MINISTERIO DE SANIDAD Y CONSUMO

agencia española de medicamentos y productos sanitarios

EMA Consultation meeting on Rheumatoid Arthritis Guideline

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Topic 2: Endpoints in clinical trials

-Disease activity criteria vs relative response

-Feasibility and need to demonstrate prevention of structural damage

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Disclaimer

This presentation reflects the current understanding within the RIWP of the CHMP-EMA on what should be the general requirements for the clinical development of medicinal products in the treatment of AR and does not necessarily reflect the final CHMP position

My DoI is public and available at EMA website

Treatment goals in Rheumatoid Arthritis

- **Control of disease activity: signs and symptoms**
- **Prevention of structural damage**

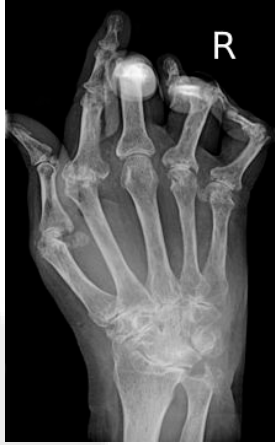
➢ **Remain unchanged**

Treatment goals in Rheumatoid Arthritis

- **Control of disease activity**
- **Prevention of structural damage**

Disease modification

- PEPs should reflect this principle
- …but in a completely new context, old requirements for the demonstration of efficacy need a revision
- Need to generate comprehensive data remains mandatory



Prevention of structural damage in RA

Current challenges:

- In the **PAST**: large mean progression in the control arm
- At **PRESENT**:
  - low disease activity and Rx progression at study entry
  - erosion is a slow progression process, long-term studies needed
  - placebo should be kept short
  - long-term non-inferiority trials

Prevention of structural damage ***highly desirable***

but feasible after all?

Prevention of structural damage in RA

Current draft EU regulatory position:

✓**Previous considerations**

✓**Strong correlation with profound level of disease activity control**

→ **Not any longer a requirement for the MA**

- Reinforce need for compelling demonstration of disease activity control
- Need to monitor by X-ray in order to rule out a possible detrimental effect due to "silent inflammation"
- Other imaging (MRI and US): optional to assess residual inflammation, supportive evidence
- but…

Prevention of structural damage in RA

Current draft EU regulatory position:

- ✓**Previous considerations**
- ✓**Strong Co-R with profound level of disease activity control**

→ **Not any longer a requirement for the MA**

- But…if demonstration of a favourable effect is sought:
  - -Short-term placebo-CT (3-6months),
  - -Preferable in patients with early RA,
  - -Mean changes from baseline in Rx scores (SvdH or GmS) (+ responder analysis)
  - -Plus long-term active control (not formal N-I testing))

Control of disease activity in RA

Thus, demonstration of efficacy will rely on the effect in the control of disease activity

•Strong coR between tight control of disease activity and prevention of structural damage

•Numerous highly effective treatment options available

•Clinical practice shift towards more aggressive/earlier treatment with a “treat to target goal”

RIWP shift from ACR 20 towards remission/LDA as PEP for confirmatory trials

Control of Disease activity

Draft proposal under discussion within the RIWP

Study population	Recommended PEP
DMARDs-naive	Remission or LDA at 3-6 m (+ maintenance)
MTX-IR	LDA at 3-6 m (+ maintenance)
b-DMARDs	LDA at 6 m (+ maintenance)
b-DMARDs (late stage)	ACR 20

**Remission ACR-EULAR criteria (Boolean or Index-based)*
*** LDA by DAS-28 <2.6*

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** LDA by DAS-28 <3.2*

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b-DMARDs IR (late stage)	**ACR 20** (+ maintenance)

Issues for discussion

1) Prevention of structural damage

1.a) Being this one of the main goals of treatment, should still be a requirement for the MA?

1.b) Are non-inferiority trials feasible?

Issues for discussion

2) Disease activity criteria vs relative endpoints as PEP

Disease activity criteria

(remission or LDA)

- Unequivocal clinical relevance
- Demonstrated co-R with prevention of structural damage
- In line with current thinking about 'treat-to-target'
- Realistic target in 1-3 Line
- N-I trials feasible, assay sensitivity
- Supportive regulatory experience
- Comprehensive clinical data package

Issues for discussion

3) Remission as a PEP for MTX-naive vs LDA for c/b DMARDs IR

2.a) Is remission a realistic/feasible goal in MTX-naive patients?

2.c) Is LDA a realistic/feasible goal in c/b DMARDs IR?

Issues for discussion

4) Definitions:

- **Remission**:
  - ACR-EULAR criteria (Boolean or index based) is acceptable?
  - Are there any others validated and generally accepted?
  - LDA by DAS-28 (CRP) < 2.6 is a reasonable alternative in MTX-naive?

- **LDA** by DAS-28 <3.2 vs SDAI/CDAI low disease activity as SEP
  - -- DAS-28 CRP vs ESR, any preference?
  - -- SDAI/CDAI more stringent and less experience

Thank you for your attention!