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NANO EMULSION (THALIDOMIDE) AS PARENTERAL: A MODERN NEW NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

This study reports the development of Nano emulsions intended for intravenous administration of thalidomide (THD). The formulations were prepared by spontaneous emulsification method and optimized with respect to thalidomide (0.01–0.05%, w/w), and hydrophilic emulsifier (polysorbate 80; 0.5–4.0%, w/w) content. The formulations were evaluated concerning physical appearance and drug crystallization; droplet size; zeta potential and drug assay. Only the formulation containing 0.01% THD and 0.5% polysorbate kept its properties in a satisfactory range over the evaluated period (60 days), i.e. droplet size around 200 nm, drug content around 95% and zeta potential around −30 mV. The transmission electron microscopy revealed emulsion droplets almost spherical in shape confirming the results obtained by photon correlation spectroscopy. Drug crystallization observed for higher content (THD 0.05%, w/w) Nano emulsions was investigated. The crystals observed at optical microscopy presented a different crystal habit compared to that of the raw material used. It was speculated whether the kind of THD polymorph employed could influence Nano emulsion formulation. Formulations were prepared with either one of THD polymorphs (- or -) and crystals were characterized by Fourier transformed infrared spectroscopy (FTIR) and X-ray diffraction (XRD)[6]. It was observed that regardless of the polymorph employed (- or -), drug crystallization occurs in the -form. THD solubility in oils

was not influenced by the polymorphic form. In addition, the in vitro dissolution profile of the selected formulation (THD 0.01%, w/w; polysorbate 0.5%, w/w) was assessed by bulk-equilibrium reverse dialysis sac technique and demonstrated a release profile similar to that of a THD acetonitrile solution, with around 95% THD being dissolved within 4 h. Finally, a pharmacokinetic simulation of an intravenous infusion of 250 mL of the selected Nano emulsion suggests that the parenteral administration of a dose as low as 25 mg might lead to therapeutic plasma concentrations of thalidomide.[15]

KEYWORD: Thalidomide THD, Nano emulsions, Spontaneous emulsification, Reverse dialysis, Pharmacokinetic simulation.

INTRODUCTION

Brief History

Thalidomide preparations in the form of tablets, syrup, suspension, capsules, drops and suppositories, marketed under different brand names, sold in Ireland between 1958 & 1962, by Messrs T.P. Whelehan, Son & Company[21] Ltd. The preparations sold through pharmacies as "over-the-counter" medicines. For a period of time it was also prescribed by general practitioners.

The Irish redress review board ultimately accepted Thirty-four children as survivors of Thalidomide. Department of Health and Children currently claim, "thirty-one Thalidomide survivors are receiving Pensions". Correspondence from Dr. Victoria Coffey sent 23rd March 1963 by to the Department of Health and subsequently on October 12th 1964 to Prof. Lenz, Germany). Stated, "The number of babies in Ireland with limb anomalies considered attributable to the drug Thalidomide was 105. Of these, 87 were actually born alive but 23 died in the neonatal period. The remainder of 64 had malformations of varying severity".

In May 1974, after a decade of intense lobbying by the parents of the Irish children, the Irish Government finally entered into a commitment of redress, the Irish government finalized their commitment with the statement, "as a matter of principle, to add to the compensation payable from the German compensation scheme to Irish Thalidomide survivors and their families". Tánaiste and Minister for Health Mr. Brendan Corish on the 9th of January 1975: "to see that the children are provided with all the services and aids necessitated by their handicaps in order for them to lead as normal a life as possible" Thus, the Irish government agreed to follow a similar path to that of the German compensation scheme.

PHARMACOLOGY

Thalidomide is a nonpolar synthetic glutamic acid derivative. Chemically, it is an a -[N-phthalimido]-glutamine consisting of a single central asymmetric carbon[11] atom with a left phthalidomide ring and a right glutamine ring. The phthalidomide ring is thought to be responsible for the teratogenic effects whereas the glutarimide ring, which is structurally similar to other sedatives, mediates sedation. It exists as optically active R (+) and S (-) enantiomers, which interconvert rapidly in vivo.

PHARMACOKINETICS

Thalidomide is slowly absorbed from the gastrointestinal tract. Peak levels in blood are reached within 2-6 hours, which could be delayed with a high-fat[7] meal. It is extensively distributed in all the tissues and fluids with higher concentrations in skin and kidneys. Bioavailability of thalidomide cannot be ascertained owing to its poor water solubility. It is primarily metabolized by nonenzymatic hydrolytic cleavage of its amide bonds. Cytochrome P-450 enzymes may have some role in metabolizing the anti angiogenic metabolite.[4] The mean elimination time is 5-7 hours[19], and it is not excreted in renal system; less than 0.7 percent of the drug is found in the urine.

MECHANISM OF ACTION

The exact mechanism of thalidomide actions is not determined. However, various theories have been proposed. theories for thalidomide embryopathy[21] have been proposed over the past 50 years and are reviewed in detail elsewhere, that include DNA mutagenesis, effects on chondrogenesis, nerve/neural crest toxicity, and inhibition of cell adhesion molecules the drug's ability to induce cell death and generate reactive oxygen species[17] (ROS); the thalidomide binding target, *Cereblon*, a ubiquitin ligase, which if prevented from binding can reduce thalidomide induced damage in embryos.[33]

METHODS

This was a retrospective case series which included only complex and proliferative AVM lesions (Schobinger grade III and IV). All patients prescribed thalidomide on a compassionate basis between September 2006 and August 2022 after attempts at embolosclerotherapy without satisfactory response were reviewed.

THD NANO EMULSIONS PREPARATION

The Nano emulsions were prepared by spontaneous emulsification (Yu et al., 1993; Bouchemal et al., 2004). Briefly, the organic phase consisting of absolute ethanol, oil (castor oil, 10.0%, w/w), lipophilic emulsifier (soybean lecithin, 3.0%, w/w) and THD (- polymorphic form) previously homogenized, were injected into the aqueous phase consisting of water, osmotic agent (glycerol, 2.25%, w/w) and a hydrophilic emulsifier (polysorbate 80), under magnetic stirring.[14] The magnetic stirring was maintained during 30 min to allow the system to reach equilibrium. The solvent proportion was 1/2, ethanol/water. Ethanol and excess water were removed by evaporation under reduced pressure until a volume of 10 mL was reached. The pH was adjusted to 5.0–5.5 with HCl 0.01 M. A first set of formulations was prepared with different concentrations of thalidomide (0.01, 0.015, 0.02 and 0.05%, w/w) and no hydrophilic emulsifier and named THD 0.01; THD 0.015; THD 0.02, and THD 0.05, accordingly. Afterwards, another set of formulations was optimized with respect to the polysorbate 80 content (0.5, 1.0, 2.0 and 4.0%, w/w) and named THD 0.01P0.5; THD 0.01P1.0; THD 0.01P2.0, and THD 0.01P4.0. Blank formulations were also prepared.

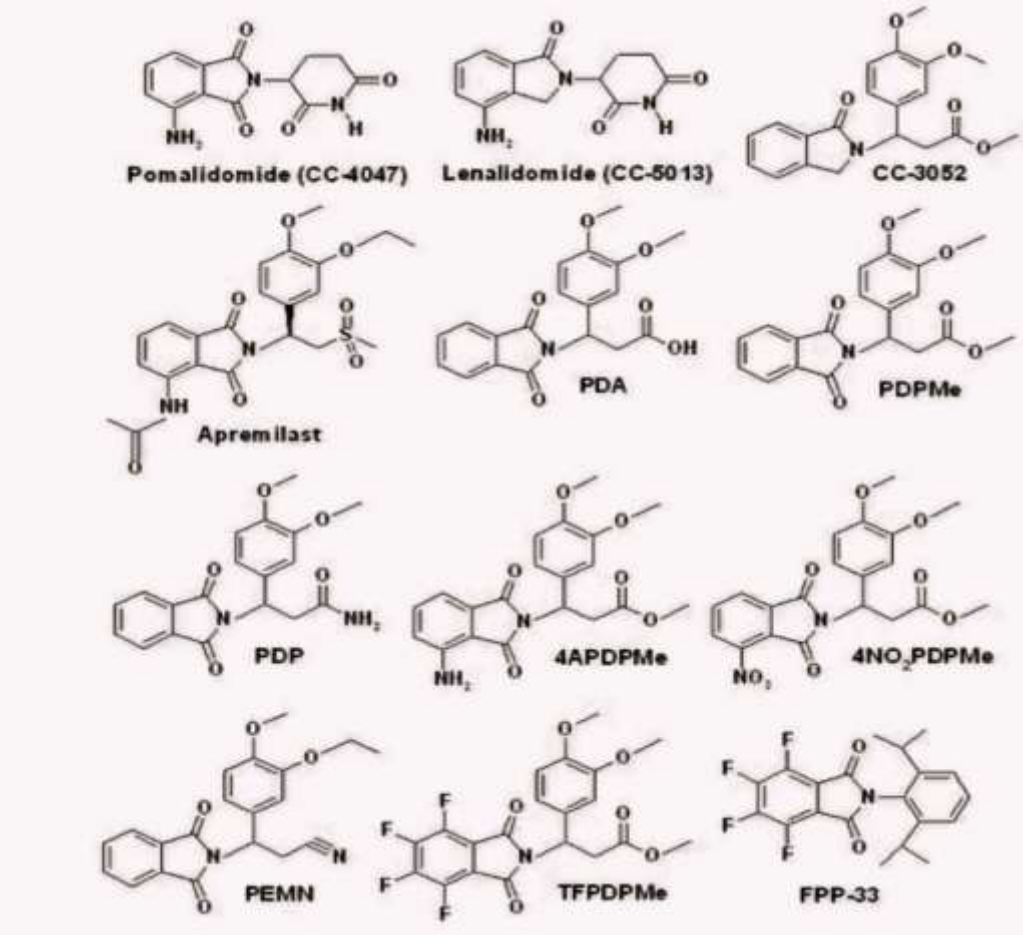

Fig no. 1: Structure analogue of thalidomide.

Anti inflammatory

It inhibits the chemotaxis, phagocytosis by Neutrophils, lymphocytes, and macrophages, stabilizes the lysosomal membranes and decreases the generation of superoxide and hydroxyl radicals.

Anti humour effects

Thalidomide has been tested in a variety of haematological and solid malignancies. It has shown remarkable efficacy in patients with advanced multiple myeloma.[17] The exact basis for thalidomide's anti-tumour[21] activity is not well-understood. It may be related to its anti angiogenic action, immunomodulatory effects, TNF-a-regulation, effect on cytokines and anti-adhesion effects,

Immunomodulatory effects

Thalidomide's immunomodulatory properties are complex. Multiple mechanisms of action have been reported. The best recognised action is its ability to inhibit the production of TNF-a, inhibit synthesis of IL-6, IL-12 and interferon- (IFN-y). It reduces expression of intracellular adhesion molecule-1 and vascular cell adhesion molecule.

Anti angiogenesis

Many tumours require new vessel formation (angiogenesis) in order to support their continuous growth. Thalidomide inhibits basic fibroblast growth factor (bFGF) (induces angiogenesis) and vascular endothelial growth factor (VEGF).[4-6] Thalidomide- induced antiangiogenic action is mediated by ceramide through depletion of VEGF receptors.[7,17] Angiogenic inhibition also results from antagonism between the following elements: E2 and F2 prostaglandins, histamine, serotonin and acetylcholine.[3]

Sedative properties

It activates the forebrain sleep centre and therefore does not cause respiratory depression, in coordination, or hangovers.

Miscellaneous Actions

Thalidomide Reduces cellular proliferation, myelin phagocytosis and sabperineural oedema. There is decrease in the capacity to release elastase and lactoferrin by lipoteichoic acid-stimulated.

2.5. Characterization of THD nanoemulsions

The formulations were stored at 4 ◦C and monitored with respect to physical appearance and formation of THD crystals, particle size, zeta potential as well as drug content.[9] The selected formulation was evaluated regarding these parameters plus viscosity and morphology.

2.5.1. Particle size analysis

The mean particle size and polydispersity index were measured at 25 ◦C by photon correlation spectroscopy (PCS) using a Malvern Nanosizer/Zetasizer® nano-ZS ZEN 3600 (Malvern Instruments, USA). Each 20 L sample was diluted in 10 mL of ultrapure water. The analyses were performed three times to determine mean values.

2.5.2. Zeta potential measurement

The zeta potential was measured by electrophoretic mobility using Malvern Nanosizer/Zetasizer® nano-ZS ZEN 3600 (Malvern Instruments, USA).[16] All analyses were done in triplicate and each 20 L sample was diluted in 10 mL of an ultra-filtered (0.22 m)solution of NaCl (1 mM).

THD assay

The THD content of the emulsions was assayed by the HPLC method as previously described (Section 2.2). A fixed amount of the emulsion (0.500 g) was diluted in a diluent solution composed of acetonitrile:ammonium acetate buffer (pH 5.5; 10 mM) (90:10,v/v) and 20 L from the resulting solution was injected into the HPLC.[19]

2.5.4. Transmission electronic microscopy

One drop of THD nanoemulsion was placed on a carbon-coated copper grid (200 mesh) overlaid with 1% formwar in chloroform, stained by 2.0% uranyl acetate aqueous solution and examined by transmission electronic microscopy using a JEM-1200 EXII instrument (JEOL, Tokio, Japan).

2.5.5. Viscosity

The rheological measurements were carried out in a AVS 350 viscometer (Schott-Geräte, Hofheim, Germany) equipped with a capillary tube Ic (viscosimeter constant, k = 0.035). The emulsion (7 mL, adjusted to 25± 0.1 ◦C) were poured into the filling tube and transferred to the capillary tube by gentle suction. The time was recorded, in seconds, for the liquid to flow from the upper to the lower mark in the capillary tube. The analyses were done in triplicate.

Uses in Dermatology Dermatological conditions have been grouped into the following categories:

(a) Very effective: ENL, aphthous stomatitis, Behcet's disease, LE, and prurigo nodularis;

(b) Moderately effective: Actinie prurigo, Langerhans cell histiocytosis, cutaneous Sarcoidosis, erythema multiforme, graft-vs-host disease (GVHD), Jessner's infiltrate, and uremic pruritus;

(c) Possibly effective: Kaposi's sarcoma, lichen planus, melanoma, and pyoderma gangrenosum;

(d) Contraindicated: Toxic epidermal necrolysis (paradoxical increase in TNF-a activity).

Thromboembolic effects Thromboembolic complications due to thalidomide are mostly associated with thalidomide's use in the cancer setting. especially when given concomitantly with chemotherapeutic agents.[2] Venous thromboembolism has emerged as the single most important complication of thalidomide in the setting of malignancy especially multiple myeloma. Venous thromboembolism was noticed in less than 5% of advanced myeloma patients taking thalidomide as a single agent.[5] It is also an emerging toxicity of thalidomide in the dermatologic setting, however. There are at least 15 cases of thalidomide- related thromboses in the noncancer setting, including among cases of sarcoidosis, lupus erythematosus, and atopic dermatitis. The risk increases when thalidomide is combined with corticosteroids (such as dexamethasone). It may be advisable to screen patients for possible thrombotic predisposition before thalidomide treatment.[2]

ACTIONS OF THALIDOMIDE

1. Inhibits leukocyte chemotaxis into site of inflammation
2. A potent sedative and increases the duration of REM sleep
3. Reduces phagocytosis by polymorphonuclear leukocytes
4. Enhances mononuclear cell production of cytokines like IL-2, IL-10 and inhibits IL-6 & IL- 12 production
5. Increases mean plasma levels of IL-2 receptors
6. Reduces TNF-a production by decreasing the half-life of related mRNA
7. Inhibits FGF-2 mediated angiogenesis[11], Possesses potent teratogenic actions.

Symptom Pattern

Phocomelia i.e. abnormal limbs

• Amelia i.e. missing limbs

Other Teratogenic Effects

• Abnormal number of digits

• Missing/malformed eye(s) and ear(s)

• Anal atresia

• Brain damage/autism

• Spinal cord defects

Cleft lip or palate

• Heart, Kidney, GIT and Genital defects.

CHARACTERISATION OF NANOEMULSION[12]

The absence of the internal phase, the elimination of flocculation, the elimination of microbial degradation, and the preservation of beauty in terms of appearance, colour, odour, and consistency are all characteristics of a stable nanoemulsion.

Flocculation and Creaming: When globules come together to create floccules, they go up or down in the emulsion more quickly as compared to the individual globules. This process is known as flocculation.

Creaming is the process of dispersed globules rising or falling to create a concentrated layer. As a result, flocculation results in creaming.

Cracking: When an emulsion breaks, the dispersed phase separates as a layer. Emulsion cracks cannot be repaired; however, shaking a creamy emulsion is possible or stirred to recombine it. Cracking will be representing permanent[15] instability.

Phase Inversion: It is physical process. It entails moving back and forth between o/w and w/o emulsions. Variations in temperature, the presence of electrolytes, and the stage volume fraction can all lead to phase inversion.

Miscellaneous Instability: If emulsions are kept at a temperature that is unusually high or low, or presence of light, they may start to degrade. Emulsions are therefore typically stored at a moderate temperature and packaged in coloured, airtight containers.

EVALUATION OF NANOEMULSIONS

Drug Content: Pre-weighed Nano emulsion is recovered by dispersing it in an appropriate solvent, and the extracted solution is then evaluated against a drug reference solution using a spectrophotometer or HPLC.

Dilution Test: This kind can be determined by diluting a nanoemulsion with water or oil. The test is predicated on the observation that a nanoemulsion can have more continuous phases added to it without having stability issues. A w/o nanoemulsion can be diluted with oil, but an o/w nanoemulsion can be diluted with water.

Viscosity Determination: The viscosity is determined using a rotational viscometer of the Brookfield type of nanoemulsions at various shear rates and temperatures.

Droplet Size Analysis: Analyzer of the size of lightscattering particles counter, the LS 230, is utilized to evaluate the diffusion method's droplet size analysis of nanoemulsion. Correlation spectroscopy, which investigates the variation in light scattering brought on by Brownian motion, can also be used to measure it. Transmission electron microscopy (TEM)[7] can also be used to analyse shrinking of the droplets in a Nano emulsion.

pH: A pH meter can be used to calculate pH of nanoemulsion.

Dye Test: An oil/water nanoemulsion absorbs the shade equally when a liquid dye is added to it.

In contrast, The emulsion only absorbs the colour in the dispersion phase, and the colour is not uniform if the dye is water-soluble and the emulsion is typeless.. By inspecting the emulsion under a microscope, this is instantly discernible.[5]

Refractive Index: An Abbes refractometer is used to calculate the nanoemulsion's reflectivity. The transparency of a nanoemulsion and how light passes through a substance are both described by the refraction. The ability to determine the medium's refractive index is based on the speed of the wave in the reference media (c) in relation to the wave's phase speed in the medium (vp) (n). i.e.n=c/vp.

The nanoemulsion is classified as transparent if its refractive index is the same as that of water.

Zeta Potential

A device called the Zeta PALS, which is used to determine zeta potential. It is used in a nanoemulsion to establish the charge on a droplet's surface.

Polydispersity

It demonstrates that the droplet diameters in the nanoemulsion are uniform. In a nanoemulsion, the droplet size is less uniform the higher the pdi value. It is called as the standard deviation to mean droplet size ratio. To measure, a spectrophotometer is utilised.

Fluorescence Test

Many oils glow when exposed to UV light. Under a microscope, a field of w/o nanoemulsion fluoresces when it is subjected to fluorescent light. The o/w type nanoemulsion is used when the fluorescence is sporadic or spotty.

Conductance Measurement

The conductivity of a nanoemulsion is tested using a conductometer. In this test, an emulsion is put on two electrodes that are wired to an electrical component and a lamp. If the emulsion is of the o/w variety, water conducts the current, which results in a flow of current between the electrodes that illuminates the lamp. Because the oil in the outer phase does not conduct electricity, the light does not illuminate when the emulsion is not present.

Percentage Transmittance

The percentage transmittance of the nanoemulsion is calculated using a UV-visible spectrophotometer.

Filter Paper Test

The theory behind this experiment is that when put on filter paper, an oil-in-water nanoemulsion will quickly spread out. On the other hand, a water-based nanoemulsion[8] will move very slowly. This method should not be used to cure very thick creams.

CONCLUSIONS

Formulations prepared with castor oil (10%, w/w) lecithin(3.0%, w/w) and increasing amounts of THD (from 0.01 to 0.05%)presented droplet size, polydispersity index and zeta potential feasible to i.v. administration. Nevertheless, drug crystallization was observed for the higher content formulation and it was demonstrated that THD always precipitated in the - polymorphic form. A significant decrease of THD content was observed for the 0.01% THD formulation at 60 days of storage and the addition of polysorbate 80 improved the stability of this formulation only at a 0.5% (w/w) level. Higher polysorbate 80 concentrations[17] led to a significant decrease on drug loading, possibly by facilitating drug interaction with the

aqueous phase. The dissolution profile of the optimized formulation was similar to that of a THD solution.

Finally, the pharmacokinetic simulation of the intravenous infusion of 250 mL of the selected formulation (0.01% THD) has showed that the parenteral administration of a dose as low as 25 mg may produce therapeutic plasma concentrations.

Thalidomide Chemical Properties

The chemical name of Tha is 2-(2,6-dioxo-3-piperidinyl)-1H-isoindole-1.3(2H)-dione and it is composed by two imide moieties, the phthalimide ring and the glutarimide ring, its empiric formula is CHNO, with a molecular weight of 258.2 g/mol. Tha is a white, tasteless crystalline powder with a melting point of 269-271°C. This drug is sparingly soluble in water (6 mg/100ml.), methanol, ethanol, acetone, and glacial acetic acid but readily soluble in acetone, dioxane, dimethyl formamide, pyridine, chloroform, and dimethyl sulfoxide. It is insoluble in ether and benzene (Somers, 1960). Its low solubility in water would suggest that its concentration in body fluids at any time would be small (Williams, 1968)[5], so the efforts to get Tha dissolved have led to prepare solutions in alkaline pli that promotes the spontaneous hydrolysis of Tha; in consequence, such solutions contain Tha in addition to its hydrolysis products. The main route of hydrolysis of Tha at pH 6, 7.4 and 8 is cleavage of the phthalimido ring to a-to-carboxybenzamido)glutarimide, this compound is reasonably stable at these pH values, however, as the pH is increased the bonds of glutarimide ring become susceptible to hydrolysis and, at pH 7.4 and 8 especially, considerable amounts of 2- and 4-phthalimidoglutaramic acids are formed (Schumacher et al., 1965a). It suggests that Tha biological effects may also be shared by its hydrolysis products or its metabolites, thus, this compound may act as a prodrug for one or more of those Tha derivatives (Fahro et al., 1965; Muller et al., 1996). In addition, Tha possesses a single chiral center in the glutarimide ring, an asymmetric carbon that originates the R and S enantiomers, thus, Tha is administered as a racemic mixture of (-)-(S) and (+)-(R)-enantiomeric forms. It has been demonstrated.

Thalidomide and its Analogs: Characteristics and Mechanisms of Action

Nowadays, Tha has showed several mechanisms of action as an antiinflammatory and immunomodulatory drug because of its broad range of inhibitory and stimulatory effects on the immune system (Zwingenberger and Wnendt, 1995; Mujagić et al., 2002). However, so far the most plausible mechanism is the inhibition on the production of the important, pleiotropic, pronecrotic and proinflammatory cytokine tumor necrosis factor-a (TNF-1)

(Sampaio et al., 1991), through enhancing the TNF-a mRNA degradation (Moreira et al., 1993). On this way, other authors have proposed that Tha has also immunomodulatory activity by two more routes: a) reducing the number of IgM plaque-forming cells and b) enhancing the secretion of the cytokine interleukin-2 (IL-2) in peripheral blood mononuclear cells (PBMC) (Shannon et al., 1997). Regarding other immunomodulatory effects, it has been observed that Tha has a costimulatory role in the upregulation of T helper 2 (Th2)-type immunity, because Tha increases the production of Th2-type (humoral) cytokines, for example interleukin-4 (IL-4) and interleukin-5 (II.-5); as well as inhibits the production of the Thi-type (cellular) cytokine interferon-y (IFN-y) in PBMC (McHugh et al., 1995; Marriott et al., 1999), while in T cells Tha induces a high production of IFN-y and IL-2 (Corral et al., 1999).

There are other possible immunomodulatory and/or regulatory mechanisms of Tha on diverse endogen mediators of the immune and inflammatory response. It deserves special consideration the first report concerning the inhibition on the activation of the nuclear factor-KB (NF-kB) in HIV-infected primary macrophages (Moreira et al., 1997). NF-B is a transcription nuclear factor that has received much attention since its discovery in 1986, because of its activation by many different stimuli and its diverse and prominent roles in maintaining the homeostasis, control of disease development, regulation of cell survival and activation of innate and adaptive immune responses, for instance, its activation provokes the production of proinflammatory cytokines including the most potent TNF-a[1] (Sun and Karin, 2008). On this way, there are reports that support that Tha strongly suppresses at different levels the NF-kB activation induced by TNF-a and reactive oxygen species (ROS) such as H_2O, besides this inhibition is apparently not cell type specific, although these effects are not seen during the NF-KB activation by other inducers (Majumdar et al., 2002; Kim et al., 2004). This likely mechanism of action has prompted the design and synthesis of NF-kB inhibitors derived from Tha (Carcache de-Blanco et al., 2007).

Cyclooxigenase-2 (COX-2) is the inducible enzyme that catalyzes the synthesis of prostaglandins (PG) which are very well known potent endogen proinflammatory agents and that regulate the cytokines expression. COX-2 is induced by bacterial lipopolysaccharides (LPS) and it has been considered as a pharmacological target for the prevention and treatment of angiogenesis and cancer, indeed, Tha has evidenced promising effects as inhibitor of LPS-induced COX-2 (Fujita et al., 2001). Furthermore, novel Tha analogs have been recently

synthesized and/or evaluated as inhibitors of COX-2 (Suizu et al., 2003; Fujimoto et al., 2006).

Current Uses for Thalidomide and Some Analogs

Thanks to the discovery by Sheskin (1965) that Tha possessed striking effects on the patients suffering from the cutaneous manifestations of ENL., in July 16, 1998, thalidomide reemerged, since the Food and Drug Administration of United States approved its use for the treatment of such disease (Annas and Elias, 1999). A short time later after 1965, Tha was successfully tried in the graft-versus-host reaction in rats and man (Field et al., 1966; Vogelsang et al, 1992), inclusive, there are current reports on this Tha application (Ratanatharathorm et al., 2001). Based on its immunomodulatory properties that evoke an antiinflammatory effect. Tha has been tested in clinical studies for treating MM wherein it has shown high efficacy[3], in addition, its analog lenalidomide gained the FDA approval in June 2006 for treating relapsed and refractory MM (Chen et al., 2009, Magarotto and Palumbo, 2009). Tha inhibitory effects on angiogenesis (D'Amato, et al., 1994) opened its potential use for the treatment of many diverse diseases depending on that process, such ascancer solid tumors (Richardson et al., 2002a) as well as for the use of Tha analogs in the management of those ailments (Marriott et al., 1999; Teo, 2005). Rheumatoid arthritis is a chronic and inflammatory autoimmune-related disease; Tha and its analogs have also been tried in this illness with hopeful results (Gutierrez-Rodriguez et al., 1989, Oliver et al., 1999). Tha and lenalidomide showed to be a successful tool in the treatment of Behçet's disease (Direskeneli et al., 2008; Green et al., 2008). Furthermore, thalidomide has beneficial properties to controlling the aphthous ulcers and cachexia associated with HIV/AIDS (Jacobson et al., 1997; Marriott et al., 1999). Crohn's disease is an autoimmune inflammatory bowel disease in which Tha has been reported to be an effective treatment for patients with refractory episodes; additionally, there are current trials to evaluate Tha analogs in such illness (Mansfield et al., 2007; Gordon et al., 2009),

As Tha and its analogs are clinically or experimentally being tried in many chronic, degenerative and inflammatory diseases, there is a potential risk of producing teratogenic outcomes in possible pregnant patients being administered with these drugs, hence, it has been created the system for thalidomide education and prescribing safety (STEPS) that is a strict as well as comprehensive program to control and monitor access to Tha or its analogs (Zeldis et al., 1999). Although Tha and some analogs display teratogenic effects it is

important to keep in mind that their main therapeutic applications are for the treatment of severe, chronic and degenerative diseases wherein patients must not get pregnant.

Thalidomide Effects on Liver Damage and Cirrhosis

Thalidomide Effects on Liver Damage

Alcoholic liver disease is maybe one of the most important hepatopathies around the world. In this regard, the effect of Tha has been studied in an animal model of alcohol- induced liver damage, the sensitization of Kupffer cells to LPS and the overproduction of TNF-a are critical for progression of alcoholic liver injury. The treatment with ethanol for 8 weeks caused marked steatosis, necrosis, and inflammation[6] in the liver. These pathologic parameters were diminished markedly by treatment with Tha. In a 4-week ethanol group, the LPS-induced liver damage was aggravated and Kupffer cells were sensitized to LPS. Coadministration of thalidomide with ethanol prevented the sensitization of those cells completely. Furthermore, thalidomide abolished the LPS-induced increase in CD14 (this is a functional LPS receptor on macrophages/monocytes and neutrophils) expression and intracellular calcium concentration (Cai elevation in the macrophages. Moreover, thalidomide reduced the LPS-induced TNF-a production by Kupffer cells by decreasing TNF- a mRNA. Thus, Tha prevented alcoholic liver injury through suppression of TNF-a production a and abolishment of Kupffer cells sensitization[6] (Enomoto et al., 2002; Enomoto et al, 2004).

Activation of Kupffer cells by LPS plays a pivotal role in the onset of pathophysiological events that occur during endotoxemia and septic shock, as well as [Caji is involved in LPS-stimulated cytokine production, as the case of TNF-a which is mostly produced by Kupffer cells. TNF-a plays a key role in the initiation and progression of multiple organ failure syndrome induced by septic shock as well as in the cholestasis provoked by sepsis (Van Amersfoort et al., 2003; Moseley, 2004). Enomoto and coworkers (2003) determined whether Tha could prevent LPS-induced liver injury, they found that LPS caused focal necrosis with neutrophil infiltration in the liver. Moreover, LPS dramatically increased ALT/AST. These pathologic parameters and increases of serum transaminases were diminished markedly by Tha. In isolated Kupffer cells, LPS-induced increases in (Ca2+Ji and TNF-a production were suppressed by treatment with Tha. To further explore the mechanism by which Tha directly abrogated Kupffer cell sensitivity to LPS, they determined the effect of Tha in vitro on LPS-induced [Ca2+]i response and TNF-a production. With the addition of Tha to the culture media before LPS, these parameters were suppressed. They concluded that Tha prevents

LPS- induced liver injury via mechanisms dependent on the suppression of TNF-a[3] production from Kupffer cells. The immunomodulatory effects of Tha have been evidenced in other two models of sepsis, the first of Escherichia coli sepsis in vive in rat as well as in in vitro by using human monocytes (Giamarellos-Bourboulis et al., 2003), and the second in sepsis by multidrug-resistant Pseudomonas aeruginosa (Giamarelles-Bourboulis et al., 2005); in those studies Tha inhibited the microbial-induced NO, TNFe and IL-1 but not IL-6, as well as increased the survival rate in septic rats.

Conceming the evaluation of Tha analogs in animal models of liver injury as hepatoprotective drugs, there are three cament reports. Thiele and coworkers (2002) synthesized and assessed the immanomodulatory and hepatoprotective properties of a Tha analog named TFBA, which was found to be an TNF-a, IL-5 and IL-10 inhibitor in isolated and stimulated monocytes, this drug is not either a PDE-4 inhibitor or costimulator of T cells. When TFBA was administered to mice with hepatic injury by galactosamine/LPS, it diminished the ALT activity, TNF-a production but not IL-6; however this drug increased the hepatoprotective IL-10. Furthermore, a serial of Tha analogs have been synthesized and evaluated as immunomodulatory agents in liver and plasma in an acute model of LPS-induced septic challenge in rat. Animal groups were twice administered with Tha or its analogs in an equimolar dese. Two hours after last dose, rats were injected with saline or LPS. The cytokines TNF-a, IL-6, -18 and -10 were quantified and studied in plasma and liver. After two hours of LPS-induction, different patterns of measured cytokines were observed with Tha analogs administration evidencing their immunomodulatory effects in both tissues. Interestingly, some analogs decreased significantly plasma and hepatic levels of LPS-induced proinflammatory[4] TNF-a and others increased plasma concentration of antiinflammatory IL-10. Tha amalegs also showed slight effects on the remaining proinflammatory cytokines in both tissues. Differences among immunomodulatory effects of analogs might be related to potency, mechanism of action, and half lives (Fernández-Martinez et al., 2004), Finally, hepatic glycogen metabolism is altered by NO during endotoxic shock and the previously tested serial of Tha analogs immunomodulate the endotoxin-induced cytokines which regulate the NO release. Therefore, the short-term effects of those Tha analogs were assessed on the hepatic glycogen store and on the plasma and hepatic NO in an acute model of endotoxic challenge in rat. Endotoxin caused inverse dose-dependent effects increasing plasma NO and lowering hepatic glycogen. Tha analogs showed short-term regulatory effects on glycogen, some of them increased it. Plasma NO was almost unaffected by analogs but

hepatic NO was strikingly modulated. Analogs slightly up-regulated the liver IFN-y (a knowa NO-coinducer) and two of them increased it significantly. Due to their interesting effects the Tha analogs may be used as a pharmacological tool due to their short-term regulatory effects on glycogen and NO during endotoxic shock, since drugs that increase glycogen may improve liver injury in early sepsis (Fernández Martinez et al., 2008).

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