Thalidomide in toxic epidermal necrolysis

Sir—The report of unexplained deaths associated with thalidomide therapy for toxic epidermal necrolysis by Pierre Wolkenstein and colleagues (Nov 14, p 1386),3 points to the need for a more complete understanding of the putative mechanism(s) of action of this drug. This issue is lent further urgency by the recent licensure of thalidomide by the US Food and Drug Administration for the treatment of erythema nodosum leprosum (ENL). This decision is likely to lead to the increased use of thalidomide in various disorders.

The dramatic efficacy of thalidomide among patients with ENL in association with inhibition of tumour necrosis factor (TNF)-α provided compelling evidence for a mechanism of action of this drug.3 The rationale for its use in toxic epidermal necrolysis was the potential of thalidomide to inhibit TNF-α.

However, thalidomide has other, unexpected effects on the immune response. The drug acts as a co-stimulator of primary human T cells in vitro, synergising with stimulation via the T-cell receptor complex,4 which leads to increased interleukin-2-mediated T-cell proliferation and production of interferon gamma. Data from clinical studies suggest that thalidomide may also have T-cell stimulatory properties in vivo. Thalidomide therapy in HIV-infected patients was associated with increases in plasma concentrations of soluble interleukin-2 receptor and CD8+ T lymphocytes.4 These responses occurred within the first 2 weeks of thalidomide therapy, a time when cutaneous and febrile reactions to the drug are most likely to occur in HIV-infected patients.

Taken together these findings suggest that thalidomide has both anti-inflammatory and immune-stimulatory activities, and may thus produce different clinical results in different diseases. In conditions characterised by monocyte/macrophage activation and high circulating concentrations of TNF-α, such as ENL, the use of thalidomide to inhibit production of TNF-α may be beneficial to the patient.5 However, in diseases where T-cell activation contributes to the pathogenic process, further T-cell stimulation by thalidomide may be detrimental and result in clinical deterioration. The latter situation may explain the findings of Wolkenstein and colleagues, as well as the finding that thalidomide caused a paradoxical increase in mortality when used prophyllactically for chronic graft-versus-host disease.6 Another possibility is that the T-cell co-stimulatory effects of thalidomide may mediate its beneficial effects in diseases where T-cell function is defective.

The use of a placebo group by Wolkenstein and colleagues led to a rapid and definitive conclusion that thalidomide was harmful in this clinical setting, underscoring yet again the importance of carefully controlled trials for the evaluation of new therapies, or old therapies for a new indication.

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Provision-of-care transmission of hepatitis B virus

Sir—Elaine Ristinen and Ravinder Mamanti (Oct 24, p 1381)1 address the ethics of transmission of hepatitis B virus (HBV) by health-care workers to patients. We would like to stress two important points. First, although it is difficult to give general risk estimates for provider-to-patient transmission of HBV, there are some reliable calculations available from the literature. With a probability model, Bell and colleagues2 assumed the chance of HBV transmission from an infected surgeon to a susceptible patient to be about 0·24% during a single invasive procedure and 57–100% during a 7-year career of the surgeon. These cumulative figures indicate that the risk of about 1 per 1000 people quoted by Ristinen and Mamanti most probably represents an underestimation of the real threat to the patient.

Second, the topics discussed not only apply to HBV, but also to various other bloodborne pathogens, including hepatitis C virus (HCV) and HIV-1. Since there are no general mandatory regulations on possible restrictions on the medical practice of infected health-care workers, there is an urgent need for the medical community to find a broad consensus that would be acceptable for both the infected worker and the patient. Such a consensus is also imperative because of possible legal consequences that might arise when an infected worker does not notify a prospective patient about his infection.