



Letter to the Editor

Drug-induced Kounis syndrome: A matter of pharmacovigilance



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We commend the review by Abdelghany and relevant debate on Kounis Syndrome (KS), including possible association with systemic mastocytosis [1,2]. As recognized, drugs represent the most common cause of KS in clinical practice. Our MEDLINE analysis (as of 25/11/2016) yielded 252 publications dealing with risk factors of KS: in 142 articles, drugs were considered directly responsible for KS; in 89 cases, KS was triggered by non-pharmacological agents and in 21 reports KS was stent related. Notably, 126 studies on drug-induced KS were case reports (89%), 14 case series and 2 studies on spontaneous reporting systems [3,4].

We would like to contribute to the debate by analyzing the FDA Adverse Event Reporting System (2004–June 2016), a consolidated pharmacovigilance source to monitor rare but serious adverse events such as KS through disproportionality analysis [5]. Out of 499 spontaneous reports of drug-induced KS, 236 cases (47%) were suspectedly attributed to a single drug. Overall, 30 drugs emerged with disproportionality, including non-steroidal anti-inflammatory drugs [e.g., ibuprofen; $N = 66$; reporting odds ratio (ROR) = 19.53; 95% confidence interval (CI) = 11.4–24.2], antibiotics such as amoxicillin ($N = 29$; ROR: 16.6; 95% CI: 11.4–24.2) also in combination with clavulanate (45; 198.42; 145.77–270.08), and anticancer drugs (fluorouracil: 10; 4.29; 2.29–8.02).

These findings are consistent with previous studies on the vasospastic and/or anaphylactic pathogenesis of KS [3,4] and underline the importance of submitting case reports to the pharmacovigilance system: increased awareness among clinicians of drug-induced KS will allow early recognition, timely management, and final inclusion in treatment guidelines of myocardial infarction.

Conflict of interest

Emanuel Raschi, Lorenzo Fertonani Affini, Ippazio Cosimo Antonazzo, Elisabetta Poluzzi and Fabrizio De Ponti declare no conflicts of interest relevant to the present manuscript. Igor Diemberger reports minor speaker fees from Bayer and Boehringer Ingelheim, on topics unrelated to the contents of this manuscript.

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References

- [1] M. Abdelghany, R. Subedi, S. Shah, H. Kozman, Kounis syndrome: a review article on epidemiology, diagnostic findings, management and complications of allergic acute coronary syndrome, *Int. J. Cardiol.* 232 (2017) 1–4.
- [2] M. Abdelghany, S. Shah, R. Subedi, H. Kozman, In reply: Kounis syndrome: a review article on epidemiology, diagnostic findings, management and complications of allergic acute coronary syndrome: Mastocytosis and post-mortem diagnosis, *Int. J. Cardiol.* 242 (2017) 39.
- [3] F. Renda, E. Marotta, G. Landoni, et al., Kounis syndrome due to antibiotics: a global overview from pharmacovigilance databases, *Int. J. Cardiol.* 224 (2016) 406–411.
- [4] F. Renda, G. Landoni, F. Trotta, et al., Kounis syndrome: an analysis of spontaneous reports from international pharmacovigilance database, *Int. J. Cardiol.* 203 (2016) 217–220.
- [5] E. Raschi, E. Poluzzi, F. Salvo, et al., Pharmacovigilance of sodium-glucose co-transporter-2 inhibitors: what a clinician should know on disproportionality analysis of spontaneous reporting systems, *Nutr. Metab. Cardiovasc. Dis.* 28 (2018) 533–542.

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