6ER-009

CAN TOLERABILITY AND SAFETY OF DAA-2 FOR HEPATITIS C BE ESTIMATED ONLY BY RANDOMISED CLINICAL TRIALS? A SYSTEMATIC REVIEW WITH META-ANALYSIS

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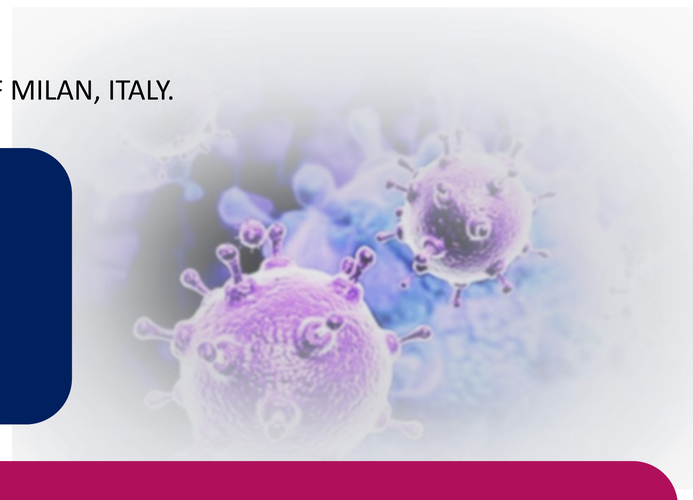


Background:
Every year an increase of new cases of patients with **chronic hepatitis C** (CHC) from HCV has been registered. The availability of **second-generation DAA (DAA-2)** has permitted a rise of SVR rates compatibly with a good safety profile.

Material and methods:
REVIEW:
- RCT and other CT concluded and published until 20 June 2017: DAA-2 in monotherapy or combined therapy vs. gold standard.
- Adverse reactions (ADR) data: not beyond 30 days from the end of treatment period.
- Databases: Cochrane-Central-Register-of-Controlled-Trials/Central, Embase and Pubmed
- Research methodology : MeSH Terms when available.

META-ANALYSIS with R for included studies

Purpose:
Literature evidence regarding existence of **tolerability and safety** data obtained from a **comparison between DAA-2 and standard of care.**

- Sofosbuvir
- Simeprevir
- Ledipasvir
- Daclatasvir
- Ombitasvir
- Paritaprevir
- Dasabuvir

PegIFN±Ribavirin (RBV)±first-generation DAA (DAA-1).

Results:
- 174 articles identified
- 9 recognized by more databases
- 168 discarded (no correspondence with primary endpoint and inclusion criteria)
- **6 studies included : 5 RCT and 1 observational study.**

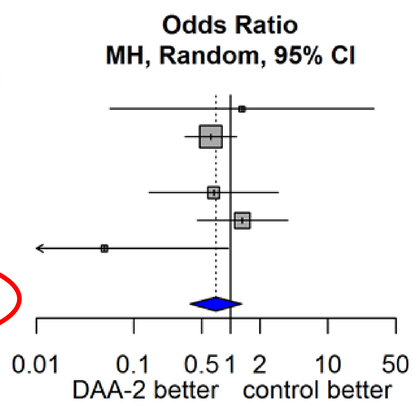
1 study excluded from meta-analysis (it didn't reported the SAE numbers for control)

The IC95% of the Odds Ratio around the evaluation of the overall effect included the value 1

Serious adverse events (SAE) data between **exposed (treated) and not-exposed (controls)** patients

Study	DAA-2 Events	DAA-2 Total	controls Events	controls Total	Weight	Odds Ratio MH, Random, 95% CI
Izumi 2014	2	34	0	8	3.70%	1.308 [0.057; 29.877]
Jacobson 2016	26	402	20	200	53.10%	0.622 [0.338; 1.145]
Pol 2012	3	36	.	12	0.00%	
Dore 2015	4	100	3	51	13.91%	0.667 [0.143; 3.099]
Zeuzem 2014	31	396	4	66	25.13%	1.316 [0.449; 3.859]
Ji 2016	0	94	4	46	4.16%	0.050 [0.003; 0.949]
Total (95% CI)	**66**	**1062**	**31**	**383**	**100.00%**	**0.702 [0.381; 1.295]**

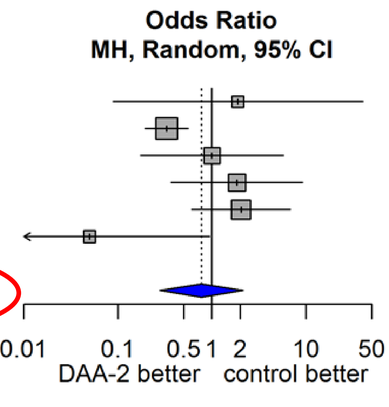
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 4.75$, df = 4 (P = 0.314); $I^2 = 15.81\%$ [0%; 82.49%]
Test for overall effect: Z = -1.133 (P = 0.257)



Interruptions of therapy data between **exposed (treated) and not-exposed (controls)** patients

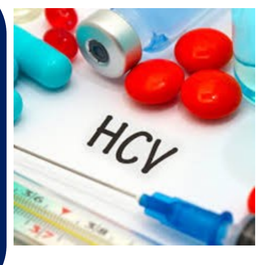
Study	DAA-2 Events	DAA-2 Total	controls Events	controls Total	Weight	Odds Ratio MH, Random, 95% CI
Izumi 2014	3	34	0	8	8.18%	1.889 [0.089; 40.225]
Jacobson 2016	28	402	37	200	28.29%	0.330 [0.195; 0.557]
Pol 2012	6	36	2	12	16.09%	1.000 [0.173; 5.772]
Dore 2015	7	100	2	51	17.39%	1.844 [0.369; 9.217]
Zeuzem 2014	35	396	3	66	21.41%	2.036 [0.608; 6.821]
Ji 2016	0	94	4	46	8.64%	0.050 [0.003; 0.949]
Total (95% CI)	**79**	**1062**	**48**	**383**	**100.00%**	**0.769 [0.277; 2.138]**

Heterogeneity: $Tau^2 = 0.89$; $Chi^2 = 13.87$, df = 5 (P = 0.016); $I^2 = 63.96\%$ [12.93%; 85.08%]
Test for overall effect: Z = -0.503 (P = 0.615)



No differences in the effect between treated and controls were observed

Conclusion:
No substantial differences subsisted in SAE and interruptions rate between the two treatments, DAA-2 and gold standard. Furthermore a significant heterogeneity between studies was observed. The introduction of large registries would be useful to value the risk of ADRs, their nature and the real frequency of SAE in the population, that can be barely estimated only by RCT.



References : R Core Team. http://www.R-project.org/

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