SHOULD MAINTENANCE THERAPY IN NMO AS A FIRST LINE INVOLVE RITUXIMAB OR IMMUNOSUPPRESSIVE DRUGS? RITUXIMAB

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Controlled clinical trials in neuromyelitis optica (NMO) are lacking (non-existent) and are necessary to establish the relative effectiveness of current "first line" treatments in NMO. Some would argue that one cannot assume that any of the treatments that we currently use for NMO are effective. Most would agree that none are entirely effective. Almost none would argue that we should not be treating patients with NMO with immunosuppressive drugs. While practices vary greatly by region, the most commonly used agents for prevention on NMO attacks around the word include corticosteroids, azathioprine, mycophenolate mofetil and rituximab. Other treatments are sometimes administered, including mitoxantrone, maintenance plasma exchange, cyclophosphamide and others, typically as second line agents. For each of the first line drugs in use, retrospective series of small to moderate size and some small prospective but uncontrolled studies have established their short term and intermediate term efficacy. However, these studies that typically compare pre-treatment attack rates to post-treatment are notorious for overestimating the treatment effect due to regression to the mean. Retrospective studies are prone to ascertainment bias, incomplete detection of events, and selective discontinuation of medication by patients who perceive that the drugs are failing them. Therefore, any preference expressed for rituximab in this debate must be based on less than adequate studies; these limitations are readily acknowledged.

The following arguments support a preference for rituximab as first line therapy:

1. There has been a prospective study that showed dramatic reduction of attacks.
2. Rituximab seems to be effective in patients who have failed other therapies, not only in treatment-naïve patients. This may be an argument that it is more effective than other drugs, albeit based on less than rigorous data.
3. Rituximab works quickly…within one month…making it a good choice in a patient who has very active disease.
4. Typically, 6 months of corticosteroids are necessary in a patient with NMO who is starting on azathioprine or mycophenolate mofetil because of the delayed onset of efficacy in these patients, making patients prone to multiple steroid-related complications, including diabetes, psychosis, avascular necrosis of the hip). Long term corticosteroids is a particular concern in children (growth effects, social consequences of severe acne, among others) and in patients with comorbidities (diabetes mellitus, hypertension, osteoporosis). Only a short period of concomitant corticosteroids is necessary in patients who are started on rituximab.
5. Rituximab selectively targets B cells, effectively sparing T cells (recognizing that T cell function may be altered by B cell depletion). This may lead to lesser immunosuppression and its consequences. Although PML occurs in patients on rituximab, it is estimated at 1/20,000 in rheumatoid arthritis, an appropriate comparator to NMO. In other patients, e.g. systemic lupus erythematosus, it is difficult to be sure that PML was not the result of the comorbidity for which the patient was receiving rituximab. Long term hypogammaglobulinemia may occur, but is treatable with IVIG. There is no clear evidence for substantially increased risk or severity for mycobacterial infections, hepatitis B (in patients with autoimmune disease), or zoster.
6. Rituximab induction has a long period of effect (6-9 months) and minimizes problems with compliance issues. It is well-tolerated in general.
7. Rituximab has been successfully and with apparent safety in pregnant patients. Its effect commonly persists for 9-12 months, and can be administered before conception. Although not advised in pregnant women, the incidence of congenital malformations is low, and when considering risk:benefit ratio, it is a reasonable consideration, and quite likely safer than azathioprine and mycophenolate mofetil, which (especially mycophenolate) are contraindicated in pregnant women and are established to cause congenital malformations.

A head-to-head comparative trial with other first line treatments would be welcome, but with advent of other promising drugs, it is not likely to happen in the near future. Accordingly, we need to use the information discussed above in reaching a decision of which first line treatment to use. Cost considerations aside, rituximab is the preferred first line treatment for NMO.