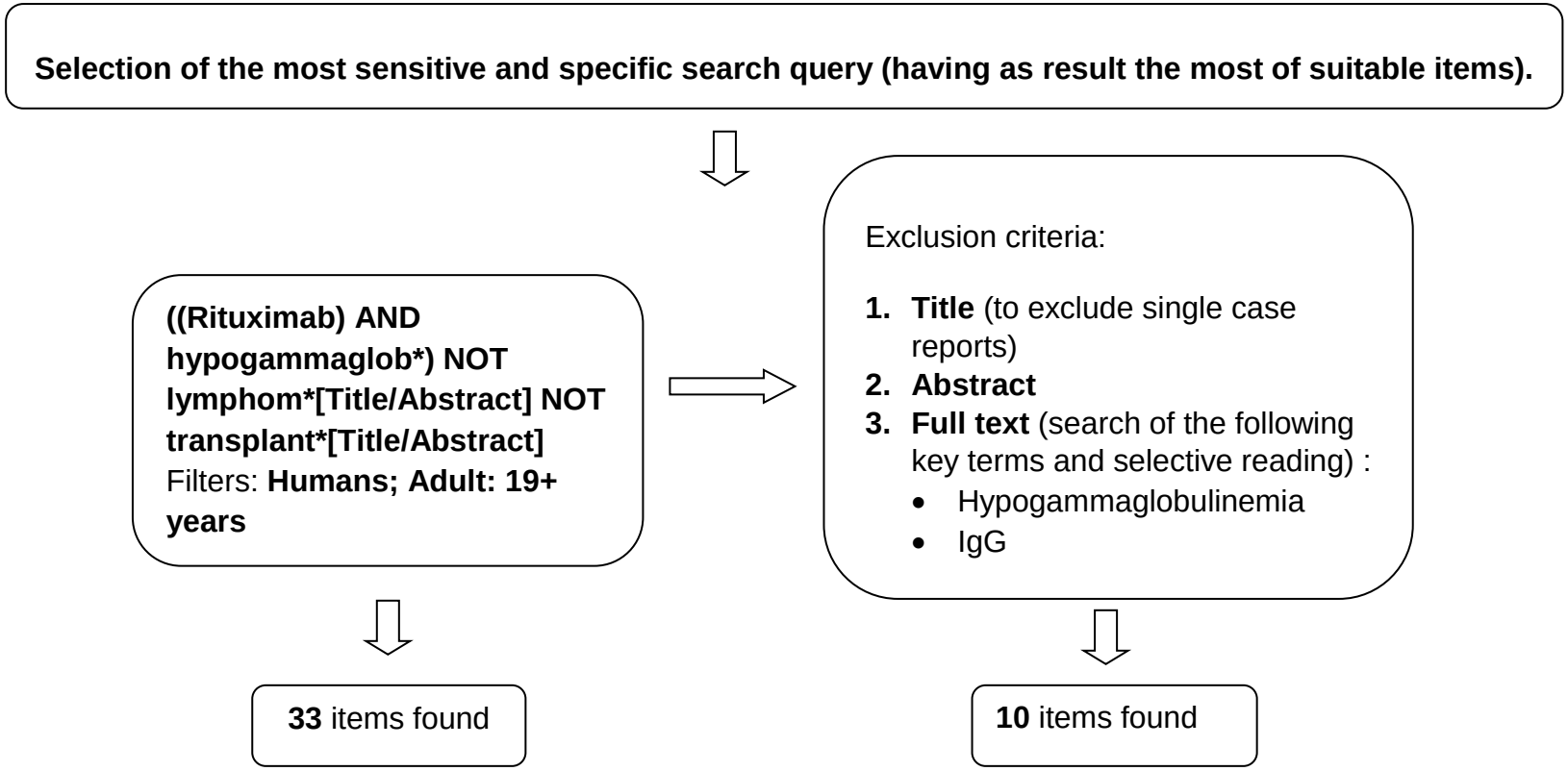
**Systematic MEDLINE search about hypogammaglobulinemia as adverse effect of Rituximab treatment.**



| Reference | Type of study | N° of patients | Population | Median follow-up | Baseline Ig dosing | Timing of Ig dosing | Type of Ig | Association with other immunosuppressive drugs | Results |
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| Roberts DM, Jones RB, Smith RM, Alberici F, Kumaratne DS, Burns S, Jayne DR. Rituximab-associated hypogammaglobulinemia: Incidence, predictors and outcomes in patients with multi-system autoimmune disease. J Autoimmun. 2015 Feb. | Retrospective case series. | 243 | Small vessel vasculitis and other multi-system autoimmune diseases. | 42 months. | Yes. | Three measurement over at least six months. | IgG IgM | Cyclophosphamide. | Ig deficit requiring IgG replacement therapy in 4.2%. |
| Marco H, Smith RM, Jones RB et al. The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease. BMC Musculoskeletal Disorders 2014. | Retrospective case series. | 177 | Multisystem autoimmune disease. | 43 months (range 2–100). Total follow-up was 8012 patient-months. | Yes. (136/177 patients (77%) | ? | IgG IgM IgA | Cyclophosphamide (and 5 other). | Cumulative rituximab dose was not associated with the incidence of hypo-Ig. Severe infections were not associated with immunoglobulin concentrations. |

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| 16. Besada E, Koldingsnes W, Nossent JC. **Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis.** Rheumatology (Oxford). 2014 Oct. | Single-center cohort study. | 29 | Granulomatosis with polyangiitis. | 4 years. | Yes. | Yearly measurement. | IgG<br>IgM<br>IgA | CYC<br>MTX<br>AZA<br>MMF | Low levels of IgG, IgA and IgM were found, respectively, in 76%, 17% and 76% of patients at any time during follow-up. In particular, 5/7, 2/7 and 6/7 (71%, 29% and 86% of patients) showed low IgG,IgA and IgM levels respectively (5.4, 1.57 and 0.13 g/l median concentration respectively) after five years of treatment, compared to none (IgA) and 8/29 (28%, both IgG and IgM) prior to RTX (7.7, 1.62 and 0.68 g/l respective median concentration). |
| Reddy V, Martinez L, Isenberg DA, Leandro MJ, Cambridge G. Pragmatic treatment of patients with Systemic Lupus Erythematosus with rituximab: Long-term effects on serum immunoglobulins. Arthritis Care Res (Hoboken). 2016 Jul 18. | Observational study. | 57 | Systemic Lupus Erythematosus. | 4 years. | Yes. | 3 months intervals up to 12 months. | IgG<br>IgM<br>IgA | Hydroxychloroquine.<br>Corticosteroids.<br>Azathioprine.<br>Mycophenolate mofetil.<br>Tacrolimus | Ig deficit restricted to the IgM class, associated with low baseline levels. |

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| Aguiar R, Araújo C, Martins-Coelho G, Isenberg D. Use of rituximab in systemic lupus erythematosus: a single center experience over 14 years. Arthritis Care Res (Hoboken). 2016 Apr 25. [Epub ahead of print]. | Retrospective analysis. | 115 | Systemic lupus erythematosus. | ? | Yes. | Six months after each RTX infusion. | IgG IgM IgA | Prednisolone/ Hydroxichloroquine/ Azathioprine/ Mycophenolate mofetil/ Cyclophosphamide/ Methotrexate. | Low levels of IgA, IgG and IgM were found, respectively, in 3.3%, 12.2% and 27.2% of patients six months after each RTX infusion. |
| Chocova Z, Hruskova Z, Mareckova H et al. Rituximab use in patients with ANCA-associated vasculitis: clinical efficacy and impact on immunological parameters. Clin Rheumatol. 2015 Jan. | Retrospective analysis. | 18 | ANCA-associated vasculitides. | 26 months (range 3–82, 15 for ≥6 months). | Yes. | Every 3 months up to 12 months. | IgG | Intercurrent treatments: Cyclophosphamide /methylprednisolone/ plasma exchange. | Total IgG levels were significantly decreased ($p < 0.01$) in comparison with baseline and 6-month values). Nadir IgG median value (5.6 g/l, range 3.1-7.1) was achieved at 3 months. Only one patient required Ig replacement therapy and none showed infectious complications. |
| 17. De La Torre I, Leandro MJ, Valor L, Becerra E, Edwards JC, Cambridge G. **Total serum immunoglobulin levels in patients with RA after multiple B-cell** | Observational prospective study. | 119 | Rheumatoid arthritis (RA). | ? range 6-120 months | Yes. | One measurement per RTX infusion. | IgG IgM IgA | ? | Considering patients achieving the fifth RTX infusion (n=18), four, three and eight of them (22%, 17% and 44%) showed respectively hypo-IgG, hypo-IgA and hypo-IgM levels. |

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| **depletion cycles based on rituximab: relationship with B-cell kinetics.** Rheumatology (Oxford). 2012 May. | | | | | | | | | |
| 18. Van Vollenhoven RF, Fleischmann RM, Furst DE, Lacey S, Lehane PB. **Longterm Safety of Rituximab: Final Report of the Rheumatoid Arthritis Global Clinical Trial Program over 11 Years.** J Rheumatol. 2015 Oct. | Pooled observed case analysis of data from a global clinical trial program. | 3595 | Moderate to severe, active rheumatoid arthritis. | 4.1 years mean follow-up. 4 mean RTX infusion. | Yes. | Every 8–16, depending on study protocols. | IgG IgM IgA | DMARD: disease-modifying antirheumatic drugs. | Low levels of IgG, IgA and IgM were found, respectively, in 14.8%, 3.9%, and 37.9% of patients at any time during follow-up. Serious infectious events occurrence was higher in patients who developed low IgG levels than in patients who never developed low IgG and higher than the corresponding infections rate in the whole trial population. |
| Venhoff N, Effelsberg NM, Salzer U et al. Impact of rituximab on immunoglobulin concentrations and B cell numbers after cyclophosphamide treatment in patients with ANCA-associated | Retrospective analysis. | 33 patients treated with cyclophosphamide and Rituximab. | ANCA-associated vasculitides. | 25 months. | Yes. | 3, 11 and 14 months after Rituximab infusion. | IgG IgM IgA | Intercurrent treatments: methotrexate; azathioprine; mycophenolate mofetil; leflunomide. | RTX therapy decreased serum immunoglobulin concentrations (significantly for IgM and IgG at any time point during follow-up). |

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| vasculitides. PLoS One. 2012. | | | | | | | | | |
| Roubaud-Baudron C, Pagnoux C, Méaux-Ruault N et al. Rituximab maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis. J Rheumatol. 2012 Jan. | Retrospective study. | 28 | Granulomatosis with polyangiitis and microscopic polyangiitis. | 38 months (range 21–97). | Yes. | ? | IgG IgM | Intercurrent treatments: prednisone;methotrexate; azathioprine; mycophenolate mofetil; leflunomide. | Considering available data at last RTX infusion (n=18), twelve and fifteen patients (67% and 83%) showed respectively hypo-IgG and hypo-IgM levels. |