Review

Clinical development of histone deacetylase inhibitor romidepsin

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ABSTRACT: Histone deactylase inhibitors have emerged as a promising epigenetic therapy for neoplasic indications. The US Food and Drug Administration granted approval to romidepsin for treatment of cutaneous T cell lymphoma (CTCL) in 2009. Phase I/II trials of romidepsin as monotherapy or hybird therapy have demonstrated substantial efficacy profoundly in CTCL and peripheral T-cell lymphoma and marginally in other hematogological malignancies and solid tumors, with a tolerable safety and toxicity profile. The current status of the clinical evaluation of romidepsin is detailed in the present contribution.

Keywords: Histone deactylase inhibitors, romidepsin, clinical activity and toxicities

1. Histone deactylases (HDACs)

A high level of interest has been focused on epigenetic regulation for cancer therapy over the past few years due to facilitated reverse of biochemical modifications in DNA or its chromatin protein complexes by chemotherapeutic intervention relative to genetic lesions in primary DNA sequence (*1*). Acetylation is probably among the best dissected epigenetic alterations and thus HDACs are recognized as an important enzyme of tumor epigenome for the corroborant competence to deacetylate histone as well as non-histone proteins (*2*). Indeed, extensive studies have recently revealed that HDACs can be tethered mechanistically to the oncogensis, maintenance, and peogression of cancer (*2*).

Eighteen HDACs have been identified in the mammalian genome and grouped to four classes based on their homology to the respective yeast transcriptional control factor sequence. Class III HDACs (Surtuin-1 to -7) share domains with yeast silencing protein Sir2 and their dependence on NAD^+ for deacetylase activity attenuates concerns here. Classical HDACs comprising Classes I, II, and IV HDAC family members are Zn^{2+}-dependent: Class I HDACs (HDAC-1, -2, -3, and -8) are closely related to yeast reduced potassium dependency-3 (Rpd3); Class II HDACs, including Class IIa (HDAC-4, -5, -7, and -9) and Class IIb (HDAC-6 and -10), possess sequence similarity to yeast histone deacetylase-1 (Hda1); HDAC11 is homologues of both Rpd3 and Hda1, consequently defining Class IV HDAC. Classes I and IV HDACs are pervasively expressed in diverse tissues and generally localized to the nucleus (*3*). Nevertheless, Class II HDACs, which are restricted to certain cell types, display an uncertain cellular localization owing to their ability to shuttle between nucleus and cytoplasm (*3*).

2. Histone deactylase inhibitors (HDACi) that have entered clinical studies

Recent research has shown that aberrant phenotypes of certain HDAC isoforms make them function nonredundantly to modulate hallmarks in several tumors (*4*). HDACi induce, to a variable extent, cell cycle and growth arrest, differentiation or apoptosis of malignant cells in *in vitro* models and *in vivo* xenografts (*2*). Strikingly, their antitumor efficacy has been clinically substantiated in broad spectrum neoplasms from both hematological and solid origins (*5*). Increasing amounts of HDACi have entered clinical evaluation for various cancers since vorinostat was first approved by FDA for the treatment of cutaneous T cell lymphoma (CTCL) (*6*). These candidates, with few exceptions, can be placed into major HDACi chemical classes including hydroxamates (vorinostat, CUDC-101, SB939, panobinostat, belinostat, resminostat, PCI-24781, givinostat, AR-42, CHR-2845, CHR-3996, JNJ-26481585, and R306465), cyclic peptides (romidepsin), benzamides (entinostat, mocetinostat, chidamide, and tacedinaline), and carboxylates (valproic acid, butyrate, AN-9, and phenylbutyrate). Their structures and clinical phases are shown in Figure 1.

Romidepsin has displayed good activity in hematogological and solid malignancies with a tolerable safety profile as monotherapy or hybird therapy in the clinic (*7-19*). On November 5, 2009, FDA granted

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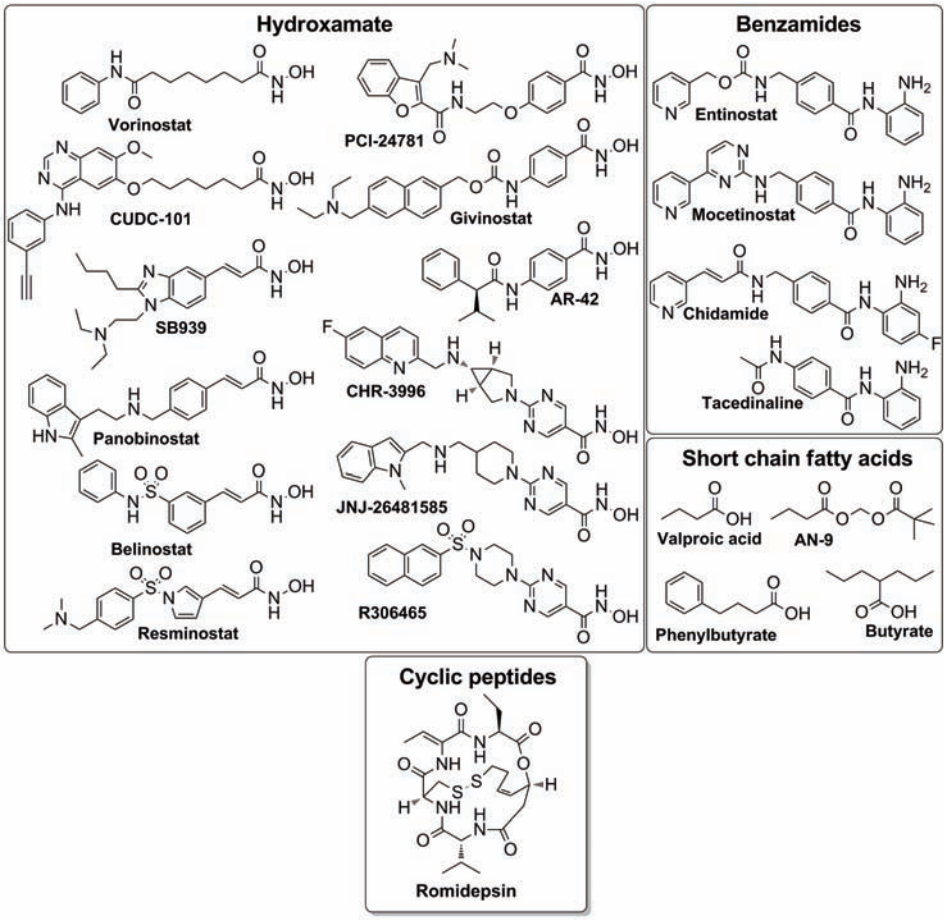

Figure 1. HDAC inhibitors under clinical development. Clinical trials for each candidate have been performed as follows: vorinostat, phase I/II/III; CUDC-101, phase I; SB939, phase I/II; panobinostat, phase I/II/III; belinostat, phase I/II; resminostat, phase II; PCI-24781, phase I/II; givinostat, phase II; AR-42, A phase I trial is not yet open for participant recruitment; CHR-3996, phase I; JNJ-26481585, phase I; R306465, A phase I trial has been completed; romidepsin, phase I/II; entinostat, phase I/II; mocetinostat, phase II; chidamide, phase II; tacedinaline, phase II/III; valproic acid, phase I/II/III; phenylbutyrate, phase I/II; AN-9, phase II; butyrate, phase II.

approval to use romidepsin for injection for treatment of CTCL in patients who have received at least one prior systemic therapy (*20*), which will hopefully accelerate the investigation of vorinostat for a broader range of cancers. We concentrate next on describing development of clinical application for romidepsin.

3. Clinical evaluation of romidepsin

In a pharmacokinetic report in T-cell lymphoma, romidepsin at doses of 14 or 18 mg/m^2 as a 4-hour intravenous (IV) infusion resulted in moderate interindividual variability in pharmacokinetics as exemplified by the population clearance of 15.9 L/h with between-patient variability of 37% (*21*).

Romidepsin demonstrated significant and durable single-agent clinical efficacy in CTCL, making it a valuable therapeutic option for treatment. It was reported that there were two phase II, open-label, multicenter trials in patients with CTCL of romidepsin at a dose of 14 mg/m^2 4-hour IV infusion on days 1, 8, and 15 every 28 days (*7-10*). One clinical trial GPI-04-0001 enrolled 96 patients with stage IB-IVA CTCL who had received one or more prior systemic therapies (*7,8*). The objective response rate (ORR) was 34% (6 patients with complete response (CR) and 27 patients with partial response (PR)) with median duration of response (DOR) of up to 15 months. Thirty-eight percent of 68 patients with advanced-stage (stages ≥ IIB) disease had a response including 5 CRs. Response was determined by a composite endpoint comprised of cutaneous disease, lymph node involvement, and abnormal circulating T-cells (*7*). Additionally, 6 patients with a ≥ 50% skin response, 5 patients with ≥ 30% of the longest diameter node, and 27 patients with ≥ 50% reduction in circulating Sézary cells did not achieve a composite response (*8*). The other clinical trial NCI 1312 involved 71 patients with CTCL at stage IA-IVB (*9,10*). There were 6 CRs and 21 PRs contributing to an ORR of 36% at all stages of disease. Responses were noted in 32% of patients at stage ≥ IIB and 20% of patients at stage IV. An additional 27% of the enrolled patients had stable disease (SD) for at least 90 days. Median DOR was 11 months and the maximum progression-free survival was more than 5.5 years (*9*). Data from these two studies were pooled for an ORR of 35% in all stages (Table 1). It is noted that there was an

ORR of 42% in stage ≥ IIB (*10*). The ORR, CR, DOR, improvement in all disease compartments, and responses at all stages make romidepsin an important therapeutic option for treatment of CTCL. Romidepsin is a robust and preferential therapy on the basis of the ORR, DOR, and improvement in total tumor burden at all stages.

A profound and sustained clinical benefit for romidepsin was observed in peripheral T-cell lymphoma (PTCL) besides CTCL as reported by Piekarz *et al.* (*11*). The ORR was 39% as shown in Table 2. The median DOR for all patients was 8.3 months (range from 1.6 months to more than 4.8 years) and that for CRs was 8.5 months (range from 4.6 months to more than 4.8 years) (*11*).

With increasing proof of limited clinical activity in other forms of hematologic and solid neoplasms (Table 2) (*12-18*), romidepsin was advanced into assessment as a combination therapy. Harrison *et al*. reported that romidepsin in combination with bortezomib and dexamethasone attained a high response rate of 95% (ORR 67% + minimal response 28%) in impressive depth (44% CR + very good partial responses) in multiple myeloma (MM) (*19*).

Romidepsin showed a tolerable toxicity profile in CTCL. The most frequent drug-related adverse events (AEs) were generally mild and included nausea (67%), fatigue (49%), anorexia (37%), electrocardiography T-wave changes (29%), anemia (26%), dysgeusia (23%), neutropenia (22%), and leucopenia (20%). Serious AEs of supraventricular arrhythmia, ventricular arrhythmia, infection, neutropenia, white blood cell decrease, hyperuricemia, and hypotension were seen in 2% of patients (*10*). As for PTCL the most common AEs attributable to the study drug were nausea (86%), fatigue (79%), decreased platelets (70%) and decreased absolute granulocyte count (63%) (*11*). Cabell *et al*. evaluated the potential cardiac effects of romidepsin and found it mild on the QT interval which is below the threshold of regulatory and clinical concerns (*22*).

Romidepsin is being clinically evaluated in multiple phase I/II investigations as monotherapy and combination therapy for cancers of the urothelium, esophageal, pleural, and neuroendocrine areas, as well as acute myeloid leukemia, chronic lymphocytic leukemia, and small lymphocytic lymphoma in addition to the indications mentioned above (Table 3) (*23*).

Table 1. Data from clinical trial GPI-04-0001 and NCI 1312 and their pooled analyses

	Clinical trials		Pooled
	GPI-04-0001	NCI 1312	
CR, *n* (%)	6/96 (6%)	4/71 (6%)	10/167 (6%)
PR, *n* (%)	27/96 (28%)	21/71 (30%)	48/167 (29%)
ORR, *n* (%)	33/96 (34%)	25/71 (36%)	58/167 (35%)
DOR	15 months	11 months	13.8 months

Table 2. Data from clinical trials of romidepsin

Indication	CR, *n* (%)	PR, *n* (%)	SD, *n* (%)	Reference
Peripheral T-cell lymphoma (PTCL)	7/43 (16%)	10/43 (23%)	NA	(*11*)
Acute myelogenous leukemia (AML)	1/11 (9%)	0	6/11 (55%)	(*12*)
Metastatic renal cell cancer	1/29 (3%)	1/29 (3%)	NA	(*13*)
Hormone refractory prostate cancer	0	1/21 (5%)	2/21 (10%)	(*14*)
Nonmedullary thyroid carcinoma	0	0	10/20 (50%)	(*15*)
Lung cancer	0	0	9/18 (50%)	(*16*)
Squamous cell carcinoma of the head and neck	0	0	2/10 (20%)	(*17*)
Colorectal cancer	0	0	4/25 (16%)	(*18*)

Table 3. Ongoing clinical trials of romidepsin (*23*)

Clinical trial	Indication	Clinical phase	Therapy
NCT00383565	Relapsed/refractory non-Hodgkin's lymphoma	II	Monotherapy
NCT00007345	Cutaneous T-cell lymphoma and relapsed peripheral T-cell lymphoma	II	Monotherapy
NCT00477698	Early stage cutaneous T-cell lymphoma	I	Monotherapy
NCT00426764	Progressive/relapsed peripheral T-cell lymphoma	II	Monotherapy
NCT00299351	Peripheral T-cell lymphoma	II	Monotherapy
NCT00062075	Relapsed/refractory acute myeloid leukemia	II	Monotherapy
NCT00963274	Chronic lymphocytic leukemia/small lymphocytic lymphoma	I	+ Bortezomib
NCT00431990	Relapsed myeloma	I/II	+ Bortezomib
NCT00066638	Relapsed/refractory multiple myeloma	II	Monotherapy
NCT00098813	Radioiodine-refractory metastatic thyroid carcinoma	II	Monotherapy
NCT00084461	Metastatic neuroendocrine tumors	II	Monotherapy
NCT00112463	Metastatic/unresectable soft tissue sarcomas	II	Monotherapy
NCT00084682	Unresectable recurrent or metastatic squamous cell carcinoma of the head and neck	II	Monotherapy
NCT00104884	Advanced malignant melanoma	II	Monotherapy
NCT00087295	Advanced cancer of the urothelium	II	Monotherapy
NCT00098644	Advanced lung, esophageal, or pleural cancer	I	+ Flavopiridol

4. Conclusions and future perspectives

HDACi create a robuse avenue in epigenetic therapy for malignant diseases. Romidepsin has shown robust activity in hematogological malignancies and solid tumors as well as tolerability in the clinic according to monotherapeutic and combined therapeutic regimens. Work is underway to continue clinical evaluation of current synergies and preclinical exploration of novel indications for optional treatment of cancers.

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