P0040

Cladribine tablets versus other highly active disease-modifying therapies in multiple sclerosis in achieving Sustained Disability Improvement (SDI) Network Meta-Analysis

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Disclosures

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- **K P-S** has received travel funding and/or speaker honoraria from Merck Serono, Sanofi-Aventis, Biogen Idec, TEVA,F. Hoffmann-La Roche. She has served on scientific advisory boards for Sanofi-Aventis and Biogen.
- **KR** has received speaking honoraria and travel expenses for participation in scientific meetings with Biogen, Merck Serono, Genzyme, Novartis, Sanofi-Aventis, TEVA, F. Hoffmann-La Roche.
- **IA** is an employee of Merck Sp z o.o., Warszawa, Poland.
- **MR, ŁK, MG, RW, MPK** have nothing to declare.

INTRODUCTION

- Relapsing-remitting multiple sclerosis (RRMS) is the most common form of multiple sclerosis (MS), affecting about 85% of all MS patients, and it is characterized by periods of symptoms worsening/improvements[1]
- A „disease-modifying" drugs are used in treatment of RRMS, in order to shorten duration of acute exacerbations, decrease their frequency and provide symptoms relief[1]
- Efficacy of those agents is assessed usually by expanded disability status scale (EDSS), a tool developed for disability assessment in MS, and most of the time efficacy is assessed in context of sustained progression according to EDSS
- A new measure based on the EDSS has been developed – **sustained disability improvement (SDI)**, that put emphasis on symptoms improvement rather than progression
- **Cladribine tablets (CT)** has a distinctive posology**.** It is administered in 2 courses – 5 days cycles in 2 consecutive months at the beginning of each of 2 years of therapy. The effects of Cladribine tablets is sustained beyond the adminstration period with the majority of patients remaining relapse-free for up to 4 years after treatment initiation.

1. Goldenberg MM. Multiple sclerosis review. P T. 2012;37(3):175-184;

OBJECTIVES

To compare probabilities of sustained disability improvement (SDI) on the EDSS in patients with relapsing-remitting multiple sclerosis (RRMS) treated with:

- **cladribine tablets (CT)**
- **fingolimod (FIN)**
- **natalizumab (NAT)**
- **alemtuzumab (ALE)**
- **ocrelizumab (OCR)**

EDSS, expanded disability status scale

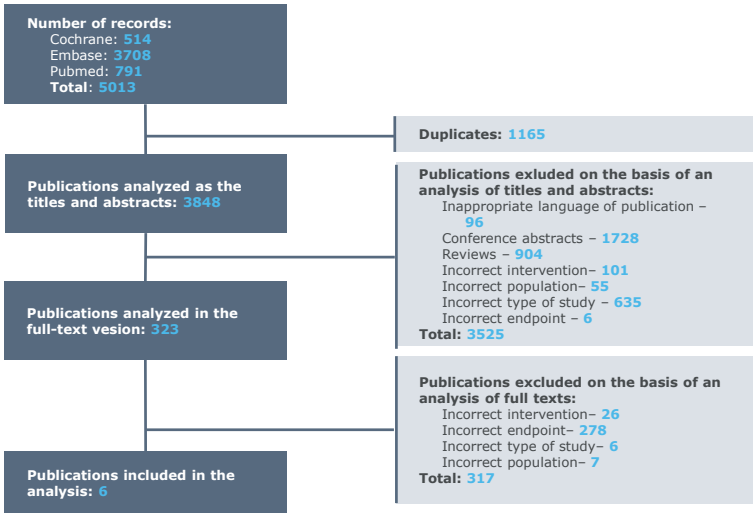
METHODS

- In compliance with the Polish HTA guidelines, a systematic review was conducted in Pubmed, Embase and Cochrane database to identify clinical trials (RCT or non-RCT) evaluating 6-month SDI:
  - among patients with RRMS
  - comparing cladribine tablets, fingolimod, natalizumab, alemtuzumab and ocrelizumab to each other directly or via a common comparator
- An indirect comparison via network meta-analysis (NMA) was performed: Bayesian inference with Markov chains Monte Carlo methods were applied; both random and fixed models were calculated and the model that better fit data was selected (according to DIC parameter value – lower indicated better fit)
- Outcome of interest was sustained disability improvement for 6 months (SDI-6 defined in general as improvement [decrease] in EDSS score ≥ 1 point that lasted for at least 6 months), and time to this event was modelled in NMA; hazard ratios (HR) from included studies for particular comparison were used as input data, and results were presented as HR for comparisons of interest

DIC, deviance information criterion; **EDSS,** expanded disability status scale

RESULTS

Systematic review



- Search was performed on April 2nd, 2019
- Total of 6 trials presenting SDI results and applicable for NMA were included:
  - 5 non-RCTs, with control groups selected by propensity score matching
    - Kalincik 2018[1] trial assessed CT, FIN and NAT
    - Kalincik 2017[2] trial assessed ALE, FIN, NAT and IFNb
    - Baroncini 2016[4], Guger 2018[5], Kalincik 2015[6] assessed NAT and FIN
  - 1 RCT - CARE MS II[3] assessed ALE and IFNb

CT, cladribine tablets; **FIN,** fingolimod; **NAT,** natalizumab; **ALE,** alemtuzumab; **IFNb,** interferon beta-1a

[1]Kalincik T et. al. Cladribine versus fingolimod, natalizumab and interferon β for multiple sclerosis. Mult Scler J 2018; 24(12):1617-1626; [2]Kalincik T et. al. Treatment effectiveness of alemtuzumab compared with natalizumab, fingolimod, and interferon beta in relapsing-remitting multiple sclerosis: a cohort study. Lancet Neurol 2017; 16(4):271-281; [3]Coles AJ et. al. Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 Clinical Trial. Neurology 2012; 78(14):1069-1078; [4]Baroncini D et. al. Natalizumab versus fingolimod in patients with relapsing-remitting multiple sclerosis non-responding to first-line injectable therapies. Mult Scler 2016; 22(10):1315-1326; [5]Guger M et. al. Real-life clinical use of natalizumab and fingolimod in Austria. Acta Neurol Scand 2018; 137(2):181-187; [6]Kalincik T et. al. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. Ann Neurol 2015; 77(3):425-435

RESULTS

NMA analysis

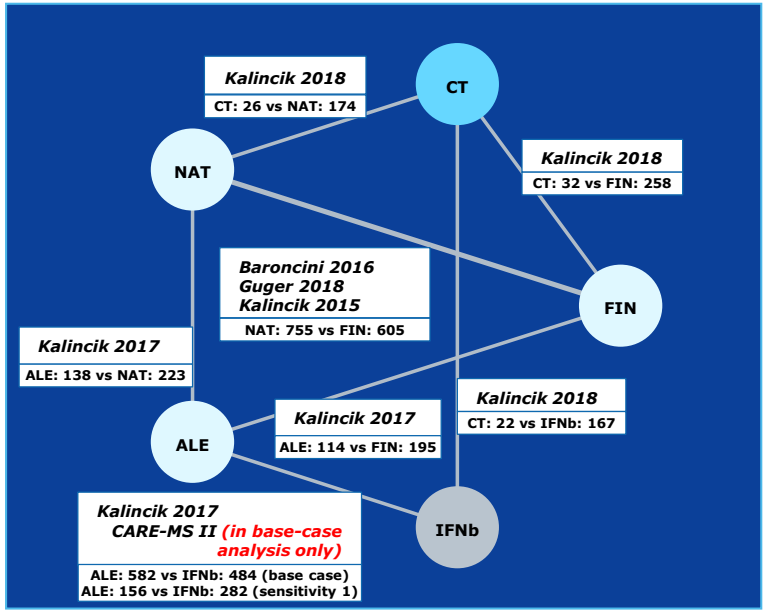
- The base-case analysis and two sensitivity analyses were planned, to explore impact of heterogeneity of included studies on NMA outcomes
- All available studies were included in the base-case analysis
- In the sensitivity analysis 1, the RCT was removed from network (CARE-MSII study), as the other trials were non-RCTs
- In the sensitivity analysis 2, studies that included patients from MSBase registry were removed from the network, as there was a high probability of included subjects overlapping (Kalincik 2015 and Kalincik 2017)
- Due to the lack of proper data, comparison with OCR was not possible. Additionally, there was also an interferon arm in the network acting as a linking element between CT and ALE (a common comparator)

CT, cladribine tablets; **ALE,** alemtuzumab; **NMA**, network meta-analysis

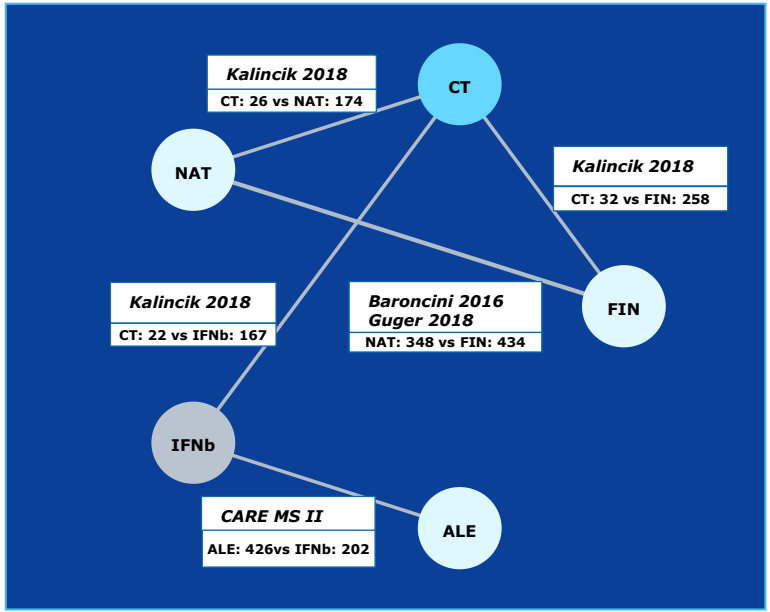
RESULTS

NMA networks

Base-case analysis and sensitive analysis 1 network



Sensitive analysis 2 network



CT, cladribine tablets; **FIN,** fingolimod; **NAT,** natalizumab; **ALE,** alemtuzumab; **IFNb,** interferon beta-1a

RESULTS

NMA results

Comparison	Base-case analysis (random model)	Sensitivity analysis 1 CARE MS II (RCT) excluded (random model)	Sensitivity analysis 2 Kalincik 2015 and Kalincik 2017 (MSBase studies) excluded (fixed model)
Hazard Ratio HR (95% CrI) for SDI-6			
CT vs FIN	5,17 (1,81; 15,01)	5,56 (2,00; 15,83)	4,27 (2,26; 7,99)
CT vs NAT	3,06 (1,06; 8,62)	3,32 (1,17; 9,24)	3,69 (1,97; 6,86)
CT vs ALE	9,45 (2,79; 31,94)	10,79 (3,24; 36,20)	5,92 (1,35; 26,44)
Likelihood that a particular intervention is in the top rank (SUCRA)			
CT	99,40%	99,28%	99,77%
NAT	73,18%	73,37%	61,98%
FIN	47,09%	48,18%	45,17%
ALE	15,98%	24,67%	40,90%

CrI, credible interval; **SDI-6,** sustained disability improvement for 6 months; **SUCRA,** surface under the cumulative ranking; **CT,** cladribine tablets; **FIN,** fingolimod; **NAT,** natalizumab; **ALE,** alemtuzumab

CONCLUSIONS

Cladribine tablets seems to be **more effective in achieving 6-month sustained disability improvement in MS patients, compared to other disease-modifying treatments** prescribed to patients with highly active disease.

The conclusion is based on clinical data of limited quality as most of included trials were not RCTs. Additionally, there were only 37 patients treated with CT with SDI data available (Kalincik 2018).