Nouveaux anti-viraux

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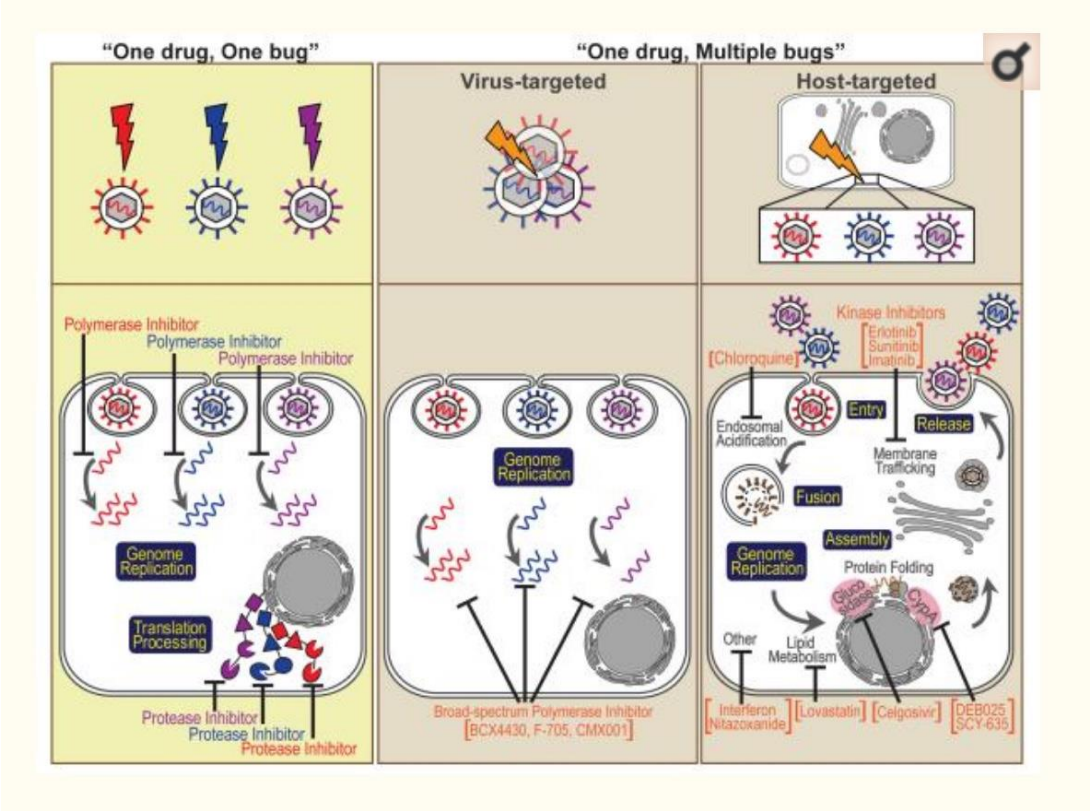
Problématique
one drug :one or multiple bugs

- Deux types d'antiviraux:
  - Spécifique d'un virus
  - Large spectre
- Conséquences:
  - Spécifique: peu d'impact écologique des résistances
  - Large spectre: utile pour l'émergence



Bekerman et col, Science 2016

Molécules à venir à “large spectre”

Dirigé sur le virus

- Nucléotides/nucleosides de nouvelle génération
  - BCX4430 inhibe au moins 20 RNA[1]
  - Favipiravir grippe et flavivirus[2]
  - Brincidofovir: Herpes et papillomavirus[3]
- Hélicase primase inhibiteurs:
  - Amenamevir: **VZV[4]** HSV 1 et 2
  - Pritelivir[5]: HSV 1 et 2

1. Warren TK, et al. Nature. 2014
2. Furuta Y, et al. Antiviral Res. 2013
3. Florescu DF, Keck MA. Expert Rev. Anti Infect. Ther. 2014
4. Kawashima et col, J Dermatol. 2017
5. Wald JAMA 2016

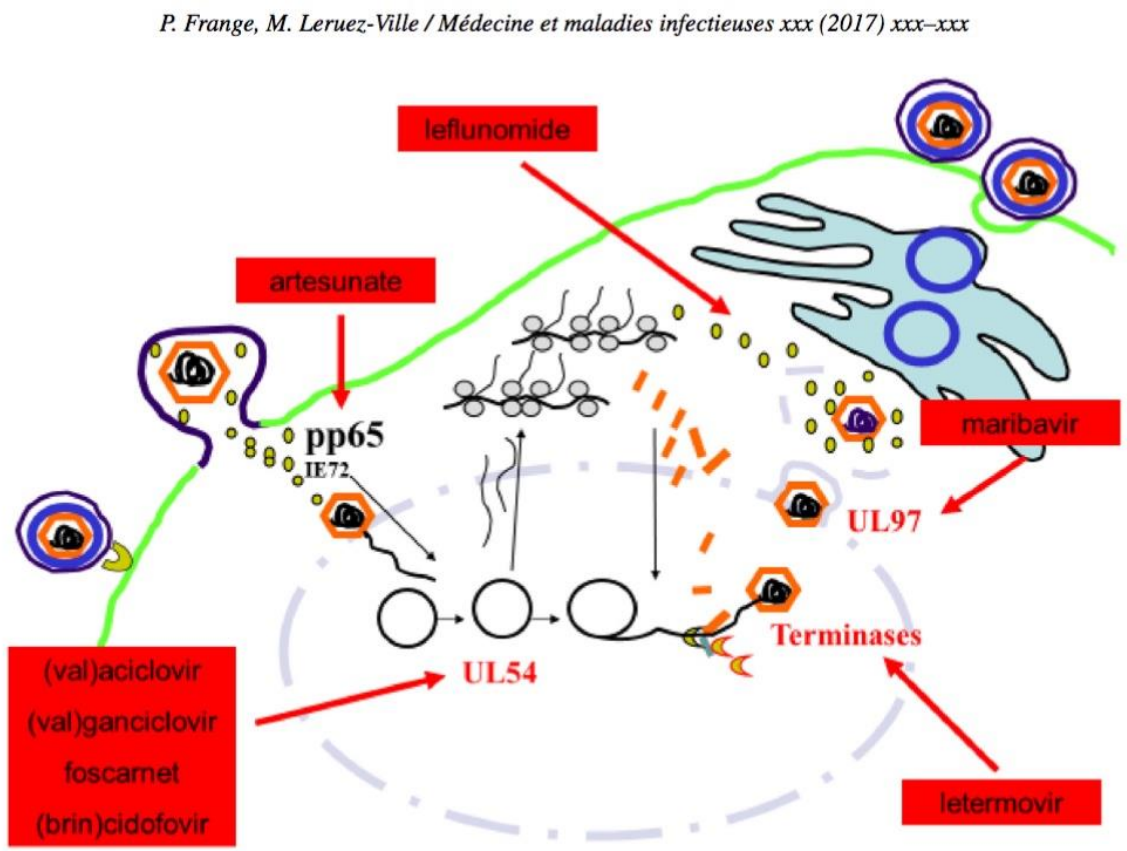
Molécules à venir à large spectre

- **Dirigé vers l''hôte**
- cyclophilin A inhibiteurs
  - DEB025[1] (Alisporivir) and SCY-635[2,3,4]
  - Activité ADN ou ARN
  - VHC, dengue virus, VIH, influenza, and MERSCoV, SARS
- ER α-glucosidase
  - Pas d'efficacité humaine pour l'heure
- Inhibiteurs du transit cellulaire:
  - erlotinib and sunitinib: testé pour Ebola et Dengue sévère[5,6]
  - Nitazoxanide: VIH, VHC, flaviviruses: diminution de la durée des symptomes[7]

1. Lin K, Gallay P. Antiviral Res.
2. Chang J, Block TM, Guo JT. Antiviral Res.
3. Neveu G, et al. PLOS Pathog. 2012;8:e1002845
4. Dyall J, et al. Antimicrob. Agents Chemother.
5. García M, et al. Sci. Transl. Med. 2012
6. Rossignol JF. Antiviral Res. 2014
7. Rolain JM, Colson P, Raoult D. Int. J. Antimicrob. Agents. 2007

Avancées cliniques récentes

Anti CMV


P. Frange, M. Leruez-Ville / Médecine et maladies infectieuses xxx (2017) xxx–xxx
leflunomide
artesunate
maribavir
pp65
IE72
UL97
Terminases
UL54
(val)aciclovir
(val)ganciclovir
foscarnet
(brin)cidofovir
letermovir

Agents spécifiques anti CMV

- Maribavir[1]
  - Per os
  - Association possible avec le foscarnet
  - Peu ou pas efficace en prophylaxie
  - Ttt curratif: phase 3 en cours (NCT02927067 et NCT02931539)

- Letermovir
  - Per os ou IV
  - Prophylaxie de troisième ligne
  - Ttt curatif en cours d'évaluation (phase 2b et 3 en cours)

1:Dropulic et col Clin pharm ther 2010
2: Lichka et col AAC 2010

Large spectre: Brincidofovir

- Prodrogue du cidofovir:
  - Biodisponibilité orale correcte
  - Actif sur le CMV, adenovirus et flavivirus
- Prophylaxie +++
  - CMV et transplanté
  - HSV et VZV en hématologie: prévention
  - Infection respiratoires à adenovirus: prevention

Marty et col. Biol Blood Marrow Transplant. 2018
Lee et col, Transpl Infect Dis. 2018
Lopez et col, Curr Opin Organ Transplant, 2018

Brincidofovir: traitement curatif

- Infection à CMV mutant (UL97)
  - Pas d'essai controlé
  - Moins nephrotoxiques mais toxique tout de même
  - Intérêt probable en association pour diminuer les posologies d'autres AV

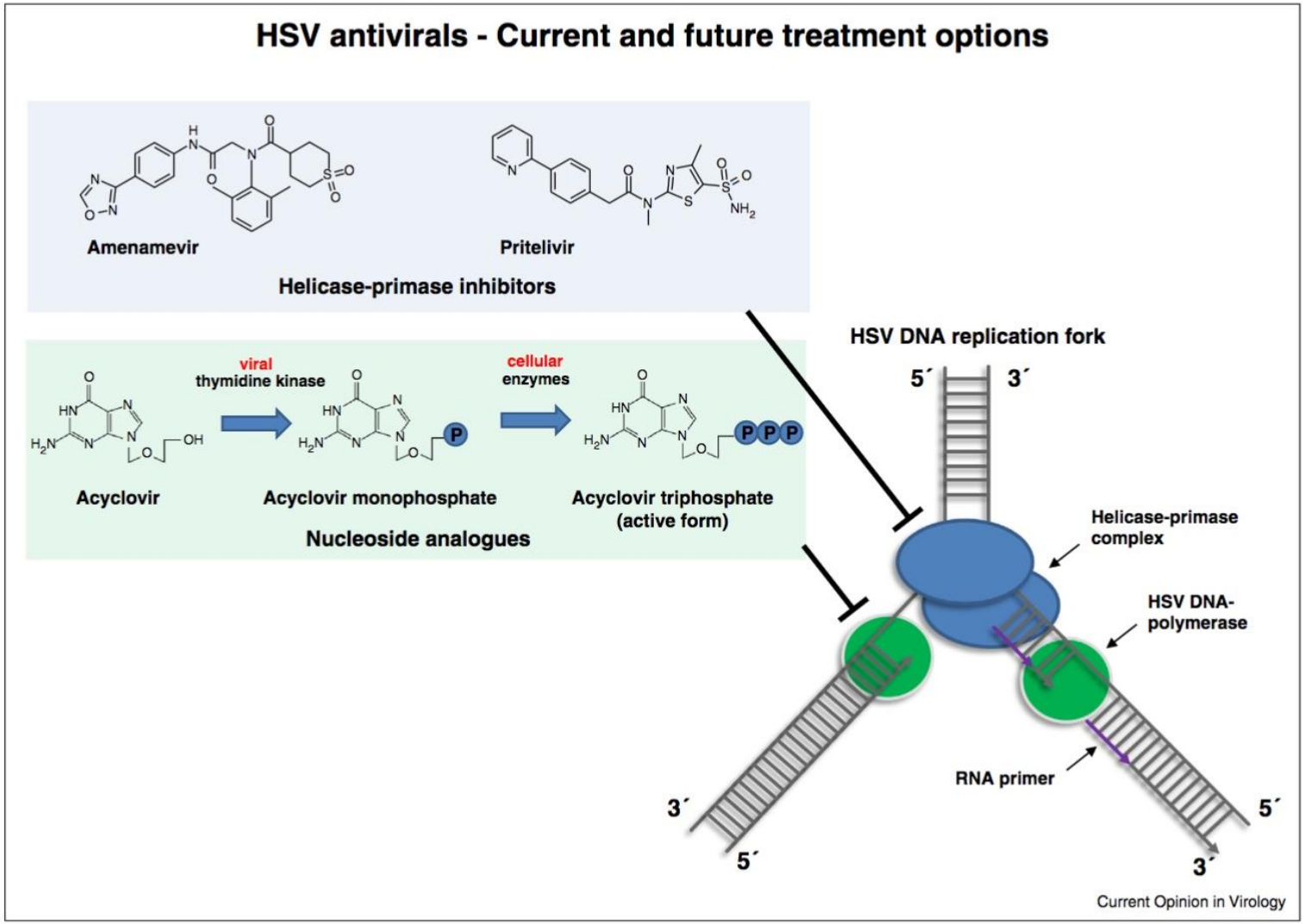
Medicine 2016
Biol Blood Marrow Transplant. 2018
Pharmacotherapy. 2018
J Clin Virol. 2017
Blood. 2017

Brincidofovir: le grand détournement

- Infections respiratoires et digestive sévères à adenovirus[1,2]
- Ebola[3,4]: essai en cours
- Variole[5]: dans la stratégie thérapeutique
- Varicelle refractaire[6]

1: Viruses 2017
2: Biol Blood Marrow Transplant. 2016
3:Clin Infect Dis. 2015
4: Front Immunol. 2018
5: Viruses. 2018
6: Transpl Infect Dis. 2016

Anti- HSV



Birckmann et col, Curr opinion Antivir Ther, 2015

Hepres genital à HSV2: Pritelivir : un essai randomisé en crossover

- Pritelivir vs Valacyclovir
- Inclusion: 4 à 9 recurrences/ans
- 76 patients
- Pas de résistance après 4 semaines de traitement

Characteristic	Pritelivir (n = 75)	Valacyclovir (n = 76)	Relative Risk or Difference in Copy No., Pritelivir vs Valacyclovir (95% CI)	*P* Value
Virologic End Points				
Genital HSV shedding, No./total (%)				
Overall[a]	173/7276 (2.4)	392/7453 (5.3)	0.42 (0.21 to 0.82)	.01
Subclinical	127/6989 (1.8)	284/6984 (4.1)	0.40 (0.20 to 0.81)	.01
Lesional	40/134 (29.9)	106/294 (37.1)	0.86 (0.22 to 3.30)	.76
Episode/person-mo	78/60	97/61	0.80 (0.52 to 1.22)	.29
Incidence rate per person-mo	1.3	1.6		
HSV DNA $\log_{10}$ copies/mL, mean (SD)				
Overall	3.2 (1.2)	3.7 (1.3)	−0.1 (−0.6)]	.83
On days with no lesions	2.8 (0.6)	3.3 (1.0)	−0.3 (−0.5)	<.001
On days with lesions	4.4 (1.3)	4.8 (1.4)	0.7 (0.3)	<.001[b]
Duration of shedding episodes, median (IQR), h	6.0 (6.0 to 12.0)	6.0 (6.0 to 36.0)		.06[c]
Clinical End Points, No./Total (%)				
Days with lesions[d]	35/1855 (1.9)	75/1900 (3.9)	0.40 (0.17 to 0.96)	.04
Recurrences/person-mo[d]	11/61 (0.2)	18/63 (0.3)	0.65 (0.35 to 1.22)	.18
Incidence rate per person-mo	72/1778 (4.0)	123/1878 (6.7)	0.53 (0.30 to 0.93)	.03
Duration, median (IQR), d				
Pain	4.0 (2.0 to 4.0)	4.0 (2.0 to 4.0)		.83[c]
Recurrences	3.0 (1.0 to 4.0)	5.0 (3.0 to 6.0)		.10[c]

Wald et col, JAMA 2016
Edlefesen, et col J inf dis, 2016

Anti-grippaux

	Therapy	Stage	Activity	Specificity	Effect on IV replication	Effect on host inflammatory response	Effect on epithelial Cells	Viability
IV	MHAA4549A	Phase II	Antibody to HA stem region, induces cellular cytotoxicity of infected cells	IAV only	Inhibitory	Inhibitory	Not reported	Good
	MEDI8852	Phase II	Antibody to HA stem region, induces cellular cytotoxicity of infected cells	IAV only	Inhibitory	Not reported	Not reported	Good
	VIS-410	Phase II	Antibody to HA stem region, induces cellular cytotoxicity of infected cells	Select IAV strains	Inhibitory	Not reported	Not reported	Good
	JNJ63623872	Phase II	Inhibits IV replication by binding PB2 and preventing 7-methyl GTP docking	IAV only	Inhibitory	Not reported	Not reported	Moderate
	Favipiravir	Approved/phase II	Inhibits generation of viable IV particles by driving mutations in IV genome	None	Inhibitory	Not reported	Not reported	Good
	JJ3297	Preclinical	Inhibits NS1 activity	None	Inhibitory	Stimulatory	Not reported	Unknown

Front Immunol. 2018

Favipavir

- Per os 1600 mgX2/j puis 600X2/j
- Actif sur influenzae A essai de phase 2b et 3 validé pour PEC des grippes non grave
- Essai de phase 3 en cours pour grippe grave
- Détournement:
  - Ebola (posologie X 4)
  - West Nile
  - Zika

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	A Pharmacokinetics Study of **Favipiravir** in Patients With Severe Influenza	• Influenza, Human • Critical Illness • Influenza	• Drug: **Favipiravir** • Drug: Oseltamivir 75Mg Capsule	• China-Japan Friendship Hospital Beijing, China
2	☐	Unknown †	Tolerance and Activity Evaluation of High Doses of **Favipiravir** Against Ebola Virus in the Semen	• Ebola Virus Survivor	• Drug: **Favipiravir**	• Conakry Conakry, Guinea • Nzérékoré Nzérékoré, Guinea
3	☐	Completed	Efficacy of **Favipiravir** Against Ebola (JIKI)	• Ebola Virus Disease	• Drug: **Favipiravir**	• The caregivers treatment center Conakry, Guinea • MSF Ebola treatment centre Gueckedou, Guinea • French Red Cross Ebola care center Macenta, Guinea • ALIMA Ebola care center Nzerekore, Guinea
4	☐	Completed	Phase 3 Efficacy and Safety Study of **Favipiravir** for Treatment of Uncomplicated Influenza in Adults - **T705**US316	• Influenza	• Drug: **favipiravir** • Drug: Placebo	• Birmingham, Alabama, United States • Birmingham, Alabama, United States

Antiviral Res 2013
Front Immunol. 2018
Antimicrob Agents Chemother. 2017
PloS med 2016

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Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

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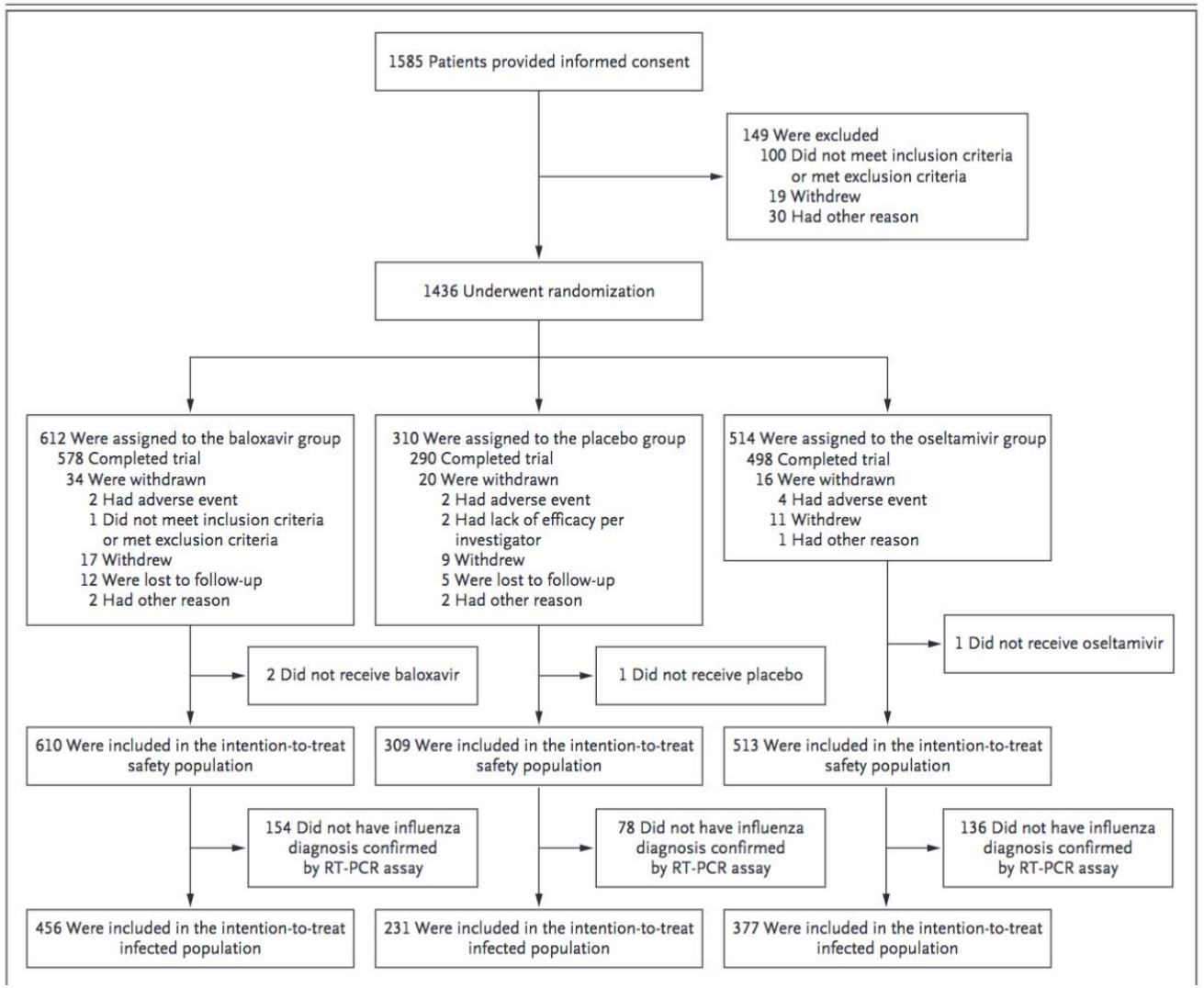
- Phase 2 double aveugle 10mg 20mg 40mg ou placebo per os
  - 20 à 64 ans
  - Japon
- Resultats
  - 400 patients
  - Grippe A (H1N1)pdm09>60%
  - Réduction significative de la durée des symptomes:
    - Différences quelque soit la dose
    - Max avec 40 mg 49.5 vs 77 heures (p=0.005)

Phase 3

- Phase 3 en double aveugle
  - Patient de 12 à 64 ans
  - Japon et USA
  - Bras baloxavir, placebo, oseltamivir
  - Baloxavir 40 mg si poids<80Kg, 80mg autrement



Résultats

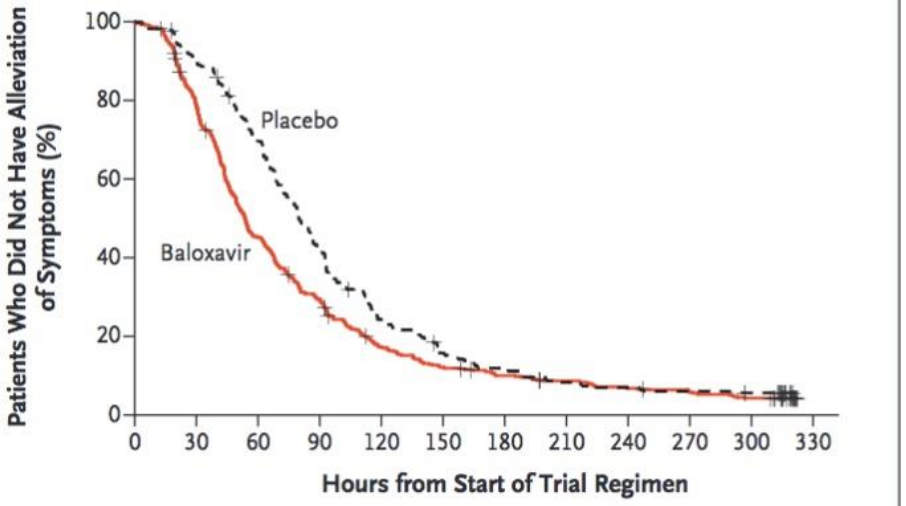
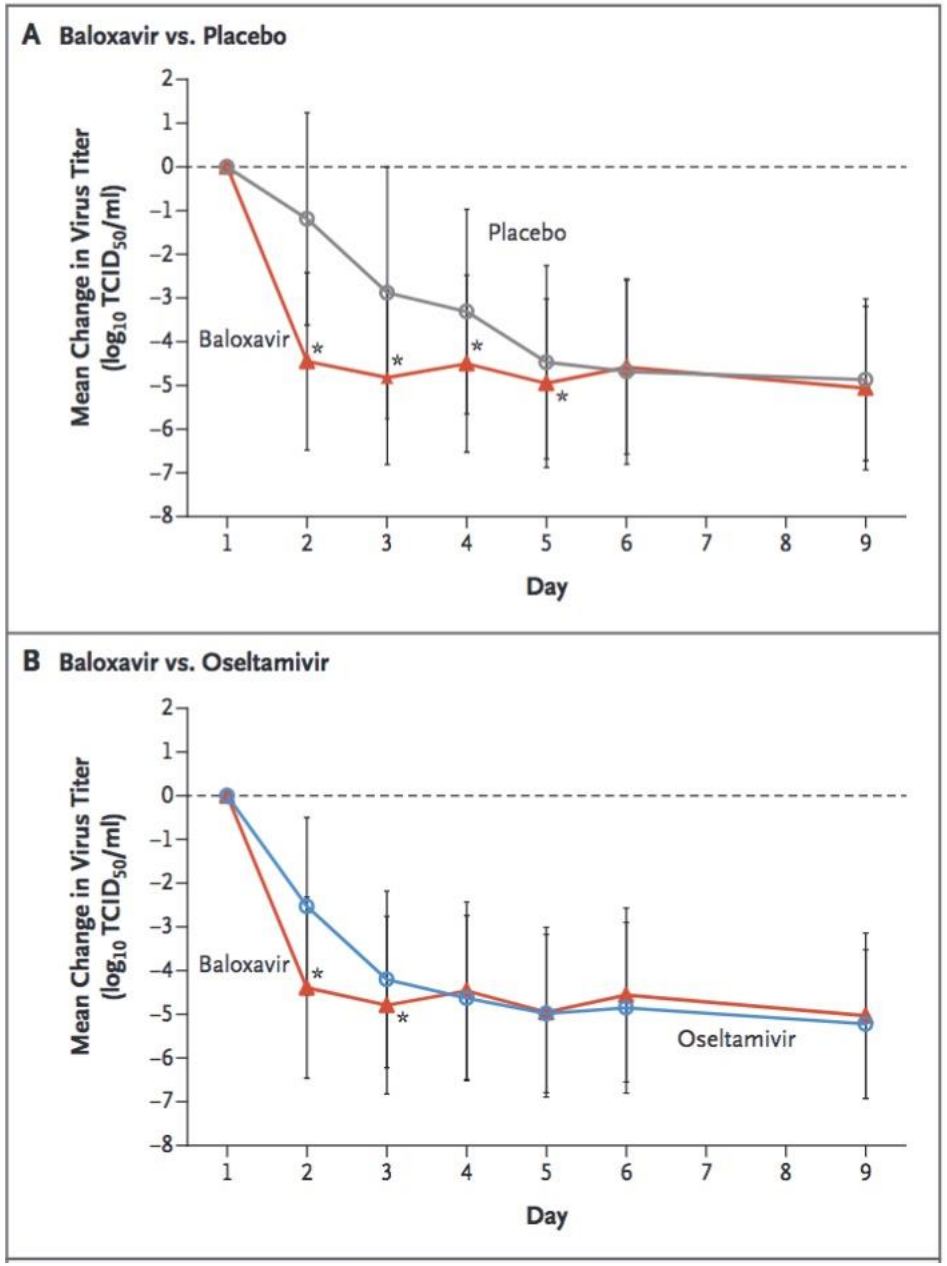


Figure 2. Kaplan–Meier Curves of the Time to Alleviation of Influenza Symptoms with Baloxavir versus Placebo in the Phase 3 Trial.



Effets secondaires?

Table 2. Adverse Events during the Phase 3 Trial (Safety Population).*

Event	Baloxavir (N=610)		Placebo (N=309)		Oseltamivir (N=513)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)					
Any adverse event	126 (20.7)	6 (1.0)	76 (24.6)	4 (1.3)	127 (24.8)	1 (0.2)
Adverse events reported in ≥1% of patients in any group						
Diarrhea	18 (3.0)	1 (0.2)	14 (4.5)	1 (0.3)	11 (2.1)	0
Bronchitis	16 (2.6)	0	17 (5.5)	1 (0.3)	18 (3.5)	0
Nasopharyngitis	9 (1.5)	0	2 (0.6)	0	4 (0.8)	0
Nausea	8 (1.3)	1 (0.2)	4 (1.3)	1 (0.3)	16 (3.1)	0
Sinusitis	7 (1.1)	0	8 (2.6)	1 (0.3)	5 (1.0)	0
Increase in ALT level	6 (1.0)	0	4 (1.3)	0	7 (1.4)	0
Headache	5 (0.8)	1 (0.2)	3 (1.0)	0	4 (0.8)	0
Vomiting	5 (0.8)	1 (0.2)	2 (0.6)	0	6 (1.2)	0
Dizziness	3 (0.5)	0	4 (1.3)	0	1 (0.2)	0
Leukopenia	0	0	3 (1.0)	0	1 (0.2)	0
Constipation	0	0	3 (1.0)	0	0	0
Adverse event considered to be related to the trial regimen	27 (4.4)	2 (0.3)	12 (3.9)	1 (0.3)	43 (8.4)†	0
Adverse events considered to be related to the trial regimen and reported in ≥1% of patients in any group						
Diarrhea	11 (1.8)	1 (0.2)	4 (1.3)	0	7 (1.4)	0
Nausea	2 (0.3)	1 (0.2)	2 (0.6)	1 (0.3)	8 (1.6)	0
Serious adverse event	2 (0.3)	2 (0.3)	0	0	0	0
Adverse event leading to discontinuation of the trial regimen‡	2 (0.3)	0	1 (0.3)	1 (0.3)	2 (0.4)	0

Conclusion

- Développements de molecules à large spectre
- Incitation au detournement des molécules
- Problèmatique de la tolerance reste au premier plan