CAN RITUXIMAB EFFECTIVELY TREAT MYELIN-ASSOCIATED GLYCOPROTEIN (MAG) NEUROPATHIES? NO

E. Nobile-Orazio

2nd Neurology, Department of Translational Medicine, Milan University, IRCCS Humanitas Clinical Institute, Rozzano, Milan, Italy

eduardo.nobile@unimi.it

Paraproteinemic neuropathies are an heterogeneous group of neuropathies that are most frequently associated with monoclonal gammopathy of undetermined significance (MGUS). Several data support the pathogenetic role of the paraprotein in the neuropathy particularly when of IgM isotype and reactive to myelin-associated glycoprotein (MAG). This has supported the use of immune therapies in this neuropathy even if their efficacy remains unclear (*Lunn et al., 2006*). A number of open pilot trials have recently suggested the efficacy of the humanised monoclonal antibody (Rituximab) directed against the CD20 antigen (*Dalakas 2008*), in patients with anti-MAG IgM neuropathy (*Pestronk et al., 2003; Renaud et al.,2003 & 2006; Benedetti et al., 2007*), with a benefit reported to last up to 2 years in 80% of the patients and 3 years in 60% of them (*Benedetti et al., 2008*). These promising results are somehow limited by the fact that several patients had a modest benefit. In one study (*Renaud et al., 2003*) for instance only two of the nine treated patients (22%) improved by more than 5 points in the Neuropathy Disability Score. A similar modest proportion of improvement was also observed in a recent uncontrolled study (*Niermeijer et al., 2010*) in whom 35% of the 17 treated patients with neuropathy associated with IgM monoclonal gammopathy, including 6 with anti-MAG IgM, had improved either in the Overall Disability Sum Score or by more than five points in the MRC sumscore. The efficacy of Rituximab was confirmed in the recently published randomized controlled trial on 26 patients with anti-MAG neuropathy (*Dalakas et al., 2009*). Four of the 13 patients treated with Rituximab (31%) had improved by at least one point in the INCAT score compared to none of the 13 patients treated with placebo. The difference only become significant when a Rituximab treated patient with baseline score of 0 (and who could not therefore improve) was excluded from the analysis, raising some criticisms on the interpretation of the study. The preliminary results of another randomized controlled trial with Rituximab on 54 patients with anti-MAG neuropathy were reported at the Satellite PNS meeting in Sydney (*Leger et al., 2010*). Even if there was no significant difference in the primary outcome (mean change in sensory score), there was a 20% absolute difference in the treated patients compared to placebo in the improvement in the Hughes disability scale (20% versus 0%) and in the self evaluation scale (26% versus 4%). Both randomized studies showed therefore a 20 to 30% absolute improvement of Rituximab compared to placebo, indicating that we probably have to treat three to four patients to improve one patient. Still, the absolute improvement compared to placebo is much higher than observed in randomized trials in other diseases such as multiple sclerosis. To remain in the same field of comparison, we should mention however the recent report on 57 patients who developed progressive multifocal leucoencephalopathy under Rituximab treatment (*Carson et al., 2009*). Even if most of these patients had a malignancy and were also treated with cytostatic agents, we should consider this at the light of the usually favourable long-term prognosis of anti-MAG neuropathy (*Nobile-Orazio et al., 2000*) and the fact that these patients might require treatment for a longer period of time compared to patients with malignant haematological diseases. Neuropathy associated with paraproteinemia remains an intriguing disease to be investigated and a challenging condition to be treated. In conclusion Rituximab s consistently effective in only a minority of patients with anti-MAG neuropathy indicating the need to search for additional therapies for this neuropathy. In addition the discrepancy observed between the consistent reduction of anti-MAG antibodies almost invariably observed in treated patients and the improvement observed in a minority of them suggest that some aspects in the pathogenesis needs to be further investigated.

References

- Benedetti L, Briani C, Grandis M, et al. (2007). Predictors of response to Rituximab in patients with neuropathy and anti-myelin associated glycoprotein immunoglobulin M. J Periph Nerv Syst 12: 102-107.
- Benedetti L, Briani C, Franciotta D, et al. (2008) Long-term effect of Rituximab in anti-MAG polyneuropathy. Neurology 71: 1742-1744.
- Carson KR, Evens AM, Richey EA, et al. (2009). Progressive multifocal leukoencephalopathy following rituximab therapy in HIV negative patients: a report of 57 cases from the Research on Adverse Drug Event and Reports project. Blood 113: 4834-4840.
- Dalakas MC (2008). Inhibition of B cell functions. Implications for neurology. Neurology 70: 2252-2260.
- Dalakas MC, Rakocevic G, Salajegheh M, et al.(2009). Placebo controlled trial of Rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. Ann Neurol 65: 286-293.
- Léger J-M, Viala K, Bombelli F,et al. (2010). Randomized controlled trial of Rituximab in demyelinating neuropathy associated with anti-MAG IgM gammopathy (RIMAG STUDY). Satellite meeting of the Peripheral Nerve Society, Sydney Australia, July 5-7, 2010. Abstract book: 51-52.
- Lunn MPT, Nobile-Orazio E (2006) Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies [Review]. Cochrane Database Syst Rev 2006 Apr 19; (2): CD002827.

- Niermeijer JMF, Eurelings M, Lokhorst HL, et al. (2009). Rituximab for polyneuropathy with IgM monoclonal gammopathy. J Neurol Nerosurg Psychiatry 80: 1036-1039.
- Nobile-Orazio E, Meucci N, Baldini L, et al. (2000). Long-term prognosis of neuropathy associated with anti-MAG IgM M-proteins and its relation with immune therapies. Brain 123: 710-717.
- Pestronk A, Florence J, Miller T, et al. (2003). Treatment of IgM antibody associated polyneuropathies using rituximab. J Neurol Neurosurg Psychiatry 74: 485-489.
- Renaud S, Gregor M, Fuhr P, et al. (2003). Rituximab in the treatment of polyneuropathy associated with anti-MAG antibodies. Muscle Nerve 27: 611-615.
- Renaud S, Fuhr P, Gregor M, et al. (2006). High-dose rituximab and anti-MAG associated polyneuropathy. Neurology 66: 742-744.