HTA254

Potential Discrepancies/Misalignments in Future EU-HTA Joint Clinical Appraisals: the Polivy and Stelara JA3 PICO Example

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INTRODUCTION

The objective of EUnetHTA Joint Action 3 (JA3) (2016-2021) was to define and implement a sustainable model for the scientific and technical cooperation on Health Technology Assessment (HTA) in Europe[1]. One of the tasks was to produce joint health technology assessments[2]. EUneHTA JA3 ultimately produced "Relative Effectiveness Assessments" (REA) for 20 medicines[3].

OBJECTIVES

The scope of this project was to assess commonalities/discrepancies between PICOs by the EUnetHTA REA JA3 project, and country assessments by regulatory/reimbursement authorities in three European countries: France, Germany and Italy, with specific reference to the patient populations identified.

METHODS

The EUnetHTA REA exercise assessed 20 medicines:

- One assessment (satralizumab) was discontinued due to changes in the EMA timelines, another (enasidenib) because the product was withdrawn from Marketing Authorization.
- Four products were Covid-19 treatments.
- Fourteen products were assigned PICOs with a huge variability in the number of comparators and outcomes (as reported in another poster4).
- Only two products were assessed for two different patient populations, Polivy (for the treatment of diffuse large B-cell lymphoma) and Stelara (for the treatment of ulcerative colitis), forming the scope of the present analysis.

This work is based on the analysis of PICOs identified in the EUnetHTA REA reports for Polivy (PTJA06)5 and Stelara (PTJA07)6 and the comparison with published HTA/P&R assessments by HAS in France, G-BA and IQWiG in Germany and AIFA in Italy.

Figure 1 The PICOS for Polivy (polatuzumab)

Population
- PICO 1a: 2L
- PICO 1b: 3+L

Intervention
- Polatuzumab

Comparators

Therapy of physician's choice, including:
- Pt and/or gemcitabine based regimens (like GemOx)
- Pt-based ICE
- Pt based DHAP +/- R
- rituximab- bendamustine (elderly or pts with comorbidities)

Therapy of physician's choice, including (after failure of >2 therapies):
- axicabtagene ciloleucel
- tisagenlecleucel
- pixantrone
- rituximab - bendamustine (elderly or pts with comorbidities)
- best supportive care (BSC)

Comparators

Efficacy [N=4]:
- Mortality
- Progression free survival (PFS)
- Complete Response
- Health-related quality of life

Safety [N=6]:
- AE
- SAE
- AE according to CTCAE
- AE resulting in withdrawal (overall and by SOCS and PT)
- Number of patients with polatuzumab antibodies
- Symptoms (e.g. like B-symptoms or fatigue)

10 outcomes for each comparison x 9 comparators = 90 analyses

Figure 2 The PICOS for Stelara (ustekinumab)

Population
- PICO 1: 3+L
- PICO 2: 2L

Intervention
- ustekinumab

Comparators
- adalimumab
- infliximab
- golimumab
- vedolizumab
- tofacitinib

Outcomes

Efficacy [N=8]:
- Clinical response after induction, after 1 year • Clinical remission after induction, after 1 year
- Inflammatory Bowel Disease Questionnaire (IBDQ) response
- Generic health-related quality of life HRQOL
- Steroid-free remission
- mucosal (endoscopic) healing after induction, after 1 year
- Surgery required,
- Hospitalization

Safety [N=7]:
- Overall adverse events (AEs) Serious AES
- Discontinuations due to AEs
- Severe AES
- Infections
- Fatal AEs
- Severe infections

15 outcomes for each comparison x 5 comparators x 2 populations = 120 analyses

RESULTS

Polivy in combination with bendamustine and rituximab (BR) was assigned **PICO-1a** [Adults with r/r-DLBCL who are not candidates for hematopoietic stem cell transplant (HSCT) – after failure of first line therapy] and **PICO-1b** [Adults with r/r-DLBCL who are not candidates for HSCT – after failure of two or more therapies] (Figure 1). Polivy was assigned different comparators for each of the PICO populations (4 vs 5 comparators respectively) and for each comparison it was assigned 10 different outcomes, potentially totaling 90 different comparative analyses.

- HAS denied reimbursement based on several factors (clinical data, relevance of comparator and primary endpoint chosen, etc.);
- AIFA approved reimbursement in PICO-1a;
- G-BA assessed a hint of non-quantifiable additional benefit, with reimbursement in PICO 1a.

Stelara was assigned **PICO-1** [Adults with moderately-severely active UC who have had an inadequate response with, lost response to, or were intolerant to, or have medical contraindication to conventional therapy and to at least one biologic therapy] and **PICO-2** [Adults with moderately-severely active UC who have had an inadequate response with, lost response to, or were intolerant to, or have medical contraindications to conventional therapy] (Figure 2). Stelara was assigned the same 5 comparators for both PICO populations and for each comparison it was assigned 15 different outcomes (8 of efficacy and 7 of safety), potentially totaling 120 different comparative analyses.

- HAS approved reimbursement in PICO-1 with a restriction vs. EMA label (in adults after failure of conventional treatments - amino-5 salicylates, corticosteroids and immunosuppressants - and at least one anti-TNFα biologic drug and vedolizumab).
- AIFA approved reimbursement in PICO-2, i.e. full EMA label.
- There is no G-BA assessment for this indication (first launch of ustekinumab was in 2009, before AMNOG came into effect), but product was fully reimbursed in EMA label.

For both products the authors of the assessments in all 3 countries lamented the lack of direct head-to-head trials versus identified comparators and the difficulty of performing Network Meta-Analyses (NMA), due to the differences in study designs, types of collected outcomes and patient populations.

CONCLUSIONS

For the only two drugs appraised in EUnetHTA REA for two different populations, authorities in France, Germany and Italy adopted different approaches, an example of the potential discrepancies and/or misalignments that companies may fear in future EU-HTA appraisals.

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CONTACT

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