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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

clearance to improve, thereby reducing relapses.[6] This hypothesis is supported by a retrospective review that found an inverse association between the duration of initial antibiotic course and subsequent rates of recurrent PBB.[9] These results raise the possibility that children with PBB might benefit from an initial 6-week antibiotic course to reduce relapses, antibiotic burden, and potentially bronchiectasis. This must be balanced against the risk that inappropriate antibiotic use will promote antimicrobial resistance. A further randomised controlled trial in children with PBB, assessing 2 weeks versus 6 weeks antibiotics using carefully chosen outcomes[10] and follow-up of at least 12 months might provide the final piece of the puzzle. Such a trial, along with other well-designed studies in children with respiratory disease, is vital to optimise children's respiratory health and improve the future respiratory health of the whole population.

We declare no competing interests.

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Azithromycin: can its benefit be ruled out in mild COVID-19?

The health emergency triggered by the COVID-19 pandemic has led to the massive use of pharmacological treatments whose efficacy has not been sufficiently evidenced. Gradually, thanks to the results of standardised clinical trials, the efficacy of the different treatments used is becoming clearer, of which only dexamethasone and tocilizumab have so far been shown to reduce mortality associated with COVID-19.[1,2]

One of the most widely used drugs in the treatment of COVID-19 has been azithromycin, since it has known antiviral properties and immunomodulatory effects, from which benefits have been obtained in the treatment of other respiratory diseases.[3,4] However, clinical trials with results published so far have not been able to show its efficacy in the treatment of COVID-19.

Large clinical trials such as RECOVERY have reasonably ruled out any benefit of azithromycin as a standalone therapy in patients admitted to hospital, in terms of reducing mortality and duration of hospital stay.[5] However, the efficacy of antiviral drugs often varies depending on the stage of the disease course at the time they are administered, because of factors related to the host's immune reaction and the existing organic damage at the time of therapy.

The ATOMIC2 study by Timothy Hinks and colleagues[6] recruited 295 patients whose symptoms brought them to the emergency room, where they were diagnosed with COVID-19, but whose condition was not considered serious enough to be admitted (participant age was 45·9 years (SD 14·9); 152 (52%) were men and 143 (49%) were women). Therefore, the study focuses on a specific stage in the evolution of COVID-19, of intermediate severity, which is not well represented in previous studies with patients admitted to hospital, nor in the PRINCIPLE study, which recruited patients diagnosed in primary care.[7]

The ATOMIC2 study did not show a reduction in the number of admissions or deaths in the first 28 days of follow-up, nor did the PRINCIPLE study show any benefit on these same results, nor did the two previous trials that tested efficacy demonstrate clinical benefits of azithromycin, in combination with hydroxychloroquine, in patients seen outside the
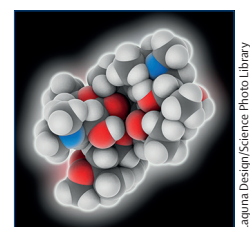
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hospital.[8,9] The most immediate conclusion is that azithromycin is not useful in any phase of COVID-19; however, many of these studies share a series of limitations, imposed by the difficult emergency situation in which they were conducted, requiring a cautious interpretation of the absence of positive results for azithromycin.

First, placebo control or the masking of patients and investigators to treatment has often not been feasible. Furthermore, many of the patients enrolled in ATOMIC2 and in other studies did not have diagnostic confirmation by PCR. Obtaining a PCR test result in patients not admitted to hospital is especially difficult, given that the test was unavailable at some points during the epidemic, and given the waiting times that have often been necessary to obtain results of the test outside the hospital. On the one hand, limiting the analyses to patients with positive PCR results would have caused the exclusion of a large number of patients who actually had COVID-19 but did not have a PCR test, or had a falsely negative result. On the other hand, the strategy of including patients on the basis of high clinical suspicion opens the door to the possibility of including patients in the efficacy studies of azithromycin who do not actually have COVID-19. In the case of the ATOMIC2 study, the authors controlled for this limitation, replicating the analyses in the subgroup of patients with positive PCR results. Although these analyses were underpowered, no substantially different results were obtained.

The adherence of patients to treatment represents another important challenge in studies with patients cared for in the community, because it is much more difficult to guarantee than in patients admitted to hospital. Low adherence, in combination with intention-to-treat statistical analyses, might cause a potential effect of azithromycin to be missed, because of its dilution in the total set of patients, of which some did not take the drug in the end, or did not take it in sufficient doses. For this reason, it is advisable to size the studies sufficiently, so that it is also possible to carry out analyses per protocol with statistical power, adding information on the potential effect that a drug might have under ideal adherence conditions. In the ATOMIC2 study, a long course of high-dose azithromycin was prescribed (500 mg for 14 days), which turned out to be partly protective against low adherence, since even the patients in the group that did not comply with

the planned schedule took an average of six doses of azithromycin—demonstrating a strength of this clinical trial.

Additionally, it is worth analysing the important difference between the expected and observed effect sizes in the ATOMIC2 study. In the ATOMIC2 study, the results show a frequency of primary outcome events (hospital admission or death) in the 28 days from randomisation of 10·3% (15 of 145 patients) in the azithromycin group and 11·6% (17 of 147 patients) in the control group. This difference represents a small risk reduction of 1·3%, which was not statistically significant, corresponding to a number needed to treat (NNT) of 77, whereas the study was sized to detect an expected risk reduction of 10%, corresponding to an NNT of ten. The question is, was a 10% risk reduction in 28 days to be expected? It has been argued that a smaller reduction would probably not change clinical practice, but against this argument is the indisputable fact that the RECOVERY study changed clinical practice worldwide when it showed that dexamethasone treatment reduced mortality by 2·9% at 28 days in patients who needed oxygen (NNT 35).[10] The RECOVERY study has also since shown that tocilizumab produces an 4·1% reduction in the risk of death in 28 days in patients admitted to hospital (NNT 24). Notably, this result contradicts those obtained in most previous trials on this drug, since these trials did not have a sufficient sample size to show such modest efficacy.[2] Thus, the actual efficacy that some drugs have shown so far in COVID-19 is not as great as the researchers who designed ATOMIC2 expected, nor the other studies with azithromycin in out-of-hospital patients. Therefore, the results of these trials, being very valuable, only establish a limit of efficacy, ruling out a prominent effect of azithromycin, but they do not have the power to detect more modest effects, which could have clinical relevance.

The ATOMIC2 adds much to our knowledge, but the body of evidence is not yet complete. There is still room for studies with power to demonstrate modest therapeutic effects, and for studies focused on other outcomes that are of great interest. For example, symptomatic persistence in COVID-19, its sequelae, and other results that need longer follow-up periods, about which we still know very little and for which we do not know therapies capable of their prevention.

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Mepolizumab for chronic rhinosinusitis with nasal polyps

Chronic rhinosinusitis with nasal polyps affects 3% of the adult population and elicits symptoms of nasal obstruction, nasal secretions, facial pressure, and loss of smell, ultimately impairing health-related quality of life.[1] Chronic rhinosinusitis with nasal polyps is a heterogeneous disease associated with different inflammatory endotypes, most frequently causing eosinophilic inflammation, but also resulting in neutrophilic and mixed granulocytic inflammation of the upper airways.[1,2] The standard of care for patients with chronic rhinosinusitis with nasal polyps includes intranasal corticosteroids, short courses of oral corticosteroids, and nasal surgery (eg, functional endoscopic sinus surgery and polypectomy). However, nasal surgery might induce mucosal damage and scarring, and is associated with high recurrence rates. Therefore, there is a high medical need for novel therapies that improve symptoms and quality of life of patients with chronic rhinosinusitis with nasal polyps and reduce the need for oral corticosteroids and surgery. In patients with a high degree of type 2 inflammation, chronic rhinosinusitis with nasal polyps tends to be more severe, recurrent, and frequently associated with late-onset eosinophilic severe asthma and respiratory disease exacerbated by nonsteroidal anti-inflammatory drugs, necessitating a holistic approach by ear, nose, and throat specialists and pulmonologists to treat this airway disease in the optimal way.[3]

Joseph Han and colleagues[4] report the results of a phase 3 SYNAPSE study of mepolizumab in patients with chronic rhinosinusitis with nasal polyps. Mepolizumab is a monoclonal antibody blocking interleukin (IL)-5, a type 2 cytokine, which promotes the proliferation and differentiation of eosinophils in the bone marrow, prolongs eosinophil survival in mucosal tissues, and activates eosinophils to release toxic granules and cysteinyl leukotrienes.[5] Because nasal polyps are often characterised by eosinophilic inflammation, Han and colleagues investigated the efficacy and safety of mepolizumab, an anti-IL-5 biological treatment, in patients with recurrent, severe, chronic rhinosinusitis with nasal polyps who were eligible for repeat nasal surgery. All patients had at least one nasal surgery in the past 10 years, before entry into the SYNAPSE study, implicating that the disease was refractory to medical and surgical treatment.

Mepolizumab 100 mg (n=206) or placebo (n=201) were administered subcutaneously once every 4 weeks, in addition to standard of care, for 52 weeks. Mepolizumab significantly improved total endoscopic nasal polyp score at week 52 (adjusted difference in medians –0·73, 95% CI –1·11 to –0·34; p<0·0001) and nasal obstruction visual analogue scale (VAS) score during weeks 49–52 (–3·14, –4·09 to –2·18; p<0·0001), the two coprimary endpoints. Importantly, mepolizumab versus placebo significantly reduced oral
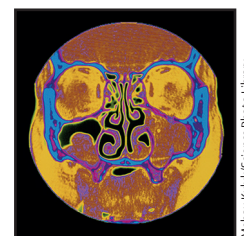
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Published **Online**
April 16, 2021
https://doi.org/10.1016/
S2213-2600(21)00133-8

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