Institution: University of Edinburgh		
Unit of Assessment: 4		
Title of case study: I: Uncovering a causative link between recombinant interferon beta therapy and thrombotic microangiopathy leads to international safety alerts and risk mitigation measures		
Period when the underpinning research was undertaken: 2011 – 2017		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
David Hunt	Chair of Neuroinflammation Medicine	2013 – present
Andrew Jackson	Professorial Fellow in Human Genetics	2005 – present
Siddharthan Chandran	MacDonald Chair of Neurology	2009 – present
Period when the claimed impact occurred: 2014 – 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Underpinning Research: Edinburgh Neuroscience researchers identified thrombotic microangiopathy (TMA), a potentially fatal disease of the small blood vessels, as a new side effect of interferon beta therapy in patients with multiple sclerosis. They demonstrated a causal association with interferon, and showed that this was linked to an evolved version of the drug resulting from incremental changes in the manufacturing process – a phenomenon known as 'biologic evolution'.

Significance and Reach of Impact: In 2014, the UK Medicines and Healthcare product Regulatory Agency (MHRA) issued a drug safety update regarding TMA from interferon beta and European Medicines Agency (EMA) ordered a warning to be included in the drug's safety data sheet. As a result, all patients taking high-dose interferon beta (50,000–100,000 patients worldwide in 2014) are now monitored for TMA as standard of care, based on "early warning signs" identified in Edinburgh Neuroscience research, enabling early preventative action to be taken. This has already prevented 2 cases of fulminant TMA in Scotland.

Edinburgh Neuroscience findings received widespread academic and mainstream media attention, raising awareness among industry regulators such as MHRA and EMA, as well as healthcare professionals, that biologic evolution may mean that a long-established safety profile does not always guarantee an absence of serious adverse side effects. This has implications for drug manufacturers worldwide.

2. Underpinning research

The Challenge: How do we know biological medicines are safe?
Biological medicines such as recombinant protein therapies are complex molecules produced in living cells, requiring multistep manufacturing processes. When doctors prescribe biologic agents, they often assume this is the same medicine that has been tested in extensive clinical trials. However, sequential manufacturing changes may accumulate to mean that none of the original components are the same. Edinburgh Neuroscience researchers have shown that that in the case of interferon beta therapy for patients with multiple sclerosis (MS), sequential manufacturing changes can affect the safety profile of the drug.

Discovery of a new side effect in multiple sclerosis patients taking interferon beta
Through clinical observation and subsequent systematic investigations, Edinburgh Neuroscience researchers have identified TMA as a new serious complication of interferon beta therapy in patients with MS. TMA is a disease of small blood vessels and can lead to fulminant multi-organ failure and ultimately death.

The Edinburgh Neuroscience researchers were the first to define the clinical syndrome of interferon-associated TMA and identify new-onset severe hypertension and impaired renal function as early warning signs. The incidence of TMA in patients treated with high-dose interferon beta was estimated to be approximately 1 per 1,000 patient-years — a major, and previously unidentified, risk [3.1].

The researchers next sought to demonstrate clinically the direct causal relationship between interferon beta and TMA: they undertook a detailed analysis of all 8 patients in the UK in whom TMA had been identified at that time, and found that no patient had any genetic, pharmacological or disease-related predisposing factors that could have explained why they developed TMA, nor were they taking any other medication associated with TMA [3.2].

Experimental evidence establishes direct causality between interferon beta and TMA

To provide explicit and unequivocal experimental evidence for the causal association between interferon beta and TMA, the researchers asked whether the recombinant protein itself could cause the small vessel abnormalities observed in the patients. Using transgenic mouse models of mild and severe interferon overexpression, they revealed a clear dose-dependent effect of interferon on the microvasculature, which mirrored phenotypes seen on patient biopsies, thus demonstrating direct causality between high-dose interferon therapies and TMA [3.2].

Increase in interferon-associated TMA is a result of incremental manufacturing changes ('biologic evolution')

The discovery of TMA as a side effect of interferon beta was unexpected since the drug had been approved for almost 20 years and was considered very safe; not only had the initial formulation been tested over many thousands of patient-years, but there had been only reports of negligible side effects for the first 10 years of use.

Together with colleagues from London School of Hygiene and Tropical Medicine, the Edinburgh Neuroscience team analysed pharmacy records and reports from national and global drug safety databases and identified a single common manufacturing source of all the interferon implicated in TMA cases. Moreover, they showed that the TMA cases were associated with the introduction of an evolved version of recombinant interferon by this manufacturer, indicating that incremental manufacturing changes, designed to improve efficiency of the process, had led to the drug having a different safety profile from that of the originally approved biologic agent [3.1; 3.3].

The Edinburgh Neuroscience researchers went on to demonstrate how current drug monitoring systems may be too limited in sample size and duration of follow-up to capture important new side effects from evolved biologics in a timely manner [3.3]. This phenomenon, whereby a complex biological drug can become less safe over time, is known as 'biologic evolution'.

3. References to the research

[3.1] Hunt DPJ, Kavanagh D, Drummond I, Weller B, Bellamy C, Overell J, Evans S, Jackson A, Chandran S (2014). Thrombotic Microangiopathy Associated with Recombinant Interferon-Beta: *N Engl Jour Med* 370:1270-1271. doi: 10.1056/NEJMc1316118

[3.2] Kavanagh D, McGlasson S… Jackson A, Chandran S, Hunt DPJ (2016): Type I interferon causes thrombotic microangiopathy by a dose-dependent toxic effect on the microvasculature *Blood*; 128(24): 2824–2833 doi: 10.1182/blood-2016-05-715987

[3.3] Casadevall N, Flossmann O, Hunt DPJ (2017) Evolution of Biological Therapeutics: How established medicines can become less safe *BMJ 357; j1707* doi: 10.1136/bmj.j1707

4. Details of the impact

The Edinburgh Neuroscience research described above has led to impacts on both the routine monitoring of patients with MS taking high-dose interferon beta and on the wider pharmaceutical industry and its regulatory bodies.

Impact on awareness among patients and clinicians
Given the potentially fatal nature of the side effect of TMA seen with the new interferon beta preparations, identified through Edinburgh Neuroscience research, it was of paramount importance to raise awareness among healthcare professionals that a long-established safety profile does not necessarily mean a drug will not have adverse side effects. This awareness has been boosted by highly supportive editorials accompanying publications [3.1] and [3.2] from high-profile figures in the field of pharmacoepidemiology: for example, the editorial of paper [3.2] noted: "*This report is remarkable for the multiple methods of their investigation, their definitive documentation of a causal association, and the importance of their findings for improved patient care*." [5.1]. In addition, in April 2017, Hunt featured in a *British Medical Journal* podcast on biologic evolution, which had been played 8,800 times by November 2020 [5.2].

Impact on UK drug safety regulators
In December 2014, MHRA issued a drug safety update on interferon beta on its website [5.3]. Citing the paper [3.1], this announcement lists the clinical warning signs of TMA, urges healthcare professionals to be vigilant for these, advises on the next steps if a case of TMA is suspected and stresses that interferon beta treatment must be discontinued immediately if TMA is diagnosed. The same warning was included in an MHRA newsletter in October 2014 [5.3].

Impact on international drug safety regulators
The Edinburgh Neuroscience reports of interferon-associated TMA triggered a European investigation into the risk. In February 2014, Hunt was invited to present evidence from his research to the EMA Pharmacovigilance Risk Assessment Committee (PRAC). Consequently, PRAC categorised TMA as an important identified risk that should be included in the risk management plan across all formulations of interferon beta.

Furthermore, PRAC recommended that the safety data sheet accompanying packages of the new formulation of interferon beta be updated to contain the following information: "*Cases of thrombotic microangiopathy […] have been reported including fatal cases with interferon beta products* […] *Therefore, if clinical features of TMA are observed, further testing […] is recommended. If TMA is diagnosed, prompt treatment with plasma exchange is required and immediate discontinuation of [product name] is recommended*." [5.4].

Crucially, PRAC also recommended the following addition to the "What you need to know before you use" section: "*Cases of formation of blood clots in the small blood vessels may occur during your treatment, from several weeks of treatment up to several years after starting [product name]. Your doctor may want to monitor your blood pressure, blood (platelet count) and the function of your kidney."* [5.4].

In addition, in August 2014, the Medicines Authority, in agreement with EMA and the manufacturers of interferon beta (Bayer, Biogen Idec, Merck Serono and Novartis), issued a "Dear Healthcare Professional" letter to all practising doctors in Europe [5.5], notifying them of the side effect.

Impact on clinical practice and patient safety
Following these explicit recommendations by EMA and MHRA, active monitoring for the early warning signs identified through Edinburgh Neuroscience research is now standard of care in MS patients taking high doses (more than 50mcg per week) of interferon beta. This has already helped to prevent the development of fulminant TMA in 2 Scottish patients.

Targeted monitoring was formally introduced in all major Scottish centres in January 2014. This involves a 3-monthly monitoring with full blood count, renal function and blood pressure checks. A clinical audit between January 2014 and January 2016 tracked 249 patients and found that since the introduction of the targeted monitoring, interferon beta was discontinued early in 2 patients who developed new severe hypertension with renal dysfunction. These abnormalities resolved fully once interferon beta was stopped, and no organ damage was observed. During the audit period, no cases presented with fulminant organ failure due to interferon-associated TMA [5.6].

In addition to preventing dangerous TMA in 2 patients in Scotland, the formal warnings by MHRA and EMA and the safety data sheet have also reduced the risk of TMA for MS patients worldwide who are taking high-dose interferon beta (50,000–100,000 patients at the time of the EMA announcement). Before the announcement, a worldwide total of 91 cases of interferon-associated TMA (7 of which were fatal) from 16 countries was documented. In the 4 months following circulation of the Dear Healthcare Professional letter in August 2014, 5 further cases were reported, with appropriate action taken in each case and no fatalities [5.7].

Impact on drug regulatory practice

Edinburgh Neuroscience's discovery of the novel side effect of interferon-associated TMA, and linking it to the evolved formulation of interferon beta, have alerted drug regulators to the risk of biologic evolution more generally. The Chief Executive of MHRA states that Edinburgh Neuroscience research has been "*influential in the drug safety field, through the description of "biologic evolution" – a process whereby biologic drugs can alter their safety profiles over time. This concept has been important in framing ongoing academic, regulatory and industry discussions about optimising biologic safety*." [5.8]. This awareness of the MHRA of the risk of biologic evolution ensures that it is now considered when new drugs or manufacturing processes are evaluated for approval.

In recognition of his contribution to drug safety, in September 2015, Hunt was awarded the Sir Derrick Dunlop Prize by the MHRA [5.9], reflecting the fundamental importance of the discovery for patient safety.

5. Sources to corroborate the impact

[5.1] Editorial for paper [3.2] doi: 10.1182/blood-2016-10-742759

[5.2] BMJ Podcast on biologic evolution, featuring Hunt, with usage metrics as at 3rd November 2020

[5.3] MHRA Drug Safety Update their website and on their newsletter

[5.4] PRAC recommendation on signals 3rd – 6th February 2014 (pages 4-5)

[5.5] "Dear Healthcare Professional" letter sent out by Medicines Authority in August 2014 to alert medical community to interferon beta side effect.

[5.6] Supplemental Data to paper [3.2] containing details of clinical audit in Scotland (figure S2 on p. 9)

[5.7] Ben-Amor et al. (2015) *Adv Ther* 32:445–454. doi: 10.1007/s12325-015-0212-6

[5.8] Letter of support from the Chief Executive of the MHRA to describe the impact of Edinburgh Neuroscience research on drug safety more generally. (The letter was written when the author was Director of Vigilance and Risk Management of Medicines, but on 20th September 2019, she became the Chief Executive of MHRA).

[5.9] Details of Sir Derrick Dunlop Prize (slide 46 of the "Changing World of Pharmacovigilance" presentation by MHRA Chief Executive on 10th June 2017)