ACTUALITE VACCINALE
Encéphalite Japonaise

SMV Septembre 2015

Encéphalite Japonaise

Rappel de la recommandation vaccinale*:

- Séjour en régions endémiques quelle que soit sa durée si exposition extérieure (notamment en zones rurales de rizières ou de marécages, pendant la période de transmission du virus)

- Expatriation et toute autre situation jugée à risque

**Avis du HCSP relatif aux recommandations de la vaccination contre l'encéphalite japonaise par le vaccin Ixiaro® 20 septembre 2013*

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Vaccin Ixiaro®

schéma court validé chez l'adulte (avril 2015)

- adulte > de **18 ans :** 1 dose (0, 5 ml) à J 0 et J 7 ou J 0- J28

- enfant : 1 dose à J0 et J28 (1/2 dose < 3 ans)

1 rappel la deuxième année chez l'adulte
non déterminé en dessous de 18 ans

Ce schéma rapide permet désormais d'immuniser des voyageurs pour des séjours à risque dans le cas d'un départ précipité ou consultation tardive

RCP Ixiaro Avril 2015

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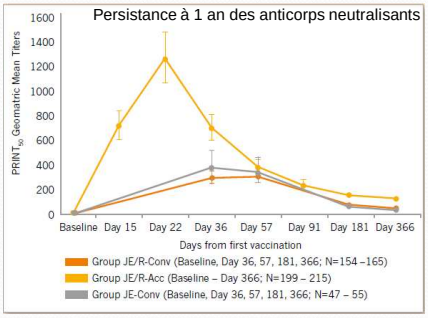
Cinétique des Ac 1 an après un schéma J0-J7

Méthode

661 adultes randomisés en 4 groupes (Autriche, Allemagne et Suisse)

Groupe	Sujets	Schéma	J 0	J 3	J 7	J 28
			Vaccins administrés			
2	217	**Accelerated** (Rabies + JE vaccine)	Rabipur **Ixiaro**	Rabipur	Rabipur **Ixiaro**	Placebo Placebo
1	167	**Conventional** (Rabies + JE vaccine)	Rabipur Ixiaro	Placebo	Rabipur Placebo	Rabipur Ixiaro
3	221	**Conventional** (Rabies vaccine alone)	Rabipur Placebo	Placebo	Rabipur Placebo	Rabipur Placebo
4	56	**Conventional** (JE vaccine alone)	Ixiaro Placebo	Placebo	Placebo Placebo	Ixiaro Placebo

Résultats



Persistance à 1 an des anticorps neutralisants avec une tendance à un maintient d'un taux plus élevé dans le bras accéléré

$PRNT_{50}$; 50% Plaque Reduction Neutralization Test;

Jelinek et al ISTM 2015

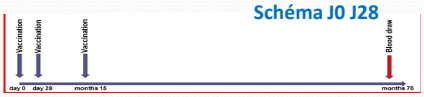
ɔipur Ixiaro IST 2015

Persistance des Ac à moyen terme après le 1er rappel chez l'adulte ?

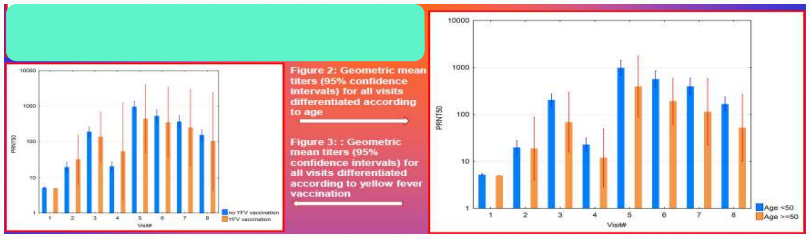
Méthode

67 volontaires randomisés après le rappel à 15 mois
Evaluation à 6 ans

Schéma J0 J28



Résultats



Plus de 6 ans après le rappel 96% des sujets testés ont des titres PRNT50 = 1:10
Les titres étaient plus bas chez les plus de 50 ans comparativement au < 50 ans
Les vaccinations anti amariles et encéphalite à tique n'ont pas eu d'interférence significative

Poster ISTM 2015, **Maria Paulke-Korinek**, LONG TERM IMMUNITY 6 YEARS AFTER BOOSTER VACCINATION AGAINST JAPANESE ENCEPHALITIS

Et chez l'enfant voyageur ?

Plénière ISTM 2015-K. Dubischar-Kastner- Valneva

Méthode

- suivi en ouvert chez 23 enfants (Europe, USA et Australie) sans booster
- titres d'anticorps neutralisants évalués par PRNT avant et 12, 24 et 36 mois après primovaccination

Résultats

- Mediane d'âge 14,3 ans, dont 1 enfant < 3ans,
- **taux de séroprotection : 91,3% (21/23 sujets) 24 mois après primovaccination**

(MGT = 75)

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Poster Number P0.03.05

ACCELERATED 1-WEEK VACCINATION REGIMENS FOR RABIES PRE-EXPOSURE AND JAPANESE ENCEPHALITIS PROPHYLAXIS

T. Jelinek[1], J. Cramer[2], G. Burchard[2], S. Bühler[3], H. Kollaritsch[4], H.-D. Nothdurft[5], E. Reisinger[6], M. Costantini[7], A. Giesen[8], E. Fragapane[7], M. Lattanzi[7], M. Pellegrini[7], K. Ahmed[9]

[1]The Berlin Center for Travel and Tropical Medicine, Berlin, Germany, [2]Bernhard-Nocht Institute for Tropical Medicine, Hamburg, Germany, [3]Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland, [4]Institute of Specific Prophylaxis and Tropical Medicine, Medical University of Vienna, Vienna, Austria, [5]University of Munich, Department of Infectious Diseases and Tropical Medicine, Munich, Germany, [6]Rostock University Medical Center, Department of Tropical Medicine and Infectious Diseases, Rostock, Germany, [7]Novartis Vaccines and Diagnostics, Srl., Italy – a GSK company, [8]Novartis Vaccines and Diagnostics GmbH, Marburg, Germany - a GSK company, [9]Novartis Healthcare Private Limited, Hyderabad, India

Conflict of interest: MC, AG, EF, ML and MP were employees of Novartis group companies when the study was conducted, and are now employees of GSK group companies. KA is an employee of Novartis group companies.

BACKGROUND AND OBJECTIVE

- The World Health Organization recommends rabies pre-exposure prophylaxis (PrEP) for travellers spending a lot of time outdoors, especially in rural areas, involved in activities such as bicycling, camping, or hiking as well as for long-term travellers and expatriates living in areas with a significant risk of exposure.[1] Japanese encephalitis (JE) vaccination is recommended for travelers to endemic areas with extensive outdoor exposure during the transmission season.[2]
- Conventional rabies PrEP and JE primary vaccination regimens each require up to 4 weeks to complete, which may not be feasible for travelers at short notice.
- This phase 3, randomized, observer-blind study evaluated the immunogenicity and safety of concomitant administration of an inactivated purified chick embryo cell culture rabies vaccine (PCECV, GSK Vaccines) and a Vero cell-derived, inactivated JE vaccine (JEV, Valneva), according to an accelerated (1 week) regimen, as compared to the conventional 4-week rabies or JE regimens (NCT01662440).

METHODS

- A total of 661 adults were randomized to 1 of 4 study groups:
  - Concomitant administration of rabies and JE vaccines following an accelerated 1-week regimen (R/JE-Acc; PCECV [1.0mL, intramuscular (IM) administration] at days 1, 4, 8; JEV [0.5mL, IM administration] at days 1, 8)*
  - Concomitant administration of rabies and JE vaccines following a conventional 4-week regimen (R/JE-Conv; PCECV [1.0mL, IM administration] at days 1, 8, 29; JEV [0.5mL, IM administration] at days 1, 29)*
  - Rabies vaccine alone following the conventional 4-week regimen (R-Conv; PCECV [1.0mL, IM administration] at days 1, 8, 29)*
  - JE vaccine alone following the conventional 4-week regimen (JE-Conv; JEV [0.5mL, IM administration] at days 1, 29)*

* Corresponding vaccination days according to official label use: PCECV: days 0, 7 and 28; JEV: days 0 and 28. To keep the observer-blind study design, placebo was matched with rabies or JE vaccination according to study group.

- Blood samples for immunogenicity analyses were drawn at baseline (day 1), and depending on the vaccine group, on days 8, 15, 22, 36, 57, 91, 181 and 366.
- For rabies, the cut-off for adequate immune response after vaccination was defined as rabies virus neutralizing antibody (RVNA) concentrations ≥ 0.5 IU/mL.[3] For JE, protective levels of anti-JE antibodies were defined as 50% Plaque Reduction Neutralization Test ($PRNT_{50}$) titers ≥ 1:10.[4]
- Solicited local and systemic reactions were collected for 7 days after each vaccination. All unsolicited adverse events (AEs), serious AEs (SAEs) and AEs leading to study withdrawal were collected through day 57. Only SAEs judged as possibly or probably related to the study vaccines were recorded from day 57 through day 366.

RESULTS

- Demography and baseline characteristics were generally comparable across the vaccine groups (**Table 1**).

Table 1. Demography and baseline characteristics

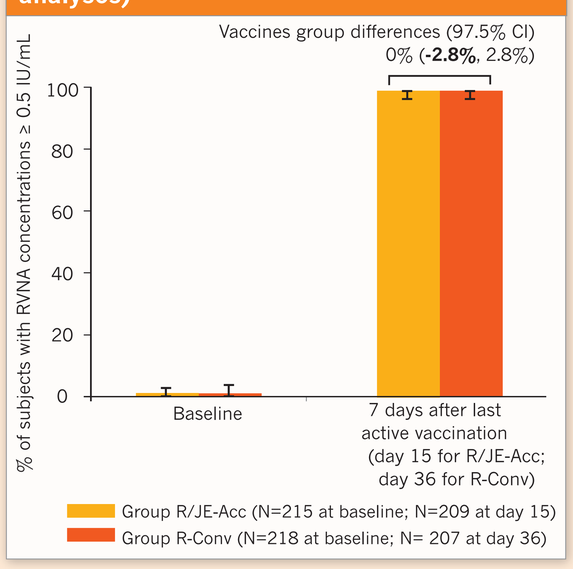
	R/JE-Acc N=217	R/JE-Conv N=167	R-Conv N=221	JE-Conv N=56	Total N=661
Age, mean±SD, years	36.8±12.7	37.3±13.4	35.7±12.6	38.8±13.3	36.7±12.9
Gender, n (%)					
Male	89 (41)	91 (54)	96 (43)	26 (46)	302 (46)
Female	128 (59)	76 (46)	125 (57)	30 (54)	359 (54)
Ethnic origin					
Asian	0	1 (<1)	1 (<1)	0	2 (<1)
Black or African American	2 (<1)	0	0	1 (2)	3 (<1)
Caucasian	213 (98)	166 (99)	218 (99)	54 (96)	651 (98)
Other	2 (<1)	0	2 (<1)	1 (2)	5 (<1)
Weight, mean±SD, kg	75.2±17.1	75.7±16.9	73.6±14.1	74.5±16.0	74.7±16.0
Height, mean ±SD, cm	172.4±8.9	174.5±9.1	172.9±9.2	172.8±8.3	173.1±9.0

SD, standard deviation.

Immunogenicity

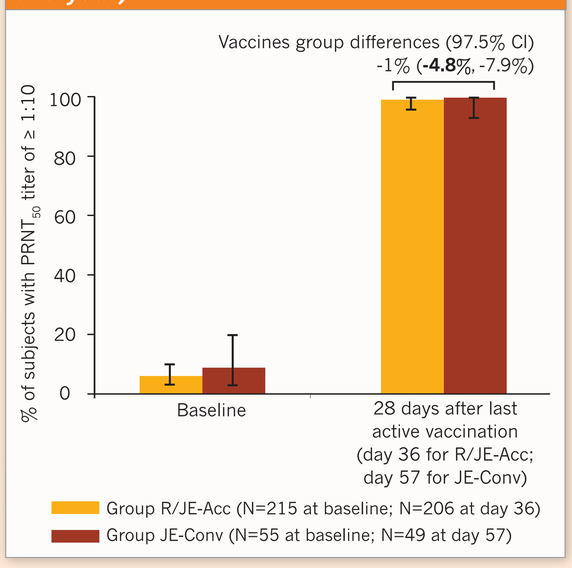
- The two primary immunogenicity objectives were met.
  - RABIES: Non-inferiority of R/JE-Acc to R-Conv at 7 days after the final active vaccination was established as the lower limit (LL) of the 2-sided 97.5% confidence interval (CI) of the difference was -2.8%, which was above the pre-specified non-inferiority margin of -5%. All subjects (100%) in both vaccine groups had RVNA concentrations ≥ 0.5 IU/mL at 7 days after the last active vaccination (**Figure 1**).

Figure 1. Percentage of subjects with RVNA concentrations ≥ 0.5 IU/mL to rabies vaccination at 7 days after the last active vaccination (primary immunogenicity analyses)



  - JE: Non-inferiority of R/JE-Acc to JE-Conv at 28 days following the final active vaccination was demonstrated as the LL of the 97.5% CI of the difference was -4.8%, which was above the pre-specified non-inferiority margin of -10%. Percentages of subjects with $PRNT_{50}$ titer of ≥ 1: 10 at 28 days after the last active vaccination were 99% and 100% for R/JE-Acc and JE-Conv, respectively (**Figure 2**).

Figure 2. Percentage of subjects with $PRNT_{50}$ titer of ≥ 1:10 to Japanese encephalitis vaccination at 28 days after the last active vaccination (primary immunogenicity analyses)



- For rabies, postvaccination RVNA geometric mean concentrations (GMCs) increased rapidly with a peak in all groups at day 15. GMCs declined thereafter, with an expected more rapid decrease for R/JE-Acc. At day 366, GMCs in R/JE-Acc were still slightly lower than those of conventional regimens (**Figure 3A**).
  At 1-year follow-up, percentages of subjects with adequate GMCs ranged from 68% (R/JE-Acc) to 80% (R-Conv) (**Figure 3B**).
- For JE, $PRNT_{50}$ geometric mean titers (GMTs) peaked at day 22 for R/JE-Acc and at days 36-57 for conventional regimens, with a steady antibody titer decline in all groups up to day 366. GMTs in R/JE-Acc were consistently higher at all time points as compared to the conventional regimens (**Figure 4A**).
  Persistence of protective anti-JE antibody levels was high in all groups. At 1-year follow-up, 94%, 86% and 88% of subjects in R/JE-Acc, R/JE-Conv and JE-Conv, respectively, had protective titers (**Figure 4B**).

Figure 3. Kinetics of neutralizing antibody responses to rabies (RVNA GMCs, 95% CI) (A) and percentage of subjects with RVNA concentrations ≥ 0.5 IU/mL (95% CI) (B) after accelerated and conventional regimens over time (day 1-366)

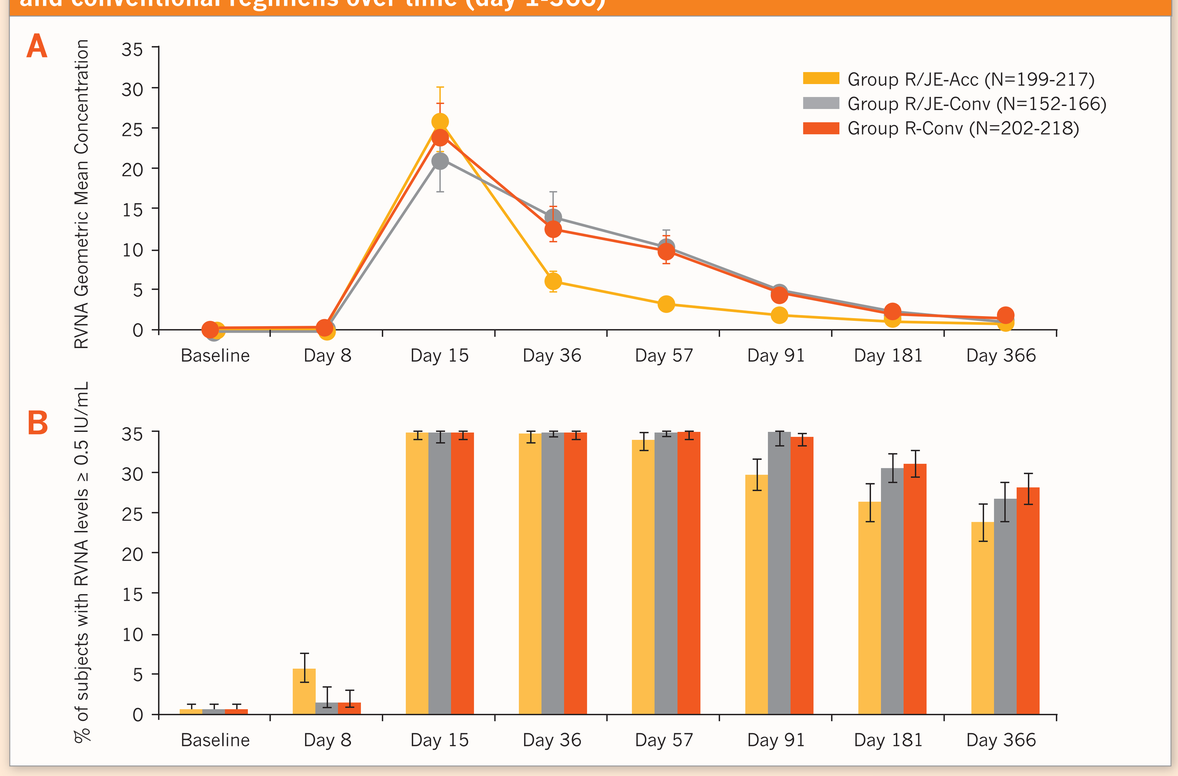


Figure 4. Kinetics of antibody responses to JE ($PRNT_{50}$ GMTs, 95% CI) (A) and percentage of subjects with $PRNT_{50}$ titer of ≥ 1:10 (95% CI) (B) after accelerated and conventional regimens over time (day 1-366)

$PRNT_{50}$ analyses were not performed at all time points in all JE groups

Table 2. Overview of subjects reporting solicited reactions (within 7 days after any vaccination) and unsolicited adverse events (day 1 through day 57)

	R/JE-Acc N=217	R/JE-Conv N=166	R-Conv N=220	JE-Conv N=56
Solicited AEs				
Any reactions	185 (85%)	137 (83%)	181 (82%)	44 (79%)
Any local reactions	161 (74%)	125 (75%)	160 (73%)	35 (63%)
Any systemic reactions	144 (66%)	99 (60%)	136 (62%)	30 (54%)
Any other reactions	36 (17%)	28 (17%)	40 (18%)	6 (11%)
Unsolicited AEs				
Any AE	108 (50%)	69 (42%)	110 (50%)	29 (52%)
At least possibly or probably related AEs	49 (23%)	30 (18%)	49 (22%)	6 (11%)
SAEs*	3 (1%)	2 (1%)	2 (1%)	3 (5%)
At least possibly or probably related SAEs	0	0	2 (1%)	1 (2%)
Deaths**	0	0	0	0
AEs leading to premature study withdrawal	0	1 (1%)	0	1 (2%)

AE, adverse event; SAE, serious adverse event.
* None of the subjects reported SAEs at least possibly related to study vaccines from day 57 to day 366
** One subject in the R/JE-Acc group died (fatal skiing accident) after day 57. This event was judged by the investigator as not related to study vaccines.

Safety

- Solicited reactions and unsolicited AEs were generally comparable between groups.
- Any solicited reactions were reported in 79% to 85% of subjects across groups, lowest in JE-Conv (**Table 2**). Severe reactions were rare and occurred in 4% or less of subjects across groups.
- Unsolicited AEs were reported in 42% to 52% of subjects across groups, of which 11% to 23% were considered at least possibly or probably related (**Table 2**).
- SAEs were reported in 1% to 5% of subjects across groups (**Table 2**). There were 3 subjects who reported possibly/probably vaccine-related SAEs: 1 subject with atrial fibrillation (R-Conv), 1 subjects with tachycardia and syncope (R-Conv) and 1 subjects with eyelid edema and generalized pruritus (JE-Con), with all cases resolved. None of the subjects reported SAEs at least possibly related to study vaccines from day 57 to day 366.
- There were no deaths from day 1 to day 57 (**Table 2**).

CONCLUSION

- The accelerated 'combined' rabies and JE vaccination regimen induced short-term strong immune responses non-inferior to those obtained with the conventional regimens, with a satisfactory safety profile. For both vaccines, immunogenicity was sustained for 1 year after the accelerated regimens.
- Concomitant administration of rabies and JE vaccines did not compromise immune responses or safety profile of either vaccine.
- Accelerated, 1-week PrEP rabies and JE vaccination regimens, could potentially be offered as an alternative to the currently recommended regimens, especially for travelers on short notice. The option to concomitantly administer these vaccines could simplify pre-travel immunization schedules and increase vaccination coverage among travelers.
- On 23 Apr 2015, the European CHMP granted positive opinion on the Ixiaro accelerated schedule and concomitant administration with Rabipur, based on the data from this study.

References

1. WHO. Rabies Fact Sheet No 99. September 2014.
2. WHO. Japanese Encephalitis Vaccines: WHO Position Paper. WER. 2015; 90: 69-88.
3. Plotkin, S. *Clin Vaccine Immunol.* 2010; 17:1055-1065.
4. Van Gessel Y, et al. *Vaccine.* 2011; 29:5925-5931.

Contact information:
michele.x.pellegrini@gsk.com

NOVARTIS VACCINES

Novartis Vaccines non-influenza business has now transferred to GSK