

## Infection Risks During Longterm Rituximab Therapy Change Over Time

To the Editor:

In the recent report from the German Registry of Autoimmune Disease (GRAID), Roll, *et al* showed that rituximab (RTX) was well tolerated with good clinical efficacy in patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis (AAV)<sup>1</sup>. However, we would like to share some concerns about their statement that RTX does not increase the rate for infections.

The rate for severe infection in our institution is 6.1 in 100 patient-years, similar to what was observed in the report from GRAID<sup>1</sup>. With our observation time being much longer (148 patient-years compared to 61.4 in GRAID), the impression is that the rate for severe infection is constant over time. However, the net status of immunodeficiency is quite different in patients over time because RTX can induce immunosuppression through several mechanisms<sup>2</sup>.

In AAV, especially when RTX is combined with other immunosuppressive drugs (mycophenolate mofetil and cyclophosphamide) at induction, the risk for severe infections is increased<sup>3,4</sup>. In longterm preemptive re-treatment, RTX can achieve immunosuppression through hypogammaglobulinemia, episodes of late-onset neutropenia, and T cell dysfunction, all through prolonged B cell depletion. In rheumatoid arthritis, hypogammaglobulinemia occurs in 10% of the patients after the first course, but this increases to 30% after the fourth course<sup>5</sup>, with lower IgG levels before RTX therapy being a risk factor for infections<sup>6</sup>. Late-onset neutropenia can increase the risk for severe infections in rheumatic diseases<sup>7</sup> because it is associated with marked B cell depletion<sup>7</sup> and hypogammaglobulinemia<sup>8</sup>. Prolonged B cell depletion from RTX maintenance also impairs T cell-mediated immunity, with increased risk for viral infections (cytomegalovirus, JC virus) and fungal infections (*Pneumocystis jirovecii*), usually associated with T cell dysfunction<sup>2</sup>. This indicates that while taking RTX over the long term, a patient's net status of immunodeficiency increases over time, together with the risk for serious infections. While the mechanism through which prolonged B cell depletion is linked to hypogammaglobulinemia, late-onset neutropenia, and T cell dysfunction is still unclear, the issue is already of great clinical relevance.

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