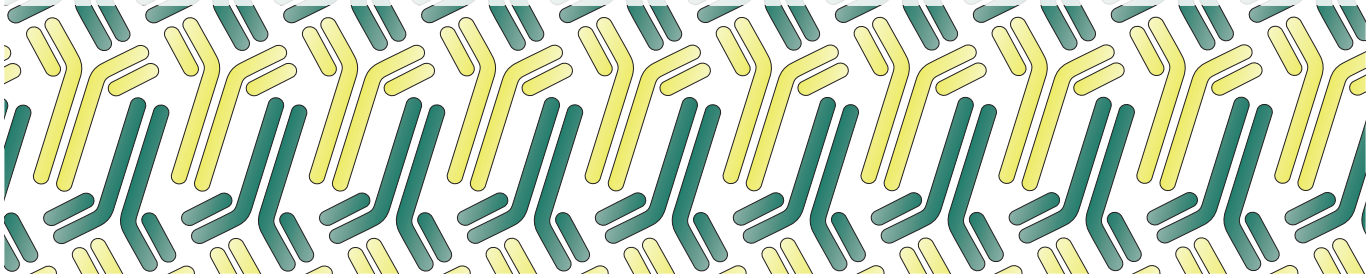
MILESTONE 5

Highs and lows with second-generation monoclonal antibodies



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Following the eventual success of natalizumab therapy for multiple sclerosis (MS; MILESTONE 3), alemtuzumab and daclizumab — two second-generation monoclonal antibodies — were approved for treatment in 2014 and 2016, respectively, although the success of daclizumab did not last.

While natalizumab prevents lymphocytes from crossing the blood–brain barrier (MILESTONE 2), the second-generation antibodies each have different biological actions. Alemtuzumab binds to CD52 on mature lymphocytes and depletes circulating T cells and B cells, which are subsequently repopulated spontaneously. This process can lead to lasting changes in adaptive immunity. Daclizumab targets CD25, the α-subunit of the high-affinity IL-2 receptor. Treatment with daclizumab reduces IL-2 signalling through this receptor and increases signalling at the intermediate-affinity IL-2 receptor. As a result, numbers of $CD56^{bright}$ natural killer cells increase and numbers of lymphoid tissue inducer cells decrease, thereby reducing immune responses.

In 2012, two clinical trials demonstrated the efficacy of alemtuzumab treatment for patients with relapsing–remitting MS (RRMS). In the CARE-MS I trial, patients with previously untreated RRMS were randomly allocated to receive alemtuzumab (12 mg daily for 5 days at baseline and for 3 days at 12 months) or interferon-β-1a (IFNβ-1a; 44 μg three times per week). Over 2 years, fewer patients in the alemtuzumab group than in the IFNβ-1a group experienced a relapse. However, alemtuzumab offered no benefit over IFNβ-1a in terms of sustained accumulation of disability.

In the CARE-MS II trial, alemtuzumab was compared with IFNβ-1a in patients with RRMS who had experienced a relapse while receiving a standard disease-modifying therapy. Among patients in the alemtuzumab group, the annual relapse rate was 49.4% lower than in the IFNβ-1a group, and sustained accumulation of disability was 42% lower. Secondary autoimmunity was the main adverse effect of alemtuzumab therapy, but this effect could be managed effectively to reduce the risk. Thus, alemtuzumab was approved for treatment in 2014.

In 2013, the randomized, double-blind, placebo-controlled SELECT trial of daclizumab in patients with RRMS was published. In this trial, patients received daclizumab (150 mg or 300 mg) or placebo every 4 weeks for 1 year. The annual relapse rate was lower in patients who received daclizumab (either dose) than in those who received placebo.

The subsequent SELECTION study was a multicentre, randomized, double-blind trial to assess the safety and immunogenicity of extended treatment with daclizumab in patients with RRMS. The conclusions were that adverse events and immunogenicity did not increase in the second year of continuous treatment with daclizumab relative to the first. In a further trial published in 2015, daclizumab was compared with IFNβ-1a. Daclizumab treatment resulted in a lower annual relapse rate than IFNβ-1a treatment.

> “fewer patients in the alemtuzumab group than in the IFNβ-1a group experienced a relapse”

On the basis of these trial results, daclizumab was approved for the treatment of RRMS in 2016, with a contraindication for patients with pre-existing hepatic disease or impairment (owing to observations in clinical trials that levels of liver enzymes were elevated in patients receiving daclizumab, and to the death of one patient from autoimmune hepatitis).

However, in 2016 and 2017 reports of immune-mediated adverse reactions in the CNS, including encephalitis and meningoencephalitis, started to emerge. Given the seriousness of these immune-mediated events and a high likelihood that they were linked to or caused by daclizumab, the drug was withdrawn from the market with immediate effect in March 2018.

Isobel Leake, Senior Editor, Nature Reviews

ORIGINAL ARTICLES Cohen, J. A. et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* **380**, 1819–1828 (2012) | Coles, A. J. et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* **380**, 1829–1839 (2012) | Gold, R. et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. *Lancet* **381**, 2167–2175 (2013) | Giovannoni, G. et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECTION): a multicentre, randomised, double-blind extension trial. *Lancet Neurol.* **13**, 472–481 (2014) | Kappos, L. et al. Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis. *N. Engl. J. Med.* **373**, 1418–1428 (2015) | Pharmacovigilance Risk Assessment Committee (PRAC). Assessment report on provisional measures. *European Medicines Agency* https://www.ema.europa.eu/documents/referral/zinbryta-article-20-procedure-assessment-report-provisional-measures_en.pdf (2018)

FURTHER READING Wiendl, H. & Gross, C. C. Modulation of IL-2Rα with daclizumab for treatment of multiple sclerosis. *Nat. Rev. Neurol.* **9**, 394–404 (2013) | Wiendl, H. & Keseier, B. Reprogramming the immune repertoire with alemtuzumab in MS. *Nat. Rev. Neurol.* **9**, 125–126 (2013)