

The story of drotrecogin alfa – evidence-based or evidence-biased?

To the Editor: In 2003, Taylor *et al.*¹ posed the question: 'Should health care money in South Africa be spent on drotrecogin alfa [Xigris]?' Based on scientific and financial considerations, they concluded that the answer should be 'no'. In addition to raising questions concerning cost-effectiveness within the South African context, the authors highlighted concerns of the validity of the evidence. Methodological flaws within the PROWESS study² were noted: the protocol was amended mid-trial, and the study's beneficial findings were only identified following this amendment, questioning the extent to which they were influenced.

Macias and Levy³ – both employees of Eli Lilly and Company (the manufacturers of Xigris) – refuted the assertions of Taylor *et al.* by implying that the granting of marketing authorisation by 40 countries defied the 'lone voice in the wilderness'.

On 25 October 2011, both the US Food and Drug Administration (FDA)⁴ and European Medicines Agency (EMA)⁵ announced their intentions to withdraw marketing rights for Xigris in the USA and Europe. This course of action followed the findings of the placebo-controlled PROWESS-SHOCK study: drotrecogin alfa did not elicit a statistically significant reduction in 28-day all-cause mortality, and also failed – in its secondary endpoint – to reduce mortality in patients with severe protein C deficiency.⁵

Ironically, we echo the concluding remarks of Macias and Levy:³ 'In evaluating new and novel therapies, health care providers and health care payers should analyse objectively and fairly all available data, be transparent in their decision-making process, and be accountable to patients and their families for their recommendations to accept or reject novel life-saving therapy'. We suggest that this same level of accountability and transparency should be extended to the manufacturing fraternity, ensuring that patients and their families are not offered false hope in the interests of profit generation.

This situation presents valuable learning opportunities for the South African healthcare community: (i) a more critical approach is required towards the analysis of clinical literature presented in support of new chemical entities; especially those that offer marginal benefit, are potentially unsafe, and come at a high cost; (ii) this critical mindset is even more pressing in a resource-poor environment, such as South Africa; and (iii) South Africa can ill afford 8 years of wasteful spending when legitimate concerns regarding safety, efficacy and affordability have been raised in the literature. These warnings need to be heeded earlier to ensure that equitable access is directed towards, rather than away from, interventions of clear clinical benefit.

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PSA screening reduces prostate cancer mortality

To the Editor: I refer to the editorial by D G Burns entitled 'Prostate cancer – is screening the solution?'¹ Although a number of relevant points are raised in his editorial, it is blatantly inaccurate to report that the European Randomised Study of Screening for Prostate Cancer (ERSPC) showed 'little or no effect on mortality from the disease over a prolonged follow-up period'. At a median follow-up of 9 years there was a 20% relative reduction in rate of death from prostate cancer among men between the ages of 55 and 69 years.² In a subsequent publication, which corrected for non-attendance in men randomised to the screening arm and contamination (having a prostate-specific antigen test) in men randomised to the control arm, the risk reduction was even greater. In the men actually screened, the risk of dying of prostate cancer was reduced by up to 31%.³ Over-diagnosis and the large numbers needed to screen and treat to prevent one death are a concern. We should not be asking whether screening improves survival as there is good evidence to support that it does. We should rather ask whether we can afford it and whether we are prepared to accept the morbidity associated with treating a large number of patients who may not benefit from treatment.

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Dr Burns replies: Lisa Kaestner is correct in pointing out that in the ERSPC there was a 20% relative reduction in mortality from prostate cancer, but the other landmark USA-based Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial failed to show a similar mortality benefit over a 7 - 10-year period.^{1,2} These were both complex trials, and it is possible that the failure to confirm the findings of the ERSPC study may have been influenced by the lower number of men entered into the PLCO study (76 693 v. 182 000), and failure to correct for 'contaminators' in the control group in the USA study. However, it also confirms that screening of very large numbers of subjects was required to demonstrate any statistical mortality benefit, with substantial overtreatment and a very small proportion of men ultimately benefiting from such interventions. Based on these studies, it indeed seems appropriate to question whether this margin of clinical benefit is worth the financial and morbidity costs of population-based screening. In fact, recently the US Preventive Services Task Force is reported to have posted a preliminary draft recommendation against PSA-based screening for prostatic cancer in all age groups, based on the publication of the above two trials.³

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