COVID-19
Sector: Hospital

HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
16 FEBRUARY 2022

The legally binding text is the original French opinion version

tocilizumab
ROACTEMRA 20 mg/ml concentrate for solution for infusion

New indication

Key points

Favourable opinion for reimbursement only in the treatment of coronavirus disease 2019 (COVID-19) in adults **who are receiving systemic corticosteroids and require supplemental oxygen**, excluding patients requiring invasive mechanical ventilation.

Unfavourable opinion for reimbursement in patients requiring supplemental oxygen by invasive mechanical ventilation.

What therapeutic improvement?

Therapeutic improvement in the management of the disease.

Role in the care pathway?

The management of COVID-19 patient is detailed in the French High Council for Public Health (HCSP) report of 28 January 2021 and is based on supportive and preventive treatments:

- Appropriate oxygen therapy,
- Analgesics and antipyretics,
- Prevention of the thrombotic risk,
- Antibacterial antibiotics in the event of arguments in favour of co-infection.

Corticosteroid therapy is an integral component of the standard of care according to national (HCSP) and international (WHO) guidelines.

According to its report of 17 June 2021 concerning the use of IL1 and IL6 receptor antagonists, the HCSP recommends the use of tocilizumab (anti-IL6), in medical units in patient requiring high-flow supplemental oxygen and with a marked inflammatory status (CRP ≥ 75 mg/L) and in the absence of improvement after 48 hours of standard of care therapy including dexamethasone (or an equivalent corticosteroid). However, in critical care units, the HCSP does not recommend the use of tocilizumab in patients requiring invasive mechanical ventilation.

As regards sarilumab (anti-IL6) and anakinra (anti-IL1), the HCSP does not recommend their use irrespective of the situation.

Role of the medicinal product in the care pathway

ROACTEMRA (tocilizumab) was granted a specific MA for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

On the basis of the available data from the English RECOVERY study conducted in hospitals and the WHO meta-analysis having demonstrated:

- a beneficial effect on the reduction of mortality at 28 days, only in hospitalised patients receiving concomitant corticosteroid therapy and requiring supplemental oxygen, excluding patients requiring invasive mechanical ventilation,
- an absence of clinical benefit in patients not receiving concomitant corticosteroid therapy or requiring invasive mechanical ventilation.

the Committee considers that ROACTEMRA (tocilizumab) could constitute, in combination with the standard of care including corticosteroid therapy, a therapeutic option in the treatment of adult patients hospitalised for COVID-19 who are receiving concomitant corticosteroid therapy and require supplemental oxygen, excluding patients requiring invasive mechanical ventilation. Early administration following hospitalisation appears to be an important factor.

The Committee does not recommend its use in patients not receiving concomitant corticosteroid therapy (population excluded from the MA) or requiring invasive mechanical ventilation.

The Committee highlights the absence of data in immunocompromised patients (a population at high risk of severe COVID-19) for whom the risk of infection not related to COVID-19 could be increased by the use of this immunosuppressive treatment.

Special recommendations

The Committee points out that demonstration of the value of tocilizumab in COVID-19 is the fruit of academic clinical research work.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ SARS-CoV-2 is an acute viral disease that is potentially life-threatening, primarily in its severe form, following complications. It is a major public health problem of global concern due to its contagiousness, its severity and its impact on healthcare system organisation and, in particular, intensive care units.

◗ The medicinal product ROACTEMRA (tocilizumab) is a curative medicinal product.

◗ The efficacy/adverse effects ratio is:

- high in the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen, excluding patients requiring invasive mechanical ventilation. However, there are uncertainties concerning the transposability of the data to current French practice in the context of the predominant circulation of the Omicron variant and the absence of data in immunocompromised patients (a population at high risk of severe COVID-19) for whom the risk of infection not related to COVID-19 could be increased by the use of an immunosuppressive treatment;
- not established in the treatment of coronavirus disease 2019 (COVID-19) in adults requiring invasive mechanical ventilation, in the absence of a demonstrated clinical benefit in these populations.

◗ There are few medicinal alternatives (see section 05 of this opinion).

◗ This is a first-line treatment in combination with corticosteroid therapy, in adult patients hospitalised for COVID-19 who require supplemental oxygen, excluding patients requiring invasive mechanical ventilation.
ROACTEMRA (tocilizumab) has no role in patients not receiving concomitant corticosteroid therapy (population excluded from the MA) and those requiring invasive mechanical ventilation, in the absence of a demonstrated clinical benefit in these populations.

Public health impact

Considering:

- the severity, contagiousness and impact on healthcare organisation, particularly in intensive care units, and the Public Health Emergency of International Concern (PHEIC),
- the major medical need to have access to effective, well-tolerated medicines in the treatment of severe and critical COVID-19 due to the absence of any available curative treatment,
- the fact that ROACTEMRA (tocilizumab) in combination with corticosteroid therapy provides a partial response to the identified medical need due to a demonstrated additional impact on morbidity and mortality and on the care and life pathway of treated patients (reduction in length of hospital stay and more frequent hospital discharge),
- an expected impact on the organisation of care (reduction in transfers to intensive care units and hospital discharge),

in view of the currently available data, ROACTEMRA (tocilizumab), in combination with corticosteroid therapy, is likely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ROACTEMRA (tocilizumab) is:

- **SUBSTANTIAL only in the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen, excluding patients requiring invasive mechanical ventilation;**

- **INSUFFICIENT in the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen by invasive mechanical ventilation.**

The Committee issues:

- **a favourable opinion for the inclusion of ROACTEMRA (tocilizumab) in the hospital formulary list of reimbursed proprietary medicinal products approved for use only in the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen, excluding patients requiring invasive mechanical ventilation, and at the MA dosages.**
- **an unfavourable opinion for the inclusion of ROACTEMRA (tocilizumab) in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen by invasive mechanical ventilation, and at the MA dosages.**

Clinical Added Value

Considering:

- demonstration of the superiority of the addition of tocilizumab (ROACTEMRA) to usual care including corticosteroid therapy compared to usual care alone in terms of reducing all-cause mortality at D28 (primary endpoint) in hospitalised patients requiring supplemental oxygen, in an English academic study (RECOVERY):
    - with a clinically relevant effect size in terms of the reduction of mortality at 28 days: 30.7% (621/2 022) versus 34.8% (729/2,094); RR = 0.85; $CI_{95\%}$ = [0.76; 0.94]; p = 0.0028; absolute difference of 4%, i.e. a relative reduction in the risk of dying of 15%,
    - with an impact in terms of reduction in the median hospital stay (19 days versus 28 days) and hospital discharge within 28 days (57% versus 50%);

But considering:

- an absence of demonstrated benefit in patients not receiving corticosteroid therapy or requiring invasive mechanical ventilation;
- limited data suggesting a favourable safety profile;
- uncertainties concerning the transposability of the data to current French practice in the context of the predominant circulation of the Omicron variant and the absence of data in immunocompromised patients (a population at high risk of severe COVID-19) for whom the risk of infection not related to COVID-19 could be increased by the use of an immunosuppressive treatment;

the Transparency Committee considers that the proprietary medicinal product ROACTEMRA (tocilizumab), in combination with corticosteroid therapy, provides a moderate clinical added value (CAV III) in the treatment of COVID-19 in adults who require supplemental oxygen, excluding patients requiring invasive mechanical ventilation.