PRS 9

ISPOR Europe 2019
2-6 November
Copenhagen, Denmark

How clinical trials incorporated outcomes relevant for health economic evaluation: an evidence gap analysis based on systematic review of clinical trials for moderate-to-severe asthma in Japan

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OBJECTIVE

To conduct a systematic literature review (SLR) of clinical trials for moderate-to-severe asthma (MSA) in Japan and assess how they incorporated economic relevant outcomes recommended by National Institute of Health (NIH), identifying evidence gaps for future economic evaluations in this field.

METHODS

- SLR of English and Japanese literature of clinical trials for MSA was conducted using the following strategy:
  - Database : MEDLINE, EMBASE, Cochrane CENTRAL
    Ichushi Web (for Japanese literature)
  - Publication year: Jan 1980-Nov 2017
  - Population : MSA patients >= 12 years old using medium to high dose inhaled corticosteroid (ICS) as basic treatment and also other concomitant drugs.
  - Intervention : methotrexate, antibiotics, NSAIDs, medical device excluded
  - Study design : randomized controlled trials (phase 1 trials excluded)
- All trials identified from SLR were divided into the following groups for assessing the incorporation rate of economic relevant outcomes :
  1) All Japan (JP) domestic trials
  2) Global trials including JP

  Group 3) and 4) identified from a published SLR of Mokoka (2019)[1] were used as benchmarks for comparison with JP trials.
  3) All trials from Mokoka (2019) SLR conducted outside JP
  4) Domestic trials among group 3
- Economic relevant outcomes for assessment were identified according to NIH (2011)[2]. (Table 1)

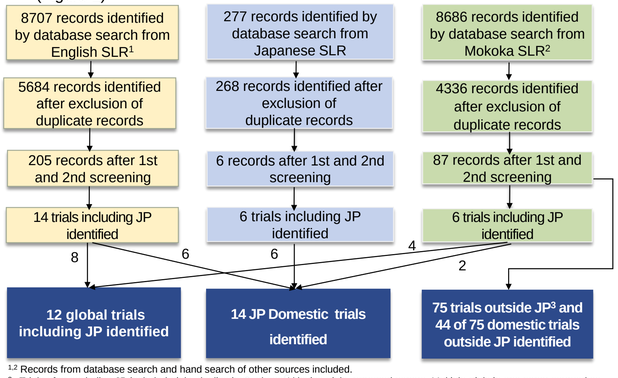
Table 1. Economic relevant outcomes for clinical trial recommended by NIH[2]

Core outcomes	Supplemental outcomes	Emerging outcomes
• Asthma-specific hospital admission • Asthma-specific ED visits • Asthma-specific outpatient visits • Asthma-specific detailed medication use • Resource use related to the intervention	• Categorization of asthma-specific outpatient visit (Primary care; Specialty care) • Respiratory healthcare use • Asthma school absences • Asthma work presenteeism and absenteeism • Cost analysis and CEA	• Remove visit • Teacher rating of student achievement • Academic standard test results

- The relationship between the incorporation of economic relevant outcomes and the trial characteristics was also analyzed.

RESULTS

- 12 global trials including JP, 14 JP domestic trials, 75 trials without JP and 44 of 75 domestic trials from Mokoka SLR were identified in this study. (Figure 1)



[1,2] Records from database search and hand search of other sources included.
[3] Trials after excluding JP-included trials, duplications, phase 1/device trials, retracted papers. Multiple trials in one paper counted as different trials.

Figure 1. Flowcharts of trials identified from SLR

- **Core outcomes**
  - Global trials including JP incorporated most detailed exacerbation-related hospitalizations/ED visits, while no JP domestic trials incorporated specific data about hospitalizations/ED visits. (Figure 2 and 3)

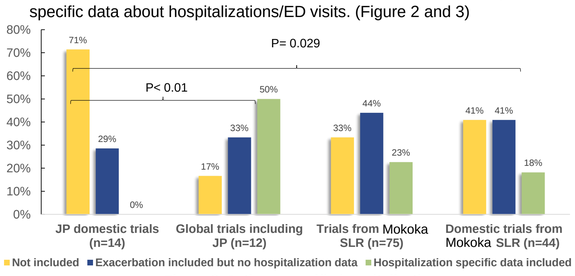


Figure 2. Asthma-specific hospitalizations

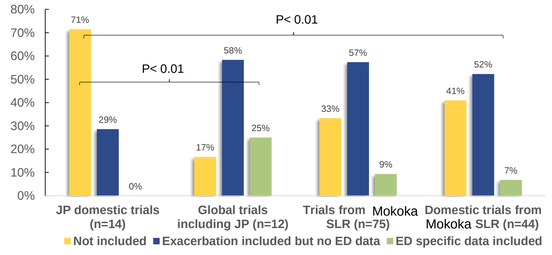


Figure 3. Asthma-specific ED visits

  - Global trials including JP incorporated outpatient visits most frequently. No JP domestic trials incorporated outpatient visits. All trials only reported unscheduled outpatient visits. (Figure 4)

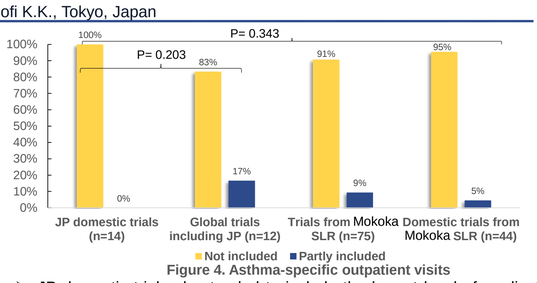


Figure 4. Asthma-specific outpatient visits

  - JP domestic trials also tended to include the lowest level of medication use although no statistical difference was found. (Figure 5)

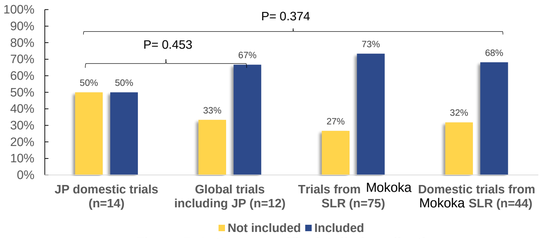


Figure 5. Asthma-specific detailed medication use

- **Supplemental outcomes**
  - School/Work absences, respiratory healthcare use were included in less than 10% of all trials (frequency: global trials including JP>trials from Mokoka>domestic trials from Mokoka. None in JP domestic trials).
- **Emerging outcomes**
  - Almost no emerging outcomes included in the trials reviewed. Only 2 trials included number of telephone visits.
- Pulmonary function was included in >98% of all trials. ACQ, AQLQ were the most included PRO scales while EQ-5D was included in only 5 trials.
- Pulmonary function was the most used primary outcome among all trials (31%), followed by exacerbation-related outcome (27%). Nearly half JP domestic JP trials didn't report clear primary outcome (43%).
- **Relationship between incorporation of economic relevant outcomes and trial characteristics (analysis using all trials)**
- Exacerbation-related outcomes reported in trials were selected as the index for the analysis with trial characteristics, and categorized as follows:
  Low level : exacerbation-related outcomes not reported at all.
  Middle level: reported but without specific data of hospitalization or ED visits.
  High level : specific hospitalization/ED visits data reported
- Trials of biotherapy, global trials, trials before product approval, trials of company sponsored were found to include higher level of exacerbation-related outcomes. (Figure 6)

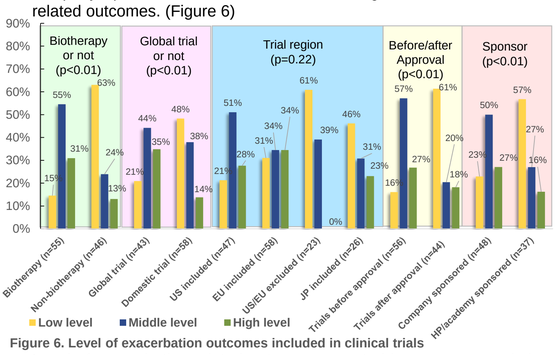


Figure 6. Level of exacerbation outcomes included in clinical trials

- Level of exacerbation-related outcomes reported increases very obviously with the increase of the timeframe and sample size of trials, while the percentage of trials including high level exacerbation-related outcomes was not found to increase very obviously with time. (Figure 7)

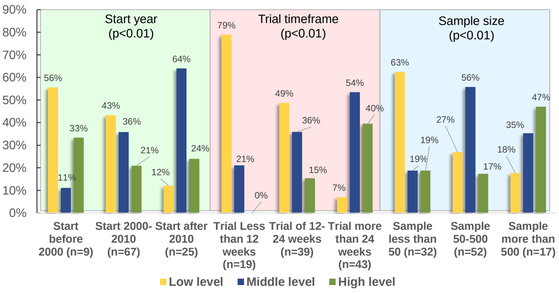


Figure 7. Level of exacerbation outcomes included in clinical trials

Discussion & Conclusions

- Generally, exacerbation-related outcomes were included in about 63.4% of all trials. Productivity loss was included in very few trials while other resource uses were almost not included.
- Global trials including JP incorporated the highest level of economic relevant outcomes, while JP domestic trials turned out to be at the lowest level to show a large contrast with global trials and also domestic trials in other single countries.
- Trials of biotherapy, global trials, trials including US/EU, trials with longer timeframe and larger sample size tended to incorporate higher level of exacerbation-related outcomes.
- Most JP domestic trials were conducted after approval, studying non-biotherapy and with very short timeframe. JP domestic trials are important for reflecting real clinical practice in JP and are expected to consider more economic relevant outcomes in future.
- Observational studies in JP were not collected by this research and how they included economic relevant outcomes remains to be explored.

Funding: This study is funded by Sanofi K.K., Japan.
Disclosure: Wentao TANG, Masanori MIYATA, Koichi SHIRAKAWA, and Yurie TAGUCHI are employees of Sanofi K.K., Japan, who may have stock options of Sanofi.
Acknowledgement: We would like to thank Creativ-Ceutical for providing support for the poster preparation.

References:
[1] Mokoka MC, McDonnell MJ, *et al.*. Inadequate assessment of adherence to maintenance medication leads to loss of power and increased costs in trials of severe asthma therapy: results from a systematic literature review and modelling study. *Eur Respir J.* 2019 May 18;53(5).
[2] Akinbami LJ1, Sullivan SD, *et al.*. Asthma outcomes: healthcare utilization and costs. *J Allergy Clin Immunol.* 2012;129(3 Suppl):S49-64.