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Review Article

Histone deacetylase inhibitors: pharmacotherapeutic implications as epigenetic modifier

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ABSTRACT

Epigenetic modifications such as acetylation and deacetylation of histone proteins play a decisive role in transcriptional alteration and expression of genes. Acetylation is catalysed by the histone acetyl transferases enzymes and activates expression of genes by converting chromatin into a less compact, transcriptionally active state. Histone deacetylases enzymes catalyze deacetylation that condenses chromatin into a closed structure .Consequently transcriptional factors are unable to access DNA and gene expression is suppressed. Balanced activity of HATs and HDACS is essential for normal gene expression. Increased HDAC activity can lead to imbalance in protein acetylation resulting in hypoacetylation, tight chromatin structure and suppression of various genes. This aberrant suppression of genes is the hallmark of several malignant and other diseases including neurodegenerative disorders. Histone Deacetylase Inhibitors (HDACIs) have potential to restore the balance of histone acetylation that reverses the silencing of pathological genes. Thus HDACIs modify expression of genes without affecting sequence of DNA and act as epigenetic modifiers. Vorinostat and romidepsin are FDA approved HDACIs. Valproic acid, belinostat and many others are in different phases of clinical trials. This review article explores the target based epigenetic mechanisms as well as existing and potential therapeutic role of HDACIs in various malignant and non-malignant diseases. Data sources were articles published in medical journals and bibliographic database Medline.

Keywords: Epigenetics, Histone deacetylase inhibitors, Vorinostat

INTRODUCTION

Histone Deacetylase Inhibitors (HDACIs) are epigenetically active, new generation target specific therapeutic agents for the treatment of various oncological and non-oncological disorders including neurodegenerative disorders. In this review article our endeavour is to explore the latest research work going on pharmacotherapeutic role of HDACIs as epigenetic modifier in various diseases. A through electronic search of bibliographic databases (pub med and science direct), electronic as well as manual search of medical journals and extensive review of references from both preclinical & clinical studies were used to incorporate all recent aspects in this field.

WHAT IS EPIGENETICS

The term epigenetics is defined as stable heritable phenotype resulting from changes in genome without any alteration in DNA sequence.[1] Thus, epigenetics is the study of mitotically or meiotically heritable changes in gene expression and functions that can't be explained on basis of changes in DNA sequence. It is based upon post-translational modifications such as acetylation of histone and non-histone proteins associated with genome.[2]

GENE EXPRESSION: ROLE OF HISTONES AND ASSOCIATED ENZYMES

Regulation of gene expression occurs on a complex structure called chromatin or genome that is composed of DNA, histones, and non-histone proteins. There are five classes of histones: H1, H2A, H2B, H3 and H4. Among

these, H1 histones are the least tightly bound to chromatin, hence are easily removable. Therefore core histones consist of only 4 classes i.e. H2A, H2B, H3 and H4. These core histones serve to wrap DNA into nucleosome that is the basic fundamental unit of chromosome. Each core histone bears one central domain and a lysine rich tail domain.[3] For gene expression, DNA must be accessible to transcriptional machinery including Transcriptional Factors (TFs) that is determined by the chromatin remodeling. Post translational modification such as acetylation or deacetylation of epsilon amino group of lysine residues in the tail of core histones affects the net electrical charges, shape and other properties of histone proteins associated with chromatin and it is the major epigenetic mechanism for chromatin remodelling that leads to the altered gene expression and response.[4]

Acetylation of histones by Histone Acetylase Transferases (HATs) resulting in a more open chromatin structure thus allows TFs to access DNA and activates gene expression. When transcription of genes is not required, the acetylation of nucleosome in that area is reduced by the Histone Deacetylases (HDACs) as a part of gene silencing process. This deacetylation condenses the chromatin into a closed structure. Thus transcription factors are unable to access the DNA resulting in suppression of gene expression.[5]

HATs & HDACs do not bind to DNA directly. Interaction of HATs & HDACs with DNA occurs with the help of multi protein complexes called co activators and co repressors respectively. These multi protein complexes are recruited to the specific regions of chromatin.[6] That's why inhibitors of HDACs can block the activity of these regions only and selectively affects the expression of small proportion of genes resulting in transcriptional activation of some genes and repression of equal or larger no. of other genes.[7]

HOW HDACIs ARE EPIGENETICALLY ACTIVE

Normal expression of genes necessitates controlled and balanced activity of HATs and HDACs. Increased HDACs activity and associated gene silencing may lead to aberrant expression of genes that is the hallmark of various pathological conditions. HDACIs correct this abnormal expression of gene through the pharmacological manipulation of epigenome by inducing hyperacetylation of lysine residues within histone proteins. This increased acetylation results in an open chromatin structure and expression of suppressed gene that restores near normal gene expression. Thus HDACIs modify expression of genes without altering DNA sequence and are termed as epigenetic modifiers. Epigenetic alterations in genome induced by HDACIs make this class of drugs therapeutically effective in various diseases including neoplasms.[8] HDACIs may induce acetylation of some non-histone proteins such as TFs and transcriptional co-regulators resulting in altered transcription of associated genes.[9]

HISTONE DEACETYLASES ENZYMES

There are total 18 HDAC enzymes available in human cells. The HDACs can be divided into two families, (1) The zinc dependent HDACs family composed of CLASS I (HDACs 1, 2, 3 and 8) localized to the nucleus of cells and comprises histone proteins as substrate , CLASS IIa and IIb (HDACs 4, 5, 6, 7, 9 and 10) have both histones and non-histone proteins as substrates which are primarily localized to the cytoplasm but can transfer to nucleus from cytoplasm and CLASS IV (HDAC 11) located in both cytoplasm and in nucleus and share features of both class I & class II. (2) The Zinc independent but NAD-dependent HDACs family includes CLASS III of sirtuins with non-histone proteins as substrates in mammalian cells.[10]

CLASSIFICATION OF HDACIs

HDACIs are categorized as hydroxamates, cyclic tetrapeptides & depsipeptides, benzamides, electrophile ketones and aliphatic acid compounds. Generally the hydroxamic acid derivatives exert nonspecific HDAC inhibitory activity and affect all classes of HDACs. Among aliphatic acid compounds (short chain fatty acid compounds) phenylbutyrate inhibits class I&II HDACs whereas valproic acid inhibits class I & class IIa but not class IIb. All these HDACIs are called broad spectrum HDACIs. Others like benzamides, cyclic tetrapeptides & dipeptides are selective deacetylase inhibitors. HDACIs act exclusively on zinc dependent classes of HDACs: Class I, II &IV HDACs by binding to the zinc-containing catalytic domain of HDACs and are classified as:[11]

First Generation[11]

- Hydroxamic acids : Trichostatin A (TSA)
- Cyclic tetrapeptides and depsipeptides: Trapoxin B, romidepsin
- Benzamides
- Electrophile ketones
- Aliphatic acid compounds: Phenylbutyrate and valproic acid

Second Generation[12]

- Hydroxamic acids: Vorinostat [Suberoylanilide Hydroxamic Acid (SAHA)], belinostat, panobinostat
- Benzamides: Entinostat, mocetinostat and givinostat

Third Generation[13]

- Nicotinamide, dihydrocoumarin, 2-hydroxynaphaldehydes.

THERAPEUTIC IMPLICATIONS OF HDACIs - ONCOLOGICAL INDICATIONS

Mechanism as anticancer

Aberrant transcriptional silencing of genes due to over expression of different isoforms of HDACs is found in many human cancers e.g. HDAC2 and HDAC3 proteins are increased in colon cancer whereas HDAC1 is increased in gastric cancer.[6] HDACs inhibition may restore the expression of specific relevant genes by inducing acetylation of histone and non-histone proteins. Hyperacetylation of histone proteins induces expression of tumor suppressor genes such as p21, p27 and other genetic markers of cell differentiation; and it decreases the expression of genes involved in cell growth such as cyclin D. Thus it leads to cell cycle arrest and limited cell growth. Hyperacetylation of some non-histone proteins such as p53, pRb, STAT 3 may impair their function and thereby arrest the cell growth and survival.[16,26] HDACIs may induce the terminal death of neoplastic cells by activating intrinsic and extrinsic apoptotic pathways, mitotic failure, and free radicals induced cell death through acetylation of associated non histone proteins. Induced acetylation of HIF-1alpha protein (non-histone) may lead to decreased production of Vascular Endothelial Growth Factor (VEGF) and consequentially decreased angiogenesis and tumor cell invasion. Thus HDACs inhibition may restore the normal cell function by interfering with multiple hall mark of cancer. Tumor-cell specificity of HDACIs allows for a tumor-selective therapeutic window and spares normal cells.[14]

HDACIs WITH ANTINEOPLASTIC POTENTIAL

Approved HDACIs are

Vorinostat: It was approved by U.S. FDA in October 2006 for clinical use in cancer patients for treatment of refractory cutaneous T-cell lymphoma. It is also being investigated for use in other haematological malignancies (Hodgkin's lymphoma, non-Hodgkin's lymphoma, and multiple myeloma) and solid malignancies (prostate, bladder, breast, colon, ovarian, and renal). Vorinostat is metabolized by glucuronidation and oxidation and is excreted in urine. It is administered as oral daily dose of 400mg. The $t_{1/2}$ of drug is 2 hrs. Drug interactions are not common as cytochrome P450 isoenzymes are not involved in its metabolism but it can interact with warfarin and valproic acid. At approved 400 mg oral dose the drug is well tolerated with common side effects as anaemia, fatigue, and diarrhoea.[14] Thrombocytopenia is a documented side effect of vorinostat that can lead to decreased synthesis of platelet dependent clotting factors (as phospholipids). In addition to this, synthesis of vitamin K dependent clotting factors in liver is inhibited by warfarin. So thrombocytopenic effect of vorinostat may potentiate the anticoagulant effect of warfarin and may increase the chances of bleeding if these two drugs are used concomitantly.[15]

Romidepsin: Romidepsin, a depsipeptide, was approved by the U.S. F.D.A. in 2009 for cutaneous T-cell lymphoma.[16] The drug is more potent than vorinostat. It is administered intravenously. The $t_{1/2}$ is 2.5 hrs. It is a substrate of P glycoprotein that mediates drug efflux. So the drug is devoid of C.N.S. effects and not effective in brain tumors unlike other HDACIs. Adverse events include nausea, vomiting, and cardiac arrhythmias. It is also being investigated for other haematological and refractory solid malignancies.[17]

HDACIs UNDER CLINICAL TRIALS[14,17-20]

HDACIs under phase III trial are

Panobinostat (LBH 589): The drug is in phase III trial for cutaneous T cell lymphoma. It is a hydroxamic acid based HDACI similar to vorinostat but has longer half-life (5hrs) than vorinostat.

HDACIs under phase II trial are

Valproic acid (VPA): VPA is currently in phase II trial for haematological malignancies and for locally advanced breast cancers.

Belinostat (PXD101): For relapsed ovarian cancer and refractory mesothelioma. It is given as intravenous infusion.

Mocetinostat (MGCD0103): For various cancers including lymphoma and acute myeloid leukaemia.

Entinostat: Currently this drug (in combination with azacitidine) is in clinical trial for myelodysplastic syndromes, chronic myelomonocytic leukaemia, acute myeloid leukaemia with multilineage dysplasia and recurrent advanced non-small cell lung cancer.

Resminostat: For Hodgkin's lymphoma.

Givinostat: For refractory leukaemias and myelomas.

HDACIS under phase I trial are

Vorinostat: For gastrointestinal tract carcinomas.

Valproic acid: For nasopharyngeal carcinoma, advanced solid tumours, neuroectodermal tumours, brain metastases and non-hodgkin lymphoma.

Combination with other anticancer agents

Therapeutic effect of HDACIs is synergistic with radiotherapy and other anticancer drugs such as docetaxel, doxorubicin, etoposide, cisplatin. imatinib, bortezomide and trastuzumab.[6,10] By modulating the histone and non-histone proteins implicated in oncogenesis HDACIs interfere with multiple hallmark of cancer, thus combined effect of HDACIs with radiotherapy and other anticancer drugs is additive.

NON-ONCOLOGICAL INDICATIONS

Disease specific epigenetic mechanism accounts for effectiveness of HDACIs in various diseases besides cancer. Decreased expression of genes involved in synthesis and post receptor signalling pathways of pro-inflammatory cytokines explicate beneficial effects of HDACIs in inflammatory and autoimmune diseases. In neurological disorders HDACIs can correct dysregulation of genes and also provide neuroprotection by their anti-inflammatory effect. De-silencing of latent virus in H.I.V. infection offers therapeutic effect in eradication of AIDS.[21]

Possible molecular mechanism may be hyperacetylation of non-histone proteins including TFs and other cytosolic proteins followed by alteration in expression of related genes.[21] For non-neoplastic indications HDACIs are being investigated mainly in preclinical trials (animal studies) except vorinostat and givinostat which are in different phases of clinical trials. The effective dose range of vorinostat is 100 – 200mg per day for Graft Versus Host Disease whereas it is 400 mg per day for neoplastic diseases.[14] So for non-oncological indications, therapeutic effect appears at doses lower than anti neoplastic doses that reduce the chances of side effects with HDACIs.

Table 1: HDACIs and their mechanism in non-neoplastic diseases.

Sr. No.	Diseases	HDCIs under trial	Type of trial	Mechanism
1.	Neurodegenerative disorder			
i	Alzheimer's disease	Valproic acid, nicotinamide	Preclinical trial	Neuroprotection
ii	Huntington's disease	Vorinostat	Preclinical trial	Reverse transcriptional dysregulation
iii	Ischemic stroke	TSA, valproic acid, givinostat	Preclinical trial	Restoration of acetylation of histone proteins in ischemic brain and neuroprotection
iv	Amyotrophic lateral sclerosis	Phenylbutyrate	Preclinical trial	Reverse transcriptional dysregulation
v	Spinal muscular atrophy	TSA, valproic acid, vorinostat, romidepsin	Preclinical trial	Increased expression of SM2 gene
vi	Parkinson's disease	Valproic acid, phenylbutyrate	Preclinical trial	Increase in tyrosine hydroxylase positive neurons in substantia nigra
2.	Psychiatric disorder	Valproic acid, phenylbutyrate, entinostat	Preclinical trial	Neuroprotection, reverse transcriptional dysregulation
3.	Ophthalmological indications	Valproic acid	Preclinical trial	Neuroprotection
4.	Rheumatoid arthritis	TSA, Givinostat	Preclinical trial Phase I clinical trial	Decreased expression of cytokines and other inflammatory mediators
6.	AIDS: HIV-1 eradication	Valproic acid, givinostat	In vitro studies	Suppression of HIV-1 gene and desilencing of latent virus
5.	Graft versus host disease	Vorinostat	Phase II clinical trial	Decreased expression of cytokines
7.	Bronchial asthma	TSA, valproic acid	Preclinical and Clinical trial	Decreased expression of cytokines and other inflammatory mediators
8.	Diabetes mellitus	Vorinostat, givinostat	Preclinical trial	Protect beta cells from autoimmune destruction
9.	Cardiac hypertrophy	TSA	Preclinical trial	Reverse the dysregulated expression of genes involved in maladaptive autophagy resulting in decreased proliferation of cardiac cells
10.	Atherosclerosis	TSA	Preclinical trial	modulate the expression of pro-atherogenic and pro-inflammatory genes involved in process of atherosclerosis
11.	Acute gout	---	---	Decreased expression of IL-1 may be helpful

NEURODEGENERATIVE DISEASES

Neurodegenerative diseases include atherosclerotic brain diseases, Alzheimer's disease and acute brain damage of cerebral stroke or blunt trauma. Recent studies suggest that epigenetic processes such as DNA methylation and histone modification play an important role in expression of genes involved in synaptic plasticity and eventually contribute to the mechanisms of memory formation and cognition. Thus histone modification can regulate the neuronal activity of brain cells by modulating the expression of concerned genes and drugs that act by histone modification such as HDACIS, can correct the epigenetic defects in brain, responsible for neurodegenerative disorders. Therefore HDACIs may be potential therapeutic agents for neurodegenerative and psychiatric diseases.[22]

Alzheimer's disease (AD)

AD is the most studied neurodegenerative disease. Neuropathological hallmarks of AD are: extracellular stores of β-amyloid and the presence of neurofibrillary tangles due to hyper phosphorylation of *Tau* protein. A class III HDACI, Nicotinamide was found to restore some cognitive deficits in transgenic mouse model of AD.[23] In a study done by Qing et al. (2008), HDAC inhibition with valproic acid was found to decrease β-amyloid production in brain of transgenic mouse model of AD. It also provided effective neuroprotection that was associated with increased acetylation of non-histone proteins.[24] Thus HDACIs may be effective therapeutic agents in AD.

Huntington's disease (HD)

Transcriptional dysregulation followed by mutation of Huntingtin's gene (*htt*) is basically involved in pathogenesis of HD. Vorinostat (SAHA), in doses of 200 mg /kg/day in drinking water, was found to improve the motor coordination in mouse model of HD disease. This drug causes hyperacetylation and corrects transcriptional dysregulation that is the cause of molecular defect in disease.[49] Steffan and colleague (2001) showed that treatment with Vorinostat suppressed on going degeneration of neuronal photoreceptors and reduced lethality in a transgenic *drosophila* model that expresses mutation in *htt* gene.[25] Thus increased *htt* acetylation may be a possible target for HDACIs to bring out therapeutic effect in HD. For this indication the drug is still in preclinical trial, but for neoplastic indications it was approved in 2006.

Ischemic stroke

Acute neurodegenerative disease, stroke, is caused by cerebral ischemia. Middle cerebral artery occlusion model is a well-studied animal model of ischemic stroke. Use of HDACIs was found to restore acetylation at lysine residues of histone proteins in the ischemic brain of rats or mice, with a concomitant decrease in infract volume.[23] Behavioural improvement was also seen with HDACIs, TSA and VPA in a study by Chuang and colleagues in 2007. Anti-inflammatory action of VPA also provided additional neuroprotective effect because of down regulation of pro inflammatory genes. These findings suggest that HDACIS may be effective in cerebral inflammation mediated by ischemic injury to brain.[26] A neuroprotective HDACIs, givinostat (ITF2357) was studied in mouse model of closed head injury where it improved functional recovery and attenuated tissue damage when administered in doses of 10 mg/kg body weight by intraperitoneal route as late as 24 hours post injury.[27]

Therefore HDACIs may be novel therapeutic agents for traumatic brain injury and ischemic stroke, for which no specific pharmacological agent is available clinically.

Amyotrophic Lateral Sclerosis (ALS)

Increasing evidences show that transcriptional dysregulation may play a role in the pathophysiology of ALS. Ferrante and colleagues (2009) showed that combined therapy with phenylbutyrate and riluzole (the only FDA approved drug for treating ALS) was found to be more effective than monotherapy with either drug in a transgenic mouse model of ALS. Phenylbutyrate, a HDACI, was reported safe and well tolerated upon administration for 20 weeks in 26 participants in a dose range of 9 to 21 gram per day. Thus HDACIs are promising newer drugs for ALS.[23,28,29]

Spinal Muscular Atrophy (SMA)

Homozygous deletion of *SMN1*gene is the genetic basis of SMA. Such patients bear at least one copy of *SMN2* gene that synthesize insufficient amount of functional SMN proteins to combat progressive motor neuron degeneration. Thus *SMN2* gene may be a potential therapeutic target for epigenetic drugs such as HDACIs. TSA, Valproic acid, Vorinostat and Romidepsin have this activity in vitro. TSA has been found to be effective in SMA by increasing expression of *SMN2* gene and consequently increased synthesis of functional *SMN2* proteins. In a pilot study, Valproic acid treatment was found to improve muscle power in SMA patients. Thus HDACIs may be potential therapeutic agents for SMA either as mono therapy or combination therapy. [23,30]

Parkinson's disease (PD)

Pathological hallmark of PD is selective loss of dopaminergic neurons in substantia nigra. Beal and colleagues (2004) showed that administration of phenylbutyrate attenuated the depletion of dopamine and loss of tyrosine hydroxylase (dopamine biosynthetic enzymes) positive neurons in substantia nigra of mouse model of PD. Hong and colleagues (2006) demonstrated that treatment with valproic acid, phenylbutyrate caused a

marked increase in tyrosine hydroxylase positive neurons in same model of PD. These studies suggest that HDACIs are potential agents for therapeutic intervention in PD.[23,31,32]

PSYCHIATRIC DISORDER

Recent studies suggest a vital role of epigenetic mechanisms such as histone modification and DNA methylation in neuronal activity of brain cells. These mechanisms also participate in expression of genes related to synaptic plasticity, memory formation and cognition such as reelin and BDNF (brain derived nerve factor). Epigenetic defects initiated during any stage of life (embryogenesis, puberty or adulthood) have been noticed in several psychiatric disorders. So epigenetic modifiers, HDACIs have potential to correct epigenetic defects that affect brain function in schizophrenia and other psychiatric disorders.[33]

Neuroinflammation may be associated with chronic depression and schizophrenia as evidenced by various studies. Valproic acid and phenylbutyrate have shown neuroprotective effect in several *in vitro* studies that may be due to their anti-inflammatory properties. Entinostat has been found to alter the mRNA expression in brain of treated mice like fluoxetine that is an established antidepressant drug. According to recent research, the nucleus accumbens (NAc), situated in limbic region of brain, is involved in the development of behavioural abnormalities as depression. A unique pattern of gene expression is induced in NAc in a chronic stress model in mouse that can be normalized to that of non-stressed control mice by chronic fluxotein treatment. Direct infusion of entinostat in NAc has been found to exert a similar effect on gene expression. Thus stress regulated gene expression in mouse model of chronic stress can be reversed by entinostat & fluoxetine in a similar pattern.[34]

OPHTHALMOLOGICAL INDICATIONS

Valproic acid, a broad spectrum HDACIs, has been found to protect the retina and optic nerve axon from ischemic damage in experimentally induced retinal ischemia and reperfusion in rats. This neuroprotection may involve induction of cytoprotective protein Hsp70 via transcriptional activation and inhibition of mitochondria-mediated apoptosis pathway.[35]

RHEUMATOID ARTHRITIS

HDACIs represent a new class of compounds for the treatment of RA by epigenetically modulating multiple molecular targets in pathogenesis of RA. HDACIs provide their anti- inflammatory effect by controlling the production of inflammatory cytokines and this is done by modulating the expression of associated genes. In animal models of arthritis, use of HDACIs was found to improve the clinical manifestations and it also prevented damage to the bone and cartilage. Increased expression of p21 and p16 in synovial cells and decreased expression of tumor necrosis factor (TNF) alpha in affected tissues in animal models of RA was observed with TSA.[36] A phase I clinical trial of givinostat, a HDACI, has confirmed its efficacy as anti-inflammatory and immunosuppressive agent in children of systemic-onset juvenile idiopathic arthritis.[21]

GRAFT VERSUS HOST DISEASE (GVHD)

In a pilot study, administration of vorinostat reduced clinical severity and mortality from acute GVHD following bone marrow transplantation. Vorinostat is presently in Phase II clinical trials to prevent or reduce disease severity in GVHD in patients with bone marrow transplants.[50]

AIDS: HIV-1 ERADICATION

Although HIV-1 infection can be treated with antiretroviral drugs very effectively but eradication of virus is not possible due to persistence of latently infected CD4 T cell reservoirs. These cells harbour transcriptionally silent but replication competent provirus. HDAC enzyme inhibits HIV -1 gene expression and contributes to the latency of virus within resting CD4 T cells. Various triggers can activate these latent cells to produce new viruses following discontinuation of antiretroviral therapy.[37]

HDACIs, valproic acid and givinostat are capable of inducing expression of dormant virus without fully activating CD4T cells or enhancing de novo infection. A study done by Matalon S. et al. (2010) confirmed the superiority of givinostat over valproic acid for inducing HIV 1 expression in latently infected cells in vitro. This study also revealed that givinostat decreases expression of co receptors CCR5 and CXCR4 which are used along with CD4 receptor by virus to enter into host cell. Hence HDACIs may be valuable futuristic drugs for HIV eradication.[38]

BRONCHIAL ASTHMA

In bronchial asthma role of HDACIs, as a potential therapeutic agent, is a bit controversial. Experimental studies with TSA indicated beneficial effects in well-established murine models of allergic airways diseases. A study by Royee et al. (2011) showed that valproic acid can reduce structural airway remodelling changes and hyper-responsiveness in a mouse model of bronchial asthma. Inhibition of airway hyper responsiveness and agonist induced contraction as well as anti-inflammatory effects of HDACIs may be useful in asthma.[39]

But some studies indicate that reduction of HDAC2 enzyme system is associated with poor response to inhaled corticosteroids and several HDAC2 enhancers as low dose Theophylline are being investigated for this purpose.[40] A study done by Mizunno et al. (2011)

explored that inhibition of HDACs causes emphysema in animal models and HDAC dependent mechanisms contribute to the maintenance of adult lung structure.[41] So further studies are needed to evaluate the effectiveness of HDACIs in bronchial asthma .

DIABETES MELLITUS (DM)

Various in vitro studies confirmed that autoimmune destruction of pancreatic beta cells in Type-1 DM may involve release of cytotoxic cytokines as IL-6, IL-1, IFN gama etc. This mechanism may be dependent on nitric oxide. HDAC inhibition prevents cytokine induced beta cell apoptosis and impaired beta cell destruction. Vorinostat was found to inhibit IL-6 induced increase in nitric oxide in mouse macrophages and in rat's primary islet cells in *in vitro* studies. A similar effect was also observed with givinostat. Thus HDACIs may protect the beta cells from autoimmune destruction by preventing cytokine mediated inflammatory and immune responses.[21,42]

Dysregulation of autophagy may also be involved in DM. Autophagy is the adaptive mechanism of cell loss by reusing intracellular components that have been generated by pathological processes. Insulin producing beta cells undergo apoptoic cell death on account of failure of autophagy. HDACIs correct this abnormal autophagy in pancreatic beta cells by altering expression of associated genes and protect pancreatic beta cells from auto destruction.[21,43]

CARDIAC HYPERTROPHY

Beneficial effect of HDACIs was observed in left ventricular hypertrophy (LVH) in various *in vivo* and *in vitro* studies. TSA was found to obtain near normal left ventricular function in a mouse model of established LVH. Similar results were also reported in animal models of ischemic and non-ischemic (doxorubicin induced) myocardial injury. The possible mechanism may be prevention of maladaptive autophagy resulting in decreased proliferation of cardiac muscles in left ventricle. Thus use of HDACIs reduces ventricular hypertrophy, fibrosis and apoptosis in LVH. But in cases of right ventricular heart failure due to constriction of aortic flow, compensatory hypertrophy of left ventricle is necessary to overcome this restriction. In such cases use of HDACIs may result in loss of this compensatory mechanism that can worsen right ventricular functions. Use of HDACIS has been found to deteriorate right ventricular functions in rats following pulmonary artery banding induced right ventricular failure. These studies suggest that HDACIs may be potential therapeutic agents for LVH, while caution should be used in cases of Right Ventricular Hypertrophy.[21,44]

ATHEROSCLEROSIS

Histone acetylation can modulate the expression of pro-atherogenic and pro-inflammatory genes involved in process of atherosclerosis. Although TSA has been found to exacerbate the atherosclerosis in LDL receptor deficient mouse model but a recent review article by Ordovas JM stated that HDACIs may reduce monocyte adhesion to the endothelium through the suppression of vascular cell adhesion molecule-1(VCAM-1). HDACIs may also reduce angiogenesis by altering vascular endothelial growth factor (VEGF) signalling in endothelium. So HDACIs with anti-inflammatory & without proatherogenic activity may be beneficial in atherosclerosis.[21,45]

ACUTE GOUT

HDACIs, being IL-1 blocker, may be potential therapeutic agent in combination with colchicin, as anakinra, a IL-1 blocker has been found to be effective in acute gouty arthritis in a study by So A et al.[46]

SAFETY AND TOLERABILITY OF HDACIs

Use of HDACIs for malignant diseases is associated with some toxicity due to high dose that is required to treat such diseases. The major dose limiting toxicity is thrombocytopenia due to impaired release of platelets from megakaryocytes. At doses used to treat cancer, all HDACIs cause gastrointestinal disturbances.[21,47] Cardiac adverse events seen with HDACIs in clinical trials are atrial fibrillation, ECG abnormalities as prolonged QT interval, T wave inversion, pulmonary thromboembolism and deep vein thrombosis.[48]

HDACIs are relatively safe and well tolerated at lower doses that are used to treat non oncological disorders as compared to higher antineoplastic doses required for killing tumor cells. But further studies are needed to evaluate the safety and tolerability of these agents.[21]

CONTRAINDICATIONS

Pregnancy, severe hepatic impairment, chronic obstructive pulmonary disease, and thrombocytopenia contraindicate the use of HDACIs.[21]

CONCLUSION

HDAC inhibitors restore back altered epigenetic pattern found in various diseases by inducing post-translational modifications as acetylation of histone and non-histone proteins associated with chromatin .These epigenetic alterations in genome induced by HDACIs make this class of drugs a therapeutically effective agents in various oncological and non-oncological diseases. Two HDACIs, vorinostat (October 2006) and romidepsin (November 2009) have been approved by FDA for cutaneous T cell lymphoma. Others as givinostat, belinostat, panobinostat,

entinostat and mocetinostat are in different phases of clinical trial for various haematological malignancies and solid tumors. Givinostat proves significant anti-Hodgkin's lymphoma activity. Panobinostat has consistent anti-leukemic effects. Belinostat seems to be promising for treatment of ovarian tumor having low malignant potential. Valproic acid has significant clinical activity as combination therapy with decitabine or azacitidine in leukaemia and myelodysplastic syndrome. Preclinical studies with valproic acid and other HDACIs have extended their potential value in diseases other than neoplasms such as neurodegenerative diseases, psychiatric diseases, autoimmune disorders, inflammatory diseases, diabetes mellitus, left ventricular hypertrophy and AIDS. HDACIs like givinostat and vorinostat are now in different phases of clinical trials for non-oncological indications. Thus HDACIs seem to be promising, newer therapeutic agents for both oncological and non-oncological diseases.

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