

# Thalidomide, treat with caution!

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Thalidomide's unique properties are now being recognised and unravelled. Various new clinical applications are being reported and two case reports in this journal are a testament to this.<sup>1,2</sup>

In 1953, thalidomide was synthesised and designed into a drug by researchers at Chemie Grunenthal in West Germany. It was a novel therapeutic agent that failed to control epileptic fits as anticipated from animal studies. However, it caused such drowsiness that it was subsequently marketed as a sedative. Its promotion ironically emphasised its safety as overdoses in animal tests failed to cause fatalities. However, in 1960 the recognition of thalidomide's neuropathic potential, and a year later its devastating teratogenic effects, led to its product license being revoked in many countries around the world. However, its unique effects in erythema nodosum leprosum, a vasculitis that occurs during the treatment of leprosy with antilepromatous therapy, facilitated its continued availability, albeit on a very limited basis. Countries around the world have struggled to manage and monitor the usage of thalidomide and specifically the USA has felt it necessary to license thalidomide and now has very strict controls and monitoring in an attempt to prevent indiscriminate use (STEPS programme).<sup>3</sup> The UK guideline for the clinical use and dispensing of thalidomide<sup>4</sup> antedated the USA guideline and offered a more balanced approach to contraceptive measures; however, as the main thalidomide producer is based in America, the STEPS programme prevails.

On this background, the renaissance of this novel and powerful immunomodulatory agent has appropriately been in clinical areas where other drugs have failed. Since the 1980s, increasing numbers of articles reporting the usefulness of thalidomide have appeared, but thalidomide's success in the treatment of severe intractable orogenital ulceration and subsequently its value in the management of the oropharyngeal ulceration seen in HIV/AIDS is particularly notable. More recently thalidomide's place in the treatment of refractory multiple myeloma has been

confirmed with polymorphisms of the TNF-alpha gene promoter predicting outcome, that is high producers of TNF- $\alpha$  are more likely to respond.<sup>5,6</sup>

Chronic graft-versus-host disease (GvHD), following allogeneic bone marrow transplantation, occurs in approximately 40% of patients. Refractory GvHD is a therapeutic challenge but initial reports of benefit from the introduction of thalidomide must now be tempered by a recent randomised controlled trial that failed to show any clear benefit from adding this agent to conventional immunosuppressive treatment.<sup>7,8</sup> Other promising indications for thalidomide are in wasting conditions, cancer cachexia, Crohn's disease, and certain dermatological/rheumatological disorders including cutaneous lupus and scleroderma.

Thalidomide's immunomodulatory actions are intriguing and incompletely understood. Many of thalidomide's actions were initially ascribed to its ability to inhibit TNF- $\alpha$  production particularly by monocytes, and more recently to its enhancement of IL-4 and IL-5 production promoting a shift from a Th1 to Th2 cytokine pattern. However, thalidomide can also act as a T cell costimulant: when added to cultures of T cells activated through the T cell receptor, there is an enhanced Th1 response with enhanced production of both IL-12 and interferon- $\gamma$  with an increase in cell proliferation.

Further research has revealed evidence of antiangiogenic effects induced by inhibiting angiogenesis, which is induced by vascular endothelial derived growth factor and basic fibroblast growth factor. This latter effect appears to be independent of TNF- $\alpha$  suppression. These antiangiogenic affects are probably the mechanism underlying thalidomide's benefit in the two case reports related to thalidomide in this journal.

Koca *et al.* describe the successful treatment of myelodysplastic syndrome-induced pyoderma gangrenosum with thalidomide in combination with interferon- $\alpha$ 2a

allowing discontinuation of corticosteroid therapy.<sup>1</sup> The dramatic before and after clinical pictures are compelling evidence of benefit in this single case report. The authors fail to mention the steps taken to ensure that conception did not occur in this 40-year-old lady whilst taking thalidomide and no mention is made of the monitoring of sensory nerve action potentials for evidence of thalidomide-induced axonal neuropathy. The authors do not give any details on how the 200 mg daily dose of thalidomide was reduced but nevertheless electrophysiological studies remain paramount.

Heidt *et al.* in this journal used thalidomide in the treatment of angiodyplasia of the bowel in an 80-year old-male with co-existing von Willebrand's disease and a past history of poliomyelitis.<sup>2</sup> Commendable attempts were made to keep the dose of thalidomide to a minimum and neurophysiological monitoring was undertaken.

There is a paramount need to develop thalidomide derivatives avoiding the teratogenic and neuropathic side effects. Many such compounds have been produced and those entering trials fall into two groups. The immunomodulatory analogues strongly inhibit TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-12 whilst augmenting production of IL-10 and are potent costimulators of T lymphocytes. The other group have more selective inhibitory effects on cytokines, predominantly TNF- $\alpha$ , with minimal effects on T cell activation.

Thalidomide continues to intrigue and mystify. As thalidomide's mode of action is unravelled and as new analogues become available, thalidomide's true place in the therapeutic armamentarium will be assured. Till then use thalidomide with caution!

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