWP01 study

Cordonnier et al, Bone Marrow Transplantation 2015
Immunogenicity, Safety, and Tolerability of 13-Valent Pneumococcal Conjugate Vaccine Followed by 23-Valent Pneumococcal Polysaccharide Vaccine in Recipients of Allogeneic Hematopoietic Stem Cell Transplant Aged 2 Years and Older: An Open-Label Study

Catherine Cordonnier,1,2 Per Ljungman,3 Christine Juergens,4 Johan Maertens,5 Dominik Selleslag,6 Vani Sundaraviji,7 Keri Clarke,8 William C. Gruber,9 Daniel A. Scott,9 Beate Schmoele-Thoma3

1 Henri Mondor University Hospital, Créteil, France
2 Université Paris-Est-Créteil, Créteil, France, 3 Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden, 4 Pfizer Pharma GmbH, Berlin, Germany, 5 Universitaire Ziekenhuizen Gasthuisberg, Leuven, Belgium, 6 AZ Sint-Jan Brugge-Oostende, Brugge, Belgium, 7 inVentiv HealthCritical, LLC, Princeton, NJ, USA, 8 Pfizer Inc, Surrey, UK, 9 Pfizer Inc, Pearl River, NY, USA

Study Design and Endpoints

Visit 1
PCV13
28–42 days after visit 1
Visit 2
PCV13
28–42 days after visit 2
Visit 3
PCV13
28–42 days after visit 3
Visit 4
28–42 days after visit 3
Visit 5
PCV13
182–224 days after visit 3
Visit 6
PPSV23
28–42 days after visit 5
Visit 7
28–42 days after visit 6
Visit 8
168–196 days after last PCV13

*One additional adult patient had PBSC (confirmed by site after study).
† Assessed using the “All Assigned Patients” population.

All Patients Assigned to Study

<table>
<thead>
<tr>
<th>All Available Immunogenicity Population</th>
<th>Age ≤ 18</th>
<th>Age 18–20</th>
<th>All (age ≥ 2)</th>
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<tbody>
<tr>
<td>n=60</td>
<td>n=189</td>
<td>n=251</td>
<td></td>
</tr>
<tr>
<td>Demographics at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age, y (min, max)</td>
<td>10 (2,17)</td>
<td>55 (65)</td>
<td>42 (2,71)</td>
</tr>
<tr>
<td>Sex: M/F, %</td>
<td>10 (13)</td>
<td>19 (39)</td>
<td></td>
</tr>
<tr>
<td>Transplant details</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditioning: myeloablative/reduced intensity, %</td>
<td>68 (10)</td>
<td>55 (65)</td>
<td>61 (39)</td>
</tr>
<tr>
<td>Source of HLA-matched/unmatched, %</td>
<td>57 (30)</td>
<td>53 (73)</td>
<td>21 (74)</td>
</tr>
<tr>
<td>Median time between HSCT and PCV13 dose 1, d (min, max)</td>
<td>97 (20)</td>
<td>90 (20)</td>
<td>90 (20)</td>
</tr>
<tr>
<td>Underlying diseases, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myeloid leukaemia</td>
<td>8 (13)</td>
<td>95 (55)</td>
<td>103 (41)</td>
</tr>
<tr>
<td>Aplastic anaemia</td>
<td>16 (27)</td>
<td>16 (25)</td>
<td>32 (13)</td>
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<tr>
<td>Other haematologic conditions</td>
<td>4 (7)</td>
<td>17 (30)</td>
<td>21 (8)</td>
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<tr>
<td>Baseline medications, n (%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Prophylactic antibiotics</td>
<td>11 (18)</td>
<td>55 (29)</td>
<td>66 (26)</td>
</tr>
<tr>
<td>Anti-infectives</td>
<td>24 (39)</td>
<td>114 (60)</td>
<td>138 (55)</td>
</tr>
<tr>
<td>Tumidina</td>
<td>4 (7)</td>
<td>29 (15)</td>
<td>33 (13)</td>
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Ljungman - Update on vaccination of oncology patients

IgG Antibody Response Curves

Percentage of Patients with Local Reactions Following PCV13

Measles is making a come-back
Measles is making a comeback

Measles Cases and Outbreaks, 1970-2013

- 397 cases in 1970
- 16 cases in 2013
- 348% increase in cases between 1970 and 2013

Measles

Safe if given 2 years after SCT (no chronic GVHD, no ongoing immunosuppression)
- King et al 1990
- Ljungman et al 1990

Effective in adults if given 2 years after SCT
- Ljungman et al 1990

Effective if given at 2 years after SCT in children
- King et al 1996

High failure rate if given at 2 years after SCT in children
- Spolou et al 2004

Safe if given at 1 year after SCT
- Machado et al 2005

Is it safe?

Most studies have shown no increased risk for side effects

Limited or any risk for increased activity of cGVHD
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"Old" vaccines against VZV

Studies with the live vaccines
Ljungman et al 2003  (varicella vaccine)
Naidus et al 2012  (zoster vaccine)

Studies with inactivated vaccines
Redman et al 1997
Hata et al 2002

IDSA recommendations

22. ZOS should be administered to patients aged ≥60 years who are receiving therapy considered to induce a low level of immunosuppression (strong, low).
23. ZOS should not be administered to highly immunocompromised patients (strong, very low).
Severe side effects - varicella vaccine

Disseminated, Persistent, and Fatal Infection Due to the Vaccine Strain of Varicella-Zoster Virus in an Adult Following Stem Cell Transplantation

New Zoster vaccines

Safety and Immunogenicity of Heat-Treated Zoster Vaccine (ZVHT) in Immunocompromised Adults

Immune response to vaccination

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>n</th>
<th>Estimated GMT</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VZV-specific IgG anti-PhytoELISPOT</td>
<td>56</td>
<td>3.0</td>
<td>1.0, 9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Influenza</td>
<td>56</td>
<td>1.4</td>
<td>0.5, 4.0</td>
<td>0.001</td>
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<tr>
<td>HIV-infected</td>
<td>60</td>
<td>1.8</td>
<td>1.2, 2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Autologous HCT</td>
<td>38</td>
<td>3.0</td>
<td>1.5, 6.0</td>
<td>Exploratory only</td>
</tr>
<tr>
<td>Allogeneic HCT</td>
<td>40</td>
<td>1.2</td>
<td>0.7, 2.1</td>
<td>Exploratory only</td>
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</table>
A common practical question

What do I do with a immunsuppressed patient travelling to

What vaccines might come up?

- HBV: No risk / data exist
- HAV: No risk / limited data
- Polio (inactivated): No risk / data exist
- BCG: Poor risk / benefit ratio?
- Typhoid (inactivated): No data / should be no risk
- Japanese encephalitis: No data / should be no risk
- Yellow fever: Limited data / risk?

Questions?