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Rationale and evidence on the use of tocilizumab in COVID-19: A systematic review. Authors' reply

Dear Editor,

We read with interest the Letter from Siang Kow et al.[1] commenting on our systematic review[2] and their discussion of the preliminary evidence from recent randomized controlled trials (RCTs) on the efficacy and safety of tocilizumab for COVID-19. We concur with the authors that it may indeed be time to divert some of our attention from IL-6 to other mediators of inflammation in COVID-19 patients. In fact, previous pharmacological attempts to modulate the inflammatory response in patients with ARDS and sepsis have repeatedly proven unsuccessful. It is therefore reasonable to also question whether suppressing the pathophysiological inflammatory response, or blocking a single mediator for that matter, will be beneficial for patients with COVID-19.

The authors commented on the absence of significant difference in mortality between patients who received tocilizumab (Actemra/RoActemra) or placebo in the industry funded COVACTA (NCT04320615 - https://www.roche.com/dam/jcr:6d8de90d-2e31-43c8-b4e1-0a24a2675015/en/29072020-mr-covacta.pdf) and EMPACTA (NCT04372186 - https://www.roche.com/media/releases/med-cor-2020-09-18.htm) trials.

The results of these trials confirm that findings from non-randomized trials should be interpreted with caution and that such caution is warranted particularly during public health emergencies when large numbers of patients may subsequently receive redundant treatments. As discussed by the authors in the context of tocilizumab and exemplified also by the hydroxychloroquine landslide,[3] experimental drugs are not always harmless, particularly when indiscriminately used. Patient safety should always be prioritized, which is why experimental drugs must be administered within the framework of registered RCTs that are accompanied by appropriate monitoring and regulation.

Research methodology may have also contributed to the negative findings of the above-mentioned RCTs. One example of a potential determinant of outcome in relation to treatment is the timing of administration in respect to the clinical phase of the disease.[4] Another is the treatment dose. Case mix may also have diluted the results; there may be sub-populations of COVID-19 patients who do actually benefit from receiving tocilizumab. Hopefully the full reports of the COVACTA and EMBACTA trials will shed some light on these questions and more. These analyses combined with additional data from the interventional tocilizumab arm of the RECOVERY trial (www.recoverytrial.net) may yet change our perspective on this drug. To summarize, although oft repeated, the following rhetoric is simply the truth: more (high quality) research is urgently needed.

Authors' contribution

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Spontaneous pneumomediastinum: Beyond the risky diving

To the Editor:

We read with great interest the letter from Cascais-Costa et al.[1] on the risk of developing pneumomediastinum as a result of diving. The authors reviewed the medical condition along with its primary risk factors. Hyperventilation due to psychological stress is one cause that is scarcely referenced in the medical literature. We introduce a case of a patient with a leptosomal phenotype body who presents a spontaneous pneumomediastinum resulting from an anxiety crisis.

Spontaneuos pneumomediastinum (SP) is an uncommon condition where air gets trapped in the mediastinum without trauma associated. The most common factors are emesis, cough or Valsava maneuvers. Other trigger situations are asthma exacerbation, barotrauma, use of illicit drugs or tracheobronchial/esophageal rupture.[2] Psychological stress with consequent altered breathing pattern are reported as a cause of SP.[3] Psychiatric diseases such anorexia nervosa or anxiety attacks, have also been shown to cause SP. This could be related to the intentional vomiting or the previously mentioned alterations in the ventilatory pattern. This generates an increase in intrathoracic pressure causing alveolar rupture, which then releases air from the peribronchial spaces to the mediastinum.[4] Similar to pneumothorax cases, those who have a leptosomic clinical phenotype with tall and thin body and are also young and predominantly male are considered to have several of the predisposing risk factors that are associated with the appearance of SP. This is due to the structure of the thoracic tissues.[5] In some cases, pneumothorax or pneumoperitoneum may appear as a pneumomediastinum complication. Usually, if no surgical interventions are needed, treatment consists of relieving symptoms and conservative management with radiological follow up.

A 34 years-old male patient, nonsmoker with other toxic habits, medical history or respiratory pathologies, was admitted to emergency room with 12 h-history of pharyngeal, cervical and thoracic oppressive pain that got worse with body movements. No fever, coughing attacks, vomiting, great efforts, Valsalva maneuvers or other findings were present. Upon admission his BMI was 19 kg/m^2. Patient expressed feeling increased levels of psychological stress resulting from job issues that arouse due to the pandemic. Patient displayed cyclic episodes of short breathing and hyperventilation patterns. His blood pressure was 145/75 mmHg, respiratory rate was 24 beats/min and oxygen saturation of 96% at room air. On examination, palpable crepitus at the neck area and upper torso were detected. There were no relevant findings on laboratories studies. Thorax radiography revealed air presence in the left paratracheal structures with no indication of a pneumothorax. Subsequent CT cervical scan showed air located in vascular, prevertebral and perivisceral spaces (figure A black arrows), which extended from the skull base to the thorax. CT thorax scan revealed air in prevascular space, supra-aortic trunks, trachea, great vessels and peribronchovascular area (Macklin effect – figure B black arrow-) to the latero-cervical region. Subcutaneous emphysema was in the supraclavicular spaces. These findings are consistent with spontaneous pneumomediastinum affecting the cervical region. Tracheobronchial and esophageal rupture were ruled out by a bronchoscopy and barium esophagography. Subsequent to the thoracic surgical evaluation, no surgical intervention was needed. After 48 h with an improved follow up, patient was discharged with good outcomes.

In conclusion, this case demonstrates that a patient with leptosomic body phenotype who is experiencing increased levels of stress could be at risk of developing a spontaneous pneumomediastinum.

Conflicts of interest

The authors have no conflicts of interest to declare.

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