Thalidomide: History, withdrawal, renaissance and safety concerns

Prof Neil Vargesson[1, *], Ph.D and Prof Trent Stephens[2], Ph.D

1. School of Medicine, Medical Sciences and Nutrition. Institute of Medical Sciences, University of Aberdeen. Foresterhill. Aberdeen. AB25 2ZD. UK.
2. Idaho Dental Education Program and Department of Biological Sciences, Idaho State University, Pocatello, Idaho, USA 83209

*Author for correspondence: email: n.vargesson@abdn.ac.uk

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1. Overview

Thalidomide is used around the world today to effectively treat inflammatory and cancer conditions. Yet, 60 years ago it was withdrawn from the market. What do we know about its mechanisms of action and how safe is it?

2. History and withdrawal

Thalidomide was marketed as a safe and effective sedative beginning in 1957 and was later found to be effective at treating morning sickness. It was believed to be so safe that it was available over the counter in several countries. However, it was withdrawn from much of the pharmaceutical market beginning in late November 1961. This was due to it being found to be the cause of an epidemic of at least 10000, and probably as high as 100000, children worldwide born with severe birth defects to mothers who used thalidomide during pregnancy [1, 2, 3, 4, 5]. The stereotypical image of a thalidomide survivor is a person with phocomelia of the arms, where the long bones of the arm are missing or shortened and the digits either articulate with the shoulder or at the end of a shortened humerus and ulna. However, thalidomide caused damage to many other tissues including legs, eyes, ears, face, cardiovascular system, gastrointestinal system, reproductive system, urinary system and the spine [1]. Sadly, due to internal organ defects such as atresia of the bowel and heart issues it is reported that up to 40% of babies died in their first year of life [1, 2]. It is also apparent that no two thalidomide survivors look identical, underlining the broad damage this drug can cause, likely due to the timing of exposure and genetic background, which would differ between pregnant women [2, 3]. The withdrawal of thalidomide led to significant and world-wide changes in the way drugs and medicines are tested [6, 7].

3. Renaissance and current uses

However, this is not the end of the thalidomide story. Since the drug's withdrawal beginning in late November 1961, it has been shown to be very effective at i) downregulating the inflammatory response and is used today as a treatment for complications of leprosy, particularly in Brazil; ii) is antiangiogenic and is in trials to treat a range of haematological malignancies, such as Haemorrhagic Hereditary Telangiectasia [8] and is also used to successfully treat Multiple Myeloma in combination with other drugs (for example, Bortezomib, Dexamethasone and Daratumumab) [9]; iii) is immunomodulatory; iv) can also be neuroprotective for some brain injuries as well as be neurotoxic following prolonged use [2, 10]. Moreover, recently its anti-inflammatory actions have made it a potential therapy to treat COVID-19 lung damage [11]. Perhaps given these clinical benefits and range of uses it shouldn't be a surprise that thalidomide is enjoying a renaissance.

4. Mechanism of action

Even after 60 years of research, how thalidomide acts to cause birth defects is still unclear. Most recent research into the actions of thalidomide have focused on the drug's anti-angiogenic, anti-inflammatory, anti-myeloma and neuroprotective actions in the adult.

Recent work has demonstrated that the drug's ability to prevent blood vessel formation which is useful for cancer treatment also underpins how the drug caused damage in the embryo [12, 13]. Recently molecular targets of thalidomide in the

embryo have been identified which include Cereblon, a ubiquitin ligase that tags other molecules for destruction. It is thought this interaction may result in misregulation of key signalling pathways in the embryo [14]. Indeed, if thalidomide can't bind Cereblon, the embryo is unaffected by thalidomide [14]. Other targets of thalidomide that seem to be Cereblon-dependent include genes involved in limb development including p63 and SALL4 [2, 14]. Yet, recent work on the action of thalidomide on the blood vessels indicate there are likely Cereblon-independent targets as well [2, 15, 16]. In addition, other targets of thalidomide have been proposed for example, interacting with GC-rich gene promoters, cell cytoskeletal proteins, NFkappaB and nitric oxide (17). Adding to this is work indicating that preventing the production of reactive oxygen species and cell death by thalidomide can prevent thalidomide-induced defects [18]. Taken together, this highlights that despite it being 60 years since the withdrawal of thalidomide from the market following the worldwide epidemic of birth defects, its mechanism of action in the embryo, is still not fully understood and is likely more complicated than we currently think. It is also possible that thalidomide caused birth defects by a combination of several mechanisms – creating a perfect storm.

5. Controversies and safety concerns

The people damaged by thalidomide while it was used between 1957 and 1961 (and even later in some countries) now suffer from early-onset age related disorders, in addition to dealling with the life style changes forced upon them due to the damage the drug caused them in utero [19].

In addition, there are populations of alleged thalidomide survivors around the world still fighting for recognition and compensation for the injuries they believe were also caused by thalidomide. The criteria for establishing if someone was damaged by thalidomide were largely created in the 1960s and based upon the most severely damaged children [1, 2, 3, 4, 5, 13]. Those children that had damage that looked similar to other clinical conditions were deemed not to be thalidomide survivors and were not followed up. On top of this, thalidomide record keeping was poor, the drug was available over the counter and was also handed out as free samples to patients. As such administration was not recorded on many medical records. Taken together, sadly, the true number of people damaged by thalidomide will never be known.

Tragically, there is a new population of thalidomide damaged children and adults in Brazil. This is due to thalidomide being used to effectively treat complications of leprosy in Brazil, where leprosy is endemic. Sadly, villages can be very far away from hospitals and medicines can then sometimes be shared amongst the population, resulting in some cases of thalidomide embryopathy [20].

However there has not been any recorded cases of thalidomide embryopathy, since the original disaster (1957-1962), in any other country, except Brazil, due to effective patient safety programmes. Indeed, thalidomide has been studied, under strict conditions, to treat leprosy since 1965 and conditions like multiple myeloma since the 1990s. It was also considered to treat HIV/AIDS at one point [7, 13]. Patient safety programmes include measures such as regular contraceptive use and regular pregnancy tests [2, 21].

Yet, with thalidomide use increasing and each year more information about its actions and potential clinical uses being discovered, for example, recently shown to be useful to treat Hereditary Hemmorhagic Telangiectasia [8] and just this year it has been proposed to be potentially effective to treat COVID-19 [11], taken altogether means the use of thalidomide continues to present a risk to the unborn child.

6. Expert Opinion

When thalidomide is used for clinical treatment with patient safety programmes in place it is a safe and effective drug [2, 21]. Yet, long term use can cause peripheral neuropathy, and there are many other side-effects including blood clots [2, 7, 13]. However, any mistakes or misuse could lead to children damaged by thalidomide, as has been seen recently in Brazil [20]. The wide range of actions this drug has on the body also means that when it used to treat a condition such as complications of leprosy it can also be acting negatively on other body systems.

Ultimately, removing thalidomide from the market again perhaps makes some sense, as thalidomide does have many side-effects and health warnings [2, 13, 20]. However, Patient Protection Programmes do and are working [7, 21] and, in particular, for the treatment of patients with Multiple Myeloma, thalidomide is successfully used in combination with other drugs and is relatively safe [9]. In this particular scenario, the withdrawal of thalidomide would be difficult to authorise, unless a better and more efficient alternative became available. Moreover, perhaps the introduction of stricter prescription measures in Brazil would reduce the risks of thalidomide embryopathy there.

Yet, while thalidomide is very effective in treating the conditions it is used for, it continues to have the risk of causing side effects to users [1, 2, 7, 13, 20]. Perhaps what would be useful is the development of a targeted version of the drug for a specific clinical condition that doesnt cause birth defect, and which are being developed [2, 22]. However, new thalidomide analogs that don’t cause birth defect may still have other side effects. Alternatively, and in the longer term, should we be devising a new drug (non-thalidomide) that targets a specific condition more efficiently and more safely than thalidomide and that does not cause birth defects or serious side-effects, particularly, if taken by mistake? For this to happen new treatments, research and understanding of the condition’s thalidomide is currently used for is needed.

Finally, a more complete and thorough understanding of the molecular mechanisms that underpin thalidomide action in the embryo is also needed. This would provide an understanding of precisely how all the differing damage patterns that thalidomide can and did cause comes about and finally explain to survivors, over 60 years later, how the drug did what it did to them. Such an understanding might also shed light on the full range of damage that thalidomide can cause and which perhaps to date has been unrecognised.

7. Conclusion

The thalidomide story has shown us that thalidomide has remarkably many clinical applications. Yet, it remains dangerous if not taken safely and carefully. In addition, and perhaps surprisingly, we still don’t understand fully how thalidomide acts in the

body or on the embryo. The repurposing of thalidomide as a potential treatment for COVID-19 lung inflammation highlights the usefulness of thalidomide. This also underlines the need to fully understand how our drugs and medicines work, to make them as safe as practicable and identify or engineer new drugs that are more efficient, targeted and safer in the treatments they are used for.

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NV and TS have independently advised lawyers representing alleged Thalidomide survivors and advised Government agencies about Thalidomide and its actions.

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