Letter to the editor

# Does concomitant methotrexate during rituximab treatment in granulomatosis with polyangiitis increase the risk of severe infections? Comment on the article of Azar et al.

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Dear Sir,

In their recent article, Azar et al demonstrated that rituximab (RTX) may be an effective remission-inducing agent in granulomatous with polyangiitis (GPA) patients. The addition of a conventional immunosuppressive agent (such as methotrexate, azathioprine and mycophenolate mofetil) to RTX and glucocorticoids decreased the risk of relapse without increasing the risk of adverse events (1). Nevertheless, their conclusions raise some important concerns. In their study, 11 patients (23 %) received methotrexate and all suffered from severe infections (1).

Rituximab can induce secondary hypogammaglobulinemia (2,3) and possibly longer B cell depletion in patients receiving additional immunosuppressive agents (3). In our cohort of GPA patients receiving RTX maintenance, 93 % were treated with an additional immunosuppressive agent during a median of 24 months (3). Although immunosuppressive agents did not seem to significantly increase the risk of severe and chronic infections and hypogammaglobulinemia, 26 % had severe infections (4) and 28 % had to discontinue RTX due to hypogammaglobulinemia (3).

While the type of RTX maintenance regimen is closely associated to adverse events in our cohort, correspondence analysis (using the R project for statistical computing www.r-project.org) shows that use of methotrexate and azathioprine during RTX maintenance could increase the risk of chronic infections (figure).

Use of immunosuppressive agent after cyclophosphamide induction with either azathioprine or methotrexate is standard in GPA (5,6), however its effect after RTX induction and especially during maintenance is not fully assessed. Azathioprine and

methotrexate could reduce the risk of relapse during RTX treatment; on the other hand, they could heighten the risk of infections and hypogammaglobulinemia.

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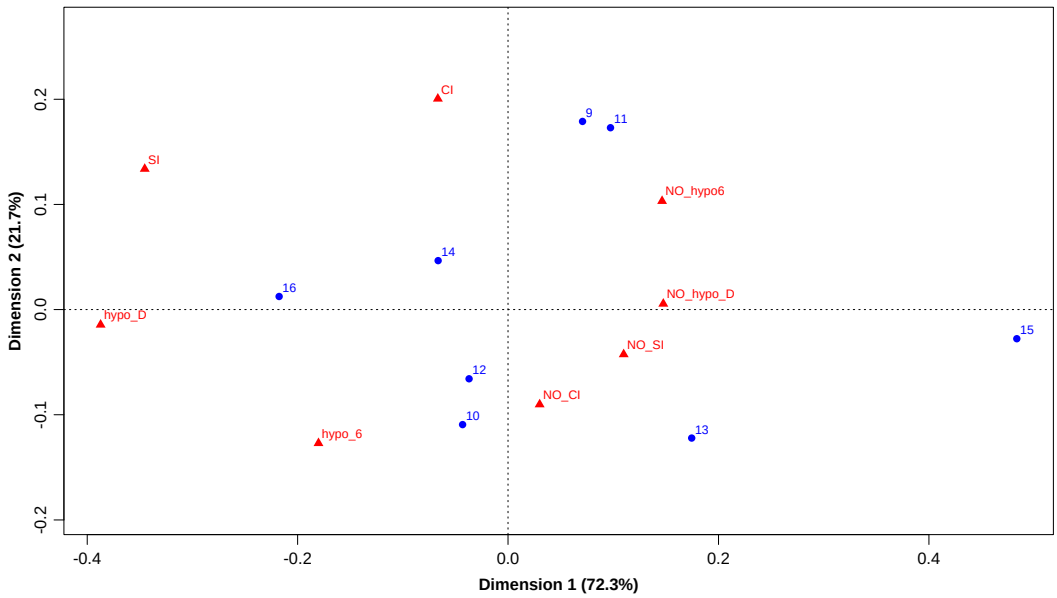
Correspondence analysis of adverse events during RTX maintenance by treatment categories.




CI: chronic infection; SI: severe infection; hypo_6: hypogammaglobulinemia defined as total Ig < 6 g/L; hypo_D: hypogammaglobulinemia leading to RTX discontinuation.
9/11/13: methotrexate/azathioprine/mycophenolate mofetil use during rituximab maintenance
10/12/14: No methotrexate/azathioprine/mycophenolate mofetil use during rituximab maintenance
15/16: RTX 2g annually /1g biannually maintenance regimen