Thalidomide in ankylosing spondylitis

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ABSTRACT

Despite potential side effects dominat - ed by teratogenicity and peripheral neuropathy, thalidomide has recently been used to treat severe ankylosing spondylitis (AS). Over 50 patients have been treated across several 6-12 month open studies. Altogether 68% of the patients improved and the drop-out rate was 19%. Inhibition of NF-κB and/or TNFα is a putative mechanism for thalidomide efficacy in AS.

History

Thalidomide (α-N-phthalimidoglutarimide) is a synthetic derivative of glutamic acid, which was originally developed by a German company and put on the market as a sedative, in Canada, South America, throughout Europe and some countries in Asia. The drug was known for rapid onset of action, lack of hangover, and absence of respiratory or skeletal muscle coordination impairment. The body's handling of this lipophilic molecule is still incompletely known. Pharmacokinetic studies in healthy human male volunteers suggest a one compartment, first order absorption and elimination model, with peak plasma levels reached within 4-5 hr and a half-life of 8.7 ± 4.1 hr. Thalidomide is metabolized mainly through non-enzymatic hydrolytic cleavage generating a multitude of active intermediates with largely unknown functions (Chen *et al.*, 1989).

In 1960, two types of major side-effects were reported, i.e. peripheral neuropathies in patients with long-term exposure, and congenital abnormalities of the limbs (phocomelia) in children born to mothers exposed to thalidomide during their first trimester of pregnancy which lead to withdrawal of the drug from the market. Unfortunately, this did not occur before 10,000 to 12,000 children with birth defects had been born from mothers exposed to the drug (6).

Since that time however, thalidomide has continuously been used under restricted conditions, because of its reported efficacy on rare refractory manifestations involving immunological mechanism, such as erythema nodosum leprosum (ENL), chronic cutaneous lupus, Behçet's disease, or chronic graft-versus-host disease (6). More recently, Food and Drug Administration has approved thalidomide for the treatment of ENL in US after strict rules and regulations were established between the agency and Celgene, the US manufacturer.

Possible mechanism of action

The mechanism of action of thalidomide is progressively broken down (6). Various anti-inflammatory, immuno-modulatory and anti-angiogenic activities have been described (Table I). Most remarkably, thalidomide is a relatively weak inhibitor of TNFα synthesis *in vitro*. At therapeutic concentrations, it reduces TNFα production by approximately 40%. This TNFα inhibitory capacity occurs at the transcriptional level through a reduction of the TNFα mRNA half-life and is selective, with no significant effect on cytokines such as interleukin (IL)-l, IL-6, and granulocyte-macrophage colony-stimulating factor, by human monocytes sti-

Table I. Immunomodulatory and anti-inflammatory properties of thalidomide

Inhibits leukocyte chemotaxis into site of inflammation

Alters density of TNF -induced adhesion molecules on leukocytes

Reduces phagocytosis by polymorphonuclear leukocytes

Enhances mononuclear cell production of interleukins-4 and -5; inhibits interferon- production

Inhibits production of interleukin-12

Inhibits production of TNFα by monocytes and macrophages by reducing half-life of mRNA.

mulated with lipopolysaccharide (LPS).

Thalidomide's inhibition of TNFα production is not always achieved *in vivo*. Decreased TNF serum concentration have been described in patients suffering from ENL or tuberculosis, treated with thalidomide (8). However, TNF levels in blood conversely increased in two randomized controlled trials demonstrating thalidomide's efficacy in healing oral aphtae in the setting of HIV infection as well as reducing HIV-associated wasting. A similar observation was made in a study of patients with toxic epidermal necrolysis, in which outcome was adversely affected by thalidomide (18). Thus, it seems that thalidomide's ability to inhibit TNF may depend on the stimulus or cellular source of cytokine production (6).

Besides pro-inflammatory cytokines inhibition, thalidomide exerts other *in vitro* immunomodulating activities, such as T-cell costimulation, thereby enhancing T cell response. This costimulatory effect appears greater on the CD8+ T cells than on the CD4+ T cells (16). There is no evidence that thalidomide possesses immunosuppressive properties, and the drug has not been associated with opportunistic infections. Antiangiogenic properties of thalidomide have also been found (9). Most recently, blocking of NF-kB activation through a mechanism that involves the inhibition of IkB kinase was shown with thalidomide, and was proposed as an upstream event responsible for the different actions of the drug (14).

Toxicity

Teratogenecity

The most serious toxicity of thalidomide is its teratogenicity dominated by phocomelia. Animal models suggest that these teratogenic effects may occur through the drug's anti-angiogenic effects on the developing fetal tissues (6). The joint effort between FDA and thalidomide manufacturer resulted in the establishment of the STEPS, (System for Thalidomide Education and Prescribing Safety) program, a stringent protocol aimed at avoiding the teratogenic effects of the drug. Women who wish to conceive, do not practice reliable contraception, or are judged by their health care provider to be incapable of practicing reliable contraception must be excluded from using thalidomide. Furthermore, patient education about the proper and safe use of thalidomide and serial pregnancy tests are mandatory (6).

Peripheral neuropathy

Thalidomide-associated peripheral neuropathy has been described in detail among the results of several large retrospective studies published throughout the medical literature (6). Frequently, patients complain of painful paresthesias and tingling sensations in the lower extremities. Motor disturbances are generally mild and reversible on discontinuation of the drug, whereas sensory symptoms may persist or incompletely resolve. The issue of irreversibility is clouded by the retrospective nature of these studies and the collection of data from patients whose conditions may themselves produce neuropathy. The reported incidence of thalidomide neuropathy varies from 0.5% to 50% between series. Gardner-Medwin and Powell have published guidelines for the use of electrophysiologic studies to monitor for neurotoxicity. They suggest baseline electromyogram and nerve conduction velocity study repeated at 10 g or 6-month intervals (which ever comes first) during treatment. A decline in the sensory nerve action potential of 50% or more, subjective neurologic complaints at monthly follow-up, or physical examination abnormalities necessitate a dose reduction or discontinuation of thalidomide. Whether electrophysiologic monitoring provides tangible benefits avoiding neurotoxicity above and beyond detailed serial clinical assessments remains to be proved (6).

Other adverse effects

Taking thalidomide at bedtime can help minimize somnolence, dizziness, and morning hangovers. These effects tend to resolve after 2 to 4 weeks of continuous therapy. Constipation, headache, nausea, weight gain, edema, and transient skin eruptions may also occur.

Thalidomide use in ankylosing spondylitis

Up to recently, there was no effective therapy for patients with severe AS, refractory to non-steroidal anti-inflammatory drugs (NSAID), especially for those with predominantly axial involvement. Given its pharmacological properties, thalidomide has been considered as a putative anti-TNFα agent. The presence of TNFα was demonstrated in inflamed sacro-iliac joints of patients affected with AS, both at messenger RNA and protein levels (3). This observation prompted one of us to examine the efficacy of thalidomide in severe refractory AS. A regimen of 100-300 mg/day was used. The first two patients who received the drug had a clear benefit from thalidomide (5). Efficacy of the drug concerned both axial and peripheral clinical manifestations, and also biological markers of inflammation (ESR and CRP). One of the 2 patients had prompt relapse after discontinuation of the drug, whereas the second was lost of follow-up. Efficacy of thalidomide resumed after reintroducing the treatment in the first patient. Since this initial description, 10 additional SpA patients have been treated by the same author (4, 10). The duration of treatment was 6 months followed by a carry-over observation period of 4 months. Of 12 patients enrolled in this small-size open-labeled study, 5 stopped thalidomide before 6 months because of side-effects. Evidence of clinical efficacy was found in 7 of 12 patients, among whom 2 achieved a reduction of Bath AS Disease Activity Index (BASDAI) greater than 50%. The most consistent efficacy however was on biological parameters of inflammation (ESR and/or CRP)

Lee *at al.* subsequently reported efficacy of thalidomide in one female patient affected with severe refractory SpA (15).

Huang *et al.* have completed a one-year open-labeled study in 30 male patients affected with severely active refractory AS, in Beijing (13). In this study, patients were required to meet six entry criteria on two occasions in the month prior to study entry: BASDAI > 4, total body or spinal pain values >2 when

Table II. Thalidomide in severe refractory SpA*.

Study	Patients treated: diagnosis (n)	HLA-B27	Dosage (mg/day)	Duration of treatment (mos.)	No. of premature discontinuations (%)	No. with clinical improve-improvement (%)	Center
Breban *et al.*	AS (9), uSpA (2), PsA (1)	10/12	100-300	6	5 (42)	7/12 (58)	Paris
Lee *et al.*	uSpA (1)	1/1	100	6	0	1/1 (100)	Sydney
Huang *et al.*	AS (30)	30/30	200	12	4 (13)	21/30 (70)	Beijing
Wei *et al.*	AS(10)	NA	200	3	1 (10)	7/10 (70)	Chia Yi

* SpA: spondylarthropathy; AS: ankylosing spondylitis; uSpA: undifferentiated spondylarthropathy; PsA: psoriatic arthrittis; NA: not available.

evaluated on a four point Likert scale, and early morning stiffness >30 minutes, ESR as well as CRP measurements higher than normal. Using a 20% improvement of 4/7 indices as primary response definition, 80% of the 26 patients who completed the one year thalidomide study demonstrated a positive response. About 50% of patients showed a >50% improvement in 4/7 indices. However, complete remission with improvement >75% in 7/7 indices was not attainable. This positive observation of primary outcome measure improvement was supported by improvement of five parameters of secondary outcome measures. Most notable were significant decreases in both ESR and CRP. ESR and CRP were high in all patients prior to therapy. They returned to normal in 4 and 14 patients respectively after 6 and12 months of thalidomide.

In Taiwan, Wei *et al.* have now completed a 3 months open-labeled study of thalidomide in 10 male patients affected with severely active AS, refractory to NSAID. According to AS assessment study criteria (1) which were used to evaluate efficacy of treatment, 7 of the 9 completers (78%) were responders (4 and 3 patients achieved 50% and 20% improvement levels respectively). Statistically significant improvement was achieved for BASDAI, patients global assessment, ESR and CRP.

Results from these different reports are summarized in Table II. In both French and Chinese studies, relapse seemed to occur after discontinuation of the drug, meaning that long-term treatment would presumably be necessary to maintain efficacy in SpA patients responding to thalidomide.

Mechanism of action

As indicated above, thalidomide was initially tried in AS because it was one of the few conventional drugs thought to target TNFα. In agreement with this hypothesis, biological agents blocking TNFα proved remarkably efficacious in refractory AS (2, 17). Parallel efficacy between thalidomide and anti-TNFα biological therapy was also observed in refractory Crohn's disease (11), as opposed to rheumatoid arthritis which seemed to respond rather poorly to similar doses of thalidomide (6).

However, as already discussed, the mechanism of action of thalidomide is more complex than just direct inhibition of TNFα. Interestingly, Huang *et al.* have demonstrated inhibition of several pro-inflammatory genes expression, in peripheral blood mononuclear cells after 3 months of thalidomide therapy. Gene expression profiles were tested by a 588-gene microarray. Seven thalidomide suppressed genes were identified: TNFα, IL-1 , M1P-1α, M1P-2α, c-jun, OX40 ligand and the T lymphocyte maturation-associated protein MAL. In contrast, such inhibition was not observed during treatment with infliximab (12, 13).

Tolerance

Overall tolerance was weaker in the French patients treated with thalidomide than in those from China or Taiwan. This could be due to genetic differences in the enzymatic capacity to detoxify the drug, but also to differences in the prescription schema. Hence in Beijing, thalidomide was started at 50 mg/day and doubled every ten days to a steady dose of 200 mg/day, which was well tolerated (none of the 30 patients dropped out because of side-

effects). Only one patient required a higher dose of 300 mg/day. In Taiwan, the initial dose was 100 mg/day for 1 week followed by 200 mg/day for 11 weeks. Only one patient dropped out after 2 weeks for skin eruption. In the French experience, a loading dose of 300 mg/day was rather used and tapered thereafter. Frequent side-effects were drowsiness, constipation, and dizziness. No major side-effect of thalidomide, such as birth defects or neuropathy, has been reported so far in AS.

Future directions

Despite its tragic past, thalidomide has recently shown promise in treating several disorders, including AS. Thalidomide is much less expensive than anti-TNFα biological agents. However, controlled studies are still needed to assess the benefits and risks from short-term and long-term use. In recent years, several structural analogues of thalidomide have been demonstrated to have increased potency at inhibiting TNFα production as well as enhanced solubility and stability. Two different groups of molecules were obtained.

The immunomodulatory imide drugs (IMiDs) inhibit the production of TNFα, IL-1 and IL-12, and enhance the production of IL-10, in monocyte stimulated by LPS. In addition, and similarly to thalidomide, these compounds exert a costimulatory effect on T cells. In contrast, the selective cytokine inhibitory drugs (SelCiDs), which are potent phosphodiesterase Type 4 inhibitors, are more selective inhibitors of TNFα. It is expected that some of these agents with increased safety profile, as compared to thalidomide, will represent useful anti-TNFα drugs in the future (8).

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