Macroglobulinemia with symptomatic auto-antibody activity: How to treat?

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Macroglobulinemia-associated symptoms likely due to auto-antibody activity of the monoclonal IgM are difficult to treat. Therapeutic options may aim to modify the IgM bio-availability, by removing it from the circulation, the IgM production, by acting on the monoclonal B cell clone, and/or the IgM effect, by deviating it from the target auto-antigen or by reducing the pathogenicity of the complex.

In an attempt to optimise depletion of IgM producing B cells, we used a regimen combining few monthly courses of fludarabine and cytoxan followed by 4 weekly injections of the anti-CD20 monoclonal antibody rituximab. Five patients with very disabling peripheral neuropathy and IgM anti-MAG have completed this treatment. Preliminary results are disappointing since a complete remission with disappearance of the monoclonal IgM was not observed in any patient. However, two patients experienced partial improvement of neurological symptoms with, in one, improvement of electrophysiological parameters.

In an attempt to modulate the IgM effect, we treated patients with symptomatic cold agglutinin disease by monthly infusions of intravenous immunoglobulins (IVIg). In 5 of 6 treated patients, high dose IVIg induced a significant immediate improvement of haemolytic anaemia that was transient but repeatedly observed. In vitro studies documented a dose-dependant inhibition by IVIg of the lysis of red blood cells in the presence of various cold agglutinin antibodies and of complement.

These preliminary data suggest that, in macroglobulinemia with symptomatic auto-antibody activity, no available therapeutic options directed towards the monoclonal B cell clone can regularly produce complete remission. Accordingly, alternative strategies aiming at modulating the pathogenic effect of the monoclonal IgM still deserve consideration.