Mechanisms of Cyclosporin A Induced Hepatotoxicity

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Abstract

Cyclosporin A (CsA); an immunosuppressive agent, is broadly used for the remedy of autoimmune diseases and after organ transplantations. However, its medical and experimental use is restrained with the aid of quite few side effects, such as nephrotoxicity, cardiotoxicity, hypertension and hepatotoxicity. Despite its toxicity, CsA remains to be one of the most usually used immunosuppressive agent due to its therapeutic efficacy. The key mechanisms involved in organ damage caused by CsA include altered redox homeostasis and chronic systemic inflammation. Indeed, various mechanisms have been suggested for CsA induced hepatotoxicity along with the development of reactive oxygen species, oxidative stress, and hepatic antioxidant system depletion. In some of the side findings, many mechanisms concerned have been appreciably explored and explained. Nevertheless, the mechanisms underlying CsA-mediated hepatotoxicity are not utterly understood. This review discusses CsA toxicity and its pathophysiology and role of oxidative stress in the initiation of the toxicity in addition to the different Therapeutic approaches for its toxicity.

Keywords: Cyclosporin A; Hepatototoxicity; Inflammation; Oxidative stress; Wnt/β-catenin signaling.

1. Cyclosporin A

1.1. Background

Cyclosporin A (CsA) discovery passed through set of stages. Starting from development as antifungal agent up to its attractive use as an immunosuppressive agent. CsA was discovered in the lab of Sandoz in Switzerland in 1972. Natural CsA was initially found within 50 soil samples in Norway collected by Hans Peter Frey within the Sandoz Screening program for natural antifungal antibiotics which started in 1958. One of these samples contained the fungus Tolypocladium inflatum (Kahan, 1999) which was isolated in 1970 for screening of its antifungal metabolites, coming to the discovery of CsA immunosuppression activity through a screening test by a Sandoz pharmacologist Hartmann F. Stähelin in 1972. CsA is also produced by other organisms (Fusarium spp., Neocosmospora spp.) as a secondary metabolite (Svarstad et al., 2000).

In the Biological and Medical Research Division of Sandoz in Switzerland in 1976, Borel set up a series of experiments for the investigation of CsA capacity for inhibition of cell-mediated cytolysis. It was found that CsA, inhibited both in vitro cell-mediated lysis as well as lymphocyte sensitization by allogeneic target cells considering its negative actions following in-vivo administration (Borel, 1976). In 1980s, CsA was
extensively studied on human to be clinically approved as an immunosuppressive agent in transplantation (European Multicentre Trial Group, 1983; Canadian Multicentre Transplant Study Group, 1986; Hariharan et al., 2000).

Despite its adverse effects, CsA is still a backbone in organ transplantation (Shah et al., 2017). Improvement of life quality and survival of transplant patient are the most attractive features (Cid et al., 2003; Li et al., 2004). In addition, reducing morbidity, graft rejection, hospitalization by CsA treatment has another economical view. Moreover, CsA has relatively non-myelotoxic immunosuppressive effects, in contrast to azathioprine (AZA) and mycophenolate mofetil (MMF) (Rezzani, 2004).

1.2. Chemical structure

Cyclosporin A is a cyclic undecapeptide (C6H11N11O12) with a molecular weight of 1203.63Da (Rezzani, 2004). As shown in Figure 1, its chemical structure comprises peculiar features. Two amino acids are unusual: 3-hydroxy-4-methyl-2-methylamino-6-octonoic acid (MeBmt) at position 1 and a-aminobutyric acid (Abu) at position 2. Seven of the 11 main chain nitrogens are methylated: MeBmt 1, Sar 3, MeLeu 4, MeLeu 6, MeLeu 9, MeLeu 10 and MeVal 11. One residue is in the d configuration (d-Ala 8) (Altschuh, 2002).

For cyclosporin A, changes of amino acids at positions 4, 6 and 11 lead to a complete loss of immunosuppressive activity. Whereas, changes at amino acids 1 retained immunosuppressive activity for CsA metabolites (Rezzani, 2004).

Figure 1. Chemical structure of CsA (Rezzani, 2004).

1.3. Mechanism of action

Cyclosporin A is classified as calcineurin inhibitor (CNI) or reversible inhibitor of T cells activation, particularly, T helper cells (Tedesco and Haragsim, 2012). As demonstrated in Figure 2, CsA can bind to an intracellular protein called immunophilin (Cyclophilin A) (CY) (Matsuda et al., 2000). CsA-CY complex effectively inhibit the dephosphorylating action of calcineurin “Calcium/calcmodulin-dependent serine threonine protein phosphatase” (Liu et al., 1991). Subsequently, CsA-CY-Calcineurin complex prevents dephosphorylation of nuclear factor of activated T-lymphocytes (NFATs), which in turn, prevents the nuclear translocation of NFAT (Rezzani, 2004). This is believed to abort activation of nuclear factors involved in the gene transcription for interleukin-2 (IL-2) and other cytokines, including interferon, which subsequently, prevent overall immune response (Tedesco and Haragsim, 2012).

Figure 2. CsA mechanism of action (Rezzani, 2006).

1.4. Therapeutic indication & dosing regimen

Cyclosporin A has been indicated for prevention of organ rejection after solid organ transplantation (Rezzani, 2006), uveitis (Nussenblatt, 1988), rheumatoid arthritis (Yoshinoya et al., 1988), psoriasis nephrotic syndrome (Reynolds and Al-Daraji, 2002), autoimmune diseases (Bach, 1999) and neurological autoimmune diseases (Belendiuk and Solch, 1988).

At dosing level, oral approved dose of CsA is 5 – 10 mg/kg, whereas, I.V. approved dose is 1.5 – 2.5 mg/kg daily. These doses were recommended for prevention of acute rejection and in conversion protocols “i.e. patients with inefficacy of other immunosuppressive agents”. I.V. route is preferable, particularly, with poor oral absorbed formulations of CsA (Sandimmune®).
It is interesting to mention that liver transplant patients may have a slight impairment in bile formation early after transplantation, which in turn, decrease absorption and/or biliary excretion of some medications “i.e. digoxin and Sandimmune®”. However, absorption of the oral CsA (Neoral®) is independent on bile which allows oral route for liver transplant patients at a dose 10 – 15 mg/kg/day (Rezzani, 2004).

1.5. Adverse effects

Generally, the toxic effects induced by CsA can be divided into acute and chronic actions (Calne, 2002). Previously, it has been reported that CsA induce several toxic effects in both transplant and non-transplant situations (Rezzani, 2006). The most notably side effects of CsA are nephrotoxicity (Olyaei et al., 2001), neurotoxicity, hepatotoxicity, hypertension, hyperkalemia, hirsutism (Hypertrichosis), gingival hyperplasia, anemia, diarrhea, infections, hyperlipidemia, hypomagnesaemia, hyperglycemia, hyperuricemia, gout, paresthesia, thrombotic microangiopathy and cardiovascular disorders. It is interesting to note that these effects could be abrogated via dose reduction, however, CsA discontinuation is still remaining the best protocol to avoid these toxic effects (Tedesco and Haragsim, 2012).

These effects may be due to decrease calcineurin levels in nonlymphocytic tissues (Williams and Haragsim, 2006). Others revealed that alterations in the renal tubular functions induced by CsA may be the underlying etiology for electrolyte disturbances “i.e. homeostasis (Naesens et al., 2009).

Additionally, CsA induces histomorphological toxicities in different organs including thymus gland, kidney, liver, heart, pancreas and nervous system resulting in multiple organ failure (Rezzani, 2006).

1.5.1. CsA- induced nephrotoxicity

The first detected nephrotoxicity induced by CsA was in 1978 (Calne et al., 1978). Two types of nephrotoxicity could be induced by CsA, (acute and chronic). Several clinical studies attempted to demonstrate the underlying reason of acute nephrotoxicity. However, there are multiple reasons which might all contribute to this side effect. It was observed that activation of the renal sympathetic nervous system concurrently with stimulation of plasma renin activity lead to subsequent, activation of Renin-Angiotensin-Aldosterone System (RAAS) followed by the characterized features of CsA-induced acute nephrotoxicity (Rezzani, 2004). This effect has been linked, later, with the imbalance in vasoconstrictor factors (i.e. endothelin and thromboxane) and vasodilator factors (i.e. prostacyclin, prostaglandin E2, and nitric oxide) (Hortelano et al., 2000). Another mechanism was strongly proved which revealed the involvement of ROS in different tissues (Akool et al., 2012).

On the other hand, chronic nephrotoxicity induced by CsA has been reported in several clinical trials which is directly related to the long-term administration of CsA (Nankivell et al., 2004).

The main histopathologic feature of CsA-induced nephrotoxicity is arteriolar hyalinosis with interstitial striped fibrosis (Naesens et al., 2009).

Collectively, pro-inflammatory and pro-fibrotic effects induced by CsA thought to be due to the upregulation of transforming growth factor-beta (TGF-β) induced by CsA (Rezzani, 2004) either directly via ROS – TGF-β – canonical Smad pathway (Akool et al., 2008) or indirectly via induction of angiotensin II (Naesens et al., 2009).

Another report mentioned that the lower expression of CYP3A4 and CYP3A5 (Joy et al., 2007) are correlated to hasten the development of CsA-induced chronic nephrotoxicity (Hesselink et al., 2010). Moreover, concomitant administration of non-steroidal anti-inflammatory agents (NSAIDs), aminoglycosides and various anti-fungal agents with CsA increase the risk of nephrotoxicity (Rezzani, 2004).

1.5.2. CsA- induced neurological disorders

It was found that 50% of patients received CsA suffer from neurological complications of CsA, particularly, high dosing therapy. The main neurological disorders induced by CsA include seizures (Rezzani, 2004), tremor, neuralgia, paraesthesia, confusion, ataxia, hemiplegia (Vellodi et al., 1987), transient cortical blindness (Rubin and Kang, 1987) and occipital seizure (Gijtenbeek et al., 1999).

Other contributing factors reported to hasten convulsions induced by CsA, are fluid retention, hypertension, high-dose steroids, graft dysfunction.
and demyelination. In addition, hypomagnesemia (Rezzani, 2004) and hypercholesterolemia (de Groen et al., 1987) are other factors that might predispose convulsions. It is believed that CsA metabolites are the underlying reason for this type of disorders (Kunzendorf et al., 1989).

1.5.3. CsA- induced hypertension

Hypertension induced by CsA is characterized by increase in systemic vascular resistance within days to weeks of administration (Taler et al., 1999), disturbed circadian rhythm, lack of the normal nocturnal fall in blood pressure (Reeves et al., 1986), nocturnal headache and nocturnal urination. The most severe form detected at night and characterized by accelerated hypertension with retinal hemorrhages, central nervous system symptoms, left ventricular hypertrophy, lacunar stroke and microalbuminuria (Rezzani, 2004).

Although, the increase of systolic blood pressure induced by CsA didn’t affect the urinary output, creatinine clearance has been significantly decreased. In addition, the lipid peroxidation by-products markedly increased indicating presence of oxidative damage induced by CsA (Rezzani, 2004).

Continues uncontrolled hypertension might lead to vascular injury including microangiopathic hemolysis, encephalopathy and seizures (Textor et al., 1994). Interestingly, it was reported that sodium intake might modulate hypertension induced by CsA (Singer et al., 1994). However, these studies lack the history of hypertension for those patients (Rezzani, 2004).

1.5.4. CsA- induced hepatotoxicity

Experimental studies and clinical observations reveal that CsA can lead to drug-induced liver injury. In CsA induced liver injury, functional and morphological changes are observed. The functional changes include elevated serum levels of liver transaminases and alkaline phosphatase, cholestasis, hyperbilirubinemia, increased production of bile salts, and impaired secretion of lipids (Hillebrand, 1999; Abboud and Kaplowitz, 2007). On the other hand, the morphological changes observed in experimental animals receiving CsA include impaired trabecular structure, hepatic sinus congestion and widening, activation of the Kupffer cells, passive congestion and oedema of portal tracts, mild mononuclear cell infiltrations within portal tracts, and degenerative changes in the hepatocytes including their focal necrosis (Kurus et al., 2009; Akbulut et al., 2015).

The mechanisms of CsA-induced liver injury involve the development of hypermetabolic state in the liver (Zhong et al., 2001) and inhibition of ATP-dependent transport of bilirubin and bile salts through the hepatocyte canalicular membranes as well as of bile secretion (Kadmon et al., 1993; Böhme et al., 1994). In addition, based on molecular mechanism(s), several studies mentioned that CsA induces oxidative stress via reduction of the antioxidant capacity (Rezzani et al., 2005). Obviously, an imbalance between oxidants and endogenously produced antioxidants have been implied in CsA-induced hepatotoxicity (Rezzani, 2006). Furthermore, the toxic effects of CsA directly leads to oxidative stress and subsequent hepatic injury (Akool, 2015). Finally, the use of antioxidants in experimental animals exposed to CsA reduces liver functional and morphological damage, which confirms the involvement of oxidative stress as one of the mechanisms of hepatotoxicity (Rezzani, 2006).

1.5.5. Pharmacological intervention on CsA hepatotoxicity

Combination therapy of vitamin E and C have been reported as the first successful intervention for CsA-induced liver injury via increasing the antioxidant capacity (Durak et al., 2004). Also, taurine, 2-aminoethanolsulfonic acid, improves the hepatic function which deteriorated by CsA (Hagar, 2004). Melatonin also has a protective hepatic effect via inhibition of the stress protein expression (i.e. Heat shock protein 60, heat shock protein 72 and metallothionein) (Rezzani et al., 2005).

Considering these studies, quercetin plus vitamin E (Mostafavi-Pour et al., 2013), trapidil plus L-arginine (Salem et al., 2010), trimetazidine plus vitamin E (Cristina et al., 2013), propolis (Seven et al., 2014), ellagic acid (Pari and Sivasankari, 2008), N-acetylcysteine (Kaya et al., 2008), sulphated polysaccharides (Josephine et al., 2008), vildagliptin (El-Sherbeeny and Nader, 2016) and wheat germ oil (Akool, 2015) were all able to significantly ameliorate CsA-induced liver injury.

Generally, these protocols involve the use of one or more immunosuppressive agents with more selective specific actions rather than CsA. This combination may include daclizumab (an IL-2
Peroxisome Proliferator-Activated Receptor Gamma role in CsA hepatotoxicity

Peroxisome Proliferator-activated receptors (PPARs) represent as a ligand-activated transcription factors which play a vital role in genes regulation in cell differentiation processes and a variety of metabolic pathways, mainly lipid and glucose homeostasis. In molecular terms, PPARs characterize a family of ligand-activated nuclear hormone receptors (NRs) belonging to the steroid receptor superfamily (Berger and Moller, 2002; Boitier et al., 2003). Once NRs interacted with the particular ligands, they are transferred to the nucleus, where they can alter their structure and also control gene transcription (Willson et al., 2000; Rogue et al., 2010).

The three-dimensional arrangement of PPARs includes a DNA binding domain within the N-terminus and also a ligand binding domain within the C-terminus. Once they interacted with agonists, PPARs are translocated to the nucleus and form a heterodimer with another nuclear receptor which is termed the retinoid X receptor (RXR) (Figure 3). The RXR forms a heterodimer with a lot of other receptors (e.g., vitamin D or thyroid hormones). The particular DNA regions of target genes to facilitate unite with PPARs are called Peroxisome Proliferator hormone response elements (PPREs) (Berger and Moller, 2002).

The PPREs are established in the promoters of PPAR responsive genes, for example the fatty acid-binding protein adipocyte Protein 2 (aP2). Generally, this process stimulates transcription of a variety of genes implicated in miscellaneous physiological plus pathophysiological processes (Willson et al., 2000).

All PPARs members covers three isoforms: PPARα, PPARβ/δ and PPAR-γ (Berger and Moller, 2002). The particular three isotopes vary from each one in their tissue distributions, ligand specificities and physiological performances. Each of them possibly stimulates or suppresses special genes with only limited overlap in action (Willson et al., 2000) (Figure 4).

Peroxisome proliferator activated receptor-γ is a member of the nuclear hormone receptor family that not only is prominently involved in adipogenesis and metabolic regulation, but also exerts an important role in the pathogenesis of CsA hepatotoxicity by interacting with three different mechanisms including oxidative stress, inflammation and Wnt/β-catenin signaling (Standiford et al., 2005).

2.2. Oxidative stress

There is a strong debate between authors about the mechanistic pathway(s) by which CsA induces its toxic actions. However, many authors develop different hypotheses to reveal this ambiguity. It is interesting to note that the imbalance between ROS formation and defense antioxidant system greatly accepted and supported by several studies through the use of antioxidants in attempting to reduce toxic effects induced by CsA in different organs, for instance, liver (Akool, 2015) and heart (Rezzani, 2006). The role of oxidative stress in chronic CsA treatment has been examined in several studies (Han et al., 2006; Erarslan et al., 2011). CsA induces intramitochondrial Ca++*, increases oxidative stress and ROS production, and inhibits mitochondrial glucose metabolism (the Krebs cycle and oxidative phosphorylation) and ATP production (Serkova et al., 2004).

It is postulated that CsA is an uncoupler and inhibitor of the mitochondrial transport system. In addition, CsA induced ROS generation is activated by NADPH oxidase, xanthine oxidase, cytochrome P450, or decreased intracellular antioxidant systems (Jeon et al., 2005). Increase in ROS results in lipid peroxidation and increases
Figure 3. PPAR-γ transcriptional activation. (1) Binding of activating ligands to PPAR-γ and to its dimer partner RXR; (2) following the ligand binding there are conformational changes of the receptors, resulting in re-arrangement of the transcriptional complex and changes in the associated transcriptional cofactors; (3) resulting from this reorganization, the transcriptional complex is activated and initiates changes in the expression of the regulated PPAR-γ target genes (Wang et al., 2014).

Figure 4. PPARs and their gene targets (Grygiel-Górniak, 2014).

its products such as MDA. Moreover, CsA treatment reduces GSH, an important antioxidant (Ay et al., 2007; Erarslan et al., 2011) which converts lipid peroxides to nontoxic products, thus maintaining the integrity of the mitochondria and cell membranes. It was previously demonstrated that CsA inhibits the glutathione reductase enzyme which is responsible for the regeneration of GSH. Therefore, the marked decreases in GSH not only were produced by engagement in ROS reduction but could also result from impaired regeneration by glutathione reductase (Korolczuk et al., 2016).

It has been shown previously that PPAR-γ exerts anti-oxidant and pleiotropic anti-inflammatory effects in the lung and liver (Standiford et al., 2005) as the transcription of antioxidant and anti-inflammatory genes were induced by PPAR-γ. From this point, the inhibition in PPAR-γ levels induce oxidative stress (Reddy and Standiford, 2010).

2.3. Inflammation

Tissue damage produced by oxidative stress is further aggravated by inflammatory changes which primarily involve infiltration of neutrophils and macrophages at the site of injury. Both cell types have been shown to be present in abundance in necrotic granulomatous and portal regions in liver as well as in renal interstitial tissue in CsA treated animals (Abboud and Kaplowitz, 2007; Selecoki et al., 2007). Neutrophil infiltration has been shown to correlate with the tissue levels of Myeloperoxidase (MPO) enzyme. This enzyme is responsible for generating hypochlorous acid during the neutrophil burst reaction which consequently increases free radical generation and compounds tissue damage. An increase in the level
of MPO is concomitant with elevated tissue levels of TNF-α and NF-κB; indicate the role of inflammatory cells in organ damage caused by CsA (Ying, 2008).

Oxidative stress and infiltration are key features of the inflammatory process that involves the release of various mediators like TNF-α and IL-1β which are well-known to contribute to tissue damage. TNF-α is one of the cytokines that plays an important role in bringing about organ toxicity in association with other tissue-derived reactive moieties. It exacerbates the damage initiated by lipid peroxidation, mitochondrial dysfunction, and the resultant generation of short-lived products like ROS and nitric oxide which is the main cause of CsA hepatotoxicity (Humphries et al., 1998).

A key ligand-activated transcription factor up-regulated by nuclear factor erythroid 2–related factor 2 (Nrf-2) is PPAR-γ (Cho et al., 2005). Notably, PPAR-γ enhances the transcription of anti-inflammatory and antioxidant genes, several of which are also up-regulated by Nrf-2. Protective effects of Nrf-2 are not limited to primary oxidative injury, as Nrf-2 knockout mice display significantly increased mortality in states of systemic inflammation, such as sepsis (Thimmulappa et al., 2016). This effect is likely accounted for by the ability of Nrf-2-induced genes to block both the direct injurious effects of oxidants and the stimulatory effects of oxidant stress on inflammatory gene transcription. In addition, PPAR-γ trans represses key proinflammatory transcription factors, including NF-κB, STAT6, and activating protein-1AP-1 (Becker et al., 2006).

A comprehensive understanding of trans repressive mechanisms is in evolution. One mechanism involves competition for coactivator molecules that these transcription factors require, whereas other evidence suggests PPAR-γ may exert trans repressive activity by directly binding to NF-κB or by a process of Simulation (Gerry and Pascual, 2008).

Peroxisome Proliferator-activated receptor-γ is also expressed in various immune system-related cell types, particularly in antigen-presenting cells such as macrophages and dendritic cells. In these cells, PPAR-γ does not only regulate genes related to lipid metabolism, but also immunity and inflammation related (Sun et al., 2008; Yang et al., 2013). Also the anti-atherosclerosis activity of PPAR-γ activating thiazolidinediones observed in animal models is thought to be generated primarily through modulation of PPAR-γ regulated gene expression in macrophages (Burkart et al., 2007). In addition to its metabolic and anti-inflammatory properties, PPAR-γ also modulates proliferation and apoptosis of many cancers cell types, and is expressed in many human tumors including lung, breast, colon, prostate, and bladder cancer (Burkart et al., 2007).

2.4. Up regulation of Wnt/β-Catenin Signaling

Another important signaling pathway that is involved in development and/or progression of liver diseases is Wnt/β-catenin pathway (Monga, 2015). It is considered as an evolutionarily conserved signaling pathway that has a fundamental role in regulating a variety of biologic processes such as organ development, tissue homeostasis, and pathogenesis of human diseases. On one side, the hepatocytes and liver-infiltrating macrophages are strongly considered as a source of Wnt ligands and hence, Wnt pathway has been suggested to have a role in liver inflammation and fibrosis progression in hepatotoxicity (Debebe et al., 2017).

On the other side, Wnt/β-catenin pathway has a significant role in controlling metabolic plasticity of the liver, whereas, canonical Wnt signaling via β-catenin in the hepatocytes affects sinusoidal oxygen gradient, mitochondrial function and hepatic fatty acid oxidation as well as systemic adiposity (Behari et al., 2014). The connection between the WNT/β-catenin pathway and PPAR-γ concerns the TCF/LEF β-catenin domain in addition to a catenin binding domain within PPAR-γ. In many mammalian cells, PPAR-γ and WNT/β-catenin signaling perform in an opposite manner (Vallée et al., 2017). In several diseases, even if the WNT/β-catenin pathway is downregulated, PPAR-γ appears to be significantly upregulated (Lecarpentier et al., 2014). This has been experimentally investigated in arrhythmogenic right ventricular cardiomyopathy (Djouadi et al., 2009), osteoporosis disease, bipolar disorder, in addition to schizophrenia and certain neurodegenerative diseases (NDs) for example Alzheimer's disease (Vallée and Lecarpentier, 2016).

In other diseases, WNT/β-catenin signaling process is upregulated while PPAR-γ expression is
downregulated. This is the case of cancers, type 2 diabetes, and certain NDs, such as amyotrophic lateral sclerosis Huntington's disease, multiple sclerosis, and Friedreich's ataxia (Vallée and Lecarpentier, 2016). In several cellular systems, β-catenin is inhibited by PPAR-γ agonists (Vallée et al., 2017). It has moreover been shown that inhibition of the WNT/β-catenin pathway triggers activation of PPAR-γ (Garcia-Gras et al., 2006). Accordingly, PPAR-γ and Wnt/β-catenin signaling work in opposite directions. so, the decrease in the level of PPAR-γ, will preferentially drive β-catenin to upregulate Wnt/β-catenin signaling which in turn induces c-myc expression. An increase in c-myc expression leads to an increase in p53, which is the main cause of hepatic apoptosis (Vallée et al., 2017).

3. Conclusion

CsA induces hepatotoxicity by inducing oxidative stress, inflammation and upregulation of Wnt/β-catenin signaling. Oxidative stress is characterized by an imbalance in the production of ROS and antioxidants in the liver, causing cellular disruption. Sustained oxidative stress can trigger inflammation by activating the transcription of NF-κB that induces production of inflammatory mediators like TNF-α. Therefore, reducing inflammation and oxidative stress and inhibition of Wnt/β-catenin signaling is the main target to manage CsA hepatotoxicity.

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