Long-term use of Ocrelizumab: maintaining benefit, minimising risk

By Sharon Edwards, Townsville Neurosciences

Introduction:
MS is generally diagnosed between ages 20-40[1]. With early introduction of disease modifying therapy (DMT) it can be anticipated patients may remain on treatment for 20-30 years. Clinical trials of immunomodulatory therapies provide efficacy and safety data for only 2-3 years. As healthcare professionals, we need to consider the long-term benefits and risks of DMTs, particularly safety implications, and how we may mitigate these over what may be decades of therapy. A potential risk management strategy for long-term use of Ocrelizumab is dose reduction and carefully monitoring MRI, haematological and clinical findings.

Background:
For Ocrelizumab, safety concerns include immunosenescence (age-related changes to the immune system) and associated infection risk, particularly in older patients. Premature immunosenescence occurs in people with MS, which may have a cumulative effect with long-term DMT use[1]. This leads to increased susceptibility to infections, autoimmune diseases, tumours, and a decreased response to vaccines[1].

Rituximab is closely related to Ocrelizumab and has been used off-label in MS for many years, as well as in other antibody mediated disorders[2]. In clinical practice dosing of Rituximab is adjusted by clinicians over time, with the dose reduced by 50-75% from initial induction, generally maintaining disease control[3]. In observational studies, such regimes in RRMS have been shown to maintain clinical and radiological remission whilst reducing infection risk; along with both cost and infusion duration[3].

Both treatments are considered safe and highly effective at treating MS; however, Rituximab is associated with the highest rate of serious infections in real world studies in people with MS treated with DMTs[2]. Infections are the most common adverse event reported with Ocrelizumab (76.2 per 100 patient years) in the latest 7-year data[4]. Serum immunoglobulin G (IgG) levels decreased at the average rate of -2.99% per year[4].

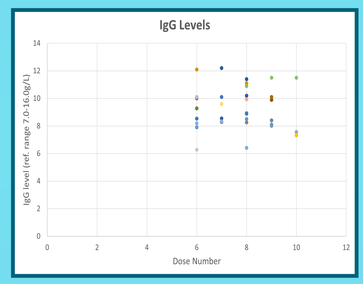
Additional Background:
Hypogammaglobulinemia is the presumed cause of higher infection risk in people with MS on Rituximab[3], and recent Ocrelizumab open-label extension data demonstrated a link between decreased IgG levels and serious infection[4]. A recent study demonstrated IgG levels dropped significantly after Cycle 5 of Ocrelizumab, whereas IgM decreased gradually over time[2].

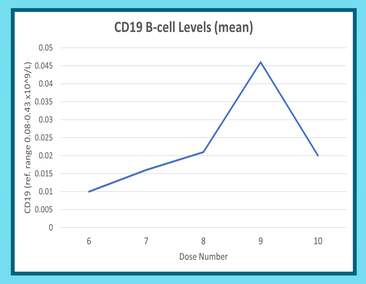
Extended interval dosing (EID) of Ocrelizumab of 6 months plus ≥4 weeks delay correlated with greater risk of MRI activity in a recent Italian multicentre study[5]. There was no impact on confirmed disability progression between standard and EID groups (n=278), however the study period was for two years and longer follow-up is needed to learn the prolonged risks to disease trajectory[5].

Pharmacokinetics and Pharmacodynamics:
CD19 B-cell depletion in the blood (pharmacodynamic marker) and other body compartments is more pronounced with longer exposure to Ocrelizumab, as most B-cells reside in tissue and a minority in the blood[6]. B-cell repletion time to the lower level of normal (LLN) (≥0.08 x10^9/L) is 27-175 weeks (median 72 weeks) [6]. Only up to 4% of Ocrelizumab patients repleted to the LLN at 6 months post their last 600mg dose, so the 6-monthly dosing interval is important to ensure continuous depletion[6]. In the other 96% of patients, B-cell depletion persists for usually 6-12 months post infusion, and 90% of patients CD19 B-cells return to the LLN by 2.5 years after their last infusion[6].

Practice Change:
Based on this knowledge, in our practice we elected to routinely reduce the ongoing dose of Ocrelizumab to 300mg every 6-months after the 2-year clinical trial defined protocol. All patients consented to this reduction after explanation of the rationale with routine testing of lymphocyte sub-sets and immunoglobulins at each infusion and annual MR scans. To date around 43% of patients (n=29) have transitioned to the lower dose, with the earliest patients now followed for up to 3 years on the low-dose regime.

Results:
The patients to date on the reduced dosing Ocrelizumab regime have demonstrated maintenance of CD19 B-cell depletion prior to each infusion, and there has been no evidence of clinical or radiological disease activity in this cohort. Most CD19 B-cell levels have remained ≤0.04 x10^9/L which is below the LLN (2 patients measured 0.08 prior to Dose 9). This demonstrates maintained depletion on reduced dosing. IgG levels remained mostly on the LLN up to Dose 10. 10% (n=7) of all patients (both 300mg and 600mg groups) have ceased Ocrelizumab due to recurrent infections.





Conclusion:
To date, this novel treatment paradigm demonstrates retained high efficacy of Ocrelizumab regarding MRI activity and disability progression. EID must be used with caution; however, dose reduction after Cycle 5 may reduce the rate of reduction to IgG levels, minimise longer term immunosenescence, and allow improved safety outcomes for people with MS on Ocrelizumab. This is a small observational study and a larger scale RCT would be needed to substantiate our findings.

References

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