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New Antiretrovirals on the Block: Pharmacological news from Croi 2017

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Introduction

The Conference on Retrovirus and Opportunistic Infections, CROI, 2017 at Seattle, USA, presented several new substances, therapy strategies and other data about the treatment of HIV/AIDS. The following article discusses a pharmacological selection of these, and shows data of new integrase inhibitors (INSTI), nucleoside (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) as well as protease inhibitors (PI), CCR5-inhibitors and several long-acting antibodies or new formulations of already widely used drugs, such as Nano particle PI and NNRTI (NANO-NNRTI, NANO-PI).

Nukleos (t) ide Reverse Transcriptase Inhibitors

Karen White and colleagues presented the new NRTI GS-9131, which reveals strong activity against NRTI-resistant HIV-1.

At a very low EC50 of only 0.16 µM (± 0.02) GS-9131 is still active against most of NRTI-resistant HIV-1, showing mutations of K65R, M184V, L74V/I, 6TAMs+184V or Q151M+M184V.

Unlike TAF, GS-3131 is an adenosine-analogue. But alike TAF it is a prodrug, which is modified by cathepsin A into its intracellular form of GS-9148 and then phosphorylated by intracellular kinases into its antiretroviral active diphosphate.

Additive effects are seen when applicate together with TAF and synergistic effects appear when coadministered with all other currently used NRTI or NVP, LPV, DRV, DTG and BIC. Earlier studies have already shown a favourable side effects profile, which didn´t show enhanced nephrotoxicity or mitochondrial toxicity as know of other NRTIs. GS-9131 is also active against HIV-2 [1].

Integrase Strand Transfer Inhibitors (INSTI)

J. Custodio discussed new data regarding the clinical pharmacology of the INSTI bictegravir (GS-9883, BIC). BIC is a new INSTI with a good oral bioavailability of >70%, and a plasma protein binding capacity of 99%. Once absorbed GS-9131 is about equally metabolized via CYP3A4 (oxidation) and UGT1A1 (glucuronidation).

Neither a moderate liver nor a higher grade renal insufficiency (eGFR 15-30 ml) rise the necessity of a dose reduction *in vivo*. The pk-profile of BIC led to the further evaluation of BIC75 mg in clinical studies, which have reached now phase 2b. The mean half-life of BIC is ~18 h, so that BIC can be taken once daily (QD). In combination with emtricitabine/tenfoviralafenamide (FTC/TAF) BIC can be dosed at 50 mg, because TAF moderately enhances the plasma concentration of BIC. Also, the influence of potent CYP3A4 inhibitors is moderate (AUC-increase of about 50%), but a concomitant induction of CYP3A4 or UGT1A1 leads to lower BIC exposure (Rifabutin: BIC AUC -38%; Rifampicin: BIC AUC -75 (Table 1). As BIC reaches about 20 fold above the IC95 for wildtype HIV-1 at the end of the dosing interval, a dose alteration is not seen as being necessary. BIC itself is a substrate but not inhibitor or inducer of CYP3A4, so that pk-studies with midazolam, norelgestromin/ethinylestradiol, ledipasvir/sofosbuvir could not detect any drug-drug interactions (DDI). Solely the elimination of metformin via the renal transmembrane transporters OCT2 and MATE1 has been inhibited leading to a higher metformin exposure of 39% (Table 2). However, since no increased incidence of side effects had been detected in these studies, a dose reduction of metformin is not suggested. Currently, BIC is further evaluated in a fixed dose combination together with FTC/TAF. [2].

Paul Sax subsequently presented first data from phase 2, when BIC+FTC/TAF+Placebo (n=65) was tested *vs.* DTG+FTC/TAF+placebo (n=33) over 48 weeks in therapy-naive patients of a median age of 30 *vs.* 36 years, respectively, in the majority caucasian with a mean viral load of 4.5 log10 copies/ml, a median CD4-cell count of 441 *vs.* 455/µl and a eGFR of 130 *vs.* 122 ml/min. At weeks 24/48, 97/97% of all patients taking BIC and 94/91% of patients taking DTG were below the detection limit for HIV of 50 coipies/mL; CD4-cell count increased 258 *vs.* 192/µl (p=0.16).

The side effects profile of both substances was comparable with focus on diarrhoea (12% in each group), nausea (8% *vs.* 12%), headache (8% *vs.* 3%), upper respiratory tract infections (8% *vs.* 0%), arthralgia (6% in both groups) and back pain (6% *vs.* 0%). Laboratory value deviations occurred especially regarding the elevation of creatin kinase (13 *vs.* 9%), AST-increase (9 *vs.* 3%), hyperglycaemia (8 *vs.* 13%), ALT-elevation (6 *vs.* 0%), LDL-elevation (6 *vs.* 9%), amylase-elevation (5 *vs.* 6%), haematuria (3 *vs.* 6%) and glycosuria (2 *vs.* 6%). The eGFR was reduced over 48 weeks on therapy 7,0 *vs.* 11,3 ml/Min. No INSTI-resistances were detected over 48 weeks in this study [3].

Non-Nukleosidale Reverse Transcriptase Inhibitors (NNRTI)

Doravirine is a new NNRTI, which could prove clinical non-inferiority in a phase 3-study when compared with a treatment consisting of darunavir/R+NRTI. These results were presented by Squires et al. t (OP45LB). Doravirine shows a distinct resistance profile, its activity remains good even when NNRTI resistance mutations such as K103N, Y181C, G190A, K103N+Y181C and E138K are detected in the HIV-1 genome. DOR can be taken QD without any food restrictions and it is evaluated currently in a fixed dose combination together with tenofovirdisoproxilfumarate (TDF) and lamivudine (3TC). In multicentre, double-blind, *double-dummy*-controlled

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	Week 24[a]		Week 48[b]	
N (%)	BIC+FTC/TAF (n=65)	DTG+FTC/TAF (n=33)	BIC+FTC/TAF (n=65)	DTG+FTC/TAF (n=33)
HIV-1 RNA<50 copies/ml	63 (96.9)	31 (93.9)	63 (96.9)	30 (90.9)
HIV-1 RNA>50 copies/ml	2 (3.1)	2 (6.1)	1 (1.5)	2 (6.1)
HIV-1 RNA ≥ 50 copies/ml	1 (81.5)	1 (3.0)	0	1 (3.0)
Discontinued due to lack of efficacy	0	0	0	0
Discontinued due to other reason and at last HIV-1 RNA ≥ 50 copies/ml	1 (1.5)	1 (3.0)	1 (1.5)	1 (3.0)
No virologic data in window	0	0	1 (1.5)	1 (3.0)
Discontinued due to AE/death	0	0	1 (1.5)	0
Discontinued due to other reason and at last HIV-1 RNA<50 copies/ml	0	0	0	1 (3.0)
Missing data in window but on drug	0	0	0	0

a) Difference in percentages (BIC+FTC/TAF *vs.* DTG+FTC/TAF) at week 24: 2.9% (-8.5% to 14.2%); p=0.50
b) Difference in percentages (BIC+FTC/TAF *vs.* DTG+FTC/TAF) at week 48: 6.4% (-6.0% to 18.8%); p=0.17

Table 1: A selection of phase 2-efficacy data of BIC vs. DTG, each plus FTC/TAF.

IC Coadministered Drug (s) and Dose (S)	Dose(s) of BIC	Geometric mean ratio % (90%CI) of BIC PK with/without Coadministered Drug (n=15 for each cohort)		
		C_{max}	AUC	C_{tau}
ATV 400 mg QD	BIC 75 mg SD fed	128 (123,134)	415 (381,451)	NA
ATV/COBI 300/150 mg QD	BIC 75 mg SD fed	131 (123,140)	406 (376,438)	NA
Voriconazole 300 mg BID	BIC 75 mg SD fasted	109 (96.1,123)	161 (141,184)	NA
DRV/COBI 800/150 mg QD	BIC 75 mg SD fed	152 (140,184)	174 (162,187)	211 (195,229)
Rifabutin 300 mg QD	BIC 75 mg SD fasted	80.4 (66.9,96.5)	62.0 (53.2,72.5)	44.0 (37.1,52.1)
Rifampin 600 mg QD	BIC 75 mg SD fed	72.2 (67.7,77.8)	24.5 (22.0,27.3)	NA

Table 2: The effects of concomitant medication on the PK of BIC.

phase 3-trial, 383 patients took either DOR+NRTI+placebo or DRV/RTV+NRTI+placebo. The median age of the mostly male (83 *vs.* 85%), caucasian (78 *vs.* 77%) patients was 34.8 *vs.* 35.7 years. Baseline CD4-cell counts were 433 *vs.* 412/µL, 87 *vs.* 88% took TDF/FTC and 13 *vs.* 13% ABC/3TC as NUC-backbone. 15 *vs.* 19% of all patients terminated this study prior to week 48 ab, whereas in the DOR-group one pregnancy and one death occurred other cases were due to therapeutic failure (n=12, 3%), *lost to follow-up* (n=17, 4%), withdrawal of informed consent (n=10, 3%), adverse events (n=4, 1%) or non-adherence (n=7, 2%) (Table 3).

The FDA-snapshot analysis stated a proportion of 84 *vs.* 80% of patients being below the HIV-1 detection limit of 50copies/ml after 8 weeks on therapy 11 *vs.* 13% showed insufficient virologic success. The stratification of the results regarding baseline viral load (<or >100.000 and<or >500.000), baseline CD4-cell count (<50, <200, >200) or comedication (ABC/3TC or TDF/FTC) could not detect any inferiority of DOR *vs.* DRV [4].

Protease Inhibitors (PI)

Link and colleagues showed preclinical data of a new PI, GS-PI1, which at a very high resistance barrier in cell cultures and at comparable potency to ATV/DRV reveals a long half-life. 24 h after its application the plasma concentrations in rats and dogs were several folds higher than those of the comparators ATV and DRV. Its stability in human microsomes is very high and a boosting with COBI/RTV is not necessary. GS-PI1 could be a favorable alternative to currently used second generation PI, if further developed [5].

CCR5-Inhibitors

PRO 140 is a humanized IgG4 monoclonal antibody, which can prevent the HIV entry into the target cell by binding directly to the CCR5-receptor. PRO 140 blocks genotypically diverse HIV, wildtype as well as MDR-resistant or maraviroc-resistant viruses. The CD01-study switched 16 patients from stable cART to a once-weekly application of PRO 140 monotherapy for 12 weeks. Patients who remained after 12 weeks under the detection limit of 50 copies/ml (n=16) subsequently received Pro 140 for further 160 weeks (CD01-extension 2b-study). The data which were presented by Lalezari et al., revealed in this small group of patients a favourable side effects profile, good tolerability and effectivity. After 60 weeks on therapy none of the patients showed the development of Pro140 antibodies. Following more than 2 years of monotherapy, 62, 5% of patients are still below DL. Further PRO140 studies have been initiated: PRO 140_CD03 investigates 300 virologic suppressed patients with CCR5trophic virus over 48 week's monotherapy. PRO 140_CD02 evaluates the application of PRO140 in 30 patients who are resistant to a number of AR*Vs.* but have CCR5-trophic virus, together with an optimized background therapy [6].

NANO-NNRTI and NANO-PI

Two new nano particle -formulations of efavirenz (NANO-EFV) and lopinavir (NANO-LPV) were introduced by Andrew Owen. Both promised the possibility for a marked dose reduction of about 50% in population pharmacokinetic modelling studies, leading to a better tolerability especially in children, in whom both AR*Vs.* are still widely used as part of cART. When only 50% of the currently recommended dose were given the exposure ratios for EFV/smEFV (GMR AUC/C24 0.88/1.32) and LPV/smLPV (GMR AUC/Cmin 0.92/1.07) GMR, measured for Cmin und AUC, were found to be in the acceptable range of bioavailability (Table 4) [7].

Capsid Inhibitors

The new capsid-inhibitor GS-CA1 can block steps of the HIV capsid

synthesis: It inhibits not only the translocation of the preintegration complex into the genome of the target cells, but also the assembly of capsid core. The EC_{50} of GS-CA1 is only 85pM, so that GS-CA1 shows up to be much more potent than current ARV*s* (Table 5). Although resistance mutations are known, these are exclusive for GS-CA1. Furthermore, viruses with these mutations at L56I, M66I do have e markedly reduced viral fitness. GS-CA1 shows comparable activity against multiple HIV-1 isolates of all subtypes. Capsid inhibitors do bind to a conserved binding site at the connection between to neighbouring monomers and speed up its assembly in *in vitro*.

All so far identified CAI are *in vitro* fully active against multi resistant HIV-mutants, by inhibiting the assembly of virions as well as the capsid functioning after cell entry as described before.

A single subcutaneous injection leads to long lasting high plasma concentrations, which were above the EC95 for wildtype HIV-1 longer than 10 weeks, so that GS-CA1 has the potential for a once-monthly application [8].

Outlook

Also, the proportion of pharmacological studies at CROI 2017 reached hardly 5%, their scientific level was nearly always high, the presented data were interesting and of clinical relevance.

New substances in clinical evaluation are scarce. Foremost, the new class of capsid inhibitors may lead to changes in future HIV therapy strategies. The new capsid inhibitor GSCA1 is reaching phase 1 now:

Endpoint	**DOR[1] (n=383)**		**DRV/r[1] (n=383)**		**Treatment difference**
HIV-1 RNA<50 copies/ml	**N**	**%**	**N**	**%**	**DOR-DRV/r (95%CI)**
Overall[2]	321	83.3	303	79.9	3.9 (-1.6,9.4)
BL HIV-RNA ≤ 100,000[§]	285	90.2	282	88.7	1.5 (-3.7,6.8)
BL HIV-RNA>100,000[§]	79	81.0	72	76.4	3.0 (-11.2,17.1)
BL HIV-RNA ≤ 500,000[§]	347	88.5	342	87.4	0.9 (-4.0,5.9)
BL HIV-RNA>500,000[§]	17	82.4	12	50.0	30.9 (-4.1,65.9)
NRTI=TDF/FTC[§]	316	88.0	312	86.5	1.3 8-3.9, 6.5)
NRTI=ABC/3TC[§]	48	89.6	43	83.7	5.9 (-9.1, 20.9)
BL CD4 ≤ 200 cells/mm³[§]	41	82.9	61	72.1	9.4 (-7.4, 26.2)
Adverse Event (AE) Summary	**% of Subjects**		**% of Subjects**		**DOR-DRV/r (95% CI)**
One or more AE	80.2		78.3		1.8 (-3.9, 7.6)
Drug-related AE	30.5		32.1		-1.6 (-8.1, 5.0)
Serious AE	5.0		6.0		-1.0 (-4.4, 2.3)
Discontinued due o AE	1.6		3.1		-1.6 (-4.0, 0.6)
Fasting Lipids, change from BL	**N**	**Mean Δ**	**N**	**Mean Δ**	**DOR-DRV/r (95% CI)**
LDL cholesterol (mg(dL)	326	-4.5	318	+9.9	-14.6 (-18.2, -11.1)
Non-HDL cholesterol (mg/dL)	329	-5.3	325	+13.8	-19.3 (-23.3, 19.9)

Table 3: Week 48 efficacy and safety outcomes.

	Geometric mean		**Geometric mean ratio**
Efavirenz	**NANO-EFV 300 mg**	**Sustiva 600 mg**	**GMR (90% CI)***
AUC_{0-24} (mg*h/L)	51.56	58.61	0.88 (0.86-0.90)
C_{12} (mg/L)	2.03	2.51	0.81 (0.78-0.83)
C_{24} (mg/L)	1.90	1.44	1.32 (1.26-1.37)
C_{max} (mg/L)	2.99	3.36	0.89 (0.87-0.91)
Lopinavir	NANO-LPV 200 mg#	Kaletra 400 mg	
C_{12} (mg/L)	4.16	4.02	1.04 (0.99-1.08)*
AUC_{0-12} (mg*h/L)	72.35	79.07	0.92 (0.89-0.94)
C_{max}	10.69	9.97	1.07 (1.05-1.10)

*Nanoformulation as reference; # boosted with 100 mg ritonavir.

Table 4: PK data of Efavirenz and Lopinavir NANO-formulations in comparison to marketed formulations.

ARV class	name	Structure	studies
NRTI	GS-9131	nucleotide-analogue	preclinical
NNRTI	Doravirine		
	NANO-EFV	nano particle Efavirenz	bioequivalence
PI	NANO-LPV	nano particle Lopinavir	bioequivalence
INI	Bictegravir (GS-9883)	Integrase Strand Transfer Inhibitor	phase 2/3
CCR5-inhibitor	PRO 140	IgG4 monoklonaler CCR5-Antikörper	phase 2b
capsid-inhibitor	GS-CA1		preclinical/phase 1

ARV=antiretroviral; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; INI=Integrase inhibitor.

Table 5: A selection of new potential ARVs. at CROI 2017.

Its very long half-life has the capacity of a once monthly subcutaneous application, So that new substance with comparably pk-profiles may lead to substantial changes in future therapy regimens: Uncomplicated application, very long dosing intervals, low/no pill burden, improved adherence.

Also, the new nanomolecular formulations of already widely used substances with the potential of decrease dosing and improved tolerability may help to improve HIV treatment especially in children. Once more, this shows the need and benefit of university-based pharmacological science, since the further improvement of both substance is of no economic interest for manufacturers.

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