Statins impair rituximab killing.

You may have missed an article by Magdelena Winiarska from Warsaw, that tells us that "Statins impair antitumor effects of rituximab by introducing conformational changes of CD20". PLoS Medicine 2008; 5:0502-0517.

The title alone makes patients receiving statins who are also receiving rituximab anxious, so before we jump to any conclusions we ought to read the paper and see if it says what the title implies.

First they demonstrated that incubating Raji cells with a statin for 48 hours reduced rituximab-induced complement dependent cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC) in a dose dependent manner. Incubation with statins reduces the binding of anti-CD20 antibody to the surface of Raji cells, but it does not reduce the amount of CD20 produced by the cells. It appears that it is the reduction of cholesterol in the cell membrane that is responsible for this effect, which is common to all statins and works for other lymphoblastoid cell lines like Daudi and Ramos and with other anti-CD20 antibodies of both type I and type II. Incubation with cholesterol after the statin treatment restores the CDC and ADCC to normal. Although, binding of rituximab to CD20 translates the antigen into cholesterol-rich lipid rafts, this mechanism is not involved in the reduction of CDC or ADCC. Using something called an "atomic force microscope" and also limited proteolysis with trypsin and chymotrypsin they were able to establish that incubation with statins induces conformational changes in the CD20 antigen that affects the binding of type I and type II anti-CD20 antibodies.

Experiments with lymphoblastoid cell lines are all very well, but does this have any meaning in clinical practice? To address this question they incubated freshly isolated tumor cells from patients with mantle cell lymphomas with MβCD (which like statins extracts cholesterol from the cells membrane) and attempted to kill them with rituximab in a CDC assay. Killing was significantly reduced.

They also demonstrated that inpatients who were receiving statins for hypercholesterolemia, the binding of anti-CD20 to normal B cells decreased by 15-20%.

So, does this have any meaning for CLL patients who are treated with rituximab?

First, I must draw attention to the fact that the clinical experiment has not been done. No-one has shown a lesser effect for rituximab in patients on statins.

Second, the reduction in killing of fresh lymphoma cells (as opposed to cells from a lymphoblastoid cell line) was after incubation with MβCD rather than a statin. I am sure they did the experiments with a statin but did not report it probably because there was no effect.

Third, as well as the incubation experiment with cells from three mantle cell lymphomas they also used cells from a patient with small B cell lymphoma (probably CLL but one

can't be sure). This patient started off with less surface CD20 on his or her cells and although incubation it was lessened significantly, but not by very much.

Fourth, if statins really did make such a difference as is implied, I would expect to see this paper in Blood or JCO or Haematologica or B J Haem – not in PLoS Medicine.

Finally, I should draw attention to a paper by Polyak et al from Canada (Leukemia 2003; 17:1384-1389). They demonstrated that the monoclonal antibody FMC7 reacts with an epitope of CD20. As most CLL students know, FMC7 is usually absent from CLL cells. Why is that? It appears that the CD20 molecule undergoes a conformational change that hides the FMC7 epitope under certain circumstances. What circumstance? When the membrane is depleted of cholesterol. It appears that in CLL the cholesterol has already been depleted, which may explain why rituximab is such a poor drug in CLL compared to its activity in other kinds of lymphoma