Rituximab for the Treatment of Common Variable Immunodeficiency (CVID) with Pulmonary and Central Nervous System Involvement

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1. GENETIC DIAGNOSTICS

There are several mutations described which can cause a CVID-like syndrome and can predispose to GLILD like LRBA, CTLA4, RAG1, BIRC4, NFKB1 or KMT2D [1 - 9]. Genetic testing was performed on one patient revealing a gain of function mutation of STAT3. GOF-STAT3-syndrome is a relatively new described syndrome and can cause a CVID-like disease with hypogammaglobulinemia, autoimmune features, lymphoproliferation, and interstitial lung disease [10].

2. HISTOPATHOLOGIC FINDINGS

Patient 1: In 2010, a lung biopsy was performed in an external clinic revealing dense lymphoid infiltrates in histologic testing. A follicular arrangement of CD20-positive B cells and CD3-positive T cells was described without S100 or CD30 positive cells. Re-biopsy in 2013, presented a heterogeneous pattern consisting of NSIP and chronic and partly follicular bronchiolitis. No evidence of malignancy.

Patient 2: In 2009, we performed a biopsy on the right lower lobe of the lung. Histologic examination presented medium-sized epithelioid cell granuloma. In the granuloma wall, loosely scattered CD20 positive B lymphocytes mixed with CD5 positive T cells were found. Poorly present plasma cells without light chain restriction. No evidence of malignancy.

Patient 3: VATS with wedge resection for histologic sampling was performed in 2017. Wedge resection on the upper lobe showed the histologic image of a lymphoplasmohistiocytic infiltration. Wedge resection of the left lower lobe also presented the same chronic lymphoplasmohistiocytic infiltration. Histologic presentation of a mixed image of dominating CD5-positive T cells with CD20-positive B cells in the background with partly loose and follicular aggregation. Low level of plasma cells without light chain restriction. No evidence of malignancy.

3. B CELL REGENERATION CORRELATED WITH GLILD RELAPSE AFTER RITUXIMAB-TREATMENT

Table 1. Flow cytometric analysis of peripheral blood during rituximab-therapy.

<table>
<thead>
<tr>
<th>Flow cytometric analysis</th>
<th>Patient 1:</th>
<th>Patient 2:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow cytometry pre-rituximab 06/2006;</td>
<td>14% B cells, 27% naïve CD10+ B cells, low count of memory B cells, 1.3% postswitch memory B cells, normal count of CD21low B cells.</td>
<td>Flow cytometry pre-rituximab 06/2010; 5% B cells. No memory B cells, normal count of transitional B cells.</td>
</tr>
<tr>
<td>Flow cytometry post-rituximab 10/2007;</td>
<td>No B cells detectable</td>
<td>Flow cytometry post-rituximab 09/2010; No B cells detectable</td>
</tr>
<tr>
<td>Flow cytometry post-rituximab 09/2014;</td>
<td>Flow cytometry post-rituximab 09/2014;</td>
<td></td>
</tr>
<tr>
<td>Flow cytometry post-rituximab 09/2015</td>
<td>No B cells detectable</td>
<td>No B cells detectable</td>
</tr>
<tr>
<td>4x rituximab 375mg/m² 09/2007</td>
<td>2x rituximab 1g abs. 08/2010</td>
<td>2x rituximab 1g abs. 08/2014</td>
</tr>
<tr>
<td>2x rituximab 1g abs. 08/2010</td>
<td>2x rituximab 1g abs. 08/2014</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Flow cytometric analysis of peripheral blood during rituximab-therapy.
Flow cytometric analysis

Flow cytometry pre-rituximab 01/2015:
1% B cells. No further sub differentiation possible.

2x rituximab 1g abs. 06/2017

Flow cytometry post-rituximab 05/2016:
No B cells detectable

Flow cytometry pre-rituximab 08/2016:
Very low count of B cells

2x rituximab 1g abs. 01/2019

Flow cytometry post-rituximab:
Not performed

Flow cytometry pre-rituximab 10/2018:
Very low count of B cells (<0.1%)

2x rituximab 1g abs. 10/2019

Flow cytometry post-rituximab:
Not performed

Patient 2:

2x rituximab 1g abs. 09/2014

Flow cytometry pre-rituximab 02/2014:
7% B cells, 5.2% transitional B cells, 8.6% preswitch memory B cells. 1% postswitch memory B cells. No CD21-positive population.

Flow cytometry post-rituximab 11/2014:
No B cells detectable

2x rituximab 1g abs. 02/2017

Flow cytometry pre-rituximab 08/2016:
3% B cells

Flow cytometry post-rituximab 08/2017:
No B cells detectable

Patient 3:

2x rituximab 1g abs. 07/2017

Flow cytometry pre-rituximab 06/2017:
2.7% B cells. No preswitch and postswitch memory B cells. Increase of transitional B cells, no increase of CD21low cells.

Flow cytometry post-rituximab 11/2017:
1.5% B cells

2x rituximab 1g abs. 01/2018

Flow cytometry pre-rituximab 11/2017:
1.5% B cells

Flow cytometry post-rituximab 03/2018:
Low count of B cells (0.2%), no sub differentiation possible

2x rituximab 1g abs. 09/2018

Flow cytometry pre-rituximab 08/2018:
8.5% B cells.

Flow cytometry post-rituximab 12/2018:
1.7% B cells. Almost complete as transitional B cells. 6.2% preswitch and no postswitch memory B cells.

Table S2. List of GLILD-patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>EUROclass subtype</th>
<th>autoimmune Cytopenia</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>male</td>
<td>B+SmB-CD21&lt;sup&gt;+++&lt;/sup&gt;T&lt;sup&gt;+++&lt;/sup&gt;</td>
<td>No</td>
<td>IgRT</td>
</tr>
<tr>
<td>2</td>
<td>male</td>
<td>B+SmB-CD21&lt;sup&gt;&lt;sup&gt;+++&lt;/sup&gt;&lt;/sup&gt;T&lt;sup&gt;+++&lt;/sup&gt;</td>
<td>Yes</td>
<td>Prednisolone, azathioprine</td>
</tr>
<tr>
<td>3</td>
<td>female</td>
<td>B+SmB-CD21&lt;sup&gt;&lt;sup&gt;+++&lt;/sup&gt;&lt;/sup&gt;T&lt;sup&gt;+++&lt;/sup&gt;</td>
<td>Yes</td>
<td>Prednisolone only</td>
</tr>
<tr>
<td>4</td>
<td>female</td>
<td>B+SmB-CD21&lt;sup&gt;&lt;sup&gt;+++&lt;/sup&gt;&lt;/sup&gt;T&lt;sup&gt;+++&lt;/sup&gt;</td>
<td>Yes</td>
<td>Prednisolone, azathioprine, rituximab</td>
</tr>
<tr>
<td>5</td>
<td>female</td>
<td>B+SmB-CD21&lt;sup&gt;&lt;sup&gt;+++&lt;/sup&gt;&lt;/sup&gt;T&lt;sup&gt;+++&lt;/sup&gt;</td>
<td>Yes</td>
<td>Prednisolone, azathioprine, rituximab</td>
</tr>
<tr>
<td>6</td>
<td>female</td>
<td>B+SmB-CD21&lt;sup&gt;&lt;sup&gt;+++&lt;/sup&gt;&lt;/sup&gt;T&lt;sup&gt;+++&lt;/sup&gt;</td>
<td>Yes</td>
<td>Prednisolone, rituximab, combination of rituximab and azathioprine, rituximab</td>
</tr>
</tbody>
</table>

Table S3. Contingency table for cytopenia and GLILD

<table>
<thead>
<tr>
<th>-</th>
<th>CVID-patients with autoimmune cytopenia</th>
<th>CVID-patients without autoimmune cytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVID-patients with GLILD</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>CVID-patients without GLILD</td>
<td>11</td>
<td>33</td>
</tr>
</tbody>
</table>

REFERENCES


[http://dx.doi.org/10.1126/science.1255904] [PMID: 25211377]

[http://dx.doi.org/10.1016/j.jaci.2018.02.007] [PMID: 29477728]

[http://dx.doi.org/10.1155/2018/3724630] [PMID: 30363934]

[http://dx.doi.org/10.1016/j.jaci.2015.06.002] [PMID: 26194542]

[http://dx.doi.org/10.1016/j.jaci.2018.02.055] [PMID: 29729943]

[http://dx.doi.org/10.1016/j.jaci.2020.07.021] [PMID: 32745555]

[http://dx.doi.org/10.1016/j.jaip.2019.02.018] [PMID: 30825606]