The Role of Lymphatic Transport on the Systemic Bioavailability of the Bcl-2 Protein Family Inhibitors Navitoclax (ABT-263) and ABT-199

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ABSTRACT

Navitoclax (ABT-263), a Bcl-2 family inhibitor and ABT-199, a Bcl-2 selective inhibitor, are high molecular weight, high logP molecules that show low solubility in aqueous media. While these properties are associated with low oral bioavailability (F), both navitoclax and ABT-199 showed moderate F in preclinical species. The objective of the described study was to determine if lymphatic transport contributes to the systemic availability of navitoclax and ABT-199 in dogs. The intravenous pharmacokinetics of navitoclax and ABT-199 were determined in intact (noncannulated) dogs. In oral studies, tablets (100 mg) of navitoclax and ABT-199 were administered to both intact and thoracic lymph duct-cannulated (TDC) dogs. The clearance of navitoclax and ABT-199 was low; 0.673 and 0.779 ml/min per kilogram, respectively. The volume of distribution of both compounds was low (0.5-0.7 l/kg). The half-lives of navitoclax and ABT-199 were 22.2 and 12.9 hours, respectively. The F of navitoclax and ABT-199 were 56.5 and 38.8%, respectively, in fed intact dogs. In fed TDC dogs, 13.5 and 4.67% of the total navitoclax and ABT-199 doses were observed in lymph with the F of navitoclax and ABT-199 of 21.7 and 20.2%, respectively. The lower lymphatic transport of ABT-199 corresponds to the lower overall F of ABT-199 versus navitoclax despite similar systemic availability via the portal vein (similar F in TDC animals). This is consistent with the higher long chain triglyceride solubility of navitoclax (9.2 mg/ml) versus ABT-199 (2.2 mg/ml). In fasted TDC animals, lymph transport of navitoclax and ABT-199 decreased by 1.8-fold and 10-fold, respectively.

Introduction

Navitoclax (ABT-263; benzamide, 4-[4-[(2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl)methyl]-1-piperazinyl]-N-[4-[(1R)-3-(4-morpholinyl)-1-[phenylthio)methyl] propyl]amino]-3-[(trifluoromethyl)sulfonyl]phenyl sulfonyl]) is a small-molecule Bcl-2 family protein inhibitor that binds with high affinity (K_i < 1 nM) to multiple antiapoptotic Bcl-2 family proteins including Bcl-xl, Bcl-2, and Bcl-w, while showing lower affinity for Mcl-1 (Park et al., 2006; Tse et al., 2008). ABT-199 (2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl]benzamide) is a first-in-class orally bioavailable small-molecule Bcl-2 family protein inhibitor that binds with high affinity (Ki <0.01 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins, Bcl-xl, Bcl-w and Mcl-1 (Ki = 48 nM, 245 nM and >444 nM, respectively) (Souers et al., 2013).

The deep and large hydrophobic BH3-binding groove of the Bcl-2 family members necessitates that small molecules occupying the space are hydrophobic and have high molecular weight (Park et al., 2006; Petros et al., 2006; Petros et al., 2010). Therefore, the physicochemical properties of both the BH3 mimetics navitoclax and ABT-199 (Table 1) do not conform to the “Lipinski rule of 5” (Lipinski et al., 2001), and it would be predicted that both compounds have low bioavailability after oral dosing. However, both compounds have reasonable exposure preclinically and clinically (Wilson et al., 2010; Seymour et al., 2012).

Overexpression of antiapoptotic Bcl-2 family proteins is associated with tumor maintenance and progression and increased resistance to chemotherapy, and are thus compelling targets for anticancer therapy (Strasser et al., 2000; Cory et al., 2003; Adams et al., 2005). Navitoclax is a first-in-class orally bioavailable inhibitor of Bcl-2 and Bcl-XL that is currently in Phase II clinical trials. To date, navitoclax has shown a reduction in tumor burden in patients with hematologic malignancies believed to be dependent on Bcl-2 for survival (Tse et al., 2008; Wilson et al., 2010; Roberts et al., 2012). ABT-199 is a first-in-class Bcl-2 selective inhibitor that has recently entered clinical trials in patients with chronic lymphocytic leukemia (CLL), where it has shown clinical activity upon oral administration (Davids et al., 2012; Seymour et al., 2012).

Abbreviations: ABT-199, 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)sulfonyl]benzamide; AUC, area under the curve; CL, clearance; F, bioavailability; HPLC, high-performance liquid chromatography; LCT, long chain triglyceride; LC-MS/MS, liquid chromatography–tandem mass spectrometry; Navitoclax (ABT-263), benzamide, 4-[4-[(2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl)methyl]-1-piperazinyl]-N-[4-[(1R)-3-(4-morpholinyl)-1-[phenylthio)methyl] propyl]amino]-3-[(trifluoromethyl)sulfonyl]phenyl sulfonyl]; TDC, thoracic lymph duct–cannulated; TFA, trifluoroacetic acid;
Davids et al., 2012; Roberts et al., 2012; Seymour et al., 2012). One possible explanation for the relatively high oral exposure observed in preclinical species as well as human patients is the high lipophilicity of these compounds, a physicochemical attribute that could contribute to oral absorption via lymphatic transport (Porter and Charman, 2001; Trevaskis et al., 2008).

While in vitro measurements, such as long chain fatty acid solubility, logD/P (Trevaskis et al., 2008), or association with plasma chylomicrons (Gershkovich and Hoffman, 2005), may provide some indication of whether a compound will undergo lymphatic transport, in vivo animal studies provide the only means of directly measuring the amount of compound in lymph. The added advantage of the conscious dog model is the ability to administer human dose forms/tablets. Therefore, the objective of this study was to determine if lymphatic transport contributes to the systemic availability of navitoclax and ABT-199 using the conscious thoracic lymph-cannulated dog model.

Materials and Methods

Navitoclax and ABT-199 were synthesized and tablets were manufactured by Abbott Laboratories (Abbott Park, IL). All other reagents or material used in these studies were purchased from Sigma-Aldrich (St. Louis, MO) unless otherwise stated.

Determination of Physicochemical Properties. The thermodynamic solubility of navitoclax and ABT-199 in aqueous or oil-based media were determined by equilibrating navitoclax or ABT-199 in excess crystalline pharmaceutical ingredient (API). For aqueous solubility, samples were equilibrated for 48 hours at 25°C (buffers) or 37°C in Fasted- and Fed-State Simulated Intestinal Fluid (FaSSIF or FeSSIF) followed by centrifugation at 3000g for 10 minutes and filtration through a syringe filter. Sample concentration in the supernatant was measured by high-performance liquid chromatography (HPLC). ABT-199 HPLC analysis was conducted on an Agilent 1100 HPLC using 0.1% trifluoroacetic acid (TFA) in water and 50:50 acetonitrile/methanol as mobile phases on a 150 × 4.6 mm 3.5-μm Xorbax XDB-C18 (Agilent Technologies, Santa Clara, CA) column with gradient from 60 to 95% B over 7 minutes with UV monitoring at 314 nm. Navitoclax HPLC analysis was conducted on an Agilent 1100 HPLC using 10 mM ammonium bicarbonate, pH 9.5, and 85:15 acetonitrile/methanol as mobile phases on a 100 × 3.0 mm, 2.5-μm Luna C18(2)-HST (Phenomenex, Torrance, CA) with an isocratic hold at 60% B for 20 minutes followed by a gradient to 85% B to 45 minutes with UV monitoring at 280 nm.

For long chain triglyceride (LCT) solubility, excess crystalline API in soybean oil was agitated at 37°C for 4 days, then centrifuged at 13,000 rpm for 10 minutes. Supernatants were diluted in acetone and concentrations were measured using HPLC (Agilent 1100) with UV detection at 254 nm. The column was a Waters X Terra RP18 3.5-μm, 50 × 4.6 mm (Waters, Milford, MA), mobile phase A was 0.05% TFA in water, and mobile phase B was 0.05% TFA in acetonitrile.

LogP and topological polar surface area (TPSA) were calculated using ACD Labs Version 11 software suite (Ontario, Canada). LogDpH7.4 was determined by HPLC method modified from the EPA method (EPA Product Properties Test Guidelines OPPTS 830.7570) for very lipophilic compounds. Briefly, the method is carried out by injecting the test compounds in a reversed phase HPLC system against a test mixture of compounds with known logD values. The logD of the test compounds are calculated from their retention factor and the calibration curve.

Studies in Beagle Dogs. This study was conducted at WuXi AppTec Co., Ltd., in accordance with the IACUC guidelines that are in compliance with the

<table>
<thead>
<tr>
<th>Physical and chemical properties of navitoclax and ABT-199</th>
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<tbody>
<tr>
<td>Molecular weight (Da)</td>
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<tr>
<td>TPSA</td>
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<tr>
<td>cLogP</td>
</tr>
<tr>
<td>cLogDpH7.4</td>
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<tr>
<td>Melting point (°C)</td>
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<tr>
<td>Soybean oil solubility /LCT (mg/ml)</td>
</tr>
<tr>
<td>Aqueous solubility; pH 1, 7.4, Fasted SSIF, fed SSIF (mg/ml)</td>
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*LogP calculated using ACD Labs Ver. 11 software.
*Experimentally determined using HPLC retention technique modified from EPA method.
Animal studies were conducted by WuXi AppTec Co. Ltd. (Shanghai, China; 10–12 kg) were used in each phase of the study. A 7-day washout period was inserted between each phase of the study with the exception of the final phase, where a 3-day washout period was used to avoid the loss of patency in the thoracic lymph cannulas. All animals were fed (50 g of a human FDA high fat meal) ~10 minutes to 1 hour prior to dosing and again at ~5 hours postdose. Animals were also administered 1 ml/kg/h of intravenous saline (25 ml) hourly for the first 12 hours postdose. For all studies, blood samples were collected predose and at 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48, and 72 hours postdose. In TDC animals, lymph was collected into drainage packs (containing 1% v/v lymph and 50% Tween 20/20% water) predose and at hourly intervals until 12 hours postdose, after which a 12–24-hour interval collection was made and the amount of lymph collected at each interval was measured gravimetrically. All plasma and lymph samples were collected with potassium (K2) EDTA and heparin sodium as anticoagulant, respectively. Blood samples were processed for plasma within 1 hour of sample collection; plasma was stored at ~70°C or lower until analyzed by liquid chromatography–tandem mass spectrometry (LC-MS/MS). All animal studies were conducted by WuXi AppTec Co. Ltd. (Shanghai, China).

LC-MS/MS Analysis. Navitoclax and ABT-199 concentrations were determined by LC-MS/MS following protein precipitation with acetonitrile, and injection of the supernatant onto the column. The column used for analysis of navitoclax was an ACQUITY UPLC BEH-C18, (50 × 2.1 mm, 1.7-μm particle size) and a Phenomenex Kinetex C-18 (50 × 2.1 mm, 12.6-μm particle size) column was used for analysis of ABT-199. An ACUITY ultra performance liquid chromatography system (Waters) coupled with a Sciex API 4000 triple quadrupole mass spectrometer (Applied Biosystems, Foster City, CA) were used for the LC-MS/MS assay. The aqueous mobile phase was water with 0.1% formic acid and the organic mobile phase was acetonitrile with 0.1% formic acid for analysis of navitoclax in plasma. For all lymph samples and plasma samples with ABT-199, the aqueous mobile phase was water with 2 mM ammonium acetate and the organic mobile phase was acetonitrile with 0.1% formic acid. The total run time was ~1.6 minutes and the ionization was conducted in the positive ion mode using the transition m/z 487.9 → 233.4 for navitoclax and m/z 868.6 → 233.4 for ABT-199. The lower and upper limits of quantitation of the assay for lymph and plasma were 0.005 μM and 10 μM, respectively.

Pharmacokinetic Analysis. Pharmacokinetic parameters were calculated by noncompartmental methods as described in Gibaldi and Perrier (1982) using WinNonlin version 5.1.1 (Pharsight, Certara, St. Louis, MO). Parameters are presented as mean ± S.D.). The % of dose recovered in lymph was calculated as the cumulative mass of navitoclax or ABT-199 in lymph divided by the oral dose. Bioavailability (% F) in both intact and TDC animals was determined by dividing the dose-normalized AUCintact of each animal dosed p.o. by the respective dose-normalized AUCDose determined from the animals dosed intravenously. The proportion of dose (% transported through the lymph was determined as the difference in AUC observed between intact and cannulated animals, [AUCintact – AUCDose] / AUCintact × 100.

Physicochemical Properties. The physicochemical properties of both navitoclax and ABT-199 are shown in Table 1. These are characterized by high molecular weight and logDpH7.4 values, which contribute to very low solubility in aqueous media. Despite the high logDpH7.4 of both compounds, the LCT solubility of both navitoclax and ABT-199 was relatively low (~9 and 2 mg/ml, respectively).

Pharmacokinetics in Intact Dogs. Following intravenous administration of both navitoclax and ABT-199, the plasma clearance (CL) of both compounds was low (<3% of liver blood flow; Fig. 1A and Table 2), which contributed to the long observed half-lives (13–22 hours; Table 2). The volume of distribution of both compounds was low, consistent with high protein binding (>99%; data not shown). After oral administration of 100 mg of navitoclax or ABT-199 to fed intact dogs, the absolute bioavailability, representing the collective portal and lymphatic transport was ~1.5-fold higher for navitoclax than ABT-199, 56.5% versus 38.8%, respectively (Fig. 1, B and C, and Table 2).

Fig. 1. Mean ± S.D. (n = 3) systemic plasma concentration–time profiles (A) after intravenous administration of 1 mg/kg of navitoclax or ABT-199 to fed dogs, (B) after oral dosing of 100-mg tablet of navitoclax to fed thoracic lymph-cannulated (TDC) and intact dogs, and (C) after oral dosing of 100-mg tablet of ABT-199 to fed TDC and intact dogs.
Pharmacokinetics in Thoracic Duct–Cannulated Dogs. As shown in Fig. 1, B and C, in TDC dogs systemic exposures of both navitoclax and ABT-199 were lower than exposures in intact animals. This is evident in the initial absorptive (from enterocyte into systemic circulation)/distribution phase, in which, for navitoclax in particular, there was a ~4-fold difference in C_{max} between intact and TDC animals. In TDC dogs, the lower initial plasma exposure of navitoclax and ABT-199 is accompanied by increasing concentrations of compound in lymph (Fig. 2A). Cumulative lymph levels of both navitoclax and ABT-199 increased linearly up to 8 hours, then plateaued (Fig. 2, A and B). The amount of navitoclax and ABT-199 in lymph represented 13.5% and 4.68% of the 100-mg dose administered, respectively (Fig. 2B). The percent bioavailability in lymph-cannulated and intact dogs and the proportion (as a %) of the absorbed dose of navitoclax and ABT-199 recovered in lymph; the plasma exposure (and corresponding % F) of navitoclax and ABT-199 in fasted animals was similar to exposures in intact dogs and the proportion (% F) of lymphatic transport of navitoclax and ABT-199 was tested; however, the % dose of navitoclax recovered from lymph in fasted animals was lower, 7.58% versus 13.5% in fed animals, and for ABT-199, 0.454% in fasted animals versus 4.68% in fed animals (Fig. 2A). Thus, in intact animals, the % F dose of navitoclax recovered from lymph in fasted animals was lower, particularly for ABT-199.

**Discussion**

It has been proposed that the prerequisite for substantial intestinal lymphatic drug transport is a $\log P > 4.7$ and a LCT solubility $> 50$ mg/ml (Trevaskis et al., 2008). However, recently it has been reported that compounds such as the cholesterylester transfer protein (CETP) inhibitor CP532,623 with LCT solubility $< 50$ mg/ml are transported

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<tr>
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<th>Navitoclax</th>
<th>ABT-199</th>
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<tr>
<td></td>
<td>i.v.</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>Intact</td>
<td>Cannulated</td>
</tr>
<tr>
<td>AUC_{0-\text{last}} (µM-h)</td>
<td>26.9 ± 0.2</td>
<td>158 ± 24</td>
</tr>
<tr>
<td>AUC_{0-\text{max}} (µM-h)</td>
<td>26.9 ± 0.2</td>
<td>164 ± 24</td>
</tr>
<tr>
<td>CL (mL/min per kg)</td>
<td>0.673 ± 0.004</td>
<td>NA</td>
</tr>
<tr>
<td>V_{ss} (l/kg)</td>
<td>0.481 ± 0.031</td>
<td>NA</td>
</tr>
<tr>
<td>C_{max} (µM)</td>
<td>22.2 ± 1.0</td>
<td>17.4 ± 1.9</td>
</tr>
<tr>
<td>T_{1/2} (hr)</td>
<td>NA</td>
<td>2.0 ± 0.0</td>
</tr>
<tr>
<td>T_{max} (hr)</td>
<td>NA</td>
<td>56.5 ± 3.8</td>
</tr>
<tr>
<td>F (%)</td>
<td>NA</td>
<td>NA</td>
</tr>
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NA, not applicable. V_{ss}, volume of distribution at steady-state.

Fig. 2. (A) Cumulative lymphatic transport of drug (as a % of dose) in thoracic lymph–cannulated dogs (mean ± S.D.; n = 3) following oral administration of 100-mg tablet of navitoclax or ABT-199 to fed or fasted dogs; (B) mean ± S.D. (%) of the absorbed dose of navitoclax and ABT-199 recovered in lymph; the plasma bioavailability in lymph-cannulated and intact dogs and the proportion (as a %) of the systemic availability from lymphatic transport.

**TABLE 2**

Pharmacokinetics of navitoclax and ABT-199 after i.v. (1 mg/kg) and oral (100 mg/dog; ~10 mg/kg) administration to intact (noncannulated) and thoracic lymph–cannulated fed dogs

Data are presented as mean ± S.D. (n = 3; for each compound the same animals were dosed after a washout period).
by the intestinal lymphatics (Trevaskis et al., 2010b, c). Therefore, it is conceivable that transport by the intestinal lymphatics could still play a role in the absorption of the Bcl-2 family inhibitors with LCT solubility < 10 mg/ml.

In intact dogs, the CL of both navitoclax and ABT-199 were low, resulting in relatively long half-lives in dogs. Moderate bioavailability and relatively high oral exposures of navitoclax and ABT-199 were observed despite their low aqueous solubility. Of note, the half-life of both compounds after oral dosing to intact animals was similar to intravenous dosing, suggesting that absorption was not rate-limiting (lack of flip-flop kinetics) (Table 1).

The clearest indication that lymphatic transport is playing a role in the disposition of both navitoclax and ABT-199 is in the observed ~2-fold decrease in plasma exposure in TDC animals compared with intact animals (Table 2). This is accompanied by a gradual and linear increase in lymph exposures over 8 hours (Fig. 2A). Interestingly, while the absorptive profile of navitoclax and ABT-199 were different in TDC animals compared with intact animals, the elimination half-lives of navitoclax and ABT-199 were similar. This suggests that lymphatic transport does not affect CL/elimination. Based on the similar % F (~20%) of navitoclax and ABT-199 in TDC dogs, portal availabilities of both compounds appear to be similar. Thus, the overall difference in F in intact animals, 56.6% and 38.8%, for navitoclax and ABT-199, respectively, (versus F of ~20% in TDC animals) reflects a difference in lymphatic transport (Fig. 2B). If this was not the case, the bioavailability of navitoclax and ABT-199 would be ~20%. The higher F of navitoclax (in intact animals) is consistent with the 4-fold higher LCT solubility of navitoclax (9.2 mg/ml) compared with ABT-199 (2.2 mg/ml).

Food may impact absorption/bioavailability by increasing the solubilization capacity due to the presence of lipids, stimulation of bile acid production, and/or slowing the GI transit time thereby increasing the absorption window. In addition, lipids in food may also promote drug access into the intestinal lymphatic system, where fat in food stimulates the formation of triglyceride-rich lipoprotein in the enterocyte and provides a lipoprotein rich environment, whereby a drug/compound can associate with lipid transport pathways (Trevaskis et al., 2008). The latter appears to apply to navitoclax and ABT-199, since similar solubilities were observed in FaSSIF or FeSSIF, which differ in their bile salt content (Table 1). The positive effect of food on dog lymphatic transport has been reported, for example, with halofantrine, CP524,515, and CP532,623, where food enhanced lymphatic transport by 67-, 2.2-, and 1.4-fold, respectively (Kho et al., 2001, 2003; Trevaskis et al., 2010b).

In fasted TDC dogs, lymphatic transport of navitoclax and ABT-199 were decreased by 1.8- and 10-fold, respectively (Fig. 2). Thus, fasting did not greatly alter the availability of either compound via the portal vein (no change in plasma exposure) but altered lymphatic transport. It is worth noting that in the animals in which the cannulas were patent, 660 ml (n = 1, navitoclax) and 1110 ml of lymph (ABT-199; mean from two animals) were collected over 24 hours. This was similar to the lymph volume collected in fed animals, suggesting that fasting did not appear to affect the flow of lymph. While in this set of studies we did not conduct an arm with fasted intact dogs, the resulting decrease in lymph transport in fasted animals for ABT-199 would predict a % F of ~20% (assuming little/no contribution from lymphatic transport) and ~40% for navitoclax (with an ~50% decrease in contribution from lymphatic transport). This is in keeping with previous data showing lower exposure in fasted versus fed (intact) animals (data on file, Abbott Laboratories). In dogs it appears that ABT-199 lymphatic transport was much more sensitive to the fed/fasted state, perhaps due to its lower lipid solubility and consequently higher reliance on an exogenous source of lipid to drive lymphatic transport. Interestingly, this observation is consistent with observations in patients, where under fed conditions, a greater food effect was observed with ABT-199 (Davids et al., 2012) compared with navitoclax (Wilson et al., 2010). Exposures (AUC) of navitoclax and ABT-199 were increased by 1.2-fold (Wilson et al., 2010) and 3- to 4-fold (Davids et al., 2012), respectively.

Apart from increasing absorption, lymphatic transport may enhance systemic exposure by avoiding hepatic first pass since the lymphatic system bypasses the liver and empties directly into the systemic circulation. This has been reported in both dogs and rats, where postprandial administration of halofantrine resulted in a decreased metabolite-to-parent ratio (Porter et al., 1996; Kho et al., 2001). In addition, it has also been suggested that enteric metabolism may be reduced by lymphatic transport (Trevaskis et al., 2006). It is unlikely, however, for navitoclax or ABT-199 that avoidance of enteric metabolism/hepatic first-pass lymphatic transport is playing a role in increasing systemic oral exposure of either navitoclax or ABT-199, as 14C preclinical data suggest that the fraction absorbed is limiting F rather than CL (data not shown). In addition to enhancing systemic exposure, it has been suggested that lymphatic transport may enhance the therapeutic effect of immune-modulatory or anticancer compounds, since drug levels are enhanced at the target site of action, e.g., lymphocytes (Trevaskis et al., 2010a; Trevaskis et al., 2011). For example, the administration of the immunosuppressant JWH-015 in a high-lipid formulation (40 mg of oleic acid) to rats elicited a significant increase in ex- vivo mitogen-stimulated release of “anti-inflammatory” cytokines (IL-4 and IL-10), relative to a low lipid formulation, despite similar systemic plasma levels observed from both formulations (Trevaskis et al., 2010a; Trevaskis et al., 2011). Further focused studies are needed to determine if clinically therapeutic advantage can be gained by targeting lymphatic transport for drugs that target lymphocytes and lymphoid compartments. In addition, it is possible that increasing lipophilic or lipid solubility may increase metabolism as well as introduce complexities such as sensitivity to changes in formulation or fed/fasted conditions. This may result in variable pharmacokinetics or, potentially, pharmacodynamics depending on the site of action.

In conclusion, we have shown that lymphatic transport plays a role in the overall systemic availability of lipophilic compounds such as navitoclax and ABT-199. These studies further indicate that lymphatic transport could be leveraged in the drug discovery process to increase the exposure of compounds with low aqueous solubility by “dialing in” lipophilicity/lipid solubility.

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Authorship Contributions

Participated in research design: Choo, Boggs, Zhu, Lubach, Catron, Jenkins, Voorman.
Conducted experiments: Zhu, Lubach, Catron.
Contributed new reagents or analytic tools: Lubach, Catron, Souers.
Performed data analysis: Choo, Boggs.
Wrote or contributed to the writing of the manuscript: Choo, Lubach, Catron, Souers.
References


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