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Commentary

Clinical observation during alemtuzumab administration

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There is growing evidence regarding the risk of cervical arterial dissection and intracerebral hemorrhage immediately following alemtuzumab infusion, for relapsing remitting multiple sclerosis (MS). Durand-Dubief et al. reported a case of multiple cervical arterial dissections days after treatment with alemtuzumab. (Durand-Dubief et al., 2019) Five cases of intracerebral hemorrhage were recently reported by Azevedo et al. (Azevedo et al., 2019) In November 2018, this concern prompted the United States Food and Drug Administration (FDA) to add the risk of stroke within three days of administration to the boxed warning on the drug's label. (US FDA Accessed 13 May; 2019) The FDA commented on the possible causative role of cytokine release syndrome, but decided there was insufficient evidence. The European Medicines Agency (EMA) have recently launched a safety review, placed interim restrictions on the prescription of alemtuzumab, and focussed on blood pressure, advising: "For patients being treated with Lemtrada®, vital signs should be monitored before and during the intravenous infusion." (EMA Accessed 13 May 2019) Azevedo et al. suggested that hypertension, or acute fluctuations in blood pressure, may be responsible for acute haemorrhagic strokes and proposed four criteria that should prompt admission for inpatient observation with strict blood pressure control. Either a 20% or 20 mmHg increase in the mean daily systolic blood pressure (SBP), or a one-off value that exceeds the patients' baseline SBP by the same extent. Chinea et al. subsequently reported their prospective observational safety study of alemtuzumab administration and found that 39% of their cohort had a SBP $\geq$160 mmHg at least once during treatment, and only half of this group had a pre-existing diagnosis of hypertension. (Chinea et al., 2019)

We audited 83 consecutive patients receiving their first course of alemtuzumab therapy for MS from our three MS centres. Blood pressure was recorded prior to infusion and at 30-minute intervals for up to four hours post infusion. The cohort was 73% female; had a mean age of 36; a median EDSS of 3.0, and 27% received alemtuzumab as first line therapy. Five patients had a pre-existing diagnosis of hypertension, two were obese, two were current smokers, one was an ex-smoker and one had type two diabetes mellitus. Pre-medication given prior to each infusion consisted of methylprednisolone 500–1000 mg, acetaminophen 1000 mg, and diphenhydramine 50 mg or cetirizine 10 mg.

While there was no significant change in mean or peak SBP or diastolic blood pressure over the five infusion days ($\leq$3 mmHg), Azevedo's proposed criteria were met by 59% of the cohort at least once across all five days of treatment (Table 1). There was no routine monitoring for evidence of cytokine release syndrome. In our cohort, there was one case of carotid artery dissection, occurring after the third day of alemtuzumab infusion in a female patient aged 25 years old. Just as with Durand-Dubief's case, she had no history of a connective tissue disorder, trauma, or a recent infection. This patient met only one of Azevedo's proposed criteria; on the day the dissection occurred the patient's SBP had a one-off value in excess of 20 mmHg of that day's baseline.

Based on this data, we believe that the clinical observations suggested by Azevedo et al. and the EMA lack clinical utility in identifying people at risk of cervicocephalic arterial dissection or cerebrovascular

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Table 1
Number of patients given alemtuzumab meeting proposed criteria for admission and strict blood pressure control.

Proposed Criteria	Patients meeting criteria (%)
Mean daily SBP >20% pre-treatment baseline	11 (13)
Mean daily SBP >20 mmHg pre-treatment baseline	13 (16)
Daily peak SBP >20% daily baseline	33 (40)
Daily peak SBP >20 mmHg daily baseline	45 (54)
Meeting any of the criteria during treatment	49 (59)

events during treatment with alemtuzumab. The proposed criteria lack specificity due to the variability of routine clinical SBP recordings and the rarity of adverse events. We believe further safety studies are needed to help mitigate the risks of therapy, exploring the value of additional monitoring for evidence of cytokine release syndrome, not just blood pressure monitoring. Monitoring for cytokine release syndrome might include a combination of clinical observation and blood testing for markers of cytokine release such as D-dimers, prothrombin time, TNF-α, IFN-γ and IL-6.

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CRediT authorship contribution statement

Christopher M Allen: Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Jenny J Feng:** Data curation, Writing - review & editing. **Mark D Willis:** Data curation, Writing - review & editing. **Marisa McGinley:** Data curation, Writing - review & editing. **Daniel Ontaneda:** Writing - review & editing. **Emma C Tallantyre:** Writing - review & editing. **Nikos Evangelou:** Writing - review & editing.

Declaration of Competing Interest

CMA and MDW have nothing to declare, JJF has participated on Consulting and Advisory Boards for Sanofi and has received a Sylvia Lawry fellowship grant from National Multiple Sclerosis Society, MM has participated on Consulting and Advisory Boards for Genzyme and Genetech and has received a Slyvia Lawry grant from NMSS. DO has received research support from National Multiple Sclerosis Society, National Institutes of Health, Patient Centered Research Institute, Race to Erase MS Foundation, Genentech, and Genzyme. He has also received consulting fees from Biogen Idec, Genentech/Roche, Genzyme, Novartis and Merck. ET reports personal consulting fees and support to attend educational meetings from Roche, support to attend educational meetings from Merck and Novartis. ET received salary from Biogen as part of a MS Registry Fellowship, and currently contributes to work in a joint-working research study funded by Novartis. NE has received honoraria and advisory fees from Merck, Novartis, Roche, Biogen and Genzyme.

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