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Case report

Rash developing after cessation of Daclizumab for relapsing remitting MS; a case series

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ABSTRACT

Daclizumab, a monoclonal antibody directed against CD25, a subunit of the high-affinity IL-2 receptor, was licensed as a disease modifying therapy (DMT) for relapsing remitting multiple sclerosis in 2017. Interference with IL-2 signalling is hypothesised to modulate T cell function. For example it results in a preferential shift of innate lymphoid cell (ILC) into $CD56^{bright}$ natural killer cells and a decrease in regulatory T Cells. We present three patients who developed urticarial papulovesicular rashes at a median of 3 months after discontinuation of Daclizumab. We propose an unexpected T cell mediated immune reaction as the cause.

Daclizumab, a monoclonal antibody directed against CD25, a subunit of the high –affinity IL-2 Receptor, was licensed as a disease modifying therapy (DMT) for relapsing remitting multiple sclerosis in 2017.

Interference with IL-2 signalling is hypothesised to modulate T cell function. Proposed mechanisms include inhibiting dendritic cell-mediated T cell activation, expansion of $CD56^{bright}$natural killer cells, and inhibition of activated T cells. Unoccupied CD25 levels return to baseline 24 weeks post discontinuation (Shirley, 2018). However the exact mechanism of action of Daclizumab is not fully understood and the full implications of disrupting IL-2 signalling are not known. Seven percent of patients in the phase 2 SELECT trial (Gold et al., 2013) and 15% of patients in the phase 3 DECIDE trial (Kappos et al., 2015) suffered serious adverse reactions including infection, autoimmune hepatitis, colitis, meningoencephalitis and cutaneous adverse events (including toxic skin eruption and cutaneous vasculitis) whilst on active treatment (Shirley, 2018; Krueger et al., 2016). Marketing authorisation was removed from Daclizumab in February 2018 due to the neurological adverse effects (Daclizumab withdrawn from the market worldwide 2018) (Fig. 1).

We present three patients who developed similar unexplained rashes within 3 months of cessation of Daclizumab treatment.

1. Case 1

A 39 year old male commenced Daclizumab in October 2017. He had previously been on Interferon Beta (Avonex), dimethylfumarate and Natalizumab, having developed an infusion reaction with the latter. He stopped Daclizumab in February 2018. Two months after cessation he developed a diffuse urticarial rash on his limbs and trunk. His ANCA, MPO and PR3 were negative. He had low titre homogenous ANA. He had a transient response to topical steroid but his rash has since rebounded.

2. Case 2

A 37 year old female had been on Daclizumab since enrolment in the clinical trial program in 2011. She had not been on other disease modifying therapy prior to this. She tolerated the treatment well until it was discontinued in February 2018. Three months after cessation she developed a papular, erythematous rash on her hands that spread over days to trunk and head. Dermatology opinion was that of an urticarial papulovesicular eruption. ANCA, MPO and PR3 were negative and she had low titre speckled ANA. She responded well to topical steroid.

3. Case 3

A 57 year old male commenced Daclizumab in May 2017. He had previously been on Dimethylfumarate and Fingolimod. He tolerated the treatment well until it was discontinued in February 2018. Three months after discontinuation he developed an erythematous, scaly rash that began on his hands and spread over days to his torso, neck and scalp. He became aware of the rash within 48 h of commencing teriflunamide but is unsure if the rash predated this. He had negative

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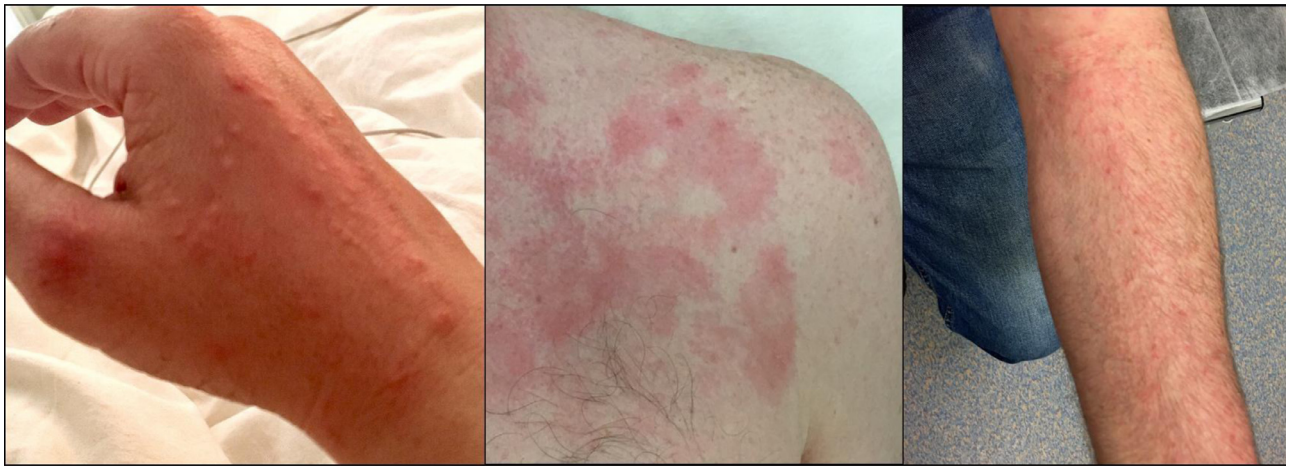

Fig. 1. Urticarial papulovesicular rash affecting limbs and torso.

ANCA, MPO and PR3 antibodies and low titre nucleolar antinuclear antibody (ANA). His rash responded well to topical steroid.

4. Discussion

The three cases we present all developed a similar rash affecting upper limbs, trunk and face within 3 months of stopping Daclizumab. All had tolerated the treatment well until discontinuation. In the three patients the rash began in the limbs and spread towards the trunk and head. All patients had at least a transient response to topical steroid. Daclizumab has a half life of 21–25 days; our patients developed their rash at 60–90 days after discontinuation. CD25 occupation by Daclizumab does not return to baseline levels until 24 weeks post discontinuation.

A limitation of our case series is that skin biopsies were not obtained. So any comments as to the mechanism of the delayed rash development are speculative. We propose that these rashes were due to a T cell mediated reaction as Daclizumab levels fell after cessation of treatment. It is known that during Daclizumab treatment there is an expansion of $CD56^{bright}$natural killer cells and that these fall back to normal levels at about 24 weeks post cessation. The $CD56^{bright}$ Natural Killer cells come from the innate lymphoid cell (ILC) lineage. Patients with RRMS have been found to have higher circulating ILC levels. Daclizumab has also been found to cause a decrease in circulating regulatory T cell (T-reg) levels. We suspect that the change in T cell and ILC subsets caused by Daclizumab (increased $CD56^{bright}$natural killer cells and decreased T-reg cells for example) and the subsequent slow return to baseline after cessation could have unpredicted systemic effects on immune function and lead to unexpected reactions. Delayed immune mediated reactions have been seen after discontinuation of other DMTs in MS patients.

In the SELECT trial skin reactions were reported in 18% of patients (compared with 13% with placebo). The majority of these were eczematous dermatitis and that on immunohistochemistry there was increased CD56 within the tissue. It would have been interesting to see if CD56 was present in our patients who developed rash after discontinuation of Daclizumab. Our patients' rashes responded to steroids at least transiently and at follow up all three patients have experienced resolution of rash.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

References

Daclizumab withdrawn from the market worldwide. DTB | vol. 56 | no 4 | April2018. DOI: 10.1136/dtb.2018.4.0604.

Gold, R., Giovannoni, G., Selmaj, K., et al., 2013. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. Lancet 381 (9884), 2167–2175.

Kappos, L., Wiendl, H., Selmaj, K., et al., 2015. Daclizumab HYP versus interferon beta 1a in relapsing multiple sclerosis. N. Engl. J. Med. 373 (15), 1418–1428.

Krueger, J.G., Kircik, L., Hougeir, F., et al., 2016. Cutaneous adverse events in the randomized, double-blind, active-comparator DECIDE study of daclizumab high-yield process versus intramuscular interferon beta-1a in relapsing-remitting multiple sclerosis. Adv. Ther 33 (7), 1231–1245.

Shirley, M., 2018. *Daclizumab: a review in relapsing multiple sclerosis*. Drugs. https://doi.org/10.1007/s40265-017-0708-2.