Predicting severe infection in repeat cycles of rituximab and effects of hypogammaglobulinaemia for the treatment of rheumatic and musculoskeletal diseases

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Background: Rituximab (RTX) is effective in treating various rheumatic and musculoskeletal diseases (RMDs). Repeat cycles are often required for disease control but may lead to hypogammaglobulinaemia. Low IgG at baseline has been associated with increased risk of severe infection event (SIE) post-RTX. However, there are limited data on predictors of SIEs in repeat cycles including immunoglobulin levels and B-cell counts as well as outcomes of hypogammaglobulinaemia.
Objectives: To assess predictors of SIEs in repeat RTX cycles and effects of hypogammaglobulinaemia in terms of rates of SIEs, infection-related mortality and its persistence post-cessation of RTX.
Methods: A retrospective study was conducted in the first 700 consecutive RMD patients treated with at least a cycle of RTX in Leeds. IgM, IgA and IgG levels were measured at baseline and 4-6 months after each cycle. For cycles 2-4 (C2-4), predictors for SIEs were analysed using mixed-effects logistic regression analysis.
Results: 550 patients were female, mean(SD) age 56(16) years and median (IQR) disease duration 7.9(3.4-15.0) years. 507(72%) had RA, 94(13%) SLE, 49(7%) AAV, 14(2%) inflammatory myopathies, 9(1%) pSS, 5(1%) APS, 6(1%) SSc and 16(3%) other CTDs. 364(52%) were biologic-naïve and 514(73%) were on concomitant DMARDs. Total follow-up: 2880 patient-years (PY). 281 SIEs were recorded in 176 patients (9.8/100 PY). In C1, we had validated that low IgG was predictive of SIE within 12 months of C1. For cycles 2-4, in multivariable analysis, non-RTX-specific comorbidities [chronic lung OR (95% CI) 2.2 (1.3-4.0), diabetes 2.6 (1.1-6.0), heart failure 5.8 (1.5-22.8), previous cancer 3.2 (1.5-7.0) and severe infection 6.3 (3.1-12.8)], higher corticosteroid dose 1.08 (1.02-1.13) and RTX-specific variables [higher IgM 1.2 (1.0-1.6) and longer retreatment time 1.01 (1.0-1.02)] were associated with increased odds of SIEs, but not B-cell counts or depletion status. Higher IgG level reduced the risk 0.88 (0.81-0.96). Of 110 patients with either low IgG at RTX baseline or for at least 4 months during therapy, SIE rates were higher in those with low baseline IgG (16.4/100 PY) or acquired it post-RTX (21.3/100 PY) versus those with normal IgG (9.7/100 PY), 10/110 (9.1%) died of infection-related complications and only 4/11(36%) had IgG normalised after switching therapies.
Conclusion: Immunoglobulin should be monitored at baseline and before each RTX cycle to identify patients at risk of SIEs. Monitoring should be done not only for below or above lower limit of normal (LLN) but also the degree of recovery or increment of IgG level (before retreatment) would reduce the risk of post-treatment infection. Vigilance is needed for those with lower IgG and comorbidities as these are consistent predictors of SIE, can increase infection risks when RTX is switched to a different bDMARDs and are associated with infection-related mortality. Low B-cell counts are not predictive of SIEs.