DEBATE

Should health care money in South Africa be spent on drotrecogin alfa?

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Drotrecogin alfa (or recombinant activated protein C) has recently been approved in most parts of the world for the treatment of severe sepsis associated with acute organ failure. Considering the poor prognosis associated with severe sepsis and the dearth of effective pharmacological interventions, such developments should be embraced. However, critical review of this drug suggests that enthusiasm for this new agent is premature.

Premature registration

Drotrecogin alfa has been registered on the basis of one double-blind placebo-controlled trial, the PROWESS study.[1] This was a phase 3 trial which enrolled 1 690 patients with systemic inflammation and organ failure due to acute infection. The primary end-point was death from any cause at 28 days. The study concluded that 16 patients had to be treated to prevent 1 death (the mortality rate was 30.8% in the placebo group, and 24.7% in the drotrecogin group). However, these results have been questioned as evidenced by the controversial process to grant marketing approval by the Food and Drug Administration (FDA). The vote of the FDAAnti-Infective Drugs Advisory Committee was split 10 to 10 as to whether activated protein C is safe and efficacious. Indeed, four of the academic consultants who opposed registration felt so strongly about the matter that they publicly voiced their concerns in the scientific literature.[2]

The reasons for scepticism regarding registration of drotrecogin alfa are many.

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1. Not only did several changes occur during the trial (amendment of the study protocol, introduction of a new placebo and change in the manufacturing process of activated protein C), but benefit of drotrecogin alfa over placebo could only be demonstrated after protocol amendment. Twenty-eight-day survival was similar for both the placebo group and the drotrecogin group prior to such changes (30% v. 28%; $p = 0.57$). Doubt remains as to whether protocol amendment could in any way have affected the final outcomes of the study.[2]

2. *Post hoc* analysis of the PROWESS trial revealed that in less severely ill patients there was a trend to excess mortality (15% v. 12%) and excess severe haemorrhage (4% v. 0%) in the drotrecogin group. It was therefore suggested that only patients with APACHE II scores of 25 or greater would be suitable candidates for administration of this therapy. However, the APACHE II score is a prognosticating system that was developed to predict mortality of severely ill patients and its validity as a screening system to identify which patients should receive specific therapy is unknown. This is of particular importance in that it was applied in an unconventional manner in the research setting. Whereas it is usually based on the most aberrant values obtained within the first 24 hours of admission to the intensive care unit, in this case it was based on the most aberrant clinical and laboratory values obtained within the 24-hour period immediately preceding the administration of study drug. This means that in the trial the APACHE II score may not always have incorporated the period of resuscitation, i.e. patients with a relatively low APACHE II score may have been severely ill.[2] This unconventional use of the APACHE II score also raises the question whether the treatment groups were indeed well matched. For example, despite similar APACHE II scores, more patients in the placebo group were receiving vasopressors (75.5% v. 71.8%) or mechanical ventilation (77.6% v. 73.3%) at time of randomisation.

3. No relation between protein C levels before infusion or measures of clotting after infusion and the efficacy of the drug could be demonstrated. Hence, the proposed mechanisms of action of drotrecogin are unproven.[2]

Apart from the above, there are other concerns.

Applicability of results in the 'real world'

1. Considering the broad exclusion criteria in the trial setting regarding bleeding risk, the true risk of severe haemorrhage with this drug in a real-life setting is probably underestimated. For example, patients with aspirin use in the previous week, trauma, thrombocytopenia ($< 30 \times 10^9/l$), chronic liver disease and chronic renal failure were all excluded from entry into the study. Indeed, it

has already been suggested that there may be a higher incidence of intracranial haemorrhage with activated protein C in uncontrolled than in controlled studies.[3]

2. From a South African perspective, there is a particular concern that the majority of patients enrolled were from the developed world. South Africa as a developing nation contributed only 2.8% of the entire study population. This is relevant in that factors influencing ICU admissions differ significantly along geographical and socioeconomic lines. For, example, HIV- and trauma-related ICU admissions are anticipated to be significantly more common in Africa than in countries in North America and Europe. Yet we do not know the impact of drotrecogin alfa in HIV-infected patients. The applicability of results to our local population is therefore particularly questionable.

Inappropriate allocation of health care resources

1. As with many other innovative drugs, drotrecogin alfa is expensive. For a 70 kg patient, current treatment costs ~R55 000. This already reflects the recent 25% price reduction which has been possible for the local distributors as a result of more than 25% strengthening of the rand / dollar exchange rate since launch of this product into the South African market (US$ / ZAR as per Standard Bank of South Africa Limited). To put this expense into perspective, it would cost in the region of R1 million to save one life assuming outcomes as per the PROWESS trial. This is in addition to the very high costs already incurred by the treatment of sepsis. Considering that 6 - 10% of all ICU admissions in South Africa may be related to sepsis (preliminary market research — Eli Lilly), the potential incremental costs for payers of health care are significant.

2. Although the only trial to date claims a mortality benefit with drotrecogin over placebo, the difference in numbers of patients alive out of hospital at 1 month is 1%. The question must therefore be posed whether deaths prevented are replaced by poor quality of life and chronic morbid sequelae.[4]

3. Critical care in South Africa is suboptimal, with non-intensivists commonly running ICUs.[5] Instead of allocating health care resources to an exorbitantly expensive drug with a dubious risk / benefit ratio, appropriate training of intensivists and accreditation of intensive care units (as suggested by Richards[5]) should be prioritised. The Critical Care Society has identified many basic intervention strategies (e.g. optimal ventilatory support, tight glucose control) which, if applied correctly, would significantly improve the outcomes of critically ill patients in South Africa, without increasing overall costs. Endeavours to elevate the training of intensivists in South Africa should therefore be supported.

Conclusions

For now, on the basis of both scientific and financial considerations we believe that allocation of health care resources towards payment of drotrecogin alfa is unwise.

From a scientific perspective, we concur with those members of the FDAAnti-infectives Advisory Board who have called for another trial that prospectively incorporates a prognostic scoring system such as APACHE II. It is always questionable in a heterogeneous disease such as sepsis to grant marketing authorisation on the basis of a single study. This has already been borne out by the case of HA-1Amonoclonal antibodies for severe sepsis. HA-1Amonoclonal antibodies were withdrawn as a result of a second trial which not only showed that treatment was ineffective, but that it was indeed dangerous in a sub-group of patients.[6]

Further, even if the scientific benefits of this drug are eventually confirmed, there still remains doubt as to whether the proposed risk / benefit in a real-life situation would mirror that in a tightly controlled clinical trial environment. This is of particular concern in South Africa with its dearth of appropriately trained intensivists, where the general standard of critical care of medical diseases has been questioned and where the demographic profile of patients is probably quite different from that of the developed world. Obviously this concern could at that point be partially managed by limiting use of drotrecogin to accredited well-trained intensivists.

The drotrecogin case also highlights the need for differential drug pricing for developing countries. Such differential pricing applies not only to the public sector, but also to the private sector. It is naïve to think that a country with a GDPone-tenth that of the USA[7] has the ability to pay the same price for a drug as the developed world. The World Bank has suggested that health care interventions may be considered cost-effective if they buy a year of healthy life for less than the national per capita GDP.[8] Although we do not propose that this value should form the absolute benchmark for health care interventions in the current South African private health care sector, it is anticipated that it will be considered by government's proposed Pricing Committee (see Medicines and Related Substances Control Amendment Bill).

It is our opinion that if we are to achieve the goals of better access to and equity in health care delivery, a wait-and-see approach should be adopted regarding funding of drotrecogin alfa in severely ill patients. We call on all stakeholders to support the principles that underpin the development of fair allocation of health care resources. This includes funders of health care.

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The value of innovation

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Xigris (recombinant human activated protein c (rhAPC), generic name drotrecogin alfa (activated) (DrotAA) has been approved for the treatment of patients with severe sepsis. Approval by regulatory authorities around the world was based on a single phase III study (PROWESS) with supporting data from a single phase II study. At the time of the drug's approval, PROWESS was one of the largest studies of patients with severe sepsis ever completed despite the study having been stopped early because of overwhelming efficacy (as determined by prospectively defined stopping rules agreed upon with the United States Food and Drug Administration (FDA)). The final dataset for PROWESS contained an estimated 160 000 000 data points and the final study report comprised 7 338 pages. The marketing authorisation application contained an estimated 26 000 pages. Marketing authorisation for Xigris has been granted in over 40 countries, and to date has not been denied in any country in which the application has been completed.

Taylor and Burns[1] provide a review of DrotAAand question whether its approval was premature. However, their review was based on limited data contained in an FDAadvisory committee briefing document (189-page high-level summary of the pre-clinical, clinical pharmacology and clinical development history of DrotAA). The issues they raise have been discussed previously and have been reviewed in depth by all regulatory agencies approving DrotAAfor the treatment of patients with severe sepsis. Taylor and Burns express the concern that an amendment to the protocol substantially modified the conduct of the study and somehow confounded the results. On this point, regulatory reviews have been consistent in their conclusions that the amendment to the study protocol did not alter the study outcome or diminish the robustness of the findings.[2-4]

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Taylor and Burns also raise questions about interpretation of *post hoc* subgroup analyses. However, the approval of DrotAA was based on results observed in the overall trial population and not on the results within any particular subgroup. For the entire PROWESS population, a *p*-value of 0.005 was achieved on the prospectively defined primary endpoint of improved survival at 28 days. The DrotAAtreatment benefit observed in PROWESS is '. . . one of the most powerful findings of mortality benefit amongst drug development trials'.[5] Subgroup analyses have been utilised by regulatory authorities only to focus use of the drug in the population of patients thought to have the most favourable benefit-risk profile. In addition, the unadjusted *p*-value of 0.005 observed in PROWESS was unchanged after adjustment for APACHE II score, age and protein C levels. Therefore, the concern expressed that potential imbalances in baseline characteristics between treatment groups influenced the outcome of the study is not well founded.

Taylor and Burns also comment that the applicability of the PROWESS results may not be extrapolated to the 'real world' or, specifically, to South Africa. Importantly, the inclusion criteria employed in the PROWESS trial were broader than those of any previous phase III sepsis study (from which these criteria were extracted), while the exclusion criteria were similar to or less exclusive than other recent trials.[6,7] Furthermore, investigators in South Africa participated in the PROWESS trial, and the administration of DrotAA was associated with a 21% reduction in the absolute risk of death and a 42% reduction in the relative risk of death in their patients (data on file, Eli Lilly). While subgroup data must always be interpreted with caution, these results do not support the suggestion by Taylor and Burns that the South African critical care system is not sufficiently sophisticated for patients to benefit from the use of DrotAA.

Finally, Taylor and Burns did not include in their review long-term follow-up data on the PROWESS survivor population, which demonstrated a reduction in in-hospital mortality of 5.2% ($p < 0.02$), and that approximately two-thirds of the survivors were discharged directly to their homes.[8] Data from the PROWESS trial indicate that the additional survivors in the DrotAAtreatment arm are not saddled with 'chronic morbid sequelae' and are as functional as placebo-treated survivors. They also did not include data from a phase IV study of DrotAA demonstrating highly comparable efficacy and safety as seen in PROWESS and that the proportion of patients experiencing a potential adverse drug reaction with commercially purchased DrotAA is lower than that observed in the phase III study.[9,10]

Benatar and Fleischer[11] raise important issues concerning how limited health care resources should be invested. We

agree entirely that health care resources should be distributed wisely, based on sound medical judgement and appropriate cost-effectiveness analyses. However, we question the notion that medical interventions in which 'each individual patient will be a direct beneficiary' are in some way inherently superior to those that produce 'a statistically demonstrable benefit for a patient population'. From a societal view, adding a year of life to an 'identifiable' individual is not inherently better than: (*i*) adding one month of life to 12 individuals; (*ii*) providing a 10% chance of adding one year of life to each of 10 individuals; or (*iii*) supplying a 1% improvement in the quality of life to 100 individuals for one year. Such comparisons are precisely the sort for which cost-effectiveness analysis was designed.

Cost-effectiveness is the ratio of the incremental cost of a therapy to the incremental benefit (e.g. cost per life-year saved) with or without adjustment for the quality of the incremental benefit (e.g. cost per quality-adjusted life-year saved). These analyses allow assessment of the comparative beneficial impact of expenditures on different health interventions and are based on the premise that 'for any given level of resources available, society . . . wishes to maximize the total aggregate health benefits conferred'.[12] For the examples provided by Benatar and Fleischer, cost-effectiveness ratios are widely disparate, with chronic renal replacement having a cost-effectiveness ratio of between $100 000 and $130 000 per quality-adjusted life-year (in year 2000 US dollars)[13] and kidney transplantation having a cost-effectiveness of up to $67 778 per quality-adjusted life-year.[14]

Unfortunately, for many commonly adopted interventions that require significant financial resources (particularly those employed in the intensive care unit), data from randomised, controlled trials are not available and, consequently, neither are cost-effectiveness analyses. This is not the case for DrotAA, for which level 1 evidence supports use of the drug in patients with severe sepsis[15] and multiple cost-effectiveness analyses indicate that its use compares favourably with other interventions ($28 000 to $33 000 per life-year saved[16] to $47 000 to $49 000 per quality-adjusted life-year saved[17]). Appropriate use in the population of patients with the most favourable benefit-risk profile will maximise the absolute benefit to patients and improve the overall cost-effectiveness of the agent (e.g. $27 400 per quality-adjusted life-year in patients with an APACHE II score ≥ 25[17]).

We agree with Benatar and Fleischer that fairness, transparency and accountability should be used when determining how limited medical resources are to be invested. 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 families for their recommendations to accept or reject novel life-saving therapies. This approach is the foundation of evidence-based medicine.

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