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.

| Flow cytometric analysis | 4x rituximab 375mg/m² 09/2007 | 2x rituximab 1g abs. 08/2010 | 2x rituximab 1g abs. 08/2014 | 2x rituximab 1g abs. 09/2015 |
|-------------------------|--------------------------------|----------------------------|--------------------------|----------------------------|
| Flow cytometry pre-rituximab 06/2006; 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. | Flow cytometry post-rituximab 10/2007; No B cells detectable | Flow cytometry post-rituximab 09/2010; No B cells detectable | Flow cytometry post-rituximab 09/2014; No B cells detectable | Flow cytometry post-rituximab 09/2015; No B cells detectable |
| Flow cytometry pre-rituximab 06/2010; 5% B cells. No memory B cells, normal count of transitional B cells. | Flow cytometry post-rituximab 09/2010; No B cells detectable | Flow cytometry post-rituximab 09/2014; No B cells detectable | Flow cytometry post-rituximab 09/2015; No B cells detectable |
| Flow cytometry pre-rituximab 03/2014; 4.7% B cells. No increase of transitional B cells, complete loss of memory B cells. | Flow cytometry post-rituximab 09/2014; No B cells detectable | Flow cytometry post-rituximab 09/2015; No B cells detectable |
| Flow cytometry pre-rituximab 08/2013; 18% B cells. No increase of transitional B cells, complete loss of memory B cells. | Flow cytometry post-rituximab 09/2014; No B cells detectable | Flow cytometry post-rituximab 09/2015; No B cells detectable |

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Flow cytometric analysis

| Strunz et al. | Flow cytometry pre-rituximab 01/2015: |
|--------------|-------------------------------------|
| 1% B cells. No further sub differentiation possible. | Flow cytometry post-rituximab 05/2016: |
| 2x rituximab 1g abs. 06/2017 |

| Strunz et al. | Flow cytometry pre-rituximab 08/2016: |
|--------------|-------------------------------------|
| Very low count of B cells | Flow cytometry post-rituximab: |
| 2x rituximab 1g abs. 01/2019 |

| Strunz et al. | Flow cytometry pre-rituximab 10/2018: |
|--------------|-------------------------------------|
| Very low count of B cells (<0.1%) | Flow cytometry post-rituximab |
| 2x rituximab 1g abs. 10/2019 |

| Strunz et al. | Flow cytometry pre-rituximab 08/2016: |
|--------------|-------------------------------------|
| 3% B cells | Flow cytometry post-rituximab 08/2017: |
| 2x rituximab 1g abs. 02/2017 |

| Strunz et al. | Flow cytometry pre-rituximab 08/2016: |
|--------------|-------------------------------------|
| 1.5% B cells | Flow cytometry post-rituximab 03/2018: |
| No B cells detectable |
| 2x rituximab 1g abs. 09/2018 |

| Strunz et al. | 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. |

**Patient 2:**

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

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

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

**Patient 3:**

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

Flow cytometry pre-rituximab 11/2017:

1.5% B cells. No preswitch and postswitch memory B cells. Increase of transitional B cells, no increase of CD21low 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.**

| Patient | Gender | EUROclass subtype | autoimmune Cytopenia | Treatment |
|---------|--------|-------------------|----------------------|-----------|
| 1       | male   | B+SmB-CD21<sup>+++</sup>T<sup>+++</sup> | No                   | IgRT      |
| 2       | male   | B+SmB-CD21<sup>+++</sup>T<sup>+++</sup> | Yes                  | Prednisolone, azathioprine |
| 3       | female | B+SmB-CD21<sup>+++</sup>T<sup>+++</sup> | Yes                  | Prednisolone only |
| 4       | female | B+SmB-CD21<sup>+++</sup>T<sup>+++</sup> | Yes                  | Prednisolone, azathioprine, rituximab |
| 5       | female | B+SmB-CD21<sup>+++</sup>T<sup>+++</sup> | Yes                  | Prednisolone, azathioprine, rituximab |
| 6       | female | B+SmB-CD21<sup>+++</sup>T<sup>+++</sup> | Yes                  | Prednisolone, rituximab, combination of rituximab and azathioprine, rituximab. |

**Table S3. Contingency table for cytopenia and GLILD**

| - | CVID-patients with autoimmune cytopenia | CVID-patients without autoimmune cytopenia |
|---|----------------------------------------|-------------------------------------------|
| CVID-patients with GLILD | 5 | 1 |
| CVID-patients without GLILD | 11 | 33 |

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