Role of biologics on vaccination in rheumatic diseases

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Sao Pedro 2015
Concerns about vaccinating PedRD

1. Is vaccination safe under medication, esp biologicals
   • Effect of vaccination on disease activity
   • Risk of inducing infection with live-attenuated virus vaccines (MMR, VZV)

2. Does vaccination induce protection?
   • Serological response
   • Infection prevention

For the audience:
Do you give MMR or VZV during
   • Inactive disease
   • Active disease
Similar immune responses to immunisation in RA, treated with biologicals and MTX

- Etanercept and MTX (retrospective, 1)
  - Response to influenza same for Etanercept as MTX
- Adalimumab and MTX (RCT, 2)
  - Adequate pneumococcal vaccine response 37.4% (controls 40%) and similar % of protective antibody titers in both groups.
  - Lower influenza vaccine response (51.5% vs 63.3%)
- Certolizumab and MTX (RCT, 3):
  - In patients without baseline antibodies: Lower pneumococcal immune responses (54.5% vs 62.5). Overall, 50.5 vs 54.1% had adequate titers
- Tociluzimab and MTX (RCT, 4)
  - 60.0% vs 70.8% responded to PPV23

Table 2  Recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases with level of evidence, strength of recommendations and results of Delphi voting per recommendation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Category of evidence</th>
<th>Increased incidence of VP infection</th>
<th>Efficacy of vaccination</th>
<th>Harms of vaccination</th>
<th>Strength of recommendation</th>
<th>Mean (SD) level of agreement by Delphi voting (VAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The vaccination status should be assessed in the initial investigation of patients with AIRD</td>
<td></td>
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<tr>
<td>Vaccination in patients with AIRD should ideally be administered during stable disease</td>
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<tr>
<td>Live attenuated vaccines should be avoided whenever possible in immunosuppressed patients with AIRD</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td>D</td>
<td>9.50 (0.97)</td>
</tr>
<tr>
<td>Vaccination in patients with AIRD can be administered during the use of DMARDs and TNFα blocking agents, but should ideally be administered before starting B cell-depleting biological therapy</td>
<td>II</td>
<td></td>
<td></td>
<td></td>
<td>D</td>
<td>8.88 (1.26)</td>
</tr>
<tr>
<td>Influenza vaccination should be strongly considered for patients with AIRD</td>
<td>III</td>
<td>Ib</td>
<td>Ib</td>
<td></td>
<td>B-C</td>
<td>9.25 (1.13)</td>
</tr>
<tr>
<td>23-valent polysaccharide pneumococcal vaccination should be strongly considered for patients with AIRD</td>
<td>III</td>
<td>II</td>
<td>II</td>
<td></td>
<td>B-C</td>
<td>9.13 (1.02)</td>
</tr>
<tr>
<td>Patients with AIRD should receive tetanus toxoid vaccination in accordance with recommendations for the general population. In case of major and/or contaminated wounds in patients who received rixivax within the last 24 weeks, passive immunisation with tetanus immunoglobulin should be administered</td>
<td></td>
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<tr>
<td>Herpes zoster vaccination may be considered in patients with AIRD</td>
<td>III</td>
<td>–</td>
<td>IV</td>
<td></td>
<td>C-D</td>
<td>9.00 (1.10)</td>
</tr>
<tr>
<td>HPV vaccination should be considered in selected patients with AIRD</td>
<td>III</td>
<td>–</td>
<td>–</td>
<td></td>
<td>C-D</td>
<td>8.19 (1.38)</td>
</tr>
<tr>
<td>In hypogammaglobulinemia or asplenia patients with AIRD, influenza, pneumococcal, Haemophilus influenzae b and meningococcal C vaccinations are recommended</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td>D</td>
<td>8.44 (1.41)</td>
</tr>
<tr>
<td>Hepatitis A and/or B vaccination is only recommended in patients with AIRD at risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D</td>
<td>9.50 (0.82)</td>
</tr>
<tr>
<td>Patients with AIRD who plan to travel are only recommended to receive their vaccinations according to general rules, except for live attenuated vaccines which should be avoided whenever possible in immunosuppressed patients with AIRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D</td>
<td>9.13 (0.89)</td>
</tr>
<tr>
<td>BCG vaccination is not recommended in patients with AIRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D</td>
<td>9.25 (1.24)</td>
</tr>
</tbody>
</table>

*For hepatitis B only

AIRD, autoimmune inflammatory disease; BCG, Bacillus Calmette-Guérin; DMARD, disease-modifying antirheumatic drug; HPV, human papillomavirus; TNF, tumour necrosis factor; VAS, visual analogue scale; VP, vaccine-preventable.
What about immunising children using biologics

Increasing numbers of indications and different biologics since 1999

JIA: most common pediatric rheumatic disease treated with biologics

Existing international network of expert pediatric rheumatology centers
Vaccinations in PedRD: Men C

Meningococcal C vaccination in JIA

Prospective observational cohort: good immunogenicity (1)
Long term follow-up (4-10y) (2)
Low numbers of patients with biologics

doi:10.1136
Anti MenC IgG levels rise after MenC vaccination

Zonneveld–Huijssoon et al. Arthr Rheum 2007;56;639
Table 2  Characteristics of different age cohorts at time of MenCC vaccination and during follow-up

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Cohort according to age at time of vaccination</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13–19 years (n=21)</td>
<td>9.0–12.9 years (n=41)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>16 (76)</td>
<td>26 (63)</td>
</tr>
<tr>
<td>Median number of available samples (range)†</td>
<td>3 (1–6)</td>
<td>3 (1–8)</td>
</tr>
<tr>
<td>JIA subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligoarticular JIA (%)</td>
<td>5 (24)</td>
<td>12 (29)</td>
</tr>
<tr>
<td>Extended oligoarticular/polyarticular JIA (%)</td>
<td>11 (52)</td>
<td>21 (51)</td>
</tr>
<tr>
<td>Other JIA (%)</td>
<td>5 (24)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Medication use at time of MenCC vaccination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients on methotrexate (%)</td>
<td>9 (43)</td>
<td>18 (44)</td>
</tr>
<tr>
<td>Patients on biologicals (%)‡</td>
<td>2 (10)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Start of treatment after MenCC vaccination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients starting with methotrexate (%)</td>
<td>6 (29)</td>
<td>17 (42)</td>
</tr>
<tr>
<td>Mean time (years) elapsed since MenCC vaccination (±SD)</td>
<td>3.2 (±2.1)</td>
<td>3.0 (±1.9)</td>
</tr>
<tr>
<td>Patients starting with biologicals (%)§</td>
<td>5 (24)</td>
<td>18 (44)</td>
</tr>
<tr>
<td>Mean time (years) elapsed since MenCC vaccination (±SD)</td>
<td>3.4 (±1.9)</td>
<td>5.5 (±1.3)</td>
</tr>
<tr>
<td>Estimated t½ MenC-specific IgG antibodies (years, 95% PI)</td>
<td>2.3 (1.7–3.4)</td>
<td>2.9 (2.3–3.9)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, frequencies (percentage) are depicted.
†Twenty-one patients only had one serum sample available.
§Six patients used tumour necrosis factor (TNF)α blocking agents (4 etanercept, 2 infliximab), and 1 patient from the 5–8.9 years cohort used an interleukin (IL)-6 antagonist (tocilizumab) at time of MenCC vaccination. In one of the patients initially treated with etanercept, rituximab and later abatacept were started during follow-up after treatment with etanercept had failed.
¶Of the patients in whom biologicals were commenced after vaccination, the IL-1 receptor antagonist anakinra was started in nine patients. Three of these patients were aged 9–13 years, 5 were 5–8.9 years, and 1 was 1–4.9 years at time of MenCC vaccination. In all other patients, TNFα blocking agents (40 etanercept, 4 infliximab) were initiated.
JIA, juvenile idiopathic arthritis; MenCC, meningococcal serotype C conjugate; n/a, not applicable; PI, predictive interval; t½, half-life.
Men C in JIA (n=127): long term follow-up

Figure 1  Kinetics of MenC polysaccharide-specific IgG concentrations according to age at time of vaccination in patients with juvenile idiopathic arthritis. All age groups are outlined in A. In B, the lines of

Figure 4  Example of MenC-specific IgG concentrations decline before and after starting treatment with biologicals in one patient. This

Stoof & Heijstek, ARD 2012,
Live attenuated Vaccinations in PedRD

- MMR vaccination in JIA patients
  - Retrospective safety analysis
  - Retrospective immunogenicity analysis (serology)
  - Prospective randomized controlled trial
    - Clinical, serological and immunological analysis
Retrospective study: No effect of MMR booster on disease activity

* All P-value Wilcoxon SR test: NS

Percentage of patients with a flare similar before and after MMR booster (n=207)

Higher MV-GMT in JIA
Mumps and RV-GMT lower

Measles-specific IgG concentrations

Mumps-specific IgG concentrations

Rubella-specific IgG concentrations

Healthy control (n=2173)

JIA (n=400)
## Prevalence of protective antibody levels lower in JIA, except for MV

Corrected for number of vaccinations, age

<table>
<thead>
<tr>
<th>Protective antibody levels</th>
<th>OR*</th>
<th>95%-CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>1.4</td>
<td>0.8-2.5</td>
<td>0.233</td>
</tr>
<tr>
<td>Mumps</td>
<td>0.4</td>
<td>0.3-0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rubella</td>
<td>0.4</td>
<td>0.3-0.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>0.1</td>
<td>0.06-0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tetanus</td>
<td>0.1</td>
<td>0.05-0.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Heijstek et al. *ARD 2012*
MMR immunisation during biological treatment

Retrospective analysis (Borte, 2009)
• MMR booster in 10 JIA children with etanercept and low dose MTX
• Similar immunogenicity compared with MTX monotherapy

Prospective analysis (Heijstek 2013)
• RCT for MMR booster in 137 JIA patients
• No worsening of disease activity
• MTX and biologics did not affect humoral responses, but low patient numbers precluded definite conclusions.
**Figure 2. Mean Disease Activity Levels During 12 Months of Follow-up by Randomization Group**

**A. Patients with JIA**

\[ \Delta \text{JADAS-27} = 0.4 \text{ (95% CI, -0.5 to 1.2)} \]

**B. Patients taking methotrexate**

\[ \Delta \text{JADAS-27} = 0.02 \text{ (95% CI, -1.1 to 1.2)} \]

**C. Patients taking biologics**

\[ \Delta \text{JADAS-27} = 0.6 \text{ (95% CI, -1.2 to 2.4)} \]

JADAS-27 indicates Juvenile Arthritis Disease Activity Score including 27 joints; JIA, juvenile idiopathic arthritis; MMR, measles-mumps-rubella. Error bars indicate 95% CIs. Δ indicates the difference in JADAS-27 scores over time between randomization groups.
What about HPV?

- HPV is associated with cervical dysplasia and cancer
- In healthy women HVP vaccination is effective
- HPV related cervical pathology is increased in adults with RA and SLE

But:
- The HPV adjuvans may cause adverse reactions (ASIA syndrome)
- Only few studies on HPV in SLE exist

Safety on vaccines, an ongoing debate

- Hawkes D (1): The current studies involving human cases are so diverse, in both external stimuli and in resulting conditions, that there is currently a lack of reproducible evidence for any consistent relationship between adjuvant and autoimmune condition.

- Schoenfeld (2) et al postulate an ASIA syndrome (autoimmune syndrome induced by adjuvants or silicone exposure)
  - Chronic fatigue syndrome, sick building syndrome, SJIA, SLE, breast implants

- In the VAERS database cases of pyrexia, myalgia and arthralgia or arthritis were reported with 3.6 cases per 100,000 doses of HPV (3)

1: J Autoimmun 2015 May;59:77-84;
2: Clin Rheumatol. 2015 Jan 22.
Disease activity does not increase after HPV vaccination.
Response rate similar for HPV 16-18
Lower HPV-antibody levels in SLE / JDM

**HPV16 titers HC, JIA, SLE and JDM**

- **Titer (GM)**
- **Days after first vaccination (GM)**

- **HC**
- **JIA**
- **SLE**
- **JDM**
**HPV vaccine in SLE**

- Mean SLEDAI scores do not increase following vaccination (low patient numbers).
- Seropositivity post-vaccine was high for HPV 6, 11, 16 and 18.
- However, vaccination-induced HPV16/18-specific antibody concentrations seemed lower.
- Quadrivalent HPV vaccine seems generally safe and well tolerated in this series of adolescents and young women with SLE, with no increase in mean SLEDAI scores, but larger studies are needed.

- Soybilgic, PROJ 2013 Aug 7;11:29
- Mok, ARD 2013;72:659-664
EULAR task force: recommendations

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Antirheumatic drugs and vaccinations

Safety
• Non-live vaccines are safe when on MTX, GCs, anti-TNF alpha, RTX
• Live-attenuated boosters seem safe when on low dose MTX or GCs
• Live-attenuated vaccines may be considered when on MTX, GCs, anti-TNF alpha, RTX on a case-by-case basis

Immunogenicity
• Good when on MTX, low dose GCs or anti-TNF alpha
  – except for PPV23 when on MTX
• Possibly lower when on high dose GCs (>20mg/day or >2mg/kg/day)
• Much lower until 6 months after RTX

EULAR Recommendations
Non-live vaccines

• Non-live vaccines safe in PedRD, including patients on GCs, DMARDs and anti-TNF alpha

• Annual influenza vaccination should be considered in all PedRD patients

• Hib, pneumococcal and meningococcal vaccines
  – recommended for patients with low complement or asplenia
  – should be considered in patients on high dose IS drugs

• HPV vaccination advised for SLE patients

• Patients on high dose DMARDS, high dose GCs or biologicals: withhold live-attenuated vaccines
  – can be considered on a case-to-case

• In patients on low dose MTX or GCs: Boosters vaccinations (MMR, VZV, YFV) can be considered

• Consider VZV vaccination in case of negative history for VZV infection / vaccination

Heijstek & Ott de Bruin, Ann Rheum Dis. 2011 Oct;70(10):1704-12
Vaccination in AIRD: Friend or foe?

**Efficacy**
- Generally effective in AIRD without drugs
- Reduced by high dose IS drugs
- Persistence of antibodies reduced
- Vaccine and disease dependent

**Safety**
- Non-live vaccines
- Live-attenuated vaccines
- Live-vaccines in high dose IS drugs
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