cant difference between these compounds. Interestingly, there is a lack of complete cross resistance between aromatase inhibitors and inactivators.[12]

Aromatase inhibitors and inactivators should not be used in premenopausal women without concomitant ovarian blockade with gonadotrophin releasing hormone analogues. This is because ovarian aromatase escapes inhibition because of stimulation by gonadotrophin.

While tamoxifen controls tumour growth only temporarily in metastatic disease, it significantly improves long term, relapse-free survival and overall survival when used as an adjuvant treatment. This suggests that even a modest improvement in the therapy of metastatic disease may translate into real survival benefit in early disease. Thus, the encouraging results seen with third generation aromatase inhibitors and inactivators have prompted trials comparing each of these compounds with tamoxifen for adjuvant therapy. These different protocols are evaluating the test compounds as monotherapy as well as in combination or in sequence with tamoxifen to find the best regimen.[13] In particular, the concept of using sequential therapy (as is done with exemestane) seems attractive. The lack of cross resistance between tamoxifen and aromatase inhibitors and inactivators in advanced disease suggests that sequential therapy could be beneficial in preventing the outgrowth of tamoxifen resistant micrometastases in some patients undergoing adjuvant therapy.

Primary medical treatment is being increasingly used not only for downstaging non-operable tumours but also for reducing the size of tumours to allow greater conservation of breast tissue. So far, most studies have used chemotherapy for this purpose, but results suggest that aromatase inhibitors could be a feasible option for postmenopausal women with oestrogen receptor positive breast cancer.[1]

Several prospective studies have found that high plasma oestrogen concentration in postmenopausal women is a risk factor for subsequent breast cancer suggesting that aromatase inhibitors and inactivators may also have a future in preventing breast cancer.[14] If ongoing adjuvant studies reveal clinical superiority and an acceptable toxicity profile for these compounds, a logical step would be to assess their role as agents to prevent breast cancer in postmenopausal women.

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PL has, over the past five years, received support for attending scientific meetings, consultancy fees, and research support from all three major pharmaceutical companies developing aromatase inhibitors and inactivators (Astra Zeneca, Novartis, Pharmacia).

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# Treatment of sepsis with activated protein C

*Encouraging news for well selected patients*

See also *Education and debate* p 923

When uncomplicated sepsis progresses to uncontrolled systemic inflammation with evidence of organ dysfunction and impaired tissue perfusion (severe sepsis) or hypotension unresponsive to expansion of the circulating volume (septic shock), mortality is high (20%-60%).[1–3] Until now attempts to improve outcome by manipulating the inflammatory response have proved disappointing and in some instances possibly harmful.[4] Failure to improve outcome with anti-inflammatory strategies can be explained partly by the limitations of the trials used to assess new treatments. These include the heterogeneity of patients in multicentre studies, the wide range in the severity of their illness, co-morbidity, standardised use of concomitant therapy (especially antibiotics), the timing of treatment, the question of attributable mortality, and the choice of outcome measures. The development of successful strategies to modulate inflammation has also been hampered by our limited understanding of the complex mechanisms

*BMJ* 2001;323:881–2

that regulate the inflammatory response, combined with a naïve assumption that mortality can be reduced by temporarily neutralising just one component of the pro-inflammatory system.

But at last it seems that an effective treatment for some patients with severe sepsis has been identified in a recent trial.[5] This trial, which used a continuous intravenous infusion of recombinant human activated protein C, a natural anticoagulant which promotes fibrinolysis while inhibiting thrombosis and inflammation, reduced the relative risk of death at 28 days by almost 20% (from 30.8% to 24.7%).

So what makes these findings persuasive and encouraging and how does this study compare with previous unsuccessful trials of inflammatory modulators in sepsis? Firstly, the hypothesis that activated protein C is effective is based on a better understanding of organ injury in sepsis and of the importance of the coagulation system and its interaction with inflammatory pathways. We now know that pro-inflammatory cytokines released in response to infection can also activate coagulation and inhibit fibrinolysis, and that the procoagulant thrombin is capable of stimulating several inflammatory pathways. This combination of procoagulant and inflammatory stimuli provides a potent mechanism for initiating and perpetuating microvascular injury, intravascular coagulation, inadequate tissue perfusion and organ failure.[6] The ability of activated protein C to target inflammatory and procoagulant pathways may therefore be central to its efficacy. Secondly, the hypothesis is supported by the observations that *(a)* reduced levels of activated protein C are found in most patients with sepsis and are associated with an increased risk of death[7]; *(b)* protein C deficiency was identified in over 90% of patients in the trial in whom levels were measured; and *(c)* giving activated protein C was associated with a reduction in circulating levels of d-dimer and interleukin 6, confirming its antithrombotic and anti-inflammatory actions.[5] Lastly, that activated protein C might be protective in sepsis has been supported by positive findings in laboratory models of sepsis and by a recent prospective open label study suggesting that treatment with activated protein C can improve outcome in severe meningococcaemia.[8 9]

Nevertheless, our excitement must be tempered by past disappointments and by the limitations of a trial involving 164 centres in 11 countries, which enrolled a heterogeneous group of patients in whom other aspects of care were not standardised.[10 11] An important difficulty with such trials is that the results can be applied only to patients who fulfil the entry criteria for the original study. Understandably, in this trial many patients were excluded because of an increased risk of bleeding. Therefore many patients with severe sepsis presenting to an average intensive care unit would not be candidates for treatment with activated protein C. Even in the population studied there was evidence of an increased risk of serious bleeding (3.5% *v* 2%, P = 0.06), including two fatal intracranial haemorrhages. Other concerns include the distribution of baseline characteristics, the timing of treatment with antibiotic, and lack of information on outcome measures other than 28 day mortality—for example, survival in hospital and in the long term progression of organ failures, time on the ventilator, and length of stay in the intensive care unit. Although this trial indicates that in the highly selected population studied one life could be saved for every 16 patients treated, this does not seem to be a universally applicable magic bullet. The impact of activated protein C on the survival of the overall population of patients with severe sepsis is likely to be less impressive. Finally, the cost of treatment with activated protein C is not yet known, but it is likely to be substantial, and it has been estimated that in the United Kingdom 10 000 patients a year could be eligible to receive activated protein C (see p 923).

One argument is that we need to wait till we have more information on the financial implications and safety of this new agent. Certainly the results of the worldwide open label study currently in progress will be awaited with interest, especially since several centres in the United Kingdom are participating in it. Nevertheless, given that randomised controlled trials are the cornerstone of evidence based practice, activated protein C can be recommended for selected patients who fulfil the criteria for enrolment in the trial.[5] Those responsible for introducing activated protein C into clinical practice must, however, ensure that it is not used indiscriminately. The decision to use this treatment should be taken by experienced intensive care clinicians guided by strict protocols designed to exclude those in whom activated protein C is unlikely to help, or be harmful, and in whom the prognosis is clearly hopeless. Particularly when intensive care resources are limited, as in the United Kingdom, we should recognise that novel treatments are most likely to succeed when given to patients who have been treated to a high standard. This includes early recognition of sepsis together with appropriately timed admission to intensive care and discharge from it.

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