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Natalizumab concentrations during pregnancy in three patients with multiple sclerosis: A clinical commentary

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It is increasingly recognised that multiple sclerosis (MS) treatment around pregnancy in people with MS should be personalised. Evaluating the risks and benefits of treatment strategies during pregnancy, taking into account the mothers' MS, potential risks to the baby from treatment, and risks to the mother from stopping treatment, is complex. At present, there are few biomarkers to guide these decisions. In the accompanying paper,[1] it is suggested that changes in serum concentrations of natalizumab during pregnancy may have clinical utility.

Serum concentrations of natalizumab have previously been studied. In the AFFIRM trial, serum concentrations at a standard dose of natalizumab (4-weekly) were 23–29 µg/mL.[2] While these vary between people, individual natalizumab concentrations are relatively consistent once established on therapy.[3] They may be influenced by body mass

index (BMI), bodyweight and dose interval (4 vs 6 weeks); plasma concentrations of 1-2 µg/mL are probably sufficient to lead to α4-integrin receptor saturation.

Extended interval dosing is often adopted when natalizumab is used in pregnancy to minimise foetal exposure. The safety profile is well-described, and many neurologists are relatively comfortable with the risk/benefit balance.[4] However, the impact of pregnancy on drug levels (and hence receptor saturation) is unknown. During pregnancy, plasma volume increases by up to 40%; this does not appear to substantially change pharmacokinetics of monoclonal antibodies (MAbs), likely due to their relatively limited volume of distribution.[5] MAbs are not renally excreted, but are catabolised into amino acids and proteins, and changes in protease expression during pregnancy may influence plasma levels.

By repeated sampling at anticipated trough levels during pregnancy, the authors[1] show that natalizumab levels in all patients decreased during pregnancy. Although all three patients remained relapse free, given our knowledge around rebound on natalizumab cessation, the theoretical risk from sustained subtherapeutic levels cannot be ignored. This study raises the question of whether natalizumab levels should be monitored in pregnancy, to identify those at risk of breakthrough disease. It highlights the need for more clinical trials and research in pregnancy, which until recently has been a neglected area in MS research despite the striking female preponderance.

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