HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
24 MARCH 2021
The legally binding text is the original French opinion version

tocilizumab
ROACTEMRA 20 mg/ml concentrate for solution for infusion

Reevaluation

Key points

Favourable opinion for reimbursement in the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.

What therapeutic improvement?

No clinical added value in the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.

Role in the care pathway?

Patients treated with chimeric antigen receptor (CAR) T cells are prone to numerous adverse events, including potentially life-threatening cytokine release syndrome (CRS). To date, two CAR T cell-based medicinal products have been granted a marketing authorisation: YESCARTA (axicabtagene ciloleucel) and KYMRIAH (tisagenlecleucel) in the third and later-line treatment of DLBCL and KYMRIAH (tisagenlecleucel) in B-cell ALL up to the age of 25 years. In clinical studies involving CAR T cells, several treatment algorithms have been developed to manage this CAR T cell-induced syndrome, with differences in terms of severity grading criteria (lack of consensual definition). Depending on the algorithm (see Annexes), the use of tocilizumab, either alone or combined with corticosteroids, may be recommended for CRS considered to be moderate.

Depending on the severity of the cytokine release syndrome, management is limited to the use of symptomatic treatments or may require a stay in intensive care in the event of severe or life-threatening syndrome. Corticosteroids may be administered.

Role of ROACTEMRA (tocilizumab) in the care pathway:

ROACTEMRA (tocilizumab) remains a first-line treatment for severe or life-threatening cytokine release syndrome (CRS) induced by chimeric antigen receptor (CAR) T cell treatments with an MA in adults and paediatric patients 2 years of age and older.

The optimum administration regimen (dosage, number of doses, optimum time), along with the role of corticosteroids, remain to be defined. Extensive use of tocilizumab in low-grade CRS or in preventive situations has been observed in the French DESCAR-T registry. However, the Committee highlights the fact that these situations are not covered by the MA for tocilizumab.

As stipulated in the SPCs for YESCARTA (axicabtagene ciloleucel) and KYMRIAH (tisagenlecleucel), its availability (at least four doses) should be ensured before infusion of CAR T cells.

It should be noted that the indication for ROACTEMRA (tocilizumab) is only validated from 2 years of age, whereas KYMRIAH (tisagenlecleucel) can be administered in children with no age restriction (in accordance with its MA).

Special recommendations

The Committee calls for the participation of all qualified centres in the DESCAR-T registry in order to obtain exhaustive, high-quality observational data for future assessments concerning CAR-T cell-based medicinal products.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) is a serious medical emergency.
◗ ROACTEMRA (tocilizumab) is a curative treatment for chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.
◗ The efficacy/adverse effects ratio has not been adequately established.
◗ There are therapeutic alternatives although they do not have a specific MA in the treatment of cytokine release syndrome (CRS).
◗ This it is a first-line treatment for chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS).

Public health impact

Considering:
- the seriousness of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS),
- its incidence,
- the inadequately met medical need at this seriousness stage,
- the partial response provided by the availability of ROACTEMRA (tocilizumab) to enable the use of CAR-T cells (its availability being required by their MAs), despite the fact that the available data does not demonstrate an impact on morbidity and mortality, quality of life or the organisation of care,

ROACTEMRA is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ROACTEMRA remains substantial in the MA indication.

The Committee issues a favourable opinion for maintenance of inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indication "the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older" and at the MA dosages.

Clinical Added Value

Considering:

- **the established use of tocilizumab in this indication, with its availability in centres qualified in the use of CAR-T cells required by the marketing authorisations of the CAR-T cell-based medicinal products on the market,**
- **but the absence of a prospective clinical study and the weaknesses of the French DESCAR-T real-world study (only 13 centres activated and data monitoring not effective) not enabling the clinical benefit of this medicine to be assessed,**
- **persistent uncertainties with respect to the optimal treatment regimen for this medicinal product with, in particular, extensive off-label use of tocilizumab observed (treatment of non-severe CRS or in preventive situations),**

the Committee considers that its previous conclusions are not liable to be modified. ROACTEMRA (tocilizumab) provides no clinical added value (CAV V) in the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.