Institution: The University of Edinburgh

Unit of Assessment: 1

Title of case study: S: Progesterone receptor modulators are effective in emergency contraception and therapy of heavy menstrual bleeding/fibroids

1. Summary of the impact (indicative maximum 100 words)

Impact: Health and wellbeing; commerce; studies and clinical trials of the effects of progesterone receptor modulators (PRMs) underpinned their application for the benefit of women of childbearing age.

Significance: UoE studies underpinned the application of PRMs as emergency contraception including over-the-counter availability and the treatment of heavy menstrual bleeding (HMB); changed clinical guidelines; influenced Pharma R&D.

Beneficiaries: Women of reproductive age; the NHS and healthcare delivery organisations; pharmaceutical companies.

Attribution: Studies were conducted by Critchley, Baird and colleagues (UoE).

Reach: Worldwide; annually 4M women seek emergency contraception in the USA, and in the UK 1M women seek help for HMB. Drugs targeting the PR are licenced in 67 countries. Multiple global Pharma are active in the field of PRM biology.

2. Underpinning research (indicative maximum 500 words)

A 20-year continuous programme of studies at UoE by Professor Hilary Critchley (Professor of Reproductive Medicine, UoE, 1993–present), Dr Alistair Williams (Reader in Pathology, UoE, 1998–present), Professor David Baird (Professor of Reproductive Endocrinology, UoE, 1977–2000; now Emeritus), Dr Pamela Warner (Reader in Medical Statistics, UoE, 1994–present), Dr Sharon Cameron (Consultant in Gynaecology and Reproductive Health, Honorary Senior Lecturer, UoE) and Professor Anna Glasier (Honorary Professor, 2004–present) has provided pivotal data for the development of progesterone receptor modulators (PRMs), most importantly as contraceptives, but also with other important clinical utilities in women's health.

Effective and safe contraception remains a major issue in women's health worldwide. Between 2000 and 2007, Baird (with Critchley, Glasier and Cameron) pioneered research in the use of PRMs for contraception by demonstrating that PRM exposure prevents the establishment of pregnancy. Glasier established that the PRM mifepristone was effective as emergency contraception, and that emergency contraception could be safely given over-the-counter (OTC; without prescription) [3.1]. These data led to UK government approval of alternative emergency contraception available OTC in 2001. A subsequent multicentre randomised trial and meta-analysis of 2221 women, led by Glasier and Cameron, showed that the PRM ulipristal acetate is the most safe and effective form of emergency contraception [3.2].

A second focus of the team's research has been menstrual complaints, specifically heavy menstrual bleeding (HMB) and uterine fibroids, which often co-occur (fibroids are present in up to 80% of women of reproductive age). HMB can cause anaemia, have a negative impact on quality of life and productivity, and cause significant morbidity in women: 1 in 3 women will complain of HMB during their reproductive years. Critchley established (1996 onwards) that progesterone receptors A and B and progesterone withdrawal play a pivotal role in regulating the cyclical remodelling occurring within the endometrium during the menstrual cycle [3.3, 3.4]. Critchley, Baird and Williams undertook formative "in human" studies of the actions of PRMs (mifepristone, asoprisnil) on uterine/endometrial tissue [3.5, 3.6], demonstrating a unique histological effect on the endometrium [3.5]. Furthermore, they reported the anti-proliferative effects on the endometrium

of low-dose continuous administration of mifepristone, when women took this class of drug for 6 months [3.6]. This highlighted the potential of this drug class to achieve morphological and functional effects that reduce menstrual bleeding.

UoE studies from 1995 onwards have also provided unique insights into the local endometrial effects of intrauterine use (i.e., slow release) of the PR agonist levonorgestrel. Levonorgestrel delivered by an intrauterine system (LNG-IUS) is currently a first-line management for HMB. Crucial data were also derived from ensuing detailed studies of uterine morphology following exposure to selected PRMs, which showed the marked anti-proliferative effects of this class of compound, along with the added health benefit of amenorrhoea, and in turn directly informed the development and refinement of the drug class, i.e., PRMs, for the treatment of fibroids and HMB [3.6].

3. References to the research (indicative maximum of six references)

3.1 Glasier A, Baird D. The effects of self-administering emergency contraception. N Engl J Med. 1998;339:1–4. DOI: 10.1056/NEJM199807023390101.

3.2 Glasier A, Cameron S, Fine P, et al. (2010). Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet. 2010;375:555–62. DOI: 10.1016/S0140-6736(10)60101-8.

3.3 Critchley H, Wang H, Kelly R, Gebbie A, Glasier A. Progestin receptor isoforms and prostaglandin dehydrogenase in the endometrium of women using a levonorgestrel-releasing intrauterine system. Hum Reprod. 1998;13:1210–7. DOI: 10.1093/humrep/13.5.1210.

3.4 Critchley H, Jones R, Lea R, et al. Role of inflammatory mediators in human endometrium during progesterone withdrawal and early pregnancy. J Clin Endocrinol Metab. 1999;84:240–8. DOI: 10.1210/jc.84.1.240.

3.5 Williams A, Critchley H, Osei J, et al. The effects of the selective progesterone receptor modulator asoprisnil on the morphology of uterine tissues after 3 months treatment in patients with symptomatic uterine leiomyomata. Hum Reprod. 2007;22:1696–704. DOI: 10.1093/humrep/dem026.

3.6 Baird D, Brown A, Critchley H, Williams A, Lin S, Cheng L. Effect of long-term treatment with low-dose mifepristone on the endometrium. Hum Reprod. 2003;18:61–8. DOI: 10.1093/humrep/deg022.

4. Details of the impact (indicative maximum 750 words)

Pathways to impact

The UoE team has disseminated the output of research endeavours extensively. Critchley, Baird, Glasier and Williams have made major contributions and provided expert consultancy to the National Institutes of Health and major Pharma: Jenapharm, TAP Pharmaceutical Products Inc, Schering, Repros Therapeutics Inc., Bayer Pharma AG, HRA Pharma, PregLem and Gedeon Richter. Glasier has engaged public opinion and lobbied government to ensure OTC availability of emergency contraception.

Impact on health and welfare, policy and the economy

Contraception: Emergency contraception is used by over 4 million women per year in the USA and 20% of women aged 18–35 per year in the UK. The UoE data on the safety and utility of PR ligands as emergency contraceptives persuaded the Scottish Government to make levonorgestrel available OTC for this purpose for free from 2008. This resulted in a 10% drop in medical abortion rates in Scotland (13,904 to 12,447) between 2008 and 2012 [5.1].

Later, the team's demonstration of the superiority of ulipristal acetate over levonorgestrel was used to support the decision in 2010 by the US Food and Drug Administration (FDA) to license the former as an emergency contraceptive [5.2]. The data are also cited in guidelines in the UK and US: the UK National Institute for Health and Care Excellence (2011) "Clinical Knowledge

Summary", endorsing the use of ulipristal acetate as an emergency contraceptive; guidelines from the UK Faculty of Sexual and Reproductive Health (updated January 2012); the Centers for Disease Control and Prevention "US Selected Practice Recommendations for Contraceptive Use, 2013" [5.3]; and the American College of Obstetricians and Gynaecologists Practice Bulletin on Emergency Contraception (November 2012). In March 2013, the WHO Family Planning steering group, chaired by Williams, agreed that ulipristal acetate should be added to the "Medical Eligibility Criteria for Contraceptive Use" when it is updated in 2014.

An independent cost-effectiveness analysis that cites ref. [3.2] suggested that the use of ulipristal acetate as an emergency contraceptive instead of the alternative levonorgestrel would result in 37,589 fewer unintended pregnancies and resultant societal savings of $116.3M in the USA each year [5.4]. This study concludes by stating that "Efforts should be promoted to increase access to [ulipristal acetate]".

Treatment of fibroids: Annual estimated direct costs of managing uterine fibroids in the USA alone are $4.1–9.4B and lost work-hours cost $1.55–17.2B. UoE work on the mechanism of action and predicted efficacy of PRMs was instrumental in the first PRM being approved for the treatment of symptomatic fibroids. Ulipristal acetate (marketed as Esmya®) received a European Medicines Agency & Medicines and Healthcare Products Regulatory Agency license in Spring 2012 for use in women for 3 months pre-hysterectomy, offering women a convenient oral treatment option to reduce heavy bleeding and fibroid size prior to surgery. The Scottish Medicines Consortium approved ulipristal acetate as a pre-operative treatment for uterine fibroids (up to 3 months) in January 2013. Drugs targeting the PR are now licensed for use in 67 countries.

Treatment of HMB: UoE researchers have formed the lead UK team deriving data on the mechanism of action of LNG-IUS and thus contributed to the development of management strategies with use of this slow-released PR agonist for the 1 million women in the UK who annually seek help for HMB. International guidance documents in the UK and USA recommend LNG-IUS for the treatment of women with HMB and state that it should be offered before invasive procedures (UK National Institute for Health and Care Excellence Clinical Guideline on Heavy Menstrual Bleeding, published in 2007 and remaining the current guideline; Institute for Quality and Efficiency in Health Care "Treatment Options for Heavy Periods", published in 2009 and updated in 2013 [5.5]).

Impact on practitioners

To provide meaningful quantitation in the studies of uterine architecture and HMB necessary to define the positive or negative effects of therapeutic PRM intervention, and critically to stratify patients with abnormal uterine bleeding for both research and therapeutic purposes, Critchley, as co-chair of the FIGO Working Group on Menstrual Disorders, with colleagues defined the PALM-COEIN classification system for abnormal uterine bleeding (2011). This is now entering clinical use worldwide (for example in North America [5.6, 5.7]), and is being adopted as the industry standard.

Impact on commerce

The UoE work on PRMs, both directly and via Baird and colleagues' input to the World Health Organization and other bodies, indirectly influenced the drug development programme of Pharma to identify PRMs, define the biology of PRMs and, crucially, to explore the potential indications of PRMs [5.8]. The expertise of the Edinburgh team continues to be sought by international pharmaceutical companies (Bayer Healthcare AG; HRA Pharma; Gedeon-Richter; TAP Pharmaceuticals Inc.). This input has been essential to inform therapeutic developments, for example through the review and classification of histological slides etc., and to conduct Pharma-supported multi-centre clinical trials [5.9, 5.10] to progress the clinical utility of PRMs in the field of benign gynaecological complaints (including HMB and fibroids).

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 NHS National Services Scotland (2013). Abortion Statistics. http://www.isdscotland.org/Health-Topics/Sexual-Health/Publications/2013-05-28/2013-05-28-Abortions-Summary.pdf.

5.2 FDA Reproductive Health Drugs Advisory Committee (2010). ella®, ulipristal acetate. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM217418.pdf. *[FDA licensing of ulipristal acetate; cites UoE research.]*

5.3 Centers for Disease Prevention and Control, Morbidity and Mortality Weekly Report (2013). U.S. Selected Practice Recommendations for Contraceptive Use, 2013. http://www.cdc.gov/mmwr/pdf/rr/rr6205.pdf.

5.4 Bayer L, Edelman A, Caughey A, Rodriguez M. The price of emergency contraception in the United States: what is the cost-effectiveness of ulipristal acetate versus single-dose levonorgestrel? Contraception. 2013;87: 385–90. DOI: 10.1016/j.contraception.2012.08.034.

5.5 Institute for Quality and Efficiency in Health Care (2009; updated in 2013). "Treatment Options for Heavy Periods". PubMed Health. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0005201/.

5.6 The Agency for Healthcare Research and Quality. Research Protocol, November 21st 2011. Primary Care Management of Abonormal Uterine Bleeding. http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=850&pageaction=displayproduct.

5.7 Society of Obstetricians and Gynaecologists of Canada Clinical Practice Guidelines (2013). Abnormal Uterine Bleeding in Pre-Menopausal Women. http://sogc.org/guidelines/abnormal-uterine-bleeding-in-pre-menopausal-women/.

5.8 Letter from the Senior Medical Director of Women's Health, AbbVie Inc., in support of the contributions made by UoE researchers in the field of reproductive health, particularly basic and clinical research with PRMs. *[Available on request.]*

5.9 Mutter G, Bergeron C, Deligdisch L,…Williams A, Blithe D. The spectrum of endometrial pathology induced by progesterone receptor modulators. Mod Pathol. 2008;21:591–8. DOI: 10.1038/modpathol.2008.19.

5.10 Wilkens J, Chwalisz K, Han C,…Williams A, Critchley H. Effects of the selective progesterone receptor modulator asoprisnil on uterine artery blood flow, ovarian activity, and clinical symptoms in patients with uterine leiomyomata scheduled for hysterectomy. J Clin Endocrinol Metab. 2008;93:4664–71. DOI: 10.1210/jc.2008-1104.