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

***Latest version: 04/10/2021***
***(Previous version: 09/12/2020)***

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

**Dexamethasone**

The use of corticosteroids should be considered the standard of care for hospitalized patients with severe COVID-19 requiring supplemental oxygen therapy (with or without mechanical ventilation).

Based on a meta-analysis of available studies and in particular of data from major randomized studies (such as RECOVERY and SOLIDARITY), this is **the only pharmacological treatment** showing a benefit in terms of **reduction of mortality**. 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) with 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**

The use of low molecular weight heparins in the prophylaxis of thrombo-embolic events in patients with acute respiratory infection, who are bedridden or have 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 retirement or nursing homes, using prophylactic doses.

To date, there is no solid evidence/sufficient information to recommend a routine use of intermediate or therapeutic doses of LMWH as an alternative to prophylactic doses in hospitalized COVID-19 patients who can be classified in Phase IIB or III of the clinical progression of the disease, in the absence of evidence of ongoing thrombo-embolic events. In this setting, the use of intermediate or high doses may be decided on a case-by-case basis, in relation to the individual patient's clinical picture after a careful assessment of the benefit-risk ratio, or may take place in clinical trials.

In case of suspected or confirmed thromboembolic events, LMWHs or unfractionated heparins should be used at therapeutic dosage and for the appropriate time, to be determined on a case-by-case basis.

As regards the possible continuation of thromboprophylaxis with LMWH at home after discharge, the evidence available in literature is still too limited to recommend whether to use them or not. However, preliminary data from retrospective studies seem to suggest its use in high-risk patients, after carefully assessing the benefit/risk ratio on a case-by-case basis.

For further information, please refer to the AIFA information sheet available at the following link: https://www.aifa.gov.it/documents/20142/0/Eparine_Basso_Peso_Molecolare_13.05.2021.pdf.

**Casirivimab and imdevimab**

Casirivimab and imdevimab are two monoclonal antibodies directed against the Spike protein of SARS-CoV-2. They have been made available pursuant to article 5.2 of Law Decree 219/2006. Since August 2021, AIFA has allowed the use of this combination of medicines, at a dosage of 4000/4000 mg, for the treatment of adult and paediatric patients over 12 years of age hospitalised for COVID-19, even on conventional oxygen therapy (non-high-flow and non-ventilated mechanical), but with negative serology for SARS-CoV-2 anti-Spike IgG antibodies.

The evidence supporting this indication derives from the results of one of the arms of the large randomised clinical trial RECOVERY, in which the use of the casirivimab/imdevimab combination was associated with significant clinical benefit in terms of clinical progression, including mortality, and shorter hospitalization periods in the seronegative population.

For further information, please refer to the AIFA information sheet available at the following link: https://www.aifa.gov.it/documents/20142/1307084/Informativa_hcp.pdf.

**Remdesivir**

Remdesvir is an antiviral medicine, approved by EMA with a conditional approval, for the treatment of COVID-19 disease in adults and in adolescents (from 12 years of age and older and weighing at least 40 kg) with pneumonia requiring supplemental oxygen. 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 the use of remdesivir can only be considered in selected cases, after a careful evaluation of the benefit/risk 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 less than 10 days.

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

Although a reduction in recovery time and mortality was demonstrated in the subgroup of subjects on standard (low-flow) oxygen therapy in pivotal study ACTT-1, this was not confirmed either by the Solidarity study or by the meta-analysis of the four available studies carried out by the WHO. On the basis of this evidence, the WHO 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 any 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_24.11.2020.pdf.

**Tocilizumab**

Tocilizumab (RoActemra®) is a humanised monoclonal antibody that binds specifically to the receptors of soluble (sIL-6R) and membrane (mIL-6R) IL-6, thus inhibiting the signals mediated by them. Already authorised in Italy for the treatment of certain forms of arthritis and of the CAR-T lymphocytes-induced cytokine release syndrome, the medicine has been included in the list of drugs of Law 648/1996 for the treatment of hospitalized adults with severe COVID-19 and/or with high levels of systemic inflammation indices.

In particular, hospitalised patients with rapidly deteriorating clinical conditions are considered candidates for treatment with tocilizumab:

- Recently hospitalised patients admitted to intensive care for less than 24/48 hours who receive mechanical ventilation or high flow oxygen; or recently hospitalised patients with rapidly increasing oxygen need who require non-invasive mechanical ventilation or high flow oxygen in the presence of high levels of inflammation indices (CRP ≥75 mg/L)

- Hospitalised patients with rapid clinical progression after 24/48 hours of dexamethasone, or other corticosteroids. Rapid clinical progression means rapidly increasing oxygen requirements, even without the need for non-invasive ventilation or high flow oxygen, and with high levels of inflammation indices (CRP ≥75 mg/L).

These indications reflect the population in which, in large randomised controlled clinical trials (RECOVERY and REMAP-CAP), a clear benefit in terms of reduced mortality with the use of tocilizumab has been demonstrated.

For further information, please refer to the AIFA information sheet available at the following link: https://www.aifa.gov.it/documents/20142/1267737/Tocilizumab_09.06.2021.pdf.

**Anakinra**

Anakinra (Kineret®) is an IL-1 receptor antagonist authorised for the treatment of rheumatoid arthritis, periodic fever syndromes, cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), and Still's disease.

In light of current knowledge, anakinra may be considered for the treatment of hospitalised adults with moderate/severe COVID-19 pneumonia (with $pO_2/FiO_2$>150, and not undergoing C-PAP or mechanical ventilation) and with Soluble Urokinase-Type Plasminogen Activator Receptor plasma levels (suPAR) ≥ 6ng/mL.

This indication reflects the population in which, in a randomised controlled clinical trial (SAVE-MORE), anakinra showed an advantage in terms of reduced mortality.

For further information, please refer to the AIFA information sheet available at the following link: https://www.aifa.gov.it/documents/20142/1123276/Anakinra_28.09.2021.pdf.

**Baricitinib**

Baricitinb (Olumiant®) is a JAK-inhibitor, already authorised for the treatment of rheumatoid arthritis and atopic dermatitis (the latter indication not reimbursed in Italy). Considering the potential lack of alternatives already available in Law 648/96 for the same indication, baricitinib can be considered for the treatment of adult subjects hospitalised with severe COVID-19, high-flow oxygen therapy or non-invasive mechanical ventilation, and/or with high levels of systemic inflammation indices.

In particular, hospitalised patients with rapidly deteriorating clinical conditions are considered candidates for treatment with baricitinib:

- Recently hospitalised patients with rapidly increasing oxygen requirements who require non-invasive mechanical ventilation or high flow oxygen in the presence of high levels of inflammation indices (CRP ≥75 mg/L).

The evidence supporting the use of baricitinib comes from two randomised clinical trials in which the use of this medicine was associated with a significant clinical benefit in terms of time to clinical recovery (ACTT-2 study) and mortality (COV study -BARRIER).

For further information, please refer to the AIFA information sheet available at the following link: https://www.aifa.gov.it/documents/20142/1123276/Baricitinib_28.09.2021.pdf .

**Sarilumab**

Sarilumab (Kevzara®), an interleukin-6 (IL-6) inhibitor authorised for the treatment of rheumatoid arthritis, shares with tocilizumab the same mechanism of action and rationale for use in COVID-19. Considering the potential lack of alternatives already available in Law 648/96 for the same indication, the use of the medicine can be considered for the treatment of adult subjects hospitalised with severe COVID-19 and/or with high levels of systemic inflammation indices.

In particular, hospitalised patients with rapidly deteriorating clinical conditions are considered candidates for treatment with sarilumab:

- Recently hospitalised patients admitted to intensive care for less than 24/48 hours who receive mechanical ventilation or high flow oxygen; or recently hospitalised patients with rapidly increasing oxygen requirements who require non-invasive mechanical ventilation or high flow oxygen in the presence of high levels of inflammation indices (CRP ≥75 mg/L)
- Hospitalised patients with rapid clinical progression after 24/48 hours of dexamethasone, or other corticosteroids. Rapid clinical progression means rapidly increasing oxygen requirements, even without the need for non-invasive ventilation or high flow oxygen, and with high levels of inflammation indices (CRP ≥75 mg/L).

NB. *Sarilumab is available as a pre-filled syringe for subcutaneous administration. For the preparation of a 400 mg dose to be infused EV, two 200 mg pre-filled syringes should be injected into a 100 ml infusion bag of 0.9% sodium chloride (invert the bag at least 10 times to ensure thorough mixing). The infusion should last at least 60 minutes.*

For further information, please refer to the AIFA information sheet available at the following link: https://www.aifa.gov.it/documents/20142/1123276/Sarilumab_28.09.2021.pdf .

| AIFA GUIDELINES ON THE MAIN CATEGORIES OF MEDICINES TO BE USED IN HOSPITAL SETTING | | |
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| **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.<br>In the advanced stages of the disease, in order to contain the effects of cytokine storm on coagulation, the most recent evidence in the literature indicates that the use of prophylactic doses may be preferred over intermediate/therapeutic doses. |
| Low molecular weight heparins: intermediate/high dosage | 🟢 | Recommended use in the treatment of thrombotic or thrombo-embolic phenomena of the venous or arterial system. In this case, LMWHs (and unfractionated heparins) should be used at therapeutic doses according to the registered indications. |
| Casirivimab and imdevimab (at doses of 4000/4000 mg) | 🟢<br>🟡 | Although they do not represent an established standard of care, the use of these medicines is recommended for the treatment of adult and paediatric patients over 12 years of age hospitalised for COVID-19, even on conventional oxygen therapy (non-high-flow and non-ventilated mechanical), but with negative serology for SARS-CoV-2 anti-Spike IgG antibodies. |
| Remdesivir | 🟡 | Use to be considered only in selected cases of subjects on standard (low-flow) oxygen therapy and with onset of symptoms <10 days. |
| Tocilizumab | 🟡 | Use to be considered only in hospitalised patients with rapidly progressing clinical conditions:<br>• Recently hospitalised patients admitted to intensive care for less than 24/48 hours who receive mechanical ventilation or high flow oxygen; or recently hospitalised patients with rapidly increasing oxygen requirements who require non-invasive mechanical ventilation or high flow oxygen in the presence of high levels of inflammation indices (CRP ≥75 mg/L)<br>• Hospitalised patients with rapid clinical progression after 24/48 hours of dexamethasone, or other corticosteroids. Rapid clinical progression means rapidly increasing oxygen requirements, even without the need for non-invasive ventilation or high flow oxygen, and with high levels of inflammation indices (CRP ≥75 mg/L). |

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| Anakinra | 🟡 | Use to be considered for the treatment of hospitalised adult subjects with moderate/severe COVID-19 pneumonia (with pO2/FiO2>150, and not undergoing C-PAP or mechanical ventilation) and with Soluble Urokinase-Type Plasminogen Activator Receptor plasma levels (suPAR) ≥ 6ng/mL. |
| Baricitinib | 🟡 | Use to be considered, in light of the potential shortage of alternatives already available in Law 648/96 for the same indication, in recently hospitalised patients with rapidly increasing oxygen requirements who require non-invasive mechanical ventilation or high flow oxygen in the presence of high levels of inflammatory indices (CRP≥75 mg/L). |
| Sarilumab | 🟡 | Use to be considered, in light of the potential lack of alternatives already available in Law 648/96 for the same indication, for the treatment of hospitalised adults with severe COVID-19 and/or with high levels of systemic inflammation indices.<br>In particular, hospitalised patients with rapidly deteriorating clinical conditions are considered candidates for treatment with sarilumab:<br>• Recently hospitalised patients admitted to intensive care for less than 24/48 hours who receive mechanical ventilation or high flow oxygen; or recently hospitalised patients with rapidly increasing oxygen requirements who require non-invasive mechanical ventilation or high flow oxygen in the presence of high levels of inflammation indices (CRP ≥75 mg/L)<br>• Hospitalised patients with rapid clinical progression after 24/48 hours of dexamethasone, or other corticosteroids. Rapid clinical progression means rapidly increasing oxygen requirements, even without the need for non-invasive ventilation or high flow oxygen, and with high levels of inflammation indices (CRP ≥75 mg/L). |
| 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 = can be used 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 randomised clinical trials are required to evaluate medicine efficacy at various levels of disease severity.*