HUMIRA (adalimumab), ENBREL (etanercept), REMICADE (infliximab), anti-TNF α

Insufficient actual benefit in the treatment of active, severe and progressive rheumatoid arthritis in adults not previously treated with methotrexate or another conventional disease-modifying drug.

Main points

- ENBREL, HUMIRA, REMICADE have Marketing Authorisation in first-line treatment of active, severe and progressive rheumatoid arthritis, in patients not previously treated with methotrexate (MTX) or for REMICADE, with another conventional disease-modifying drug.
- It is preferable, at an early stage, to expect a response to first-line treatment with methotrexate, with a treatment adjustment strategy, and to introduce, where applicable, a targeted treatment in case of insufficient response or intolerance of methotrexate.
- ENBREL, HUMIRA, REMICADE have no role in the treatment strategy for patients who have not been previously treated with MTX or with other conventional treatments.

Pre-existing indications *

- ENBREL, HUMIRA, REMICADE have other indications in rheumatology, dermatology or gastroenterology (HUMIRA, REMICADE).

Therapeutic use

- As first-line treatment, MTX is the standard disease-modifying drug for RA. If there are contraindications or intolerance to MTX, leflunomide or sulfasalazine may be considered.
- For second and subsequent lines of treatments, in patients who have responded insufficiently or are intolerant to methotrexate:
  - If there are no poor prognostic factors, a combination of synthetic disease-modifying drugs (methotrexate/sulfasalazine/hydroxychloroquine) or even a change to a different synthetic disease-modifying drug (leflunomide, sulfasalazine) may be offered. If these fail or are contraindicated, a biologic should be considered.
  - If there are poor prognostic factors (especially if there is structural damage), adding a biologic may be offered (anti-TNF, abatacept or tocilizumab and in some circumstances rituximab).

Use of any biologic is preferably carried out in combination with MTX. However, if a biologic must be prescribed in monotherapy, it seems logical to favour tocilizumab, because the literature has not shown the clinical superiority of an anti-TNF, rituximab or abatacept as monotherapy compared to methotrexate alone, unlike tocilizumab.

- Role of anti-TNFs in the therapeutic strategy

Considering the current therapeutic strategy, the prescription of any biopharmaceutical (in combination with methotrexate or as monotherapy) is not justified in the first line of treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other disease-modifying drugs (DMARD). Other biologics, adalimumab, etanercept and infliximab have no place in first-line treatment of rheumatoid arthritis in patients not previously treated with methotrexate or other disease-modifying drugs (DMARD).

* This summary does not cover these indications.
Clinical data

- The available data do not provide any clinically relevant evidence for the first-line use of adalimumab, etanercept or infliximab in adult patients with active, severe RA who are naïve to DMARD treatment. Moreover, in clinical studies, patients could be treated with methotrexate (first-line reference treatment in RA), so the transposability of the observed results to the recommended practice is not assured.
- No new safety signals for adalimumab, etanercept or infliximab were observed in the available data.
- Given the available safety and efficacy data, an impact of adalimumab, etanercept and infliximab on morbidity is expected, if the current therapeutic strategy that favours the use of MTX or another conventional DMARD in first line is respected.

Special prescribing conditions

- **ENBREL**
  Medicine requiring initial annual hospital prescription. Initial prescription and renewal reserved for specialists in rheumatology, in internal medicine, in paediatrics or in dermatology.
  Exception drug status.
- **HUMIRA**
  Medicine for initial hospital prescription.
  Prescription and renewal restricted to specialists in rheumatology, gastroenterology and hepatology, dermatology, paediatrics and internal medicine.
  Exception drug status.
- **REMICADE**
  Medicine reserved for hospital use.

Benefit of the medicinal product

- The actual clinical benefit* of ENBREL, HUMIRA, REMICADE is insufficient to justify reimbursement by national health insurance in rheumatoid arthritis in patients with an active, severe and progressive disease, not previously treated with methotrexate (MTX) or other DMARDs (for REMICADE).
- Does not recommend inclusion on the list of reimbursable products for supply by pharmacists (ENBREL, HUMIRA) and for hospital use.

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* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV (equivalent of "no CAV") means "no clinical added value".