Commentary
Tanovea® for the treatment of lymphoma in dogs
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Abstract
Tanovea® (first named GS-9219, then VDC-1101, generic name: rabacfosadine) is a pro-drug or “double” prodrug of PMEG [9-(2-phosphonylmethoxyethyl)guanine], which has been conditionally approved by the US FDA (Food and Drug Administration) for the treatment of lymphoma in dogs. Tanovea has been demonstrated to be effective against non-Hodgkin’s lymphoma (NHL) in dogs, as well as canine cutaneous T-cell lymphoma, spontaneous canine multiple myeloma, naive canine multicentric lymphoma and relapsed canine B-cell lymphoma. As a double prodrug of PMEG, GS-9219 is first converted intracellularly by hydrolysis to cPr-PMEDAP, then deaminated to PMEG, which is then phosphorylated twice to its active metabolite PMEGpp, acting at the level of the cellular DNA polymerases.

1. Introduction
The acyclic nucleoside phosphonates (ANPs: [1]) have received major attention and clinical usefulness as antiviral drugs in the treatment of HIV (human immunodeficiency virus) and HBV (hepatitis B virus) infections. Foremost have been TDF (tenofovir disoproxil fumarate) [2] and TAF (tenofovir alafenamide) [3], which became the cornerstone for the treatment of HIV and HBV infections; TDF and TAF in combination with various other anti-HIV drugs, in the treatment of HIV infections, and TDF (Viread®) and TAF (Vemlidy®) as such for the treatment of HBV infections. In combination with emtricitabine, TDF has also been approved, as Truvada®, in the US in 2012, and 4 years later in the EU, for the prevention (PrEP: pre-exposure prophylaxis) of HIV infections.

What is widely accepted is that, being ANPs, both TDF and TAF, which qualify as antiviral agents for the treatment of HIV and HBV infections, stem from Dr. Antonín Holý’s legacy [4]. What is hardly recognized, however, is that the first anti-tumor drug, Tanovea® (rabacfosadine), ever approved by the US Food and Drug Administration (FDA) for the treatment of lymphoma in dogs also originates from the same class of compounds, referred to as ANPs [1]. Where did Tanovea® come from? What are its credentials? How does it work? And where it may lead to? This will be the subject of the present Commentary.

2. History
The era of the ANPs started with the demonstration that (S)-HPMPA [(S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine] and its closely related analogue PMEA [9-(2-phosphonylmethoxyethyl)adenine] had broad-spectrum anti-DNA virus activity [5]. In the follow-up paper [6], various other phosphonylmethoxyalkyl derivatives of purines and pyrimidines, including the guanine counterpart of PMEA, 9-(2-phosphonylmethoxyethyl)guanine (PMEG), were described as antiviral agents, PMEG being the most cytotoxic of the series.

PMEG was subsequently found effective against Shope papilloma virus infection in rabbits and human papilloma virus type 11 infection in human foreskin xenografts in athymic nude mice [7]. Kreider noted that “drug toxicity paralleled the therapeutic effects in rabbits but there was much less toxicity in athymic mice”. Of (S)-HPMPA, PMEA and PMEG, the latter was the most active in inhibiting intraperitoneal P388 leukemia in mice [8]. The in vivo antitumor activity of PMEG was noteworthy as the compound was considered “representative of a new class of antitumor antimetabolites heretofore recognized only for their antiviral properties”.

PMEG was then shown to owe its cytotoxic activity to the inhibitory effects of its diphosphate (PMEGpp) on the cellular DNA polymerases, particularly α, δ and ε [9], and the incorporation of PMEG into DNA by DNA polymerases δ and ε [10].

Holý reported on the inhibition of murine lymphocyte proliferation by N5-substituted acyclic purine nucleoside phosphonates [11]. One of these N5-substituted derivatives, cPr-PMEDAP [9-(2-phosphonylmethoxyethyl)-N5-cycloprenyl-2,6-diaminopurine] was then found to block choriocarcinoma in rats, thereby acting as a prodrug of PMEG [12]. Apparently cPr-PMEDAP was converted to PMEG through an as yet unidentified cellular enzyme, as both adenosine deaminase and adenylyl deaminase proved unable to deaminate cPr-PMEDAP [13]. Later on, Schinkmanová et al. [14,15] would identify the enzyme responsible for converting cPr-PMEDAP to PMEG. It would be the same
enzyme as that responsible for converting abacavir 5′-monophosphate to carbovir 5′-monophosphate. Unlike cPr-PMEDAP that is converted to PMEG, PMEDAP would not be deaminated to PMEG but directly phosphorylated to PMEDApp and PMEDAppp [16].

In addition to cPr-PMEDAP, a few other N^2-substituted PMEDAP derivatives have been described [17], but they were not considered superior to the parental PMEDAP for the treatment of hematological malignancies. Yet, transdermal or topical application of cPr-PMEDAP has been considered as an attractive alternative route for the administration of this potentially useful antitumor/antiviral agent [18].

6. Efficacy of Tanovea® in canine T- and B-cell lymphoma and multiple myeloma

Tanovea® (alias VDC-1101 and GS-9219) was shown to be effective against spontaneous canine multiple myeloma at well-tolerated doses [24]. In vitro, it exhibited antiproliferative activity against several human multiple myeloma-derived cell lines (H-929, RPMI-8226, and U-266) [19,27]. In vivo, it proved effective against canine cutaneous T-cell lymphoma (CTCL), a malignant disease with a poor prognosis, where it achieved an objective response rate (ORR) of 45% [25].

The current standard of care for the treatment of dogs with multicentric lymphoma is combination chemotherapy including cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) [26]. Objective response rates (ORR) of ≥85% and median response durations of 6–10 months, and median response durations of 8–12 months have been reported with CHOP-based protocols (see Section 1 in Thamm et al. [27]). Most dogs that achieve remission after a CHOP-based chemotherapy protocol eventually relapse, with <25% of dogs experiencing survival times ≥2 years. Since treatment of lymphoma in dogs is not curative, owners may be hesitant to commit the time and financial resources necessary to complete a lengthy multidrug protocol [28].

Dogs with naïve multicentric lymphoma that received alternating Tanovea® (rabacfosadine) (1 mg/kg iv at weeks 0, 6, 12) and doxorubicin (30 mg/m^2 iv at weeks 3, 9, 15) showed an overall response rate of 84% and an overall median progression-free interval (PFI) of 194 days [27]. Alternating rabacfosadine/doxorubicin generally was well tolerated, with a PFI comparable to standard doxorubicin-based treatment regimens (CHOP, and fewer treatment cycles). Most adverse events were mild and moderate and self-limiting. Fig. 4 illustrates the effect of the immunophenotype on the progression-free survival of dogs with naïve multicentric lymphoma following treatment with alternating rabacfosadine/doxorubicin [27].

In dogs with relapsing canine B-cell lymphoma, rabacfosadine, dosed at either 0.82 mg/kg or 1.0 mg/kg as a 30-min iv infusion every 21 days for up to 5 treatments, achieved an overall response rate of 74%, with 45% of dogs experiencing a complete response, with PFIs up to 203 days [29]. It was concluded that rabacfosadine is an effective treatment for dogs with B-cell lymphoma that relapsed following an initial doxorubicin-based chemotherapy regimen.

7. Perspectives

In general, chemotherapy protocols, i.e. CHOP, are first evaluated in humans before, if successful, to be applied in animals, i.e. pet dogs. Here, the compound Tanovea® was conditionally approved by the US FDA, without being pursued for its potential usefulness in humans. The question to be raised is whether the information gathered by the use of Tanovea in dogs would facilitate its application in the appropriate conditions in humans?

The compound has been indicated for the treatment of lymphoma in dogs. Its efficacy has been demonstrated in the treatment of NHL (Non-Hodgkin’s lymphoma) and multiple myeloma. Should it also find utility in the chemotherapy of other malignant diseases in dogs and other pet animals?

For the treatment of HIV infections in human, ANPs are, as a rule, combined with other anti-HIV drugs, whereas for the treatment of HBV infections the antivirals are generally used as single drugs. For the treatment of malignancies, so as to reduce the likelihood of relapses, it may be advocated to use Tanovea in combination with other antitumor drugs, either simultaneously or sequentially (as has already been done
Fig. 1. Metabolism of GS-9219 (Tanovea®), via cPr-PMEDAP, to PMEG and its active form, PMEGpp, the diphosphate of PMEG. PMEGpp then inhibits the DNA polymerase(s) and/or is incorporated, as PMEG, into DNA [9,10].

Fig. 2. Representative FLT-PET/CT of a dog with non-Hodgkin's lymphoma before and after GS-9219 treatment. FLT-PET/CT scan before (A) and 5 d after a single 0.66 mg/kg dose of GS-9219 (B) in a dog with stage V, B-cell non-Hodgkin's lymphoma. A third scan was done 3 wk following completion of five cycles of GS-9219 (C). Bottom, whole-body FLT-PET/CT scans at three time points; top, cross-sectional FLT-PET/CT. Whole-body PET scan before therapy (A) shows significant proliferative response in affected lymphoid tissues (popliteal, mesenteric, mediastinal, prescapular, submandibular lymph nodes, and spleen). Scans repeated 5 d after initial therapy (B) and 3 wk following completion of all treatment cycles (C) clearly indicate biological response as measured by significantly diminished uptake of tracers. Data taken from Vail et al. [23].
with alternating rabacfosadine/doxorubicin [27].

Tanovea has so far been used only for iv infusion, as GS-9219 was specifically formulated for this purpose. Yet, the use of a permeation enhancer DDAK (dodecyl 6-dimethylaminohexanoate) may provide an attractive alternative route of topical or transdermal administration for cPr-PMEDAP, the prodrug of PMEG to which GS-9219 is converted [18].

Finally, novel acyclic nucleotide analogues GS-343074 and GS-424044, both produgs of PMEG, for which the chemical structures were not revealed, have been reported to demonstrate antiproliferative and pro-apoptotic activity in canine neoplastic cell lines [30]. Hence, compounds similar to Tanovea® are at the horizon, which could be further explored for their potency and/or safety.

8. Conflict of interest

The author is co-inventor of Tanovea.

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References


