Reviewer's report

Title: Superior antigen-specific CD4+ T-cell response with AS03-adjuvantation of a trivalent influenza vaccine in a randomised trial of adults aged 65 and older

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Reviewer: Xavier Saelens

Reviewer's report:

The authors compared AS03-adjuvanted TIV with TIV in a cohort of people over 65 years of age. A third group of 18-40 year old adults who received TIV was also included, allowing comparison of immune responses to TIV between young adults and elderly. CD4 T cell responses, as determined by the expression of CD40L, IL-2, TNF, and IFN-gamma (two or more of either of these) were significantly higher in the AS03-adjuvanted TIV recipients compared to the other two groups on days 21 and 42. This difference remained significant on day 180 after vaccination when comparing the two elderly groups. Vaccine antigen-specific CD8+ T cell responses were not altered after vaccination and the frequency of GrzB+ CD4 and CD8 T cells responsive to vaccine antigen remained constant over the study period. Based on the observation that GrzB+ and IFN-gamma and or IL-2 positive CD4 and CD8 T cell frequencies following restimulation with CMV in CMV carriers were comparable in all groups, it is concluded that the differences in CD4 T cell responses directed against influenza vaccine antigens, are specific to these antigens and do not reflect a bystander effect. Interestingly, there was no correlation between the increased CD4 T responses and influenza virus-specific serum antibody responses, as determined by HI, SPR and MNT assays.

Comments:
This is an interesting study that provides additional knowledge on the use of adjuvanted inactivated influenza vaccines, which may increase protection in more at risk groups for influenza-associated illness, such as the elderly.

Major compulsory revision

1. I am not sure that the conclusion that the significant increases in CD4 T cell responses in the AS03 group are merely split antigen-specific, as suggested by the comparison with the CMV responses. The authors should compare the flu and CMV-specific responses of the CD4 T cells that express CD40L, IL-2, TNF, and IFN-gamma (two or more of either of these). This is important because Fig. 4 shows that GrzB and IFN-gamma/IL-2 expressing CD4 and CD8 T cells do not differ between the three TIV groups.

Minor essential revision

2. The authors should mention if the volunteers were allowed to use medication to try to mitigate the adverse events that appeared in some cases following
vaccination and, if so what kind of medication.

3. In the introduction or the discussion, it would be helpful if the authors could clarify the (surmised) mechanism of action of the AS03 adjuvant.

4. Page 7, line 15: please be more precise on “short term”: how many hours of stimulation

5. Page 8, line 20: please provide details on the antibodies used for cell staining

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests