"Thalidomide Revisited: Historical Tragedy, Regulatory Reform, and Modern Therapeutic Roles"

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Abstract

Thalidomide was initially introduced to the market in 1957 but was promptly retracted due to its infamous teratogenic effects. Research on the mechanism of action of thalidomide has uncovered the many features of this medication class, encompassing anti-inflammatory, antiangiogenic, and immunomodulatory effects. Thalidomide and its equivalents, lenalidomide and pomalidomide, have been repurposed to treat erythema nodosum leprosum, multiple myeloma, and other hematological malignancies due to their significant activity. Recent discoveries indicate that thalidomide analogues use the CRL4CRBN ubiquitin ligase to direct various cellular proteins for ubiquitination and subsequent proteasomal destruction. The degradation of SALL4 and p63, transcription factors vital for embryonic development, induced by thalidomide, presumably contributes significantly to thalidomide embryopathy. This study offers a concise retrospective overview of thalidomide-induced teratogenesis, the mechanism of thalidomide's action, and recent advancements in understanding the molecular mechanisms behind thalidomide-induced congenital abnormalities. The harrowing sight of thousands of newborns born with malformed limbs in the early 1960s astonished the world. The public's mind has been indelibly marked by the image of young individuals grappling with limb deformity. Thalidomide, a medication utilized by women for morning sickness and insomnia, was identified as the cause of limb and organ malformations. Thalidomide was marketed in more than 40 countries and was approved for prescription use in Canada from April 1961 to March 1962. While the actual figure was probably higher due to spontaneous miscarriages and stillbirths, it led to around 115 instances of malformations in this nation. This medicine, having been removed from the medical arsenal, became a derogatory phrase for many years. Nonetheless, thalidomide has resurfaced from the depths of profound sadness. Despite rigorous restrictions, it has achieved a spectacular recovery and integrated into the present therapeutic regimen. Due to the revelation that thalidomide and its derivatives positively influence several cellular activities, they are presently advised for the treatment of several conditions, including leprosy and multiple myeloma. Prior to reintroducing the medicine to the market, the US FDA performed several clinical investigations. The fatalities associated with this agent prompted legislation that enhanced patient informed consent procedures, restructured the FDA regulatory framework, and mandated greater transparency from pharmaceutical corporations.

Keywords: Thalidomide, Teratogenicity, Phocomelia, Drug Regulation, Frances Kelsey, FDA, S.T.E.P.S. Program, Lenalidomide.

1. Introduction

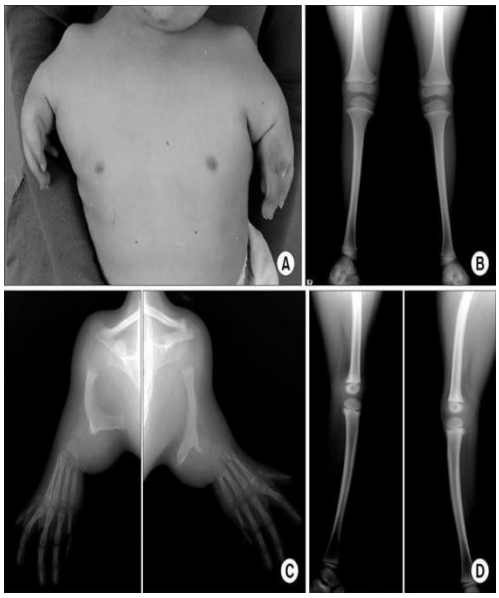
Thalidomide was created by the Swiss pharmaceutical firm CIBA in 1953 and subsequently launched by the German pharmaceutical business Chemi Grunenthal in 1956.Originally branded as Contergan, thalidomide was administered as a nonbarbiturate hypnotic sedative capable of inducing profound sleep without residual effects or dependency risks. Experiments in animal models did not determine a median lethal dose, and the medication was widely considered innocuous to humans . Unlike the comprehensive testing conducted today, formal assessments for detrimental teratogenic consequences were not carried out during that period. Soon to be marketed globally, the medicine gained popularity for its anti-emetic properties in pregnant women experiencing morning sickness. The drug's appeal stemmed mostly from its easy accessibility without a prescription and its relatively low cost. In Germany, it rapidly emerged as a leading sedative, with approximately 14.6 tons marketed in 1960 .

In 1961, Dr. William McBride, an Australian obstetrician, and Dr. Widukind Lenz, a German pediatrician and geneticist, independently observed a correlation between thalidomide use during pregnancy and congenital abnormalities. These findings were corroborated by numerous global cases, leading to the eventual withdrawal of thalidomide from the market. Preliminary reports documented limb and skeletal anomalies, including amelia, phocomelia, syndactyly, and hypoplasia of long bones, among other deformities . Further observations encompassed esophageal, duodenal, and anal atresia, alongside cardiac anomalies and aplasia of the gallbladder and appendix . Most abnormalities arose when thalidomide was consumed between 34 and 49 days following the last menstrual period, with even a solitary dose linked to heightened risk. As many as 40% of impacted newborns succumbed within one year.

Thalidomide was temporarily accessible as an investigational drug in the United States. The medicine was endorsed as an anxiolytic but was never authorized for commercialization. Dr. Frances Kelsey, a physician and pharmacologist, was the FDA officer responsible for evaluating the medication application; she rejected approval due to insufficient safety data.

Central to Kelsey’s judgment were new findings associating thalidomide with neurologic toxicities, particularly peripheral neuritis. In recognition of her efforts to prevent the marketing of thalidomide and so avert a significant tragedy in the United States, Dr. Kelsey received the President’s Award for Distinguished Federal Civilian Service from President John F. Kennedy in 1962 .

An estimated 10,000 newborns were impacted globally, with additional unquantified stillbirths or miscarried pregnancies. A significant consequence of these tragic incidents has been the positive transformation in the drug regulating process. Issues with animal models and inefficiencies in the pharmaceutical approval process were addressed by new laws that reformed the FDA regulatory framework, enhanced patient informed consent protocols, and mandated greater transparency from medication producers. Committees were established in Germany to allocate compensation to the individuals most adversely impacted. Comparable organizations were established in Britain, Canada, and Sweden. Thalidomide was removed from most commercial markets by 1961 and prohibited globally by the end of the decade. [1]



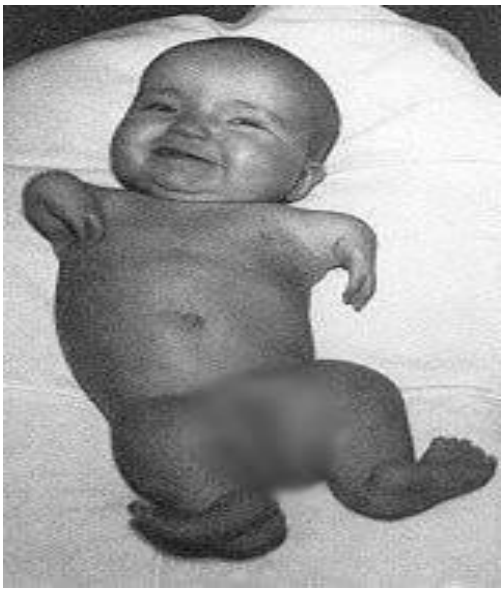


Fig1:[a]single view of patient upper and lower extrimites

[b]phocomelia in baby

2. Development of Thalidomide

Thalidomide was initially formulated as a sedative by the Swiss pharmaceutical firm Ciba in 1953. In 1954, Ciba discontinued the product, which was subsequently acquired by the German pharmaceutical firm Chemie Grünenthal. The company was founded by Hermann Wirtz Sr, a member of the Nazi Party, post-World War II as a subsidiary of the family's Mäurer & Wirtz enterprise. The company's primary objective was to provide antibiotics to address an urgent market demand. Wirtz appointed scientist Heinrich Mückter, who evaded prosecution for war

crimes related to his experiments on captives in Nazi concentration camps, to lead the development program because to his expertise in developing and producing an anti-typhus vaccine for Nazi Germany. He appointed Martin Staemmler, a physician and prominent advocate of the Nazi eugenics program, as head of pathology, along with Heinz Baumkötter, the chief medical officer at Sachsenhausen death camp, and Otto Ambros, a chemist and Nazi war criminal. Ambros served as the chairman of Grünenthal's advisory group throughout the development of thalidomide and was a board member during the sale of Contergan. [2]

Fig 2: Dr Frances Kelsey is awarded the presidents for distinguish fedral civilian service from president John F. kennedy in 1962.

2.1. Reintroduction of thalidomide into clinical practice

Thalidomide has been reintroduced into clinical practice as an anti cancer drug. In the first clinical trial conducted at the university of Arkansas, 25% of patients with advanced relapsed refractory multiple myeloma achieved a partial response to therapy.

Shortly after the teratogenic properties of thalidomide became known, astute physicians considered the drug as a possible cancer treatment. They reasoned that a drug powerful enough to cause severe defects in rapidly growing fetal tissues & organs, Probably have similar effects against malignant tumors.

At least, 3 large scale clinical trials involving approximately 200 patients were undertaken in the United States to investigate thalidomide use for treatment of advanced cancer, no notable activity was seen with this drug in any of these early trials, and enthusiasm for continuing research of thalidomide as an anticancer agent disappeared for about 3 decades.

In clinical trial phase III, thalidomide plus dexamethasone demonstrated significantly superior response rates in newly diagnosed myeloma compared with dexamethasone alone.

Thalidomide represents a new era in therapy for this incurable and fatal malignancies.

The drug also is being studied in nonmalignant conditions including inflammatory bowel disease, reflex sympathetic dystrophy syndrome, and certain autoimmune disorders.

Lenalidomide has shown considerale promise in treatment of relapsed and refractory myeloma.[3]

2.2. Birth defect crisis

It is believed that over 10,000 embryos were harmed by thalidomide use during pregnancy, perhaps reaching up to 20,000; of these, around 40 percent perished at or shortly after delivery. Survivors exhibited problems in limbs, eyes, urinary tracts, and hearts. The U.S. market entry was obstructed by Frances Oldham Kelsey at the U.S. Food and Drug Administration (FDA). The teratogenic effects of thalidomide prompted the establishment of enhanced drug control and oversight in numerous nations.

The severity and site of the deformities were contingent upon the gestational age at which the mother commenced treatment; thalidomide administered on the 20th day of pregnancy resulted in central brain damage, on day 21 it affected the eyes, on day 22 it impacted the ears and face, on day 24 it caused arm deformities, and leg damage could occur if taken until day 28.

Thalidomide did not adversely affect the fetus if administered after 42 days of gestation.

2.2.1. United Kingdom

Prosthetic limbs designed for a disabled youngster in the 1960s by the Limb Fitting Centre of the Department of Health and Social Security in Roehampton, London .The medication was authorized in the UK in 1958 and retracted in 1961. Of the approximately 2,000 infants born with congenital anomalies, about half perished within a few months, while 466 endured until at least 2010.In 1968, following an extensive campaign by The Sunday Times, a compensation agreement for the UK victims was established with Distillers Company (now a subsidiary of

Diageo), who had distributed the drug in the UK. Distillers Biochemicals disbursed around £28 million in compensation subsequent to a legal dispute.

The British Thalidomide Children's Trust was established in 1973 as a component of a £20 million legal settlement between Distillers Company and 429 children with disabilities connected to thalidomide. In 1997, Diageo, established via the merging of Grand Metropolitan and Guinness (which had acquired Distillers in 1990), pledged long-term financial support to the Thalidomide Trust and its beneficiaries. The United Kingdom government gave survivors a grant of £20 million, to be distributed through the Thalidomide Trust, in December 2009.

2.2.2. Spain

Thalidomide was extensively accessible in Spain during the 1970s, and possibly into the 1980s. Two explanations accounted for this. Initially, regulatory oversight and protective measures were inadequate; it was not until 2008 that the government acknowledged the country's prior importation of thalidomide. Secondly, Grünenthal neglected to compel its Madrid-based sister business to notify Spanish physicians and allowed it to refrain from alerting them about the problems. The Spanish support organization for thalidomide sufferers estimates that in 2015, there were between 250 and 300 live victims of thalidomide in Spain.

Australia and New Zealand

While Australian physician William McBride is credited with expressing concerns about thalidomide, it was midwife Sister Pat Sparrow who initially believed that the medicine was responsible for birth deformities in the infants of women under McBride's care at Crown Street Women's Hospital in Sydney. German pediatrician Widukind Lenz, who also hypothesized the association, is recognized for completing the scientific investigation that demonstrated thalidomide was responsible for birth abnormalities in 1961. McBride subsequently received several accolades, including a medal and monetary award from L'Institut de la Vie in Paris; however, he was ultimately removed from the Australian medical registration in 1993 due to scientific misconduct associated with his research on Debendox.

Additional animal experiments were performed by George Somers, Chief Pharmacologist of Distillers Company in Britain, revealing fetal anomalies in rabbits. Comparable findings were also reported demonstrating comparable effects in rats and more species.

Lynette Rowe, born without limbs, spearheaded an Australian class action lawsuit against the medicine maker, Grünenthal, which sought to have the case adjudicated in Germany. In 2012, the Supreme Court of Victoria rejected Grünenthal's motion, and the matter was adjudicated in Australia.On 17 July 2012, Rowe received an out-of-court settlement, estimated to be in the millions of dollars, establishing a precedent for class action claimants to obtain additional compensation. In February 2014, the Supreme Court of Victoria approved a settlement of $89 million AUD for 107 victims of the drug in Australia and New Zealand.

2.2.3. Germany

In East Germany, thalidomide was disapproved by the Central Committee of Experts for Drug Traffic in the GDR and was never authorized for usage. No thalidomide-affected infants have been documented in East Germany. In West Germany, a considerable duration elapsed before the rise in dysmelia at the conclusion of the 1950s was linked to thalidomide. In 1958, Karl Beck, a former pediatrician in Bayreuth, authored an article in a local newspaper asserting a correlation between nuclear weapons testing and instances of dysmelia in infants. Consequently, FDP whip Erich Mende solicited an official statement from the federal government. For statistical purposes, the primary data set utilized to investigate dysmelia patients coincidentally commenced concurrently with the approval date of thalidomide. Following the Nazi regime's implementation of the Law for the Prevention of Hereditarily Diseased Offspring, which employed compulsory statistical surveillance to perpetrate several atrocities, West Germany exhibited considerable hesitance to monitor congenital diseases with comparable rigor. The legislative study dismissed any correlation between radiation and the anomalous rise in dysmelia. The DFG study project established following the Mende request proved unhelpful. The project was directed by pathologist Franz Büchner, who conducted it to advance his teratological theory. Büchner saw inadequate nutrition and maternal conduct as more significant than hereditary factors. Moreover, the appointment of a Surgeon General in Germany was delayed; the Federal Ministry of Health was established in 1962, many months subsequent to the prohibition of thalidomide from the market. In West Germany, some 2,500 infants were born with congenital anomalies due to thalidomide.

2.2.4. Canada

Notwithstanding its significant adverse effects, thalidomide was available in Canadian pharmacies until 1962. The consequences of thalidomide heightened concerns about the safety

of pharmaceutical medications. The Society of Toxicology of Canada was established following the public revelation of thalidomide's consequences, emphasizing toxicology as a distinct specialty from pharmacology. The necessity for the evaluation and authorization of toxins in specific pharmaceutical medications intensified following the accident. The Society of Toxicology of Canada oversees the Conservation Environment Protection Act, concentrating on investigating the effects of chemical pollutants on human health. Thalidomide prompted modifications in drug testing protocols, influenced the selection of pharmaceuticals administered during pregnancy, and heightened awareness of potential adverse effects associated with medications.

As reported by the Canadian news magazine show W5, the majority of thalidomide sufferers, but not all, get annual compensation payouts from the Government of Canada. Those unable to furnish the requisite papers mandated by the government are excluded.

A collective of 120 Canadian survivors established the Thalidomide Victims Association of Canada, aimed at obstructing the endorsement of pharmaceuticals that may pose risks to pregnant individuals and infants.The members of the thalidomide victims organization participated in the STEPS programme, which sought to avert teratogenicity.

2.2.5. United States

In 1962, FDA pharmacologist Frances Oldham Kelsey was awarded the President's Award for Distinguished Federal Civilian Service by President John F. Kennedy for preventing the sale of thalidomide in the United States.

The FDA in the U.S. denied approval for the marketing of thalidomide, citing the necessity for additional studies. This diminished the effects of thalidomide in U.S. patients. The rejection was primarily attributable to pharmacologist Frances Oldham Kelsey, who resisted pressure from Richardson-Merrell Pharmaceuticals Co. Despite thalidomide not receiving approval for sale in the United States, more than 2.5 million tablets were delivered to over 1,000 physicians during a clinical trial program. Approximately 20,000 people, including several hundred pregnant women, used the drug to mitigate morning sickness or as a sedative, resulting in at least 17 children born in the United States with thalidomide-related abnormalities. During her pregnancy, children's television host Sherri Finkbine ingested thalidomide, which her husband had acquired over-the-counter in Europe.. Upon discovering that thalidomide was inducing fetal malformations, she sought to terminate her pregnancy; however, Arizona's laws permitted

abortion solely in instances when the mother's life was at risk. Finkbine flew to Sweden to undergo the abortion. Thalidomide was discovered to have caused fetal deformities. Kelsey was awarded the President's Award for Distinguished Federal Civilian Service in 1962, following his rejection of the application despite pressure from Richardson-Merrell Pharmaceuticals Co., during a ceremony with President John F. Kennedy.In September 2010, the FDA bestowed upon Kelsey the inaugural Kelsey Award, presented yearly to a member of the FDA staff. This occurred 50 years after Kelsey, then a newly appointed medical officer at the agency, initially evaluated the application from the William S. Merrell Pharmaceuticals Company of Cincinnati.

Cardiologist Helen B. Taussig became aware of the detrimental effects of the medicine thalidomide on neonates and, in 1967, testified before Congress regarding this issue during a visit to Germany, where she collaborated with infants suffering from phocomelia (severe limb abnormalities).Her efforts led to the prohibition of thalidomide in the United States and Europe.

2.2.6. Austria

Ingeborg Eichler, a participant in the Austrian pharmaceutical admission conference, implemented limits on the sale of thalidomide (brand name Softenon) under prescription drug regulations, resulting in a relatively low incidence of affected children born in Austria and Switzerland.

Thalidomide Memorial located near Cardiff, Wales the extensive reports of congenital abnormalities in infants heightened awareness of the drug's adverse effects on pregnant women. The teratogenic effects of thalidomide might vary from modest malformations to more severe anomalies. Potential congenital anomalies including phocomelia, dysmelia, amelia, bone hypoplasia, and various other problems impacting the ear, heart, or internal organs. Franks et al. examined the impact of the medicine on neonates, the severity of their malformations, and conducted an evaluation of the drug during its initial years. In 1963, Webb further examined the historical context of the medicine and the various types of birth abnormalities it had induced. The predominant type of birth problem associated with thalidomide is limb reduction, particularly affecting the arms more frequently. This syndrome is characterized by malformations of the long bones in the limbs, leading to shortening and other anomalies.[4]

2.3. Grünenthal criminal proceedings

In 1968, a significant criminal trial commenced in West Germany, accusing multiple Grünenthal officials of negligent homicide and bodily harm. Following Grünenthal's settlement with the victims in April 1970, the trial concluded in December 1970 without a determination of culpability. Grünenthal contributed 100 million DM to a designated foundation, while the West German government supplemented this with an additional 320 million DM. The foundation compensated sufferers with a one-time payment ranging from 2,500 to 25,000 DM, according upon the severity of their handicap, in addition to a monthly allowance of 100 to 450 DM. The monthly stipends have been significantly increased and are now fully funded by the government, as the foundation has depleted its financial resources. In 2008, Grünenthal contributed an additional €50 million to the charity.

On 31 August 2012, Harald F. Stock, the chief executive officer of Grünenthal GmbH from January 2009 until 28 May 2013, issued an apology for the production of the medicine and for remaining silent regarding the associated birth problems. During a ceremony, Stock revealed a statue of a deformed kid to represent those affected by thalidomide and expressed regret for failing to contact sufferers for more than 50 years. At the time of the apology, approximately 5,000 to 6,000 individuals continued to live with Thalidomide-related congenital anomalies. Victim groups deemed the apology "insulting" and "insufficient," criticizing the firm for failing to compensate victims and for asserting that the harm caused by the medicine was unforeseeable, contending that several warning signs were evident at the time. [5]

2.3.1. Australian National Memorial

On 13 November 2023, the Australian Government declared its intention to issue a formal apology to individuals impacted by thalidomide alongside the inauguration of a national memorial site. Prime Minister Anthony Albanese characterized the thalidomide tragedy as a “dark chapter” in Australian history, while Health Minister Mark Butler stated, “Although we cannot alter the past or alleviate the physical suffering, I hope these significant subsequent Measures of acknowledgment and apology will assist in healing some of the emotional scars. [6]

3. Thalidomide Embryopathy (Thalidomide Syndrome)

More than 10,000 children were born from 1957 to 1962 with significant congenital anomalies due to thalidomide exposure in utero. Thalidomide exposure during early embryonic development can impact the limbs, ears, eyes, genitals, and various internal organs, including the heart, kidneys, and intestines, as well as the central nervous system and overall nervous system of the embryo, potentially resulting in facial pals. This medicine is commonly referred to as thalidomide embryopathy or thalidomide syndrome due to the extensive array of disorders it induced. The mortality rate for infants with thalidomide embryopathy during their first year is estimated at approximately 40%, primarily because to severe internal abnormalities, including cardiac and renal problems. Numerous infants with severe interior deformities would have either miscarried or perished in utero or shortly after delivery, elucidating why survivors predominantly exhibit limb, ear, and eye anomalies rather than internal defects .

3.1. Urgent Critical Period of Maximum Sensitivity during Embryonic Morphogenesis

A certain developmental period exists during which the human embryo is particularly vulnerable to the teratogenic effects of thalidomide, leading to birth abnormalities. This interval spans 20 to 36 days post-fertilization, or 34 to 50 days following the last menstrual cycle . Thalidomide exposure after 36 days post-fertilization does not exhibit any discernible morphological effects on the fetus . Conversely, thalidomide administration prior to the critical developmental window results in miscarriage in both humans and rats . Estimates indicate a substantial risk (up to 50%) of recurrent congenital anomalies following thalidomide exposure during the critical period from a single 50 mg pill, underscoring the considerable potency of thalidomide. The duration of thalidomide sensitivity was established through interviews with mothers of children affected by thalidomide. A multitude of women were aware of the precise dates of drug administration and the quantities consumed, enabling a reliable link to be established between the duration of exposure and the occurrence of anomalies, so facilitating the determination of the timing of deformity induction .

All morphological birth abnormalities associated with thalidomide embryopathy can be attributed to exposure within this specific time frame. The utilization of thalidomide for treating morning sickness was determined to be the cause of the thalidomide disaster and the resultant birth abnormalities that occurred during a brief developing period The auditory and visual systems are impacted by thalidomide ingestion during the initial days of the sensitive period

(days 20–24), succeeded by the upper extremities (days 24–31) and the lower extremities (days 27–33), respectively .

Nerve damage can lead to facial palsies, hearing loss, autism, and epilepsy, which may manifest from the onset of the critical time- sensitive window; however, the diagnosis of such damage may be delayed until after birth, yet it can be associated with thalidomide usage during this period. Thalidomide was administered to alleviate morning sickness symptoms during pregnancy, generally from the fourth week forward, coinciding with the critical period of limb development. This elucidates why the limbs are the most frequently impacted tissue in thalidomide survivors, as the drug was administered during a period when limb development is predominant . Recent research indicates that late fetal exposure to thalidomide may result in neurological impairment in brain regions associated with autism and epilepsy .These findings suggest that there is no safe period during pregnancy for thalidomide exposure.

3.2. Limb defects

Most thalidomide survivors display limb deformities , typically characterized by reduction defects that are predominantly symmetrical . Defects may be moderate, impacting solely the fingers, or they may be severe, including amelia (total absence of limbs) to phocomelia, characterized by significant limb shortening . Phocomelia exhibits a spectrum of severity, from the most extreme variant characterized by the absence of long bones, resulting in a flipper-like structure consisting primarily of a handplate directly articulating with the body, to milder manifestations where the long bones are shortened but present .

The spectrum and nature of limb malformations resulting from thalidomide exposure have a distinctive pattern. The thumb is the initial structure impacted, succeeded by the radius, humerus, and finally the ulna. Phocomelia or amelia may occur in the lower limb; however, lower limb abnormalities are less frequently observed than those of the upper limbs, and isolated lower limb deformities are uncommon . The femur is the bone most frequently impacted in the lower limb, and akin to the ulna, the fibula is typically the last bone to retain normalcy . Thalidomide embryopathy impacts both the upper and lower limbs, including the limb girdles. In children with significant upper limb reduction deficits, the typically smooth and curved contour of the shoulder becomes accentuated, since the acromioclavicular joint is more pronounced in cases of shoulder deformity . The hip joint may be hypoplastic or entirely missing, as is the case with the pubic bone . The participation of the limb girdles in

thalidomideinduced limb reduction anomalies is a hallmark of thalidomide embryopathy and, in certain instances, assisted physicians in distinguishing thalidomide deformities from sporadic or inherited limb malformations.

3.3. Eye and ear defects

The second most prevalent category of impairments in individuals affected by thalidomide is observed in the ocular and auditory systems. Ocular anomalies encompass cataracts, microphthalmos (congenital diminutive eye), anophthalmos (absence of the eyeball), impaired vision, aberrant lacrimation issues, and predominantly, colobomas (malformation of the iris and retina). Ocular abnormalities typically manifest unilaterally, although diminished vision may still be present in the unaffected eye . Thalidomide may induce abnormalities in ocular movement, typically occurring alongside auditory problems and facial muscular weakness .

Ear anomalies resulting from thalidomide embryopathy are often symmetrical, varying from total loss of the outer ear or pinna (anotia) to partial presence of the outer ear . Anotia is associated with abnormalities of the external auditory meatus, resulting in deafness in affected children . Thalidomide-induced auditory anomalies are concomitant with cranial nerve dysfunctions, leading to facial paralysis .

3.4. Internal organ defects

Defects of internal organs including anomalies of the heart, kidneys, genitals, and intestine. The exact prevalence of these malformations is uncertain, as such anomalies sometimes do not manifest until later in life. Cardiac defects were believed to be accountable for numerous intrauterine and postnatal fatalities. Many thalidomide survivors experience cardiac issues, primarily ventricular and atrial septal abnormalities, alongside pulmonary stenosis and patent ductus arterios The urinary tract and kidneys may also be impacted, with occurrences of horseshoe, hypoplastic, rotated, and ectopic kidney malformation. A significant number of children impacted by thalidomide experienced genital anomalies, both internal and external. Males exhibited absence of the testes, testicular abnormalities, and hypospadias, whereas females presented with uterine malformations and anomalies in the reproductive system. Thalidomide-induced abnormalities in the colon including anorectal stenosis, intestinal atresia, pyloric stenosis. [7]

4. History And Withdrawal

Thalidomide was promoted as a safe and efficacious sedative starting in 1957 and was subsequently discovered to be beneficial in alleviating morning sickness. It was considered sufficiently safe to be sold over the counter in multiple countries. Nevertheless, it was retracted from a significant portion of the pharmaceutical market starting in late November 1961. This was attributed to its identification as the cause of an epidemic affecting at least 10,000, and maybe up to 100,000, infants globally who were born with significant congenital anomalies to mothers who consumed thalidomide during gestation . The archetypal representation of a thalidomide survivor depicts a someone with phocomelia of the arms, characterized by the absence or reduction of the long bones, resulting in digits either articulating with the shoulder or terminating at the end of a shortened humerus and ulna. Thalidomide adversely impacted various tissues, including the legs, eyes, ears, face, cardiovascular system, gastrointestinal system, reproductive system, urinary system, and spine. Regrettably, due to variations in internal organ development, including intestinal atresia and cardiac anomalies, it is believed that up to 40% of infants succumb within their first year of life. No two thalidomide survivors exhibit identical characteristics, highlighting the extensive harm this drug may inflict, largely influenced by the timing of exposure and the genetic backgrounds of pregnant women, which vary significantly.The retraction of thalidomide has resulted in substantial global alterations in the methodologies employed for drug and medicine testing. [8]

5. Pharmacology, Pharmacokinetic and Mechanism of action.

5.1. Pharmacology

Thalidomide, a-(N-phthalimido) glutarimide, is a racemic derivative of glutamic acid comprising equal proportions of R-(þ) and S-(-) enantiomers . The enantiomers experience swift chiral interconversion in physiological settings . The (S)-isomer inhibits the release of tumor necrosis factor (TNF)-α from mononuclear blood cells, while the (R)-form is associated with sedative effects . These variations are not clinically significant due to the swift interconversion between enantiomers. The thalidomide molecule undergoes spontaneous hydrolysis .

The conversion to active metabolites seems to account for the drug's efficacy. Notably, these metabolites are species-specific, which partially elucidates the species-dependent effects of thalidomide. No systematic dose escalation studies have been performed; nonetheless,

singledose thalidomide investigations demonstrate that bioavailability, absorption, distribution, and elimination are contingent upon dosage andconcurrent medical conditions. The average time to reach peak plasma concentrations varies from 2.9 to 5.7 hours, with peak levels being roughly 1 mg/ml.

The average elimination half-life is around 5 to 7 hour. The precise metabolic pathway of thalidomide remains incompletely elucidated. are predominantly eliminated The precise metabolic pathway of thalidomide remains incompletely elucidated, with the majority being removed via urine; ultimately, less than 1% is eliminated as Nonenzymatic hydrolysis results in the production of hydrolysis products, predominantly eliminated via urine; less than 1% is excreted as the unmodified medication . Hepatic metabolism seems to be limited, and the pharmacokinetic features in hepatic impairment remain undetermined. No dosage adjustments are required for people with renal impairment. Single clinical doses have varied from 50mg to 1200mg; yet, optimal clinical efficacy seems to be observed within the 50 to 400mg per day range. [9]

5.2. Pharmacokinetics

Thalidomide is gradually absorbed from the gastrointestinal system.Peak blood concentrations are attained between 2 to 6 hours, sometimes delayed by the consumption of a high-fat meal. It is widely disseminated throughout all tissues and fluids, with elevated amounts in the skin and kidneys.

The bioavailability of thalidomide cannot be determined due to its limited solubility in water. It is chiefly metabolized through nonenzymatic hydrolytic breakage of its amide bonds. Cytochrome P-450 enzymes may have a function in the metabolism of the antiangiogenic metabolite. A portion of the medicine is excreted in the bile, whereas less than 1% is eliminated in the urine.[10]

5.3. Mechanism of action

The molecular processes underlying the effects of thalidomide remain incompletely elucidated. Thalidomide exhibits immunomodulatory, anti-inflammatory, and anti-angiogenic properties associated with the intricate control of inflammatory cytokines . Thalidomide primarily exerts its effects by selectively inhibiting TNF-a production in human monocytes, likely through the increased degradation of TNF-a mRNA . Moreover, thalidomide has demonstrated the capacity to limit nuclear factor (NF)-kB activity via the suppression of I-kB kinase activity . NF-kB is

a DNA- binding transcription factor that regulates the production of genes contributing to the immune response, such as TNF-a, interleukin (IL)-8, and IL-12 . Thalidomide also suppresses the production of IL-6 and IL-12 . Additional anti- inflammatory capabilities encompass the deactivation of Caspase-1, which activates pro- inflammatory cytokines such as IL-1 .

Thalidomide effectively activates T cells, particularly promoting proliferation in the CD8þ T-cell subset. Moreover, thalidomide effectively regulates T helper cell (Th) activity by selectively promoting Th2 cytokine production while suppressing Th1 cytokine production in peripheral mononuclear cells. This action alters T lymphocyte-dependent immunological responses by augmenting IL-4 production and suppressing interferon (IFN)-g production.

In 1971, Dr. Judah Folkman posited that tumors necessitate angiogenesis for sustenance; hence, approaches aimed at obstructing the formation of new blood vessels could serve as successful cancer therapies . Following this revelation, understanding of the distinct characteristics of tumor vasculature in contrast to normal vasculature has expanded significantly. The identification of multiple signaling pathways implicated in tumor angiogenesis, including Hypoxia-inducible factor-1, vascular endothelial growth factor, platelet-derived growth factor, and basic fibroblast growth factor (bFGF), has resulted in the creation of innovative therapeutic agents. The robust anti-angiogenic characteristics of thalidomide were initially elucidated through a rabbit cornea model of FGF-induced neovascularization. D'Amato and associates hypothesized that thalidomide-induced congenital anomalies resulted from suppressed angiogenesis in the developing fetal limb bud, suggesting a comparable mechanism may impede vasculogenesis inside the tumor microenvironment . Kenyon and associates characterized thalidomide as an angiogenesis inhibitor in a murine cornea model, positing that thalidomide markedly suppresses bFGF and vascular endothelial growth factor (VEGF)-induced ocular neovascularization. The S(-) enantiomer was further defined as the agent responsible for anti-angiogenic properties, with phthaloylglutamic acid identified as a metabolite that preserves anti-angiogenic action in the corneal model .

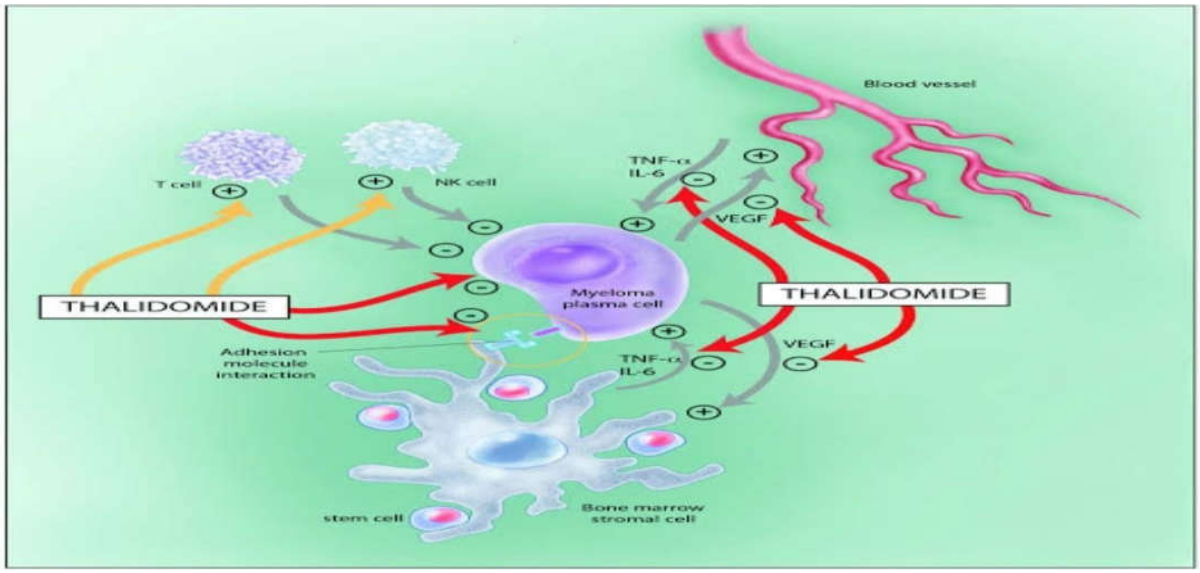


Figure 3. Proposed mechanisms of action of thalidomide upon tumorous plasma cell and surrounding micro environment

Ito and colleagues posited that the mechanism underlying thalidomide's anti-angiogenic effects, and consequently its teratogenic characteristics, is associated with the direct binding of thalidomide to cereblon, a constituent of an E3 ubiquitin ligase complex . The ligase activity is crucial for FGF production and is consequently involved in the regulation of angiogenesis, cell signaling, and limb outgrowth . Besides its anti-angiogenic capabilities, thalidomide exhibits many effects against plasma cell myeloma. Thalidomide obstructs tumor cell adhesion and intercellular communication essential for proliferation and survival. Cytokines essential for plasma cell proliferation in the bone marrow microenvironment include IL-6, IL-10, and TNFα, all of which are suppressed by thalidomide. Finally, thalidomide may directly inhibit myeloma cell proliferation by generating DNA damage mediated by free radicals. These diverse Twenty-nine properties have validated the application of this drug for anti-myeloma therapy.

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5.4. Chirality of Thalidomide

- The thalidomide tragedy would probably never have occurred if, instead of using the racemate, only the R- (+) enantiomer had been brought to the market.
- Researches revealed that, only R-(+) form was therapeutically active; the S-(-) form was not only ineffective; it was the source of the birth defect: embyotoxic and teratogenic effect.[1,2]
- The two enantiomers caused distinctly different effects from one another; R-(+) enantiomer is devoid of any of those effects under the same experimental conditions.
- Unfortunately, dosing a single enantiomer of thalidomide doesn't have a unique therapeutic value, because the drug converts to the racemic compound in vivo.[12]

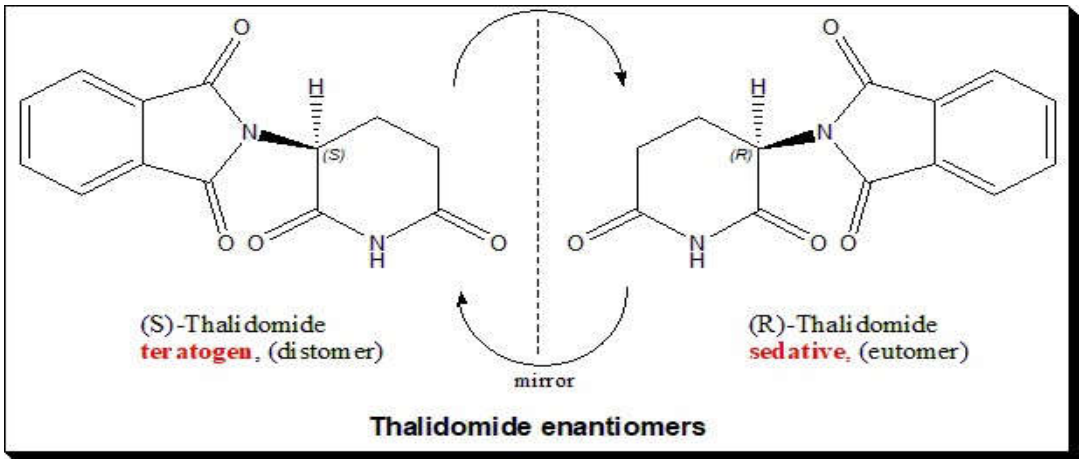

Fig 4: Thalidomide interconverts between (R) and (S) enantiomers with protein binding off 55% and 65% respectively.The (R) form is responsible for sedative effects and the (S) ferm is responsible for immunomodulatory effects.

5.5. Thalidomide complications

Plasma cell myeloma is linked to a heightened incidence of thrombotic events. Proposed mechanisms include anomalies in coagulation factors such as elevated levels of von Willebrand factor and factor VIII, resistance to activated protein C, and hypofibrinolysis . Thalidomide, especially when utilized in combination therapy for plasma cell myeloma, significantly elevates the risk of thrombotic events. The risk is exacerbated by the incorporation of conventional cytotoxic drugs, especially anthracycline chemotherapy Venous and arterial thrombotic episodes have been documented . Thalidomide monotherapy little elevates the risk of

thrombosis; however, in extensive randomized studies assessing thalidomide in conjunction with dexamethasone, the incidence of deep venous thrombosis rises to 17-19% .

A proposed mechanism by which thalidomide may facilitate thrombosis is the alteration of thrombomodulin levels during the initial month of treatment . Thrombomodulin forms complexes with thrombin during the anticoagulant interactions with protein C; a temporary reduction in thrombomodulin plasma concentration may induce a thrombophilic condition. Moreover, thalidomide-derived immunomodulatory agents downregulate PU.1, a transcription factor implicated in granulocyte differentiation. This action results in the buildup of promyelocytes and elevated amounts of cathepsin G, a platelet aggregation agonist contained in promyelocyte granules, thus heightening the risk of thrombotic events.

Strategies for coagulation prevention encompass the use of aspirin, low or therapeutic dosages of warfarin, and low molecular weight heparin (LMWH). A randomized, phase III trial conducted in Italy assessed the prophylactic use of aspirin (100mg/day), warfarin (1.25mg/day), or low molecular weight heparin (40mg/day) in previously untreated individuals with plasma cell myeloma undergoing treatment regimens that included thalidomide. The rates of serious thrombotic events were 6.4% for the aspirin group, 8.2% for the warfarin group, and 5% for the LMWH group .[13]

6.Thalidomide Revival

Although prohibited in commercial markets, thalidomide continued to be accessible mainly in developing nations. Clinical interest in thalidomide reemerged following Dr. Jacob Sheskin's initial prescription of the drug in 1964 as a sedative for a patient suffering from erythema nodosum leprosum (ENL). Sheskin was at Hadassah University Hospital and Hansen Leper Hospital in Jerusalem. He noted an unforeseen and dramatic remission of the patient's leprosy skin eruption after 48 hours of medication. This action was subsequently replicated and documented by Sheskin in 1965 . In 1971, the World Health Organization released the findings of a randomized experiment that validated the efficacy of thalidomide in ENL.

Following the documented efficacy in treating ENL, thalidomide received experimental endorsement from the FDA in the 1970s, largely for other dermatological and inflammatory disorders. The medication was also made accessible via several compassionate use programs for its sedative properties. Thalidomide was subsequently investigated for various inflammatory conditions, including sarcoidosis, cutaneous lupus, Behçet’s syndrome,

inflammatory bowel diseases, ankylosing spondylitis, and refractory or high-risk chronic graftversus-host disease (GVHD). Response rates varied from 20% to 79% with rising dosages ranging from 200 to 1600 mg per day . In a trial including 59 participants randomized to receive either thalidomide or placebo for GVHD prophylaxis, the thalidomide group exhibited a greater incidence of GVHD and poorer survival outcomes . Thalidomide has demonstrated efficacy in treating chronic GVHD; however, its prophylactic application led to a paradoxical effect, resulting in an increased incidence of chronic GVHD and diminished overall survival. The scientists determined that early thalidomide administration altered the equilibrium between graft-versus-host disease and the induction of tolerance.

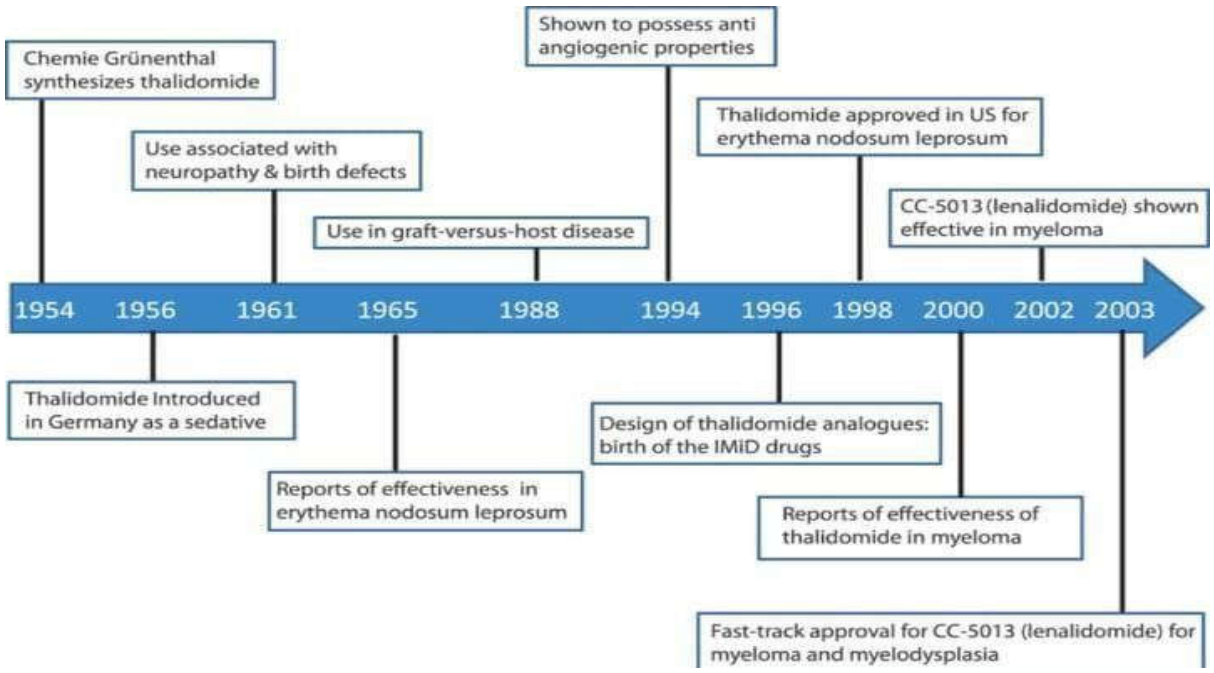

Fig 5: Timeline of events in thalidomide and immunomodulatory drug (IMiD) development

A fresh utilization of thalidomide's anti-emetic, sedative, and analgesic qualities has emerged in palliative care, specifically for cancer cachexia and HIV wasting syndrome . Thalidomide has re-emerged as an effective treatment for problems associated with HIV illness, including HIV wasting syndrome, Kaposi’s sarcoma, and aphthous ulcers . These discoveries resulted in the sustained availability of thalidomide in regulated clinical studies and through compassionate use protocols. At this point, 'drug buyer' clubs were being founded in prominent cities. These groups were distributing occasionally adulterated forms of thalidomide via the expanding illicit market in South America, particularly in Brazil, where thalidomide had mainly

remained accessible since its introduction. The largely unregulated distribution of thalidomide compelled the FDAto request drug applications from multiple firms researching the substance. Celgene Corporation received authorization to officially commercialize the medication. In 1998, the FDA sanctioned thalidomide for the treatment of ENL, so ensuring the drug's ongoing availability for other conditions .[14]

6.1. Brand name

Brand names under which thalidomide is being marketed include Contergan, Thalomid, Talidex, Talizer, Neurosedyn, Distaval and many other.

6.2Approval of FDA

1954: Thalidomide was introduced to the market by the company of Chemie Grunenthal.

1956: first known victim, daughter of grunenthal employee was born 1961: Thalidomide was discovered by Dr Jacob Sheskin to treat complications associated with erythema nodosum leprosum (ENL).

1998: Thalidomide was approved by the FDA for treatment of ENL.

May 2006: a combination of thalidomide and dexamethasone was FDA approved for the treatment of multiple myeloma.

June2006: Lenalidomide (Revlimid) and Pomalidomide (Actimid) derivative of thalidomide, were FDA approved for the treatment of multiple myeloma.

In U.S, the new regulations strengthened the FDA, among other ways, by requiring applicants to prove efficacy and to disclose all sie effects encountered in testing.

In 2006 the U.S Food and Drug Administration granted accelerated approval for thalidomide in combination with dexamethasone for the treatment of newly diagnosed multiple myeloma.this cpmbination of drug probably results in an increase of the overall survival.

The use of thalidomide is incredibly restricted and requires participation in the System for Thalidomide Education and Prescription Safety (STEPS) program.[15]

6.3. S.T.E.P.S.

System for Thalidomide Education and Prescribing Safety

Developed by the Calgene Corporation, Warren, New Jersey. To ensure that fetal exposure to this teratogenic agent does not occur, the manufacturer has instituted a comprehensive program to control prescribing, dispensing, and use of the drug. This program, known as the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S). In an attempt to minimize the number of women exposed to this drug during pregnancy.

To achieve its goal of the lowest possible incidence of drug assaociated teratogenecity, S.T.E.P.S uses three step program that must be followed with all the patients who are potential candidates for the drug:

Patient must receive education regarding the potential benefits and side effects of thalidomide. Contraceptive counseling must be provided, including emergency contraception measures, and women of childbearing potential must be given pregnancy tests Patients must complete an informed consent form and participate in an ongoing mandatory and confidential survey. Clinicians who wish to prescribe the drug must be registered in the STEPS. Prescriber Registry and agree to prescribe the drug in accordance with S.T.E.P.S patient eligibility criteria and monitoring procedures. Pharmacies must also register and agree to comply with patient identification and monitoring procedure.[16]

6.4. Anticancer properties

The potential advantages of thalidomide in oncological therapy were initially postulated in the 1960s, immediately following the documentation of its teratogenic effects. Investigators posited that the processes underlying teratogenicity may potentially serve as possible avenues for cancer therapy. The initial clinical trials investigating thalidomide as an anticancer drug did not demonstrate considerable efficacy for several reasons . Recent observations indicate encouraging outcomes in castrate-resistant prostate cancer. A phase II trial including 60 patients assessed thalidomide as an alternate anti-angiogenic drug in conjunction with conventional chemotherapy and bevacizumab, resulting in a prostate-specific antigen (PSA) reduction of at least 50% in 90% of participants . In other solid tumors associated with angiogenesis, such as renal cell, hepatocellular, and ovarian malignancies, mixed findings have been documented.Numerous phase II and phase III trials are presently investigating thalidomide as an adjuvant treatment for various solid cancers. Access to thalidomide is

regulated through the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program to mitigate the risk of teratogenicity. All prescribing physicians, pharmacies, and patients are required to register with the program and adhere to safety protocols to regulate the prescribing, dispensing, and utilization of thalidomide. This approach not only mitigated the possible risk of fetal injury linked to thalidomide medication but also established a framework for future instances where pharmacological treatment presents significant advantages yet entails substantial dangers without stringent distribution controls.[17]

7. Hematological Malignance

Plasma cell myeloma The identification of effective anti-angiogenic properties revitalized interest in thalidomide as an anticancer drug. Plasma cell myeloma is linked to heightened bone marrow microvascular density and higher blood VEGF levels. These characteristics resulted in the acknowledgment that angiogenesis is a significant pathogenic process in this condition and stimulated clinical application . Researchers at the University of Arkansas initially documented a 32% overall response rate with single-agent thalidomide in a cohort of 84 refractory plasma cell myeloma patients . A further investigation with escalated doses indicated an overall survival rate of 48% at two years . Updated data at a median follow-up of 9.2 years indicated improved overall survival in individuals administered greater cumulative doses of thalidomide, implying a dose-dependent impact . Further prospective studies with single-agent thalidomide corroborated the advantages of thalidomide monothera. Systematic assessments of phase II trial results indicate response rates of 30% and an overall median survival of 14 months in patients with refractory illness treated with thalidomide . Subsequently, the combination therapy of thalidomide and dexamethasone was found to improve response rate A literature review by von Lilienfeld-Toal and colleagues of 12 studies involving 451 patients receiving thalidomide and dexamethasone combination therapy revealed an overall response rate of 46% in relapsed/refractory plasma cell myeloma patients, with a toxicity rate similar to that of thalidomide monotherapy . The combined therapy of thalidomide for newly diagnosed plasma cell myeloma has yielded an enhanced overall response rate and an extension of the time to disease progression; these combinations have established themselves as the norm.

A trial including thalidomide into high-dose therapy and autologous hematopoietic cell transplant reported complete response rates of 62% and 5-year event-free survival rates of 56%. Two randomized controlled studies have evaluated the efficacy of thalidomide combined with

dexamethasone vs dexamethasone monotherapy as induction treatment in newly diagnosed, untreated individuals. The combination treatment yielded a markedly improved overall response rate of 63% and prolonged time to progression from 6.5 to 22.6 months.

Incorporating bortezomib into thalidomide and dexamethasone induction therapy enhances full response rates. A phase III trial with 474 patients shown that bortezomib, thalidomide, and dexamethasone (VTD) induction treatment resulted in a full or near-complete response rate of 31% . Bortezomib, thalidomide, and prednisone administration had a median progression-free survival of 25 months and a 65% overall three-year survival rate .

In older patients or those unsuitable for hematopoietic cell transplantation, the combination of thalidomide with melphalan and prednisone markedly enhances event-free and overall survival rates. Median progression-free survival rates vary from 15 to 28 months, while overall survival rates range from 40 to 52 months . These individuals were typically aged over 65 to 75 years.

Recent studies have assessed the efficacy of thalidomide maintenance medication; nonetheless, the findings have yielded inconsistent results, since the therapeutic advantages remain ambiguous while the adverse effects typically escalate. A study assessed the combination of thalidomide and dexamethasone for maintenance therapy. The two-year progression-free survival increased from 32% to 63%, while the two-year overall survival rose from 68% to 84% . In a separate research, thalidomide combined with IFN maintenance therapy enhanced progression-free survival from 13.2 to 27.7 months, although did not yield a meaningful improvement in overall survival.

The maintenance treatment of thalidomide has also been investigated in the post-transplant context. A clinical trial randomized 556 patients to receive vincristine, doxorubicin, and dexamethasone induction (VAD) followed by interferon maintenance, vs thalidomide, doxorubicin, and dexamethasone induction (TAD) followed by thalidomide post-transplant. The thalidomide cohort exhibited an enhancement in progression-free survival, increasing from 25 to 34 months; yet, no statistically significant change in overall survival was seen. A second trial allocated 269 individuals to receive thalidomide in conjunction with prednisolone, compared to prednisolone alone, following autologous transplantation.

At the three-year follow-up, participants in the thalidomide group had enhanced progressionfree survival (42% compared to 23%) and overall survival (86% compared to 75%). Thalidomide was administered for a duration of 12 months and can thus be regarded as a

consolidation rather than a maintenance effect. Neurological effects resulted in the cessation of thalidomide in as many as 60% of patients. Consequently, it remains ambiguous which demographic derives the greatest advantage from maintenance therapy.

Thalidomide therapy has also been assessed in conjunction with standard chemotherapeutic drugs, including anthracyclines and alkylating agents such as cyclophosphamide. Notwithstanding claims of elevated response rates in certain studies, the absence of compelling survival advantages, along with increased toxicity, particularly thrombotic and infectious problems, renders these regimens less appealing . In May 2006, thalidomide received approval for the treatment of newly diagnosed plasma cell myeloma in conjunction with dexamethasone.[18]

7.1. Phocomelia

The phocomelic limbs of the surviving are arguably the most notable and characteristic feature of thalidomide embryopathy. Phocomelia refers to the loss or considerable shortening of the long bones in the limbs (upper and/or lower). The majority of individuals who have survived thalidomide embryopathy have some sort of limb deformity. Current hypotheses suggest that phocomelia arises from the early developmental loss of cells responsible for forming the long bones of the leg. Indeed, early chick limbs subjected to X-rays develop without proximal elements (humerus). CPS49 induces significant mesenchymal cell apoptosis, vascular degeneration in the developing chick leg, disruption of limb signaling pathways, and a range of markedly shortened limbs, some of which closely resemble phocomelia. Following thalidomide exposure and the depletion of cell populations responsible for forming proximal limb elements, signaling between the apical ectodermal ridge (AER) and limb mesenchyme resumes, allowing the remaining cells to shape distal elements under AER regulation.

Examples of Phocomelia sufferers.

Category: People with Phocomelia:

Notable cases:

- Lorraine Mercer of the United Kingdom, born with phocomelia of both arms and legs, is the only thalidomide survivor to carry the Olympic Torch.

- Thomas Quasthoff, an internationally acclaimed bass-baritone, who describes himself: "1.34 meters tall, short arms, seven fingers — four right, three left — large, relatively well-formed head, brown eyes, distinctive lips; profession: singer".
- Mercedes Benegbi, born with phocomelia of both arms, drove the successful campaign for compensation from her government for Canadians who were affected by thalidomide.
- Mat Fraser, born with phocomelia of both arms, is an English rock musician, actor, writer and performance artist. He produced a 2002 television documentary "Born Freak".
- Michaelina Argy (born 1962) is an English thalidomide survivor and activist. She is a past chair of the National Advisory Committee of the Thalidomide Trust.
- Terry Wiles Terrence 'Terry' Wiles (born 12 January 1962) was one of the most disabled thalidomide babies born in the UK.
- Ronan Tynan Born14 May 1960 an Irish singer & former Paralympics athlete. Born with phocomelia, both of his lower legs were underdeveloped unusually short, feet were splayed
- outward, had three toes on each foot. He was one of set of twins; his twin brother died at months old.
- Dave Stevens (amputee sportsman) He is currently a reporter for the Disability Channel and interviews some of the biggest names in sports and entertainment history.[19]

7.2. Myelofibrosis

Thalidomide has been utilized as an efficacious drug in the management of myelofibrosis. Initial data indicate enhancement in cytopenias and splenomegaly. A research involving 36 patients with a median follow-up of 25 months revealed that 28% exhibited a sustained response to thalidomide.

7.3. Myelodysplastic syndromes

Thalidomide has been utilized in the treatment of myelodysplastic syndromes due to its anticytokine immunomodulatory and anti-angiogenic effects. The erythroid response in transfusion-dependent patients has been favorable; nevertheless, patients exhibit poor tolerance to effective (larger) dosages. Thalidomide dosages administered in clinical trials

ranged from 200 to 1000 mg per day. This variability in dose may account for the uneven study outcomes and the differing toxicities observed in this context.

7.4.Waldenstrom macroglobulinemia

Phase II studies have demonstrated remarkable efficacy of thalidomide, either as monotherapy or in conjunction with other medicines, in the treatment of Waldenstrom macroglobulinemia . Treon and colleagues documented a 72% overall response rate in predominantly untreated individuals utilizing thalidomide and rituximab for symptomatic illness . The median serum IgM dramatically dropped from 3670 mg/dl to 1590 mg/dl, while the median hematocrit increased from 33.0% to 37.6% (p=0.004) at the time of optimal response; for responders, the median time to progression was 38 months. Thalidomide's antitumor efficacy has been limited in non- Hodgkin lymphoma, acute myeloid leukemia, and chronic lymphocytic leukemia[20]

8. Thaliodmide Analogues

Owing to anti-angiogenic properties of thalidomide, researchers the entire world over explored its therapeutic potencies for different sorts of cancers. During this period, it was observed that thalidomide lacks good water solubility and spontaneously undergoes hydrolytic cleavage. To overcome this problem along with an augmentation of therapeutic efficiency, chemically modified analogues of thalidomide were designed, synthesized and screened for various cancers. Some of the analogues have been discussed as follows: Lenalidomide (CC-5013), is also known by the names of (RS)-3-(4-amino-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione and Revlimid®) in IUPAC system and commercial systems, respectively. Lenalidomide is a structural analogue of thalidomide as shown in Fig. (4). It shows immunomodulatory actions and has demonstrated higher potency in the proliferation and tube formation assays of human umbilical vein endothelial cells (HUVEC) . The inhibition of proliferation responded in a dosedependent manner with increasing concentrations of the drug. Besides, antimigratory effects and tumor growth inhibition in vivo have also been demonstrated . However, metabolism studies showed no effect on cytochrome P-450 activity, and no phase I and II metabolism by human liver microsomes or supersomes was detected . Lenalidomide was initially patented by Muller et al. for its ability to inhibit TNF- and now has entered clinical trials in a variety of hematologic and solid tumors. Lenalidomide is rapidly absorbed following oral administration in human beings and about 67% is excreted unchanged in urine in less than 24 hours; with a mean half-life of 8 hours. It was well tolerated in healthy volunteers with only

minor adverse immunologic events noted . In a phase I study of lenalidomide in individuals with multiple myeloma, multiple doses did not alter the pharmacokinetic profile, with a time of maximum concentration (Tmax) of 1 hr or 1.5 hrs on day 1 and day 28 of each dose level (5, 10, 25, 50 mg/day) . The t1/2 of lenalidomide is 3 hrs. Pomalidomide (CC-4047) is commercially known as Actimid with IUPAC name; 4-Amino-2-(2,6-dioxopiperidin3-yl)isoindole-1,3-dione. This co-stimulatory thalidomide analogue initiates protective, long-lasting and tumorspecific in vivo Th1-type responses . CC-4047 was used in a phase I study where 24 relapsed or refractory multiple myeloma patients were treated with a dose- escalating regimen of oral CC-4047 . The treatment was associated with significantly increased levels of serum interleukin (IL)- 2 receptor and IL-12, which is consistent with activation of T cells, monocytes and macrophages. Clinical activity was noted in 67% of patients, and a more than 25% reduction in paraprotein content was noted, 13 patients experienced a greater than 50% reduction in paraprotein, and four of 24 patients were reported to enter complete remission. The treatment related thrombosis incidence was 12.5%, similar to treatment with thalidomide alone in multiple myeloma . Similar to CC-5013, the dose- limiting toxicity was myelo suppression, with neutropenia occurring in 6 patients within 3 weeks of starting therapy. The maximum tolerated dose was 2 mg/day. Half-life of pomalidomide is 8 hrs. ENMD-0995 is a small molecular analogue of thalidomide with IUPAC name; (S-3-Amino-phthalimido-glutarimide) and stereo chemically has the S-(-) configuration . This thalidomide derivative was found to have improved angiogenesis inhibiting activity and no evidences of the toxic side effects were found. S-(-) enantiomer (ENMD-0995) has been preclinically tested to inhibit angiogenesis more efficiently than thalidomide in a murine corneal micropocket model . ENMD-0995 has entered Phase I clinical trials with 6 patients that followed an initial dosing regimen of 20 mg/day. The dosage was then reduced to every 10 mg per other day when excessive myelo suppression was seen in the first cohort .

Despite myelo suppressive toxicity, all 6 patients had a decrease in M-spike seen with very good partial response (VGPR) (>90% decrease in M spike). Therefore, ENMD-0995 has shown activity against multiple myeloma. In 2002, ENMD-0995 was granted Orphan Drug designation from the Food and Drug Administration for the treatment of patients with multiple myeloma. Entre Med. Inc., Maryland, the manufacturer of ENMD-0995, announced the licensing of the company’s thalidomide analogue programs to Celgene Corporation, USA, in 2003. It was demonstrated by earlier studies that thalidomide metabolites are responsible for

its antiangiogenic functions. For example, 5'-OH-thalidomide is one of the products of cytochrome P450 2C19 isozyme biotransformation of thalidomide retains some antiangiogenic activity. On the basis of the structure of such metabolites, several classes of thalidomide analogues were synthesized. The rat aortic ring assay was used to screen the newly synthesized analogues for their antiangiogenic activity. Seven analogues from the N- substituted and tetrafluorinated classes significantly inhibited microvessel growth in this assay. Human umbilical vein endothelial cell (HUVEC) proliferation and tube formation experiments were used to confirm the antiangiogenic activity of the newly developed analogues of thalidomide. One N-substituted analogue, CPS11, and two tetrafluorinated analogues, CPS45 and CPS49 (Fig. 6) consistently exhibited the highest potency and efficacy in all three assays. The initial patent application for these compounds, as well as related analogues, was filed in 2002, and subsequently licensed to Celgene Inc. . As a result of promising in vitro and ex vivo properties of these analogues, their therapeutic potentials were subsequently determined in vivo. Their effects were studied on severely combined immunodeficient (SCID) mice bearing subcutaneous human prostate cancer xenografts, at the determined Maximum tolerance dose (MTD) for daily dosing. Among all the three analogues, CPS49 was the most potent. However, all three analogues significantly showed significant inhibition of PC3 tumor growth. Besides, Platelet derived growth factor- AA (PDGF-AA) levels in these tumors were significantly reduced by both CPS45 and CPS 49. Moreover, it was observed that intra tumoral micro vessel density (MVD) was efficiently decreased by CPS 49.

8.1. THALIDOMIDE VS ANALOGUES

New thalidomide analogues were developed to overcome the therapeutic problems associated with thalidomide therapy (water solubility, bioavailability, stability in plasma, toxicities etc.). This quest resulted into the development of new thalidomide analogues with improved therapeutic activities and considerably lower side effects. Lenalidomide, the first commercially useful thalidomide analogue, shows 2000 times more potency than thalidomide in inhibiting tumor necrosis factor-alpha (TNF-) and has significantly less severe adverse drug reactions . In addition, it is not teratogenic in rabbit, a sensitive species for thalidomide induced birth defects, making lenalidomide a more desirable therapeutic drug candidate than its parent. Similarly, pomalidomide is 20,000 times more potent than thalidomide in causing the inhibition of TNF- . There are no reports of conventional drug resistance and thalidomide like side effects

(sedation, constipation, peripheral neuropathy) in relapsed multiple myeloma patients at 5 to 50 mg/day doses of lenalidomide.

However, other cytokines, IL-1, IL-6, and granulocyte macrophage-colony stimulating factor (GMCSF) are also inhibited by lenalidomide and pomalidomide to the same extent as thalidomide does; without fewer side effects . Besides, thalidomide analogues are more potent in co-stimulating T-cells that have already been partially activated by the T-Cell receptor (TCR). For example, the costimulatory action of pomalidomide is thought to produce the prolonged antitumor response seen in mice implanted with colorectal cancer cells. Additionally, ENMD-0995 analogue is found to have improved angiogenesis inhibiting activity with no or very less toxic side effects . Recently, described the inhibitory activity of thalidomide analogues; derived through Sonogashira or Suzuki reactions against proinflammatory cytokine TNF. The compounds with aryl-isobutyl or arylisopropoxy groups were the most effective in the inhibition of TNF expression with several fold higher potency than thalidomide. An apoptotic response was associated with five of the more active derivatives while one of these compounds with an aldehyde group showed possible influence of cell cycling effects. Guirgisa et al. reported new thalidomide dithiocarbamate analogues as potential anti-tumor agents. They studied the anti-tumor effects of the synthesized thalidomide analogues against transplantable experimental tumor, Ehrlich ascites carcinoma (EAC) in mice. It was observed that the thalidomide dithiocarbamate analogue (a) had more potent anti-tumor activity as compared to thalidomide or its dithiocarbamate analogue (b). However, both the analogues were significantly more potent as anti-tumor agents than thalidomide. Li et al. determined in vitro anticancer profiles and pro apoptotic properties of a sugar-substituted thalidomide derivative, STA-35 through inhibition of NF-B activation in HL-60 cells. They observed that STA-35 inhibited HL-60 cell proliferation at a rate much higher than thalidomide with an IC50 of 9.05 μmol/L. The authors proposed that the higher growth-inhibition rate of this novel N-sugarsubstituted phthalimide might be due to N-sugar substitution of thalidomide. To overcome the water insolubility problems, Marriott et al. described CC- 3052 as water soluble analogue of thalidomide with better anti-TNF activity as compared to thalidomide. Moreover, this analogue exhibits increased stability in human plasma (t1/2; 17.5 vs 1.5 h for thalidomide). Furthermore, this analogue is found to be non-toxic, non- mutagenic and non-teratogenic in nature. A keen observation of therapeutic properties comparison of thalidomide with its

analogues suggests a serial evolution of thalidomide generations, with superior properties of the analogues. [21]

9. Alternative uses

The vascular effects of thalidomide have resulted in other creative applications. Thalidomide has been effectively utilized to manage recurrent, enigmatic gastrointestinal hemorrhage or refractory bleeding due to angiodysplasia . These findings have been applicable to patients with von Willebrand's disease . Lebrin and associates documented the effective application of thalidomide medication to diminish the incidence of epistaxis in a cohort of hereditary hemorrhagic telangiectasia (HHT) patients. They hypothesized that thalidomide circumvents an endothelial cell regulatory system, therefore promoting vascular development and averting vessel wall abnormalitie

ENL, Multiple Myeloma, Myelodysplastic syndrome

- Promising uses: Prostate Cancer, Aphthous ulcers(in HIV)
- Potential uses: Autoimmune conditions, Bechet’s disease, Inflammatory bowel disease
- Dermatological conditions: Actinic pruritis, Pyroderma gangrenosum, Leprosy
- Rheumatological: Rheumatoid Arthritis, Sarcoidosis Cachexia and weight loss: HIV associated, Tuberculosis, Cancer Cachexia, Heart failure
- It works in Hansen’s disease by reducing swelling and redness (inflammation)
- Graft vs host disease
- Pancreatic Cancer
- Ovarian Cancer
- AIDS related Kaposi’s Sarcomas: anti neoplastic effectHodgekin Lymphoma
- Bronchial Asthma (SeICIDs)
- Macular degenerationInflammatory bowel disease [22]

10. Adverse effect and complication

- Common side effects include sleepiness, rash, and dizziness, dry mouth, vomiting.
- Severe side effects include tumor syndrome, blood clots, interfere with formation of various kinds of new blood cells, creating a risk of infection via neutropenia, leukopenia, and lymphopenia and peripheral neuropathy.

- Several cardiovascular adverse effects including risk of heart attacks, pulmonary hypertension, bradycardia
- Can cause liver damage and skin reactions
- Can prevent menstruation
- Reduced coordination, interstitial lung disease, lung inflammation
- Use in pregnancy, result's in malformation of the fetal limbs.[23]

10.1. Contraindication

- Thalidomide should not be used by women who are breastfeeding or pregnant, trying or able to conceive a child, or cannot or will not follow the risk management program to prevent pregnancies.
- The prescribing doctor is required to ensure that contraception is being used, and regular pregnancy tests are taken.
- Those allergic to thalidomide should not take it.

11. Conclusion

The story of Thalidomide is both tragic and transformative, marking a turning point in the history of medicine and pharmaceutical regulation. Initially marketed in the late 1950s as a mild sedative and treatment for morning sickness in pregnant women, Thalidomide was believed to be safe. However, within a few years, it became clear that the drug caused severe birth defects, including limb malformations and organ damage, in thousands of babies worldwide. This global disaster not only devastated families but also exposed serious gaps in drug testing, particularly concerning safety in pregnancy.

The Thalidomide tragedy served as a wake-up call to the scientific and medical communities. It led to the establishment of stricter laws, guidelines, and regulatory bodies across the world. Drug approval processes became more rigorous, especially in relation to teratogenicity and long-term side effects. The disaster also emphasized the importance of informed consent, transparency in clinical trials, and ongoing post-market surveillance to protect patient safety.

Surprisingly, Thalidomide's story did not end in disgrace. Decades later, researchers discovered that it possessed powerful anti-inflammatory and immunomodulatory properties. Under strict regulations, it was reintroduced to treat diseases like erythema nodosum leprosum (a complication of leprosy) and later, multiple myeloma, a type of blood cancer. Its derivatives— lenalidomide and pomalidomide—have further extended its therapeutic impact in oncology and autoimmune disorders.

In conclusion, Thalidomide represents both a warning and a lesson in medical history. It teaches us the high cost of scientific oversight but also highlights the potential of modern research to repurpose and redeem even the most controversial drugs. Today, Thalidomide stands not only as a symbol of tragedy but also of progress, reminding us that safety, ethics, and innovation must always go hand in hand in the pursuit of better healthcare.

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