Use of Thalidomide in Rheumatic Diseases
For the vast majority who won’t start it

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Ended with tragic side effects & revived for desperate conditions
Thalidomide was synthesized in 1954 and prescribed as a sedative, tranquiliser, and anti-emetic for morning sickness. It is chemically similar to barbiturate, but with much less hang-over, and thus soon became very popular. However, after the emergence of reports of teratogenicity, in particular foetal limb malformation, including pregnant women who took, as little as a single dose of the drug, it was withdrawn from the European and Canadian markets in 1961 - 62.

A few years later, an Israeli physician administered some old supplies of thalidomide to a patient with leprosy and mania for sedation. Surprisingly, it gave dramatic and near complete resolution of the patient’s cutaneous symptoms. However, it was not until the discovery to thalidomide’s anti-tumour necrosis factor-α (TNFα) activity in 1991 and experimental evidence of its ability to interfere with vasculogenesis in 1994 that interest in re-emergence of the drug was rekindled. Now it has been extensively studied for use in many refractory malignant or inflammatory conditions.

Between nasty poison and last card - immunomodulatory action
The immunomodulatory effects of thalidomide are complex and incompletely understood. Its key ability is to inhibit the production of TNFα, primarily on monocytes and also T-lymphocytes, alveolar macrophages, lamina propria mononuclear cells and microglial cells. How thalidomide inhibits TNFα production remains unclear but it seems to involve the enhancement of TNFα mRNA degradation and inhibition of NF (nuclear factor)-κB activation. Besides its effects on TNFα production, thalidomide can also enhance the production of IL (interleukin)-4 and IL-5, while inhibiting IL-12 production. It also acts as a T-cell co-stimulant, which is potentially beneficial to anti-tumour activity. Moreover, it is capable of inhibiting angiogenesis induced by vascular endothelial derived growth factor and basic fibroblast growth factor.

The molecule
Thalidomide is a derivative of glutamic acid. It is administered clinically as a 1:1 racemic mixture of S and R enantiomers (mirror image isomers) that interconvert under physiological conditions. It is well absorbed after oral administration, eliminated by spontaneous hydrolysis to multiple chemically inactive metabolites, and has a half-life of around five hours.

Recent convert of an ex-convict
Thalidomide is particularly useful in treatment of mucocutaneous diseases. Erythema nodosum leprosum was the first approved indication by Food and Drug Administration of the United States. Resistant oral aphthous ulceration, whether idiopathic or associated with human immunodeficiency virus infection, and the granulomatous skin lesions of sarcoidosis all respond very well to thalidomide.

Another major application of thalidomide is in haematological malignancies. The most promising results to date have been in the treatment of multiple myeloma. Up to 35% response rate in refractory cases had been reported. Thalidomide can also be useful in high-risk myelodysplasia, acute and chronic myeloid leukaemia, and other myeloproliferative disorders. In contrast, the efficacy of thalidomide in solid organ tumours is less well documented, because increased thromboembolic disease has also been reported. Thalidomide has also been reported to be beneficial in Crohn’s disease, wasting and cancer cachexia.

Use of thalidomide in rheumatic diseases
In non-randomised studies, thalidomide was moderately effective for the treatment of refractory cutaneous lesions of lupus, which otherwise had inadequate response to treatment with anti-malarial agents, steroid or other immunosuppressive drugs. Overall, clinical response rates ranged from 84% to 100% at daily doses of 50 - 400 mg, with the possibility of subsequent maintenance therapy after initial response. The effects of thalidomide on visceral and articular involvement of lupus are conflicting. In short, thalidomide is considered second-line therapy in cutaneous lupus, as its usefulness is mainly limited by potential neurotoxicity and extent of relapse after discontinuation of therapy.

Ankylosing spondylitis, a chronic inflammatory disease of axial skeleton (spine and particularly sacroiliac joints) and occasionally other peripheral joints, also shows good response to thalidomide. An open-label study was conducted in Mainland China which involved 30 male patients suffering from severe and active ankylosing spondylitis refractory to non-steroid anti-inflammatory
drugs, sulphasalazine, methotrexate and even corticosteroid. Thalidomide 200 mg daily was used. As a result, 80% of the 26 patients who completed the study experienced at least 25% improvement in the functional and disease indices. Prompt improvement was noticed at 3-6 months. Nine patients (30%) became pain-free. Decreased expression of several pro-inflammatory genes, including TNFα and IL-1 in peripheral blood mononuclear cells from these patients after thalidomide treatment was also noted. The common side effects in this study were slight drowsiness in first dry month, and these gradually subsided upon continued treatment. Only one patient in this study stopped thalidomide at 2nd month because of tingling sensation over fingers for two days lasting for three days.

Behcet’s disease is an inflammatory disease of unknown aetiology characterised by episodic exacerbation of oral ulcers, genital ulcers, uveitis, arthritis, erythema nodosum and other skin lesions. Several uncontrolled studies have shown that thalidomide is effective in both treatment and prevention of recurrence of orogenital ulceration in Behcet’s disease. In a placebo controlled trial, oral and genital lesions of Behcet’s disease improved after treatment with thalidomide (100mg or 300mg) versus placebo, with complete response rates of 9% on treatment versus 0% on placebo. Typically, oral lesions healed in 3-4 weeks, but recurrences were common in the drug. Despite its effectiveness in orogenital ulcers, thalidomide appears to offer little help on uveitis in Behcet’s disease.

For some unclear reasons, the effect of thalidomide is not so impressive in refractory rheumatoid arthritis, a chronic inflammatory arthropathy mediated in part by TNFα. Thalidomide has also been tried, but without major success, in a limited number of patients suffering from other rheumatic diseases such as Still’s disease, scleroderma and Sjögren’s syndrome.

Side effects

Thalidomide is notorious for being extremely teratogenic. In utero exposure of the drug, even with a single 50 mg dose taken in first trimester, could cause 10% - 50% risk of birth defects. Common foetal abnormalities are phocomelia (short limbs) or amelia (absent limbs), central skeletal or craniofacial abnormalities and visceral malformation. The mechanisms of teratogenicity may involve free radical mediated embryonic DNA oxidative damage, and disturbed cellular recognition through interaction with adhesion molecules.

Peripheral neuropathy is the next serious side effect and it occurs at a rate ranging from 1% to 70% in different series, depending on whether it is documented on clinical ground or with more sophisticated electrophysiological studies. Age and cumulative dose were identified to be associated factors in a large prospective study, though not so in another retrospective study. Typical presentation is painful or burning sensory neuropathy in association with mild proximal myopathy. Upon cessation of thalidomide, weakness rapidly resolves but sensory changes are usually slow to recover and in some cases may be irreversible.

Other side effects include somnolence (ironically the originally intended “effect”), constipation, dizziness, macular rash, decreased libido and rarely neutropenia.

Taming the shrewd - Precautions

Thalidomide should only be used to treat severe disabling conditions refractory to conventional treatment. In many public hospitals and clinics, the drug is available on a named patient basis. Patients should be encouraged to take part in the decision making process of resorting to thalidomide therapy. They should be well informed to consider such major undertaking, by striking the balance between possible benefit of controlling a refractory disease versus potential side effects and the absolute willingness to prevent pregnancy.

Any women of childbearing potential must be aware of the risk of birth defects and they should have a negative pregnancy test done shortly before starting thalidomide. They must abstain from intercourse or use two forms of contraception at the same time, which must begin one month before starting thalidomide and continued for at least one month after stopping treatment. Male patients must use a condom every time they have intercourse, even if they have undergone vasectomy.

Baseline nerve conduction studies may be useful, and patient should be advised to stop thalidomide should any neuropathic symptom arise. Bedtime dosing can minimise the side effect of somnolence.

The case for a special role in Asia

Roughly speaking, thalidomide can be regarded as an oral anti-TNFα agent, and supposedly less expensive than biologic agents specifically designed for such purpose. Indeed, anti-TNFα therapy is currently the breakthrough for treating refractory ankylosing spondylitis. However, TNFα is also a key cytokine in the body’s defense against infection. Sepsis, including active tuberculosis, is a contraindication to anti-TNFα treatment. Chronic hepatitis carriers were excluded from clinical trials on use of anti-TNFα agents in refractory ankylosing spondylitis in western countries, as there were reported cases of fatal hepatitis C exacerbation after such treatment. There are only scattered reports on the safety of thalidomide use in hepatitis B and hepatitis C carriers in the literature. Here is the tantalising question - is thalidomide a safer anti-TNFα agent in concomitant tuberculosis infection and chronic hepatitis carriers? More intriguing is whether thalidomide can be a temporary substitute for biologic agents, the cost of which is certainly prohibitory.

Conclusion

Thalidomide has been demonstrated to be useful in some rheumatic conditions such as cutaneous lupus, ankylosing spondylitis and Behcet’s disease when conventional treatment fails. However, contraception must be faithfully exercised, as teratogenicity remains the ultra concern.

References