AGENZIA ITALIANA DEL FARMACO

TREATMENTS TO BE USED IN COVID-19 PATIENTS IN HOSPITAL SETTING

Considering the numerous scientific evidence gathered in the last months of the COVID-19 pandemic for the treatment of patients hospitalized with COVID-19, **the current standard of care is use of corticosteroids and heparin**.

Dexamethasone

Use of corticosteroids should be considered a standard of care in patients hospitalized for severe COVID requiring supplemental oxygen therapy (with or without mechanical ventilation).

Based on a meta-analysis of the available studies and in particular of data from major randomized studies (such as RECOVERY and SOLIDARITY), this is **the only pharmaceutical treatment** having shown a benefit in terms of **mortality reduction**. On 18 September 2020, at the end of a referral procedure, EMA approved the use of dexamethasone in the treatment of subjects, both adults and adolescents (from 12 years of age and weighing at least 40 kg) affected by COVID-19 needing supplemental oxygen therapy (both standard oxygen therapy and mechanical ventilation). Although the most significant results were obtained with dexamethasone, the clinical benefit is also evident with other molecules, suggesting an overall class effect.

For further information also regarding the recommended dosages and the duration of treatment, please refer to the AIFA information sheet available at the following link:

https://www.aifa.gov.it/documents/20142/1123276/Corticosteroidi_06.10.2020.pdf/075c9302-895c-4d7e-11bc-0e2319082ffc .

Heparins

Use of heparins can provide for two different conditions:

- **Use of prophylactic dosage** (according to the related authorized indications)
  Use of low molecular weight heparins in the prophylaxis of thrombo-embolic events in patients with acute respiratory infection and reduced mobility is recommended by the main guidelines in the absence of contraindications. This applies, in the presence of the aforementioned characteristics, both to hospitalized patients and to patients managed at home or in nursing homes. Such use can be considered a standard of care.
- **Use of intermediate/high doses**
  Use of intermediate/therapeutic doses in severe cases of COVID-19, classifiable in phase IIB or III of the clinical evolution of the disease, can be considered by evaluating the risk/benefit ratio in the individual patient. In particular, levels of D-dimer much higher than normal (4-6 times) and/or a SCI score>4, high ferritin (>1000 mcg/L) or a high BMI (>30) seem to identify conditions whereby use of intermediate/high doses correlates with clinical benefit even if there is no evidence from RCTs.

For further information, please refer to the AIFA information sheet available at the following link: https://www.aifa.gov.it/documents/20142/1123276/Eparine_update_01_26.11.2020.pdf/0ae7552a-2bee-3981-eeeb-ae3acc8abe6e .

Remdesivir

Remdesvir is an antiviral medicine, approved by EMA with conditional approval, for the *treatment of COVID-19 disease in adults and adolescents (from 12 years of age and older, weighing at least 40 kg) with pneumonia requiring supplemental oxygen therapy.* Remdesivir cannot be considered an established standard of care as currently available data do not agree and overall do not demonstrate a clear clinical benefit in terms of mortality or use of mechanical ventilation.

AIFA has therefore established that use of remdesivir can only be considered in selected cases, after a careful evaluation of the risk/benefit ratio, in subjects with COVID-19 pneumonia under oxygen therapy, not requiring high-flow oxygen or mechanical ventilation or ECMO and with onset of symptoms for less than 10 days.

All studies agree on the lack of efficacy in the most severe patients (who need oxygen delivery through high-flow devices, mechanical ventilation - non-invasive/invasive - or ECMO).

Although a reduction in recovery time and mortality was demonstrated in the subgroup of subjects on standard (low-flow) oxygen therapy of the pivotal study ACTT-1, this was not confirmed by the Solidarity study nor by meta-analysis of the four available studies carried out by WHO. On the basis of this evidence, WHO has issued a WEAK NEGATIVE recommendation on the use of this drug in the entire population of patients with COVID-19 regardless of severity (*"We suggest against administering remdesivir in addition to usual care for the treatment of patients hospitalized with Covid-19, regardless of disease severity; weak or conditional recommendation*. A living WHO guideline on drugs for Covid-19 | The BMJ").

Studies to date have not shown a difference in efficacy between the 5-day and the 10-day treatment, either in patients with moderate disease or in the severe disease cohort.

For further information, please refer to the AIFA information sheet available at the following link:

https://www.aifa.gov.it/documents/20142/1123276/remdesivir_update01_26.11.2020.pdf/242569e8-5ab0-70e6-bd74-9ee3937922b2.

Other treatments

The use of immunomodulatory drugs is still undergoing clinical trials and it is not currently possible to define guidelines; their use should therefore be limited to randomized clinical trials. FDA recently granted the *Emergency Use Authorization* (EUA) for the use of baricitinib (JAK inhibitor) in combination with remdesivir for the treatment of subjects suffering from COVID-19 requiring supplemental oxygen therapy, mechanical ventilation or ECMO. Data relating to the use of such combination have not yet been published and are currently not sufficient to recommend its use in clinical practice.

Evidence available from clinical studies relating to use of other immunomodulators, such as anti-IL-6 (tocilizumab and sarilumab) does not seem to show a clinical benefit. However, further evidence is needed to be able to conclusively define the role of these drugs in the management of COVID-19 in different clinical scenarios.

AIFA GUIDELINES ON THE MAIN CATEGORIES OF MEDICINES TO BE USED IN HOSPITAL SETTING		
Medicine		**Notes**
Dexamethasone		Standard of care in patients requiring supplemental oxygen therapy (with or without mechanical ventilation)
Low molecular weight heparins: prophylactic dosage		Recommended use, in the absence of specific contraindications, in the prophylaxis of thrombo-embolic events in patients with acute respiratory infection and reduced mobility.
Low molecular weight heparins: intermediate/high dosage		Use to be considered in severe cases of COVID-19 (classifiable in phase IIB or III of the clinical evolution of the disease) by evaluating the risk/benefit ratio in the individual patient.
Remdesivir		Use to be considered only in selected cases of subjects on standard (low-flow) oxygen therapy and with onset of symptoms <10 days
Immunomodulating therapies (anti-JAK, anti-IL1, anti-IL6)		Not recommended in clinical practice *
Hydroxychloroquine/chloroquine +/- antibiotic therapy		Not recommended in clinical practice **
Lopinavir/ritonavir or darunavir/ritonavir		Not recommended in clinical practice ***
Routine use of antibiotics		Not recommended
Key: green=standard of care; yellow=usable in selected cases; red=not recommended in clinical practice ** use is possible in the context of clinical studies* *** use is possible in the context of local clinical studies* **** Further randomized clinical trials are required to evaluate drug efficacy at various levels of disease severity.*		