Development of a novel, anti-drug antibody screening platform to detect neutralizing responses following alemtuzumab treatment in relapsing multiple sclerosis

Short Title: Detecting alemtuzumab neutralizers

Gauri Saxena[1] (Main Author), Liquat Ali[1], James Moore[2], Samantha Loveless[2], Neil P Robertson[2], Sharmilee Gnananpavan[1], Gavin Giovannoni[1], David Baker[1], Emma Tallantyre[2], Angray S. Kang[1]

1Blizard Institute, Barts & the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom, 2Division of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Cardiff, United Kingdom.

Alemtuzumab was the first humanized monoclonal antibody to be licensed for the treatment of relapsing multiple sclerosis (MS). It was designed to reduce the immunogenicity seen with the rodent CD52-specific antibody. However, since commercial development of alemtuzumab began anti-drug antibodies (ADA) responses are generally portrayed as being of limited clinical significance. However, data within European Regulatory Submissions suggests that alemtuzumab generates the highest frequency of binding and neutralizing ADA of all current, clinical, humanized antibodies. These ADA appear to be an inherent issue of the biology of the molecule and target, such that avoidance of immunogenicity related-effects seems to have driven the dosing-schedule adopted in clinical practice.

In order to adequately monitor our patients' immunogenicity to alemtuzumab, we generated an adherent CD52-expressing cell line and engineered a novel reporter molecule, which consist of the two single chain variable fragments specific for alemtuzumab bridged via a luciferase containing linker. We then generated light-based, antibody-binding and neutralization assays in a multi-well assay format. These were used to retrospectively screen, blinded, banked-serum samples from people with MS who had received three or more cycles of alemtuzumab (Welsh Neuroscience Research Tissue Bank [Rec Ref: 19/WA/0058).

Results suggest that the dosing schedule allows the drug to work in most people, but at the individual level it was evident that a number of people stop deleting lymphocytes. In some people antibody neutralization was persistent and severe, notably in some people with disease-breakthrough. Therefore, ADA appear to be clinically relevant for some individuals. It is imperative that the degree of lymphocyte depletion and the anti-drug response are monitored in people requiring additional cycles of alemtuzumab, particularly in cases who show evidence of disease breakthrough. ADA detection technology may help inform whether to re-treat or switch to another disease modifying treatment.

Conflicts of Interest: GS, has nothing to declare. ASK has filled patents on the assay technology. SG, GG and NPR have received consultancy and or speaker honoraria from Sanofi-Genzyme within the past 3 years. Others, multiple are considered irrelevant.