Rituximab tunes desmoglein-3-specific follicular T cells in patients with pemphigus vulgaris

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Abstract

Background: Pemphigus vulgaris (PV) is characterized by pathogenic auto-antibodies targeting interkeratinocytes desmoglein (Dsg) 1 and 3, and by the HLA-DRB1-0402 predisposition allele. Treatment using rituximab (RTX) combined with short-term corticosteroids (CS) allows disease control and long-lasting remission. The aim of this study is to evaluate the impact of RTX on the circulating subpopulations of Dsg-3-specific T lymphocytes that specifically regulate B cell responses: follicular helper (Tfh) and follicular regulatory T (Tfr) lymphocytes. Methods: Using the HLA-DRB1-0402 tetramer loaded with the Dsg-3 immunodominant peptide, we analysed by flow cytometry the frequency, the polarisation and the activation status of blood Dsg-3-specific follicular T cell populations at baseline, Month 6 and long-term follow-up (Month 60-90) from PV patients. Results: At baseline, we observed a predominance of Tfh1* and Tfh17 subsets and an underrepresentation of the Tfh2 subset among autoreactive Dsg-3-specific Tfh cells as compared with non-autoreactive Tfh cells. RTX treatment induced a decrease of autoreactive Tfh cells with no effect on their polarisation during patients’ follow-up. In parallel, we observed the emergence of a Dsg-3-specific Tfr subpopulation with a significant overexpression of the surface activation markers PD1, ICOS, and CD25 that was not observed at the surface of autoreactive Tfh and non-autoreactive Tfr cells of the same PV patients. In contrast, a very few Dsg-3 specific Tfr cells were observed in PV patients treated with CS alone. Conclusion: Here we show that the emergence of activated autoreactive Dsg-3-specific Tfr cells is associated with the long-term efficacy of RTX in PV patients.

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Figure 1

<table>
<thead>
<tr>
<th>Present study</th>
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<td>57 available blood samples from patients carrying the HLA-DRB1*04:02 susceptibility allele</td>
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**Baseline**
- 20 patients
- Anti-Dog-3 positive in all patients

**RTX at M0:**
- 13 patients
- 13/13 in complete remission
- Anti-Dog-3 Abs negative in all patients

**RTX at M1:**
- 20 patients
- 20/20 in complete remission off-therapy
  - 19/20 patients received their last RTX infusion at M1
  - 1 patient received RTX at M0 due to a relapse
- Anti-Dog-3 Abs negative in 17 patients and positive in 3 patients

**CS alone at the LTfu-date**
- 4 patients
- 4/4 in complete remission off-therapy
  - 2 patients never received RTX
  - 2 patients needed RTX infusions for relapses in their history
- Anti-Dog-3 Abs negative in 2 patients and positive in 2 patients

Figure 2

**A)** Hem; CLP 87.1H

**B)** Dcr-1 150.284

**C)** CD8x

**D)** TB1

**E)** TB1x