EDITORIALS

Editorials are usually commissioned. We are, however, happy to consider and peer review unsolicited editorials
See http://resources.bmj.com/bmj/authors/types-of-article/editorials for more details

Statins in pregnancy

New safety data are reassuring, but suspension of treatment is still advisable

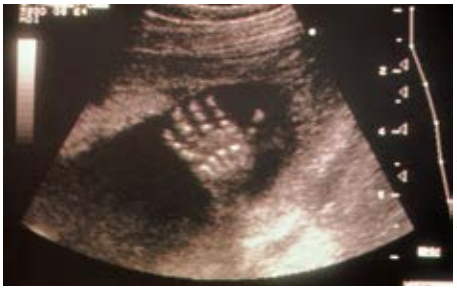
Françoise Haramburu director
francoise.haramburu@u-bordeaux.fr
Amélie Daveluy consultant
Ghada Miremont-Salamé associate director, Bordeaux Regional Pharmacovigilance Centre, CHU de Bordeaux, France, INSERM U657, France

The linked study by Bateman and colleagues[1] is an important contribution to our knowledge about the teratogenic potential of statins in early pregnancy. It is a well designed epidemiological study of pregnancy and childbirth among a large cohort of US women enrolled in the US Medicaid programme between 2000 and 2007.

The authors analysed 886 996 pregnancies that ended with a liveborn infant, representing approximately 40% of all births in the United States during the study period. They used sophisticated analytical techniques, including high density propensity scoring, to compare otherwise similar women who did or did not use a statin during their first trimester. Propensity scoring helps minimise confounding by adjusting for the many important differences between exposed and unexposed women, such as prevalence of diabetes (which is higher among women taking statins) and use of other drugs. These techniques are rarely used in studies of medicines in pregnant women and are an important strength of the new work.

Bateman and colleagues' study evaluates the teratogenic potential of statins taken in the first trimester of pregnancy. The primary outcome was any major congenital malformation, but the authors also looked for organ specific malformations. While unadjusted results suggested a slight increase in the risk for any malformation associated with statin use (relative risk 1.79, 95% confidence interval 1.43 to 2.23), this increase disappeared in adjusted analyses that controlled for a wide range of potential confounders (1.07, 0.85 to 1.37).

The study was conducted in a cohort of women on low incomes, all of whom were eligible for government funded health insurance, Medicaid. Generalisability to other more affluent populations may be limited, but the demographic profile of the studied population arguably represents a "worst case scenario" for pregnancy outcomes. If results are reassuring among those on lowest incomes, they are likely to be equally reassuring for women living in a more favourable social and economic environment.



P S AADA/EURELIOS/SPL

Women who unintentionally use statins in the early weeks of an unidentified or unplanned pregnancy can now be reassured about the risk

Despite using sophisticated methodology, database studies such as this one share several limitations, including the classification of statin use based on dispensed prescriptions and not consumption, and analyses confined to data available in the chosen database. The precise time of use of statins during pregnancy is difficult to assess from data on dispensed prescriptions. Misclassification can easily occur if, for example, adherence is poor (a common problem during long term primary prevention). As with most studies on drug use during pregnancy, Bateman and colleagues' study does not have all the answers. Questions remain about statins and other outcomes related to congenital malformation (medical terminations, miscarriages, and intrauterine fetal deaths) and longer term effects on the neonate and beyond.

Practical implications

What are the practical implications of this new work for clinical practice, including the evaluation of risk among women taking statins who are pregnant or planning a pregnancy?

Statins are a preventive treatment for long term cardiovascular complications, seldom used in women of childbearing age (just 0.13% of women in this cohort were taking statins). Despite some pharmacokinetic differences, all statins share a common mechanism of action, so combining them in more than 1000 pregnancies makes pharmacological sense. The authors found no evidence of increased risk associated with statins, reinforcing similar results from most previous studies,[2-8] except one.[9 10]

The US Food and Drug Administration currently designate statins in pregnancy as category X, or contraindicated. Statins in pregnancy are also contraindicated in Europe and in many other countries worldwide. Regulators will now have to update their information and potentially revisit a blanket ban. Women who unintentionally use statins in the early weeks of an unidentified or unplanned pregnancy can now be reassured about the risk. But how should treatment be managed once pregnancy is confirmed? In most women an interruption to treatment during pregnancy and breast feeding will not have serious consequences for the mother's health, and despite Bateman and colleagues' largely negative findings, interrupting treatment during pregnancy remains the best option. The benefits of statins are not established among women of childbearing age. Statin treated women who are planning a pregnancy can be advised to continue their treatment until pregnancy is confirmed.

Bateman and colleagues' study does not consider the use of statins later in pregnancy so cannot inform choices beyond the first trimester. We have limited information about the safety of statins used "off label" for the prevention of pre-eclampsia, an indication currently under study.[4-8] More information is also needed about safety outcomes beyond teratogenicity and the possibility of harm to the fetus or neonate from prolonged exposure to statins throughout pregnancy.

Bateman and colleagues' well designed study is a welcome addition to the literature informing risk assessment during pregnancy. However, single studies are never enough. Teratogenic risks are notoriously difficult to detect, and absence of risk is even harder to establish with confidence. Women and their providers must make informed use of all available data when making decisions about treatment during pregnancy. Tragic outcomes from drug use during pregnancy such as those due to thalidomide or diethylstilboestrol must not be forgotten. It would be unwise to make wholesale changes to recommendations and advocate wider use of statins during pregnancy on the basis of reassuring results from one or more single studies, however well conducted. The latest study along with its predecessors cannot eliminate uncertainty, a now familiar aspect of all therapeutic discussions about the risks of drug use in pregnancy.

Cite this as: *BMJ* 2015;350:h1484

RESEARCH, p 13

thebmj.com

- News: Cost of hospital prescribing rose 15% in a year owing to new rheumatoid arthritis and cancer drugs (*BMJ* 2014;349:g6867)
- Research News: Conventional triple therapy as good as etanercept for uncontrolled rheumatoid arthritis (*BMJ* 2013;346:f3846)
- Practice: Management of rheumatoid arthritis: summary of NICE guidance (*BMJ* 2009;338:b702)

Drugs for rheumatoid arthritis: looking backwards to move forwards

New combinations of older drugs can be effective and affordable

Pierre Miossec professor of clinical immunology, Department of Clinical Immunology and Rheumatology and Immunogenomics and Inflammation research Unit, University of Lyon, Edouard Herriot Hospital, 69437 Lyon, France pierre.miossec@univ-lyon1.fr

Over the past 40 years the clinical picture has improved for patients with rheumatoid arthritis thanks to key steps in drug development and care strategy. These steps include the introduction of methotrexate in 1980 and the first inhibitors of tumour necrosis factor (TNF) in 2000. This was followed by the development of new biotechnology products to target other cytokines, cell subsets, and cell interaction pathways. All these products are expensive drugs with obvious consequences for health systems with limited resources.

In parallel, trials have also continued to test old drugs used in new more modern ways, starting with the combination of methotrexate, sulfasalazine, and hydroxychloroquine. The real surprise came from a recent demonstration that this combination was as effective as the combination of methotrexate and the TNF inhibitor etanercept.[1 2] The linked paper by Scott and colleagues is another example of a trial of TNF inhibitors compared with intensive treatment comprising a combination of conventional disease modifying anti-rheumatic drugs.[3] The primary objective of this non-inferiority trial was to examine whether the drug combination could achieve similar clinical benefits to a TNF inhibitor but at lower costs.

This open label pragmatic trial (called the TACIT trial) included patients with rheumatoid arthritis who were eligible for TNF inhibitors under current guidance from the National Institute for Health and Care Excellence. Of 432 patients screened, 101 started treatment with a TNF inhibitor and 104 started treatment with the drug combination. Various drugs were used during the trial, to reflect routine practice. The most common TNF inhibitor was adalimumab (58/101) and the most common drug combination was methotrexate and leflunomide (62/104).

Newer drugs not necessarily better

The primary outcome was the change in disability scores (health assessment questionnaire, range 0.00 to 3.00) over 12 months. Scores decreased in both groups, but slightly more in the group treated initially with disease modifying drugs (−0.45 *v* −0.30). The difference was below the authors' prespecified threshold for non-inferiority (0.22). Changes in quality of life, progression of erosions, rate of induction of remission (44/101 with TNF *v* 36/104 with combination drugs), and serious adverse events (18/101 *v* 10/104) were comparable in both treatment arms. In conclusion, drug combinations resulted in non-inferior outcomes compared with starting TNF inhibitors. There were also differences. At six months, TNF inhibitors were associated with lower disease activity relative to drug combinations, a difference not seen at 12 months, and indicating the rapid effect of TNF inhibition. Conversely, drug combinations were associated with lower health and social care costs, saving £3615 (€4930; $5585) per patient during in the first six months and £1930 per patient during months 6-12.

ALAIN POL, ISM/SPL

New trial challenges orthodoxy

The good news is that a combination of traditional drugs was not inferior to a biological option as found in previous trials.[1 2] It is too early to say, however, which combination of disease modifying drugs is likely to work best. This remains an important question for future studies, preferably in larger populations with adequate power for firm conclusions. Further questions remain about the long term effects of treatments on joint destruction and disability. When researchers compared methotrexate head to head against the TNF inhibitor etanercept, participants treated with etanercept had fewer joint changes on repeat radiographs.[4] In the TACIT trial, 12 months of follow-up is far too short to assess long term safety or the balance of benefit and risk. Long term studies are needed, again in larger populations. In the end, we might never get the clear answers needed to make therapeutic choices.

When two treatment options for rheumatoid arthritis look equally good in a trial, the reality for patients is that they are often equally bad. Whatever new compounds are tested, usually 30% of the patients will not respond. Another limitation is that rheumatoid arthritis is a chronic disease.[5] When active treatment stops, active disease often restarts. One option, at least in responders, is to continue treatment, but at a reduced dose.[6]

Timing is important in the treatment of rheumatoid arthritis, and we might be using drugs in the wrong sequence. Progress in cancer treatment finally came when drugs were combined, given intravenously at high dose during the early phase of treatment, then simplified later. If we were to take the same approach to rheumatoid arthritis then we would combine drugs at the start of treatment and not wait for traditional monotherapies to fail.[7] Economic analysis will have to balance the extra cost of drugs against potential savings made by society as a consequence of reduced disability. We must also invest in research to help to improve understanding of disease heterogeneity. None of the studies described here has assessed the use of biomarkers and personalised medicine in this context.[8]

Considering rheumatoid arthritis care today, the best way to improve overall outcomes is to act earlier.[9] This is common sense, but now we know why. Over the years, the daily pressure of chronic inflammation induces molecular changes in cells at the disease site, leading to reduced response to cell death signals.[10] Over time, the disease pathways change, starting with an immunological disease with classic interactions between immune cells and their derived soluble products. Later, the disease is less immunologically driven while remaining immunologically induced.[11] Today we don't focus on the late targets responsible for chronicity.

The future of treatments for rheumatoid arthritis used to be seen as progressing through research evaluating new biomarkers and testing new expensive drugs. The TACIT trial challenges this orthodoxy and gives fresh hope to more patients around the world that they can achieve equal or better disease control with combinations of established, low cost, and easy to produce alternatives.

Cite this as: *BMJ* 2015;350:h1192

RESEARCH, p 12

thebmj.com

- News: EU-US trade treaty threatens vital health gains, warn public health experts (*BMJ* 2015;350:h1438)
- Editorial: The Transatlantic Trade and Investment Partnership and UK healthcare (*BMJ* 2014;349:g6552)
- Feature: Trade secrets: will an EU-US treaty enable US big business to gain a foothold? (*BMJ* 2013;346:f3574)

European Commission's proposals on trade secrets

Risk undermining public health and must be modified

Martin McKee professor of European public health, London School of Hygiene and Tropical Medicine, London WC1H 9SH, UK martin.mckee@lshtm.ac.uk
Ronald Labonté Canada research chair in globalization and health equity, University of Ottawa, Canada

In late 2013 the European Commission published proposals to harmonise elements of existing national legislation on trade secrets.[1] These will shortly be debated in the European parliament but, in their present form, they have created serious concerns among non-governmental organisations concerned with health policy.[2]

Strengthening protection against disclosure of trade secrets is the most recent step in a process whereby multinational corporations have increasingly sought to commodify knowledge. Thus, the drug industry has lobbied to strengthen the protection given to it by the patent system—for example, by persuading governments to increase the duration of protection for so called orphan drugs[3] and using international trade negotiations to enable it to claim rights in previously unprotected markets such as India. A diverse range of industries has exploited the opportunities provided by transfer pricing, whereby operations selling a trademarked commodity in one country pay large sums to another part of the same corporation based in a low tax jurisdiction for the right to use the brand name and associated imagery.[4]

Maybe the European Parliament will be able to redress the balance in favour of the citizens of Europe whose interests it is meant to represent

The arguments in favour of such arrangements are well rehearsed. Patent law gives corporations rights over intellectual property and enables them to innovate without the risk that others might profit from their ideas. This reflects a social contract whereby those innovating will obtain a time limited degree of protection, based on the idea of a fair return on their investment, in return for the contribution that their products, such as new medicines, make to society or to economic growth. The same principles underpin the use of copyright. Trademarks are also considered to offer a societal benefit, placing owners under an implied responsibility to ensure the quality of their product. However, many trade secrets are not protected by patent, copyright, or trademark legislation and, within Europe, their protection varies greatly from country to country. At present, there is not even a common definition of trade secrets.

The proposed directive would remedy this, adopting the definition used in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which draws on the US Uniform Trade Secrets Act.[5] A trade secret is defined as something that is "not generally known among or readily accessible to persons… that normally deal with the kind of information in question." It must also have some commercial value, and reasonable steps must have been taken to preserve secrecy. Interestingly, the directive treats trade secrets differently from other forms of intellectual property in that there is no owner as such. Instead it uses the term "holder," which confers no exclusive right to possess the information concerned.

Although the benefits of the proposals to large corporations are apparent, there are also important criticisms. Some have questioned whether there is even any need for them. Member state governments argue that the existing lack of legal harmonisation is a barrier to innovation, reducing competitiveness as companies fearing their secrets will be misappropriated apply costly measures to protect them.[6]

Yet the survey of businesses used in the case for legislation provides little support for these arguments,[7] and the commission's impact assessment finds that most companies already share trade secrets using their own disclosure agreements.[8] Nor is it clear that the proposals will provide legal certainty because many elements remain vague.[7 9] They may not even be directed at the right targets, given the growing evidence of industrial espionage by certain governments.[10]

More questions than answers

It is, however, in health policy where many unanswered questions are now emerging. Do the harms to patients associated with non-disclosure of trial results and adverse drug reactions by the pharmaceutical industry argue for less rather than more trade secrecy?[11] The European Food Safety Agency depends on manufacturers' assessments of safety, but those manufacturers regard the results as trade secrets, so could these become even more difficult to access? Could whistleblowers and undercover reporters highlighting threats to public health—for example, by exposing grossly unhygienic practices and adulteration of foodstuffs—lose what few safeguards they have? Could researchers studying tactics used by the tobacco, alcohol, and junk food industry to market their products to children find themselves in breach of the law? Will proposed limits to disclosure of trade secrets in civil litigation constrain the ability of protestors to cite evidence that might justify their actions?

It may be argued that the proposals contain sufficient protection for the public interest. There is a provision for whistleblowers to "reveal misconduct or wrongdoing." Yet this would be permitted only when such action was strictly "necessary" to reveal wrongdoing. This test may not be met if it was already known that the corporation had done wrong but the secrets were acquired to illustrate the scale and scope of its actions.[7] Nor might it protect an investigative reporter who went undercover following reasonable suspicion that wrongdoing was occurring but who discovered that it was not, or when additional material, not strictly relevant to the alleged misconduct, was inadvertently obtained.

In recent years the European Commission has given a much greater priority to economic growth and competitiveness than to social policy. This is exemplified by the recent proposal, abandoned in the face of widespread protests, to move pharmaceutical policy from the health directorate general to the internal market, industry, and entrepreneurship directorate.[12] The European parliament will return to the proposals on trade secrets in April. Maybe it will be able to redress the balance in favour of the citizens of Europe whose interests it is meant to represent.

Cite this as: *BMJ* 2015;350:h1369

thebmj.com

- Research News: Teenagers want schools to give them more information about sex (*BMJ* 2015;350:h1256)
- Research News: Sexually transmitted infection control strategies should target "swingers" (*BMJ* 2014;349:g6407)
- Feature: Online sexual health advice? Access denied (*BMJ* 2014;349:g6271)

Digital media interventions for sexual health promotion

A great way to reach people, particularly those at increased risk of sexual ill health

Julia Bailey clinical senior lecturer, eHealth unit, Research Department of Primary Care and Population Health, University College London, London NW3 2PF, UK
Julia.bailey@ucl.ac.uk
Sue Mann consultant, King's College Hospital NHS Foundation Trust, London, UK
Sonali Wayal researcher, eHealth unit, Research Department of Primary Care and Population Health, University College London, London NW3 2PF, UK
Charles Abraham professor, Psychology Applied to Health (PatH) Group, University of Exeter Medical School, Exeter, UK
Elizabeth Murray professor, eHealth unit, Research Department of Primary Care and Population Health, University College London, London NW3 2PF, UK

CORNELIA SCHAUERMANN/CULTURA/SPL

Promoting sexual health is a public health priority in the UK, but there are many challenges. For example, universal access to comprehensive sex and relationships education in schools is lacking; prevention and health promotion are less of a funding priority than diagnosis and treatment; sexual health services struggle to meet demand; and teachers, pupils, clinicians, and patients can be reluctant to discuss sexual health in school or clinic settings.

Interventions delivered through the internet or mobile phone could help with some of these challenges. Most people in the UK have access to these technologies,[1] and some of those at highest risk of sexual ill health (young people, men who have sex with men, sex workers) may also be heavy users of digital technology. Digital media are particularly appropriate for promoting sexual health because access can be private and convenient and learning can be self paced and personalised.[2] The reach and scalability of digital interventions is potentially excellent, and interest in digital media technology for health has exploded over the past decade or so. Nevertheless, the NHS has lagged behind other institutions and commercial companies in terms of information and communications technology.[1] There is now impetus to exploit digital media to facilitate patient access to information and self care, and to reduce the costs of healthcare.[1]

Interactive digital interventions have been shown to increase knowledge of sexual health and to promote safer sexual behaviour.[3 4] Interactive designs can promote active learning by using imaginative multimedia features such as quizzes, games, stories, scenarios, simulations, virtual characters, animations, audio, and video. Material can also be customised for individuals in various ways, including tailoring by demographics, risk behaviour, or factors such as knowledge, motivation, or skills.[5-7] Best practice for designing interventions includes involving users, drawing on empirical evidence on mechanisms of change, and addressing implementation from the outset.[8 9] However, there is still much to learn about the design of interventions (for example, the choice of change techniques and interactive features), the best models of delivery (for example, optimum settings, modes of delivery, "dosage," support, or facilitation), and how to address barriers to implementation and engagement.

Digital media are particularly appropriate for promoting sexual health because access can be private and convenient

Although the UK has pockets of innovation, there are no national programmes to roll out interactive digital interventions for sexual health promotion in clinics, in schools, or online. Hundreds of websites and apps for health are available, but most are not evidence based. Sexual health websites and school curriculums on sex and relationships often focus on physical health (safer sex, contraception, sexually transmitted infection, etc) and do not cover content that users would like (such as building good relationships and sexual pleasure).[10]

Innovation outstripping evaluation

The pace of innovation is outstripping capacity to evaluate the safety and efficacy of most digital interventions. The NHS Choices Health Apps Library is working with developers to ensure the safety of health apps, but there is no approval system for information websites that are not medical devices for diagnosis or treatment. We need to ensure that the health benefits of digital interventions can be evaluated and realised within reasonable timescales. Faster mechanisms are needed for commissioning research, for ethics committee and administrative approval, and for publication and dissemination of the results of evaluations.

While sexual health websites and mobile phone text services are available for particular local populations, knowledge needs to be shared nationally to avoid duplication of effort. We also need to build on evidence and experience to ensure that interventions are engaging and effective. Evaluation should be planned from the beginning to build knowledge of what works. Healthcare settings, schools, and colleges need to be able to offer reliable, fast access to digital technology, and healthcare staff and teachers need training and support to be confident in facilitating patient and pupil access to digital resources for sexual health.

Most digital systems linked with health services are designed to enhance the treatment of health problems rather than to promote health or prevent disease. However, sexual health promotion could easily be added to digital systems that are already in use—for example, electronic history taking and risk assessment, triage (with the option of self testing), and electronic decision aids before an appointment. Digital interventions can exploit "teachable moments"—for example, providing tailored sexual health advice via interactive websites or health promotion videos in waiting rooms.[11 12] Health promotion interventions could be added to systems such as online ordering of chlamydia and HIV test kits, automated recall systems, online partner notification for sexually transmitted infections, and digital systems to enhance adherence with HIV treatment or oral contraceptives.[2] Interactive digital interventions can also offer self help—for example, with sexual problems.

The UK government has laid out a vision for realising the potential of digital health systems,[1 13] and exciting possibilities exist. Coordinated national efforts are needed to realise the potential of interactive digital interventions for health promotion.

Cite this as: *BMJ* 2015;350:h1099