Re: Cardiotoxicity of immune checkpoint inhibitors: A systematic review and meta-analysis of randomised clinical trials

Joe-Elie Salem, Stephane Ederhy, Agnès Dechartres

Answer to Cardiotoxicity of immune checkpoint inhibitors: A systematic review and meta-analysis of randomised clinical trials – An enigmatic discordance resolved

Joe-Elie SALEM, MD, PhD[1]; Stephane EDERHY, MD[2]; Agnès DECHARTRES, MD, PhD[3]

Correspondence: Joe-Elie Salem, M.D., Ph.D, Centre d'Investigation Clinique Paris-Est, Hôpital Pitié-Salpêtrière, Bâtiment Antonin Gosset, 47-83 Bld de l'hôpital, 75013 Paris, France. Secretariat: +33 1 42 17 85 31, Fax: +33 1 42 17 85 32; Email: joe-elie.salem@aphp.fr

[1] *Sorbonne Université, INSERM, AP-HP, Pitié-Salpêtrière Hospital, Department of Pharmacology, CIC-1901; Sorbonne Université, INSERM, APHP.Sorbonne UNICO-GRECO Cardio-oncology Program, F-75013 Paris, France.*

[2] *Sorbonne Université, INSERM, AP-HP, Saint-Antoine Hospital, Department of Cardiology, CIC-1901; APHP.Sorbonne UNICO-GRECO Cardio-oncology Program, F-75013 Paris, France.*

[3] Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, UMR-S 1136, AP-HP, Hôpital Pitié-Salpêtrière, Département de Santé Publique, Paris, France

968/1000 words

10/10 references

1 Figure

Disclosures: None

Immune-checkpoint inhibitors (ICI) are revolutionary anticancer drugs approved in an expanding variety of cancer types.[1] ICI restore the activity of the immune system and primarily of T-cells to destroy neoplastic cells.[1] Currently, approved ICI are monoclonal antibodies blocking CTLA4 (cytotoxic T-lymphocyte associated protein 4) and PD1 (Programmed cell Death protein 1), which are immune-checkpoint brakes expressed on the T-cells.[1] ICI also include anti-PDL1 (PD1 ligand located on cancer cells) normally interacting with PD1 to tone-down T-cells.[1] Though, ICI may induce immune-related adverse events (irAE) with auto-immune reaction targeting potentially any organ and eventually being fatal in ~0.5-1% of ICI treated patients.[2] IrAE, when symptomatic, are generally treated by withholding ICI and start of immunosuppressants including glucocorticoids in the first place.[2] IrAE affecting the cardiovascular system mainly includes myocarditis, pericarditis, arrhythmias and vasculitis.[3] Myocarditis is fortunately a rare event but is the top life-threatening irAE with fatality rates reaching up to 50% in the first cohorts reported.[3] Johnson et al. first described two fatal ICI-myocarditis cases with on autopsy, activated T-cells and macrophages leading to heart and peripheral muscles necrosis, providing the main pathophysiological processes of this novel condition.[4] Incidence of myocarditis have been estimated around 0.03% in first clinical trials evaluating ICI monotherapies and up to ~1% in real-life cohorts involving aware medical teams including oncologists and cardiologists.[3,4] But, with the increased use of ICI and the multiplication of cancer indications, numbers of deadly and glucocorticoids-resistant ICI-myocarditis have exploded, representing an important concern for clinicians and regulatory institutions.[5-7] Combination of ICI, including an anti-CTLA4 and anti-PD1, have been repeatedly shown to be a risk factor for ICI-myocarditis using multiple study designs.[3,4,8] First, an analysis of Bristol-Myers Squibb corporate safety databases as of April 2016 showed a significantly higher incidence of myocarditis in patients who received combination therapy (an anti-PD1 and an anti-CTLA4; 8/2,974 (0.27%)) than in those who received an anti-PD1 alone (10/17,620 (0.06%); P<0.001).[4] Second, in a query of VigiBase, the WHO pharmacovigilance database, ICI-myocarditis was overreported in patients treated with ICI combination therapy versus those treated with monotherapy (Reporting odds-Ratio=4.31[2.86–6.38]).[3] Thirdly, in an U.S. Food and Drug Administration

pooled analysis of 59 trials (N=21,664), ICI therapy was associated with higher rates of myocarditis, vasculitis, ischemia, arrhythmia, and pericardial disease compared to non-ICI therapy.[7] When ICI were used in combination (N=1,533), cardiovascular adverse events increased across most categories compared to ICI monotherapy (N=17,072), and particularly myocarditis (0.13% vs. 0.02%; Relative-risk=7.42).[7] Lastly, in preclinical models, the deleterious interaction between PD1 and CTLA4 was further confirmed. Wei et al identified a dose–dependent genetic and functional interaction between the T cell–negative costimulatory genes Ctla4 and Pdcd1, which manifests as fatal myocarditis in $Ctla4^{+/-}$ $Pdcd1^{-/-}$ mice contrasting with absence of this phenotype in $Ctla4^{+/+}$ $Pdcd1^{-/-}$ or $Ctla4^{+/-}$ $Pdcd1^{+/-}$ mice.[8] In this context, results of the systematic review and meta-analysis of randomized clinical trials by Agostinetto et al, showing no association between ICI monotherapies, or even ICI combination therapies compared to non-ICI controls patients stands out remarkably.[9] Herein, we investigated the reason of such discordant findings.

Since ICI-myocarditis are rare events, many ICI trials did not report any such events in either ICI and non-ICI arms and these trials should not have been included in meta-analysis. Indeed, the Cochrane handbook (the well-recognized reference for conducting systematic reviews and meta-analyses, www.training.cochrane.org/handbook) specifically states that for studies with no events in either arm (#section-10-4-4-2), the standard practice in meta-analysis of odds ratios and risk ratios is to exclude such studies. "*This is because such studies do not provide any indication of either the direction or magnitude of the relative treatment effect. Whilst it may be clear that events are very rare on both the experimental intervention and the comparator intervention, no information is provided as to which group is likely to have the higher risk, or on whether the risks are of the same or different orders of magnitude (when risks are very low, they are compatible with very large or very small ratios). Whilst one might be tempted to infer that the risk would be lowest in the group with the larger sample size (as the upper limit of the confidence interval would be lower), this is not justified as the sample size allocation was determined by the study investigators and is not a measure of the incidence of the event. Bradburn and colleagues*

undertook simulation studies which revealed that all risk difference methods yield confidence intervals that are too wide when events are rare, and have associated poor statistical power, which make them unsuitable for meta-analysis of rare events (Bradburn et al 2007). This is especially relevant when outcomes that focus on treatment safety are being studied, as the ability to identify correctly (or attempt to refute) serious adverse events is a key issue in drug development. Furthermore, it is likely that outcomes for which no events occur in either arm may not be mentioned in reports of many randomized trials, precluding their inclusion in a meta-analysis". This recommendation was not respected in the meta-analysis by Agostinetto et al, leading as expected to falsely negative results.[9] When reperforming the meta-analysis after removing the trials with no events in ICI and non-ICI arms, and keeping the same events data extracted,[9] results are much different and confirm the well-consolidated association between ICI and myocarditis (Risk-ratio~2.3-2.7, with significance depending on type of model used (fixed or random effects models) and possible correction methods for ICI monotherapies vs. non-ICI groups in **Figure-1**). Lastly, Agostinetto et al. only extracted the adverse events data from publications whereas results posted at ClinicalTrials.gov especially adverse events and serious adverse events are generally more completely reported.[10] Therefore, reperforming a more comprehensive meta-analysis with methods adapted to rare events and search of clinical trial registers as ClinicalTrials.gov might be desirable to further assess cardiovascular toxicities spectrum induced by ICI.

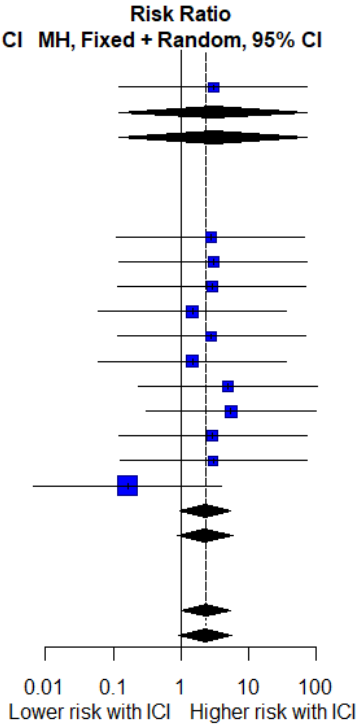
REFERENCES

1. Geraud A, Gougis P, Vozy A, et al. Clinical Pharmacology and Interplay of Immune Checkpoint Agents: A Yin-Yang Balance. *Annu Rev Pharmacol Toxicol* 2020.
2. Wang DY, Salem JE, Cohen JV, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. *JAMA Oncol* 2018; **4**(12): 1721-8.
3. Salem J-E, Manouchehri A, Moey M, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *The Lancet Oncology* 2018; **19**(12): 1579-89.
4. Johnson DB, Balko JM, Compton ML, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. *N Engl J Med* 2016; **375**(18): 1749-55.
5. Salem JE, Allenbach Y, Vozy A, et al. Abatacept for Severe Immune Checkpoint Inhibitor-Associated Myocarditis. *N Engl J Med* 2019; **380**(24): 2377-9.
6. Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B, Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. *Lancet* 2018; **391**(10124): 933.
7. Amiri-Kordestani L, Moslehi J, Cheng J, et al. Cardiovascular adverse events in immune checkpoint inhibitor clinical trials: A U.S. Food and Drug Administration pooled analysis. *Journal of Clinical Oncology* 2018; **36**(15_suppl): 3009-.
8. Wei SC, Meijers WC, Axelrod ML, et al. A genetic mouse model recapitulates immune checkpoint inhibitor-associated myocarditis and supports a mechanism-based therapeutic intervention. *Cancer Discov* 2020.
9. Agostinetto E, Eiger D, Lambertini M, et al. Cardiotoxicity of immune checkpoint inhibitors: A systematic review and meta-analysis of randomised clinical trials. *Eur J Cancer* 2021; **148**: 76-91.
10. Riveros C, Dechartres A, Perrodeau E, Haneef R, Boutron I, Ravaud P. Timing and completeness of trial results posted at ClinicalTrials.gov and published in journals. *PLoS Med* 2013; **10**(12): e1001566; discussion e.

Figure. Forest-plot for myocarditis events in single immune checkpoint inhibitors group (ICI) versus non-ICI group. Meta-analysis was performed after adding 0.5 cell only to studies with no event in one of the two compared groups (ICI vs. non-ICI) but after excluding the studies with no event in both groups (A); and using the correction proposed by Sweeting applying the reciprocal of the opposite arm size (B).

A

Study or Subgroup	ICI Events	ICI Total	NON-ICI Events	NON-ICI Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
Subgroup = Anti-CTLA4							
EORTC-18071, 2016	1	471	0	474	6.2%	8.1%	3.02 [0.12; 73.92]
Total (fixed effect, 95% CI)		471		474	6.2%	--	3.02 [0.12; 73.92]
Total (random effects, 95% CI)					--	8.1%	3.02 [0.12; 73.92]
Heterogeneity: not applicable							
Subgroup = Anti-PD(L)1							
JAVELIN Lung 200, 2018	1	393	0	365	6.4%	8.1%	2.79 [0.11; 68.19]
JAVELIN Renal 101, 2019	1	434	0	439	6.2%	8.1%	3.03 [0.12; 74.29]
KEYNOTE-042, 2019	1	636	0	615	6.3%	8.1%	2.90 [0.12; 71.08]
KEYNOTE-048, 2019	1	576	0	287	8.3%	8.1%	1.50 [0.06; 36.61]
KEYNOTE-181, 2019	1	314	0	296	6.4%	8.1%	2.83 [0.12; 69.15]
KEYNOTE-189, 2020	1	405	0	202	8.3%	8.1%	1.50 [0.06; 36.61]
KEYNOTE-426, 2019	2	429	0	425	6.2%	9.0%	4.95 [0.24; 102.87]
KEYNOTE-522, 2020	5	781	0	389	8.3%	9.9%	5.48 [0.30; 98.89]
NCT02362594, 2018	1	509	0	502	6.3%	8.1%	2.96 [0.12; 72.46]
NCT03051659, 2019	1	44	0	44	6.2%	8.2%	3.00 [0.13; 71.67]
PACIFIC, 2017	0	475	1	234	24.9%	8.1%	0.16 [0.01; 4.02]
Total (fixed effect, 95% CI)		4996		3798	93.8%	--	2.30 [0.97; 5.46]
Total (random effects, 95% CI)					--	91.9%	2.27 [0.88; 5.86]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.48$, df = 10 (P = 0.97); $I^2 = 0\%$							
Total (fixed effect, 95% CI)		**5467**		**4272**	**100.0%**	**--**	**2.34 [1.02; 5.40]**
Total (random effects, 95% CI)					**--**	**100.0%**	**2.32 [0.93; 5.77]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.50$, df = 11 (P = 0.98); $I^2 = 0\%$							



B

Study or Subgroup	ICI Events	ICI Total	NON-ICI Events	NON-ICI Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
Subgroup = Anti-CTLA4							
EORTC-18071, 2016	1	471	0	474	7.0%	8.7%	3.01 [0.12; 73.36]
Total (fixed effect, 95% CI)		471		474	7.0%	--	3.01 [0.12; 73.36]
Total (random effects, 95% CI)					--	8.7%	3.01 [0.12; 73.36]
Heterogeneity: not applicable							
Subgroup = Anti-PD(L)1							
JAVELIN Lung 200, 2018	1	393	0	365	7.0%	8.4%	2.93 [0.11; 74.66]
JAVELIN Renal 101, 2019	1	434	0	439	7.0%	8.7%	3.01 [0.12; 73.28]
KEYNOTE-042, 2019	1	636	0	615	7.0%	8.5%	2.97 [0.12; 74.03]
KEYNOTE-048, 2019	1	576	0	287	6.2%	6.4%	2.50 [0.06; 103.04]
KEYNOTE-181, 2019	1	314	0	296	7.0%	8.5%	2.94 [0.12; 74.33]
KEYNOTE-189, 2020	1	405	0	202	6.2%	6.4%	2.50 [0.06; 102.84]
KEYNOTE-426, 2019	2	429	0	425	7.0%	9.6%	4.98 [0.24; 104.04]
KEYNOTE-522, 2020	5	781	0	389	6.2%	7.2%	8.49 [0.26; 279.84]
NCT02362594, 2018	1	509	0	502	7.0%	8.6%	2.99 [0.12; 73.68]
NCT03051659, 2019	1	44	0	44	7.0%	8.8%	3.00 [0.13; 71.67]
PACIFIC, 2017	0	475	1	234	25.1%	10.3%	0.25 [0.01; 4.66]
Total (fixed effect, 95% CI)		4996		3798	93.0%	--	2.70 [1.08; 6.72]
Total (random effects, 95% CI)					--	91.3%	2.52 [0.94; 6.73]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.14$, df = 10 (P = 0.98); $I^2 = 0\%$							
Total (fixed effect, 95% CI)		**5467**		**4272**	**100.0%**	**--**	**2.72 [1.13; 6.54]**
Total (random effects, 95% CI)					**--**	**100.0%**	**2.56 [1.00; 6.54]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.15$, df = 11 (P = 0.99); $I^2 = 0\%$