Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept

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Introduction

Juvenile idiopathic arthritis (JIA) represents a heterogeneous group of disorders characterized by chronic inflammatory arthritis and turns out to be the commonest rheumatic disease seen in childhood worldwide. In Northern European countries and the United States the incidence ranges between 5 and 21 per 100 000 children, with a prevalence of ~1–2 per 1000 [1, 2].

Immunization in JIA using attenuated live vaccines poses a debatable problem because of the very limited data on safety, efficacy and immunogenicity in particular. Even amongst experienced clinicians in the field of paediatric rheumatology there is uncertainty with regard to the efficacy of attenuated live vaccines in patients receiving low-dose MTX or the TNF-α receptor antagonist etanercept [3–7].

Previous studies on protection against measles, mumps and rubella (MMR) virus have been based solely on antibody levels, whereas the protective effect of MMR immunization is conferred by the interplay of humoral and cell-mediated immune (CMI) responses [8, 9]. In the present study, a cell-based enzyme-linked immunospot assay (ELISPOT) was employed for detection of long-lived protective T cells [8, 10, 11]. IFN-γ production by T cells specific for the three components of MMR vaccine and seroprevalence of virus-specific IgG antibodies were investigated following MMR revaccination in children with JIA treated with either low-dose MTX therapy alone or in combination with etanercept.

Patients and methods

Patients

A prospective nested case–control study was performed in which three investigational groups of JIA patients were compared each with a group of age-based healthy controls. In total, 22 healthy individuals and 15 children with JIA were included consecutively. We confirmed the diagnosis according to International League of Associations for Rheumatology (ILAR) criteria. Baseline characteristics of JIA patients are specified in Supplementary Table 3, available as supplementary data at Rheumatology Online. All individuals were scheduled for MMR vaccination according to recommendations of the vaccinations committee of Saxony, Germany [12]. These recommendations advise MMR-I vaccination between 13 and 24 months of life and MMR-II revaccination following the fifth birthday at the age of 6.

Investigational Group 1 represented JIA patients with completed MMR-I and -II vaccination, being treated with low-dose MTX therapy (10 mg/m² body surface, once weekly, s.d.: 7.5–15 mg/person) that was started on average 4 yrs later than MMR revaccination. Group 2a consisted of children with JIA that received MMR revaccination whilst being treated with low-dose MTX therapy for at least 6 months before vaccination date. Group 2b included JIA patients being treated with low-dose MTX in combination with the TNF-α receptor antagonist etanercept (0.4 mg/kg body weight, twice weekly) for at least 6 months before receiving MMR revaccination. Treatment with etanercept was not interrupted before MMR revaccination.

Parents were informed about the considerable side-effects of MMR revaccination with regard to children’s treatment and were asked for written, informed consent (treatment on demand). All patients were asked to comment on side-effects after vaccination (patient’s diary book), to visit the health care centre periodically every 8 weeks for 6 months following vaccination or immediately in case of any symptoms of infection, the need to increase medication or worsening of self-reported health. Disease activity and medication use were documented every visit.
The population of healthy individuals included 9 boys and 13 girls, mean age 11.2 yrs (range 1-20 yrs). Blood samples were taken upon patients’ or parents’ written consent in the course of preparation for scheduled operations. This study was done according to the approval of the ethics committee of the University of Leipzig.

Disease activity and medication use

Disease activity and medication use were compared during the period of 6 months before revaccination vs 6 months after MMR revaccination for Groups 2a and 2b. Disease activity was assessed by a paediatric rheumatologist and measured as the number of joints with active arthritis, the physician’s global assessment (PGA) of disease activity on a 3-cm visual analogue scale (VAS), and the ESR [5, 13-15].

Sample collection

Heparinized peripheral venous blood (4.5 ml) was obtained from all included individuals. Blood sampling was done at least 6 months after initiation of low-dose MTX therapy (Group 1) or 6 months following MMR revaccination (Groups 2a and 2b). Healthy controls were selected based on age at blood sampling within matched patient groups. Peripheral blood mononuclear cells (PBMCs) were isolated as described elsewhere [16]. The plasma phase was centrifuged at 900 g for 15 min. Afterwards 1 ml of supernatant was stored at −80°C. To maintain full functionality of CD4 and CD8 T cells in cryopreserved PBMCs, freezing and thawing of PBMCs was performed following an evaluated protocol [16].

MMR virus antibody assays

Specific IgG antibody content was measured in all collected plasma samples. Commercial EIA kits for detection of antibodies against MMR (Dade-Behring, Marburg, Germany) were used on the automated BEP III instrument according to the manufacturer’s recommendations. The IgG content was provided in IU/ml for measles and rubella, and as titre for mumps. Cut-off values were adapted from international standards (rubella: 15 IU/ml, for measles and rubella, and as titre for mumps). Cut-off values were adapted from international standards (rubella: 15 IU/ml, for measles and rubella, and as titre for mumps). Cut-off values were adapted from international standards (rubella: 15 IU/ml, for measles and rubella, and as titre for mumps). Cut-off values were adapted from international standards (rubella: 15 IU/ml, for measles and rubella, and as titre for mumps). Cut-off values were adapted from international standards (rubella: 15 IU/ml, for measles and rubella, and as titre for mumps).

ELISPOT assays and viral antigens

ELISPOT assays were performed according to MultiScreen MTS Filter Plate (Millipore, Billerica, MA, USA) technical notes for IFN-γ-ELISPOT [17]. Both IFN-γ capture and detection antibody were purchased from Mabtech (Stockholm, Sweden). Thawed PBMCs were resuspended in RPMI medium with 1% l-glutamine, HEPES and 10% fetal bovine serum (PAA Laboratories, Pasching, Germany) and plated at 150 000 PBMCs/ well in triplicate for each antigen and controls. Antigens of measles virus (Edmonston strain), mumps virus (Enders strain) and rubella virus (Judith strain) were obtained from infected Vero cells (Institut Virion/Serion, Würzburg, Germany). Antigens were added in final concentrations previously established optimal for T-cell stimulation. Phytohaemagglutinin (PHA-M, Sigma, St Louis, MO, USA) served as positive control. ELISPOT plates were incubated at 37°C for 24 h in the presence of 5% CO2. Plate analysis and enumeration of cell counts was done using an AID EISSpot 04 HR Reader and appropriate AID reader software, release 4.0 (Autoimmun Diagnostika, Strassberg, Germany).

Statistical methods

All compared case-control groups were statistically similar in terms of population characteristics. Because numbers of subjects in each group were small, the Kruskal–Wallis test was run with a two-sided P-value <0.05 considered significant. Statistical analysis was carried out on XLSTAT2007 for Windows, release 2007.1 (AddinSoft SARL, Paris, France).

Results

Protective immunity of completed MMR vaccination is not affected by low-dose MTX therapy

To evaluate the influence of low-dose MTX treatment on existing humoral and cell-mediated immunity to MMR we draw comparison between children with JIA, treated with low-dose MTX therapy starting on average 4 yrs later to completed MMR-II revaccination (Group 1, n = 5), and untreated healthy individuals. The comparison group was statistically similar in terms of age, sex and time of blood sampling. Overall, there was a trend towards lowered antibody titres in children with JIA, whereas virus-specific IFN-γ producing T cells were augmented (Fig. 1 and Table 1, similar data for mumps and rubella virus not shown). These findings reached statistical significance for the measles component of MMR vaccine.

Low-dose MTX and etanercept therapy do not interfere intended outcome of MMR revaccination

We studied a total of 10 children with JIA receiving MMR revaccination whilst being treated with either low-dose MTX alone (Group 2a, n = 5) or low-dose MTX in combination with etanercept (Group 2b, n = 5). Neither low-dose MTX nor etanercept was interrupted before MMR revaccination. Population characteristics of compared, untreated healthy individuals did not differ from JIA patients in terms of age, sex and time of blood sampling. Within the group of children treated with low-dose MTX alone (Group 2a) whilst receiving MMR revaccination we observed no statistical relevant differences in antibody titres or virus-specific IFN-γ producing T cells when compared with untreated healthy controls, as shown in Fig. 1 and Table 1. Admittedly, there was a slight trend for JIA patients to have both lower levels of virus-specific IgG antibodies and IFN-γ producing T memory cells. The treatment group of children receiving low-dose MTX plus etanercept therapy during MMR revaccination (Group 2a) tended towards a decline of virus-specific IFN-γ producing T cells, but not within the range of statistical significance. Humoral immunity, in terms of virus-specific IgG antibodies, on the other hand seemed to be slightly increased (Fig. 1 and Table 1).

Disease activity, medication use and safety notes

No worsening of mean disease activity parameters was seen over the period of 6 months after MMR revaccination when compared with 6 months before vaccination date, as shown in Table 2. Further, no increase in medication use was observed for oral or IA steroids or MTX. The mean dose of MTX or oral steroids administered following vaccination was unchanged, too (Table 2). Within all groups no overt measles, mumps, rubella or secondary severe infections were noted during the observational period of 6 months after MMR revaccination.

Discussion

Immunization in children with JIA using attenuated live vaccine has been a matter of controversy and is still handled on individual operating experience [3–6]. In this study, we investigated features of humoral and cell-mediated immunity following MMR
revaccination in JIA patients being treated with DMARDs or biological agents.

Children with JIA, not treated with low-dose MTX therapy until they had completed MMR vaccination, showed a trend for lowered MMR IgG seroprevalence, concomitant with a slight increase in numbers of virus-specific IFN-γ producing T cells when compared with healthy children. These findings are in structural agreement with several studies demonstrating lowered antibody titres in children with JIA following hepatitis B, meningococcal C or influenza vaccination. Antibody responses to vaccination were not affected by prednisone, MTX or infliximab treatment [18–20].

In JIA patients receiving low-dose MTX treatment continuously during MMR revaccination, both virus-specific IgG seroprevalence and numbers of IFN-γ-producing T cells were reduced. However, this effect did not interfere statistically with development of humoral or cell-mediated immunity to MMR virus. In view of our results in children with JIA that received MMR revaccination without simultaneous DMARD treatment, we would endorse findings that low-dose MTX therapy
Efficacy of MMR revaccination in JIA

Table 1. Effects of anti-rheumatic treatment on humoral and cell-mediated immunity to MMR virus

<table>
<thead>
<tr>
<th>Disease activity parameters</th>
<th>Group 1</th>
<th>Controls</th>
<th>P-value</th>
<th>Group 1</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles virus</td>
<td>194.3 (0–410)</td>
<td>1231.7 (461–1730)</td>
<td>0.045</td>
<td>32.3 (26.5–42)</td>
<td>14.3 (5.5–21)</td>
<td>0.038</td>
</tr>
<tr>
<td>Mumps virus</td>
<td>588.6 (0–760)</td>
<td>974.3 (310–590)</td>
<td>0.258</td>
<td>45.4 (31.5–47)</td>
<td>31.8 (22–42.5)</td>
<td>0.522</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>19.4 (14–19)</td>
<td>49.2 (21–73)</td>
<td>0.110</td>
<td>14.1 (8–20)</td>
<td>8.7 (5.5–11.5)</td>
<td>0.176</td>
</tr>
</tbody>
</table>

*Mean value and interquartile range.

Table 2. Disease activity and medication use before and after MMR revaccination in JIA patients receiving MTX or MTX and etanercept

<table>
<thead>
<tr>
<th>Disease activity parameters</th>
<th>Group 2a Before MMR</th>
<th>Group 2a After MMR</th>
<th>Group 2b Before MMR</th>
<th>Group 2b After MMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active joints</td>
<td>1 (0–5)</td>
<td>1 (0–4)</td>
<td>1 (0–3)</td>
<td>1 (0–4)</td>
</tr>
<tr>
<td>PGA</td>
<td>0.6 (0.0–1.8)</td>
<td>0.5 (0.0–1.3)</td>
<td>0.7 (0.0–2.1)</td>
<td>0.4 (0.0–1.1)</td>
</tr>
<tr>
<td>ESR</td>
<td>10 (1–27)</td>
<td>8 (2–29)</td>
<td>8 (1–21)</td>
<td>7 (1–17)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX dose/person (mg/m²)</td>
<td>9 (7.5–20)</td>
<td>9 (8–20)</td>
<td>12 (7–22)</td>
<td>11 (7–17)</td>
</tr>
<tr>
<td>Oral steroids (mg/kg/day)</td>
<td>0.0 (0.0–0.2)</td>
<td>0.0 (0.0–0.2)</td>
<td>0.0 (0.0–0.3)</td>
<td>0.0 (0.0–0.2)</td>
</tr>
<tr>
<td>Patients on NSAIDs (n)</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

PGA: physician’s global assessment of disease activity (0–3 scale), where 0 = inactive, 0.1–1.4 = mildly active, 1.5–2.4 = moderately active and 2.5–3.0 = severely active; values given as mean and range unless indicated otherwise.

Counteracts Th1 T-cell enhancement related to the immunopathology of JIA, resulting in a balance of humoral and cell-mediated immunity almost the same as that seen in healthy children [21, 22].

Children with JIA, receiving TNF-α receptor antagonist etanercept and low-dose MTX continuously during MMR revaccination, featured a notable trend towards fewer MMR virus-specific IFN-γ-producing T memory cells, accompanied by a slight increase of virus-specific IgG serore prevalence. To our knowledge, this represents the first report of tightly monitored MMR revaccination during treatment with the TNF-α receptor antagonist etanercept in children with JIA.

In our patients, neither vaccine failure nor occurrence of overt measles, mumps and rubella or secondary severe infections was observed within 6 months of observation since MMR revaccination. Admittedly, as our study groups are limited in size serious adverse events were potentially not explored [5, 23, 24]. Involvement of substantial numbers of children with JIA being treated with DMARDs and biologic agents and receiving two MMR vaccinations at specified time is exceedingly complicated, e.g. because of legal circumstances.

Further, because of limitation in cell numbers available, virus-specific production of IFN-γ was measured in a whole lymphocyte population instead of isolated CD4 and CD8 populations. We excluded analysis of Th2-like T-cell cytokines for the same reason. It should be mentioned that laboratory testing of in vitro responses to vaccine antigens might differ in results from in vivo responses.

Recapturing, our results provide evidence for the efficacy of MMR revaccination in children with JIA being treated with low-dose MTX or the TNF-α receptor antagonist etanercept. Anti-rheumatic treatment did not seem to interfere with intended outcome of MMR revaccination or to increase disease activity or medication use. However, further studies are needed to provide a safety basis for the use of MMR vaccine in JIA.

Rheumatology key message

- MMR revaccination is effective in children with JIA treated with low-dose MTX and/or the TNF-α receptor antagonist etanercept simultaneously with vaccination.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at Rheumatology Online.

References

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