



COVID-19 hazard in patients with rare diseases. What drugs to take with caution?

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Rare patients are most vulnerable. Which pharmacological treatment to be maintained or to be used with caution in rare non-oncological diseases.

Rare patients are worried about COVID-19

The COVID-19 pandemic and related health emergencies have highlighted the problems of fragile populations, such as the elderly, chronic and multi-pathological patients and, not least, patients with rare diseases. This represents a composite category of patients with different degrees of disability and requiring multiple and complex therapeutic and physiotherapeutic approaches. It is not clear the impact that these approaches can have on COVID-19 infection and its management. In addition, some rare pathologies alter organs and systems that can predispose to a greater risk of complications related to the infection. This generates great concern and many questions in patients and families.

The case of rare neuromuscular diseases (NMD) is taken as a paradigm. International experts establish NMD at high risk due to various factors, many of which can be translated to other rare diseases. For this reason, patient associations, healthcare professionals and expert scientists have produced documents, guidelines, webinars etc. to help patients and caregivers as well as family doctors.

The paradigm of NMD pathologies. Which factors increase the risk (or danger) of COVID-19 in rare NMD patients? What are the preventive measures?

The main risky conditions for the rare neuromuscular patients in case of Sars-CoV-2 infection are related to muscle weakness that can affect the oropharynx, respiratory muscles and diaphragm. This reduces respiratory volumes, causes non-expulsive cough, requires assisted ventilation and tracheostomy, favors the risk of lung complications. Furthermore, many NMD patients have cardiovascular alterations, considered a negative prognostic factor, and states of atrophy, physical deterioration and dysmetabolisms. Some patients are on immunosuppressive drugs and steroids.

It is therefore useful to implement all precautions to reduce the risk of contagion: the increase in hygiene rules, the use of personal protective

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equipment and social isolation, that may also include remote physiotherapy. It is important to be prepared for any emergency, including how to treat the patient without hospitalization.

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What are the consequences of the risk of Covid-19 infection for treatments used in people with NMD?

Although specific therapies are not available for the majority of rare NM pathologies, NMD patients are treated with different drugs and ventilation systems to manage the primary and secondary symptoms of the pathology. The supply of these treatments must be guaranteed during the isolation period. Ongoing therapies must be maintained and, in case of COVID-19 infection, possible changes of therapy must be evaluated by specialists in relation to the state of neuromuscular disease and respiratory function. This includes immunosuppression in inflammatory muscle diseases, myasthenia gravis and peripheral nerve diseases, and steroid therapy in patients with Duchenne muscular dystrophy. It is necessary to continue taking vitamin D, in case of deficiency, also for its potential role to sustain immune function. Similarly, therapies to support cardio-respiratory function, such as ACE inhibitors, should not be discontinued unless specifically indicated, as clear evidence about the increased risk in COVID-19 is not currently available. Even in the case of Myotonia Congenita, a rare disease characterized by painful muscle stiffness, it is recommended do not alter the symptomatic drug regimen with mexiletine. Social distancing can interfere on treatment regimens that require hospital procedures (e.g. nursinersen, alglucosidase alfa, intravenous immunoglobulin (IVIg) and rituximab or other treatments related to clinical trials). These treatments generally should not be stopped, but whenever possible, transferred to a non-hospital setting. Similarly, the numerous ongoing clinical trials can be guaranteed thanks to specific agreements with sponsors and the remodeling of clinical evaluations with non-risky procedures.

Can Covid-19 treatments negatively affect the patient with rare neuromuscular disease?

Numerous treatments and vaccines for Covid-19 are in pre-clinical and clinical study and is now considered the use of drugs approved for other pathologies (off-label), such as anti-viral used for HIV and other viral infections, antibiotics, antimalarials, as well as immunosuppressants and monoclonal antibodies to control the cytokine storm. Some of these drugs can adversely affect neuromuscular function: for example, chloroquine and azithromycin are not safe in myasthenia gravis, except when ventilatory support is available.

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Furthermore, the use of these drugs, mostly in combination, as well as of anti-HIV lopinavir / ritonavir and other antivirals should be carefully monitored, especially in DMD patients or in rare cardiological patients with long QT tract syndrome, due to the risk of severe arrhythmias and heart failure due to QT prolongation (a parameter on the electrocardiogram called QT interval). Other treatments may have effects on specific neuromuscular diseases (metabolic, mitochondrial, myotonic and neuromuscular disorders). Although regulatory agencies have recently pointed out that there are no scientific evidence for the restriction of the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in COVID-19, it should be noted that many NMD patients are on steroid therapy (DMD) or on immunosuppressants (myasthenia gravis) suggesting paracetamol as a first choice drug for the treatment of fever. Although COVID-19 pneumonia is characterized by an inflammatory state, acetazolamide and phosphodiesterase inhibitors could be considered, with caution, to improve oxygenation and lung ventilation.

Emergency treatments for COVID-19 are added to standard or novel under study treatments in NMD patients. They should therefore only be taken after consulting specialists, for possible pharmacodynamic and pharmacokinetic interactions.

The recommendation of the experts is therefore to maintain the pharmacological standards of care in rare patients in order to support vital functions and to strengthen prevention rules. It is always important to limit self-medication, even for the simple decision to take dietary supplements, and to rely on institutional and medical sites to get protection from incorrect information circulating in the media. The synergy between doctors, scientists and patients aims to accelerate the adoption of specific treatment options and to reduce the uncertainties due to the pandemic.

Sitography

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