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Systematic review and network meta-analysis (NMA) for cladribine tablets in achieving sustained disability improvement (SDI) in multiple sclerosis

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ABSTRACT

Introduction. This study was performed to compare probabilities of SDI on the Expanded Disability Status Scale (EDSS) in patients with relapsing-remitting multiple sclerosis (RRMS), treated with cladribine tablets (CT) or fingolimod (FTY), natalizumab (NAT), alemtuzumab (ALE) and ocrelizumab (OCR).

Clinical rationale for the study. Progression of neurological disability as measured by the EDSS has been a common endpoint in multiple sclerosis (MS) trials. Novel therapies can not only slow this process, but in some patients even reverse it. This effect can be measured by the sustained disability improvement (SDI) — an endpoint that seems to continuously gain importance in clinical practice. Despite that, SDI has rarely been explored as an outcome in MS clinical studies, mostly as post-hoc analyses from randomised trials or as retrospective analyses based on patient registry records.

Material and methods. A systematic review was conducted in Medline, Embase and Cochrane to identify clinical trials (RCT or non-RCT) evaluating 6-month SDI. An indirect comparison via network meta-analysis (NMA) was performed. Bayesian inference with Markov chains Monte Carlo methods were applied.

Results. Eight trials presenting SDI results and applicable for NMA were included: six non-RCTs, with control groups selected by propensity score matching, and two RCTs. NMA results revealed that probability of achieving 6-month SDI with CT was significantly higher compared to all other high efficacy disease-modifying drugs with available data — HR (95% CrI - Bayesian Credibility Interval) *vs.* FTY: 4.98 (2.11–11.79); *vs.* NAT: 3.12 (1.31–7.27); *vs.* ALE: 9.29 (3.40–25.21). The main results were confirmed in the sensitivity analyses.

Conclusions. Of all considered therapies, treatment with cladribine tablets was associated with a higher probability of sustained disability improvement in RRMS patients. As this conclusion is based on available clinical data of limited quality, future studies, as well as real-world data, would be valuable to provide further evidence regarding the comparative effectiveness of RRMS therapies.

Key words: multiple sclerosis (MS), sustained disability improvement (SDI), cladribine in tablets (CT), network meta-analysis (NMA), systematic review

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Introduction

Multiple sclerosis (MS) is an immune-mediated inflammatory demyelinating disease of the central nervous system [1]. MS affects mostly younger people (between 20 and 40 years old), eventually resulting in disability and cognitive impairment, therefore early and precise diagnosis is of particular importance with room for improving existing techniques and implementing new ones [2]. Relapsing-remitting MS (RRMS) is the most common type of MS, accounting for c. 85–90% of cases at onset and affecting especially young people [3]. Its course is characterised by fully or partially reversible episodes (relapses) of neurological disability and differential involvement of motor, sensory, visual, and autonomic systems [4]. Typically, there is observed slight disease progression between relapses, although they can leave residual or sometimes severe disability [5]. However, as no medication fully prevents or reverses progressive neurological deterioration [1], delaying or stabilising disability progression is one of the most important goals in treating MS. While more effective therapies for MS appear, it is reasonable to anticipate potential treatment effects on sustained improvements in physical disability [6].

Progression of neurological disability as measured by the Expanded Disability Status Scale (EDSS), has been a common endpoint in MS clinical trials [7]. Sustained (confirmed in a defined time interval e.g. 3 or 6 months) improvements in disability (i.e. decreases in punctation in EDSS) have rarely been explored as an outcome in MS clinical studies. Therapies with SDI might lead to improved quality of life and provide a better prognosis [6, 8]. Most of the evidence on this endpoint comes from post hoc analyses of data from pivotal RCTs. However, control arms in those trials have usually comprised first-line disease-modifying drugs (e.g. interferon beta) or a placebo. This is a factor limiting the possibility of comparison between drugs aimed at high activity disease. Additional data comes from analyses of MS patient registers with the methodology of cohort matched studies.

Clinical rationale for study

This study aimed to compare cladribine tablets (CT) and the other disease-modifying therapies (DMTs) indicated for highly-active MS, such as fingolimod (FTY), alemtuzumab (ALE), natalizumab (NAT) and ocrelizumab (OKR), in their potential for achieving sustained disability improvement, as measured by EDSS. Cladribine tablets are one of the new therapeutic options for MS; this treatment produces selective B and T lymphocyte reduction followed by reconstitution with no known effect on innate immunity. CT are considered as an immune reconstitution therapy (IRT) [9–11]. Concerning the remaining analysed drugs, it should be noted that ocrelizumab reduces the antigen presentation from B lymphocytes to T lymphocytes and affects the secretion of pro-inflammatory molecules from B lymphocytes and their reactivity, fingolimod prevents infiltration of adaptive immune cells into the CNS, natalizumab averts leukocyte infiltration into the CNS, and alemtuzumab leads to long-term depletion of CD52-positive B and T cells [12].

Material and methods

A systematic review was performed in Medline/Pub-Med-not-MEDLINE and EMBASE (via Elsevier) and CENTRAL (Cochrane Central Register of Controlled Trials); references of the included studies were also analysed. The search was performed on 6 July 2021 by two independent analysts, including a third person if consensus was required (for details, see Fig. 1 and Table S.1 in Supplementary Materials).

The search was focused on studies evaluating cladribine tablets or chosen comparators (alemtuzumab, fingolimod, natalizumab, and ocrelizumab) in MS patients and reporting the results of 6-month improvement in disability on the EDSS scale. However, the exact definition of this endpoint and the period of confirmation of the improvement in EDSS was required, and studies in which this period was anything other than six months were excluded. Studies presenting results for SDI in any way different than that in the Kalincik (2018) publication [13] (the only one evaluating cladribine tablets) were also excluded. Specifically, this was the case if only percentages of patients with improvement in EDSS score were given (not as the time-to-event measure) and comparative assessment against comparators was not possible or publications presented results of comparisons that were not included in the indirect comparison network.

The 2018 study by Kalincik [13] was the only one to present direct comparisons of cladribine tablets with natalizumab, fingolimod and interferon β, and therefore to allow an indirect comparison with alemtuzumab and to strengthen the observed results, a network meta-analysis (NMA) was performed. Calculated inter-study effect (HR) was adopted in the indirect comparison computation assuming a normal distribution of its logarithm. The logarithmic value of this effect, with its standard error, was introduced into the model. Results of the analysis were presented with 95% Bayesian credibility intervals (CrI), i.e. considering the analysed data, intervals in which the true (unknown) value of the analysed parameter lies with 95% probability. A different approach is applied to the calculation of 95% confidence intervals (CIs), which are a measure of uncertainty around the estimated effect and consist of lower and upper bounds indicating that, taking into account hypothetically repeated measurements, 95% of the confidence intervals calculated from random samples will contain the true value. The results are considered significant when 95% CrI doesn't include the value '1' [14].

The calculations were performed with R software (ver. 4.1.0; R 2021) with the *gemtc* package version 1.0–1 [15]. The model parameters, in line with Bayesian inference, were treated as random variables, and their posterior distributions

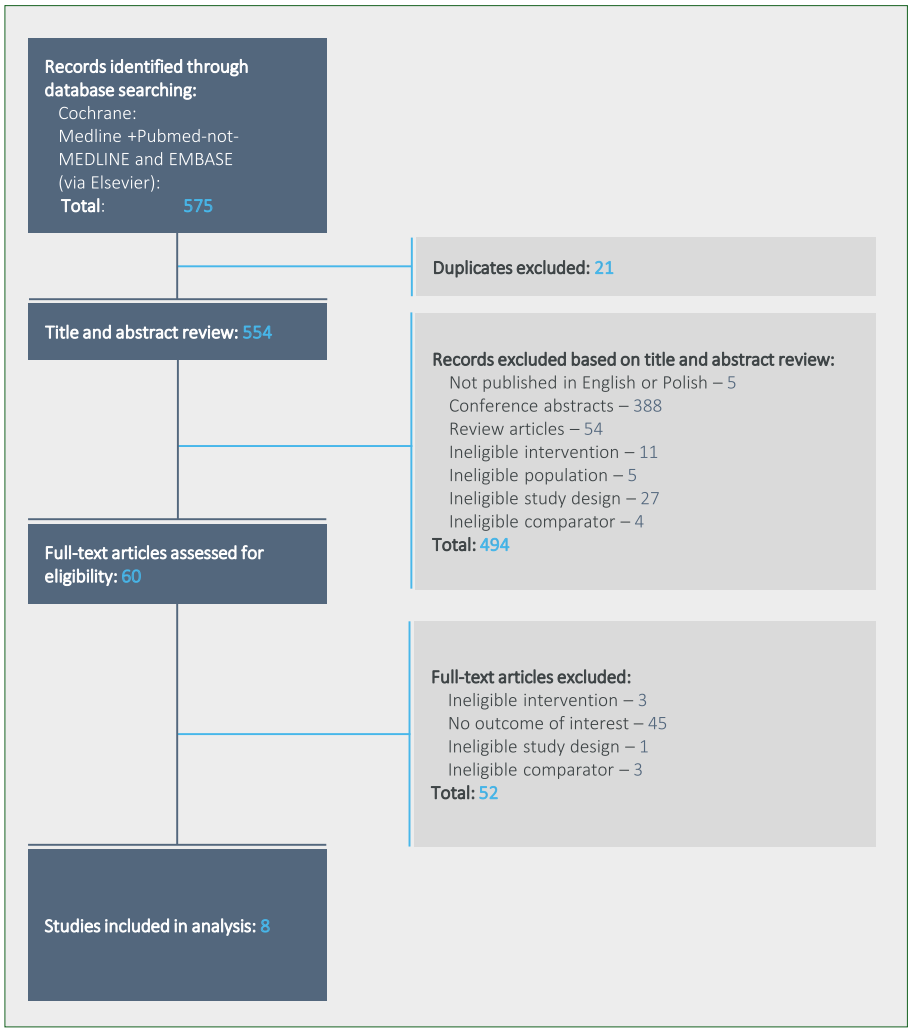

Figure 1. Flow diagram of literature review process

were estimated by the Markov Monte Carlo chain method (MCMC). This iterative process involved 450,000 repetitions (of which the first 200,000 were rejected from the final analysis as uncertain) and was carried out in four parallel different chains (so, in total, 1,000,000 samples were calculated). *A priori* distributions for estimated parameters were chosen to introduce as little information as possible into the model (non-informative priors) — default values of these parameters, determined automatically by the *gemtc* package were adopted. The calculations were conducted with the use of two statistical models — the fixed effects model (fixed) and the random-effects model (random). Herein, we report only those results that were obtained by the model characterised by a lower value of the DIC parameter; however in the case when DIC values for both fixed and random models were very similar, the fixed effects model was preferred.

In the indirect comparison analysis, the included treatments were ranked according to their comparative effectiveness — for each drug, probability of being the best drug among the all under assessment (rank No. 1), the second one (rank No. 2), etc. Additionally, the SUCRA parameter, i.e. the surface under the cumulative ranking curve, was also determined. This parameter is a numerical result of all ranks, rescaled for the range from 0 to 100 (zero being 100% probability of obtaining the worst rank by a given treatment, and 100 being 100% probability of obtaining rank No. 1). Therefore, the SUCRA value indicates the belief that the drug will be the best or worst in the network, and the higher its value, the more likely that the drug will be the most effective. This parameter can also be interpreted as the mean proportion of therapies worse than the benchmark [16, 17]. To confirm the main results, two sensitivity analyses were conducted. In the first, studies with a different methodology were excluded, and in the second one, studies with potentially overlapping subjects were not considered.

Results

The systematic review resulted in eight publications included in the analysis: in two of them, the results of SDI assessment coming from randomised controlled trials were

presented: CAMMS223 [18] and CARE-MS II [19], while the remaining six publications stated SDI results from cohort studies, where the propensity score matching method was applied with matching the characteristics of the assessed cohorts [13, 20–24]. The results for cladribine tablets were presented only in Kalincik 2018 [13], where the total cohort comprised only 37 patients. No studies were found to allow for the inclusion of ocrelizumab in the indirect comparison network, while interferon β (INFβ) needed to be included in the network as a common comparator allowing for the comparison of cladribine tablets with alemtuzumab.

In addition to the direct comparisons present in Kalincik 2018 [13] (CT *vs.* FTY or *vs.* IFNβ or *vs.* NAT), the remaining studies incorporated into the NMA comprised the following comparisons: NAT *vs.* FTY — Andersen 2021 [20], Baroncini 2016 [21], Guger 2018 [22] and Kalincik 2015 [24], ALE *vs.* NAT and *vs.* IFNβ — CAMMS223 [18] and Kalincik 2017 [23], and ALE *vs.* FTY — Kalincik 2017 [23] and CARE-MS II [19]. Kalincik 2018 [13] reported the sustained improvement in disability defined as: reduction in EDSS score ≥ 1 point (1.5 points if the baseline value was 1.5 and 0.5 points if the baseline value was > 6) confirmed in an interval of ≥ 6 months. A change from 1 to 0 EDSS was not interpreted as an improvement in disability. A similar definition was adopted in Andersen [20] and Kalincik 2017 [23], except that it did not specify the criteria for patients with a baseline EDSS 1 score. The definition of the sustained improvement in disability in other included studies differed slightly in details - they are presented in Table S.2 in the Supplement.

As part of the indirect comparison, there were three analyses performed. The main analysis included all eight studies identified in the systematic review. The first sensitivity analysis (1) excluded the CARE-MS II [19] and CAMMS223 [18] trials, which differed from the other trials in terms of methodology due to the random assignment of patients (RCTs). To avoid multiple inclusion of the same patients, studies other than Kalincik 2018 [13] were removed from the calculations in the second sensitivity analysis, because those might in part include the same patients from the MS Base registry — Kalincik 2015 [24] and Kalincik 2017 [23] — that were already covered by Kalincik 2018 [13]. In the case of Andersen [20], the main results obtained in the population comprising the MS Base registry were excluded as well. However, the results of additional analysis restricted to DMSTR and OFSEP registries data were included in this NMA.

The network of relations between the interventions from the studies that entered the main indirect comparison analysis is presented graphically in Figure 2A. The networks of evidence for the sensitivity analyses are presented in Figure S.1 and S.2 in Supplementary Materials.

It should be noted that the study assessing cladribine tablets [13] comprised a mixed population, with secondary progressive MS course as well, although the vast majority were patients with relapsing-remitting MS (75–90% depending on the cohort). In the remaining studies, only patients with RRMS were enrolled — the CARE-MS II study [19] specified that the diagnosis was made according to the 2005 McDonald criteria, and Kalincik 2017 [23] was also based on the McDonald criteria, but from 2010, while the CAMMS223 [18] trial adopted an even older (2001) version of the criteria. Two of the included studies defined also the number of previous relapses — in CAMMS223 [18] and CARE-MS II [19] trials it was assumed to be ≥ 2 relapses in the last two years — including ≥ 1 in the last year in CARE-MS II [19]; the last criterion was also in accordance with Kalincik 2017 [23]. Patients with disease duration ≤ 10 years were included in both of these trials, and the criteria for baseline EDSS performance were presented — only patients who scored ≤ 5.0 points were included in the CARE-MS II trial [19], and Kalincik 2017 [23] accepted patients with EDSS ≤ 6.5. Slightly different inclusion criteria were adopted in the CAMMS223 study [18], where patients with disease duration ≤ 3 years and baseline EDSS score ≤ 3.0 were enrolled.

The average age of patients in different subgroups ranged from 33 to almost 40 years in most of the analysed studies. One exception was Kalincik 2018 [13], which enrolled older patients; depending on the selection and matching of patients in individual groups of this study, their average age was within the range 44–50 years. Populations of the studies predominantly consisted of women (65–81%). As indicated by the baseline characteristics of the included populations, the mean baseline EDSS score was within the range 2.0–3.4, which is characteristic of moderate performance impairment. The exception, again, was Kalincik 2018 [13] that assessed cladribine tablets, where a higher EDSS value compared to other studies was observed — a median baseline EDSS score was 3.5–4.5 depending on the cohort.

A detailed summary of the methodology, inclusion criteria, patient baseline characteristics, and quality assessments of the included studies is set out in Tables S.3 and S.4 in Supplementary Materials. The numbers of subjects in individual cohorts under evaluation are presented in Figure 2B. In the case of studies where propensity score matching methodology was applied, those numbers may vary depending on the given comparison.

Direct comparison

All of the comparisons that were carried out based on matched cohorts of patients from the MS Base registry presented in Kalincik 2018 [13] showed a significant benefit from the use of cladribine tablets in terms of increasing the probability of obtaining a sustained (≥ 6 months) disability improvement (Tab. 1).

Indirect comparison

The main result of the performed NMA shows that the probability of obtaining a sustained (≥ 6 months) disability improvement (SDI6) with CT compared to ALE is over nine

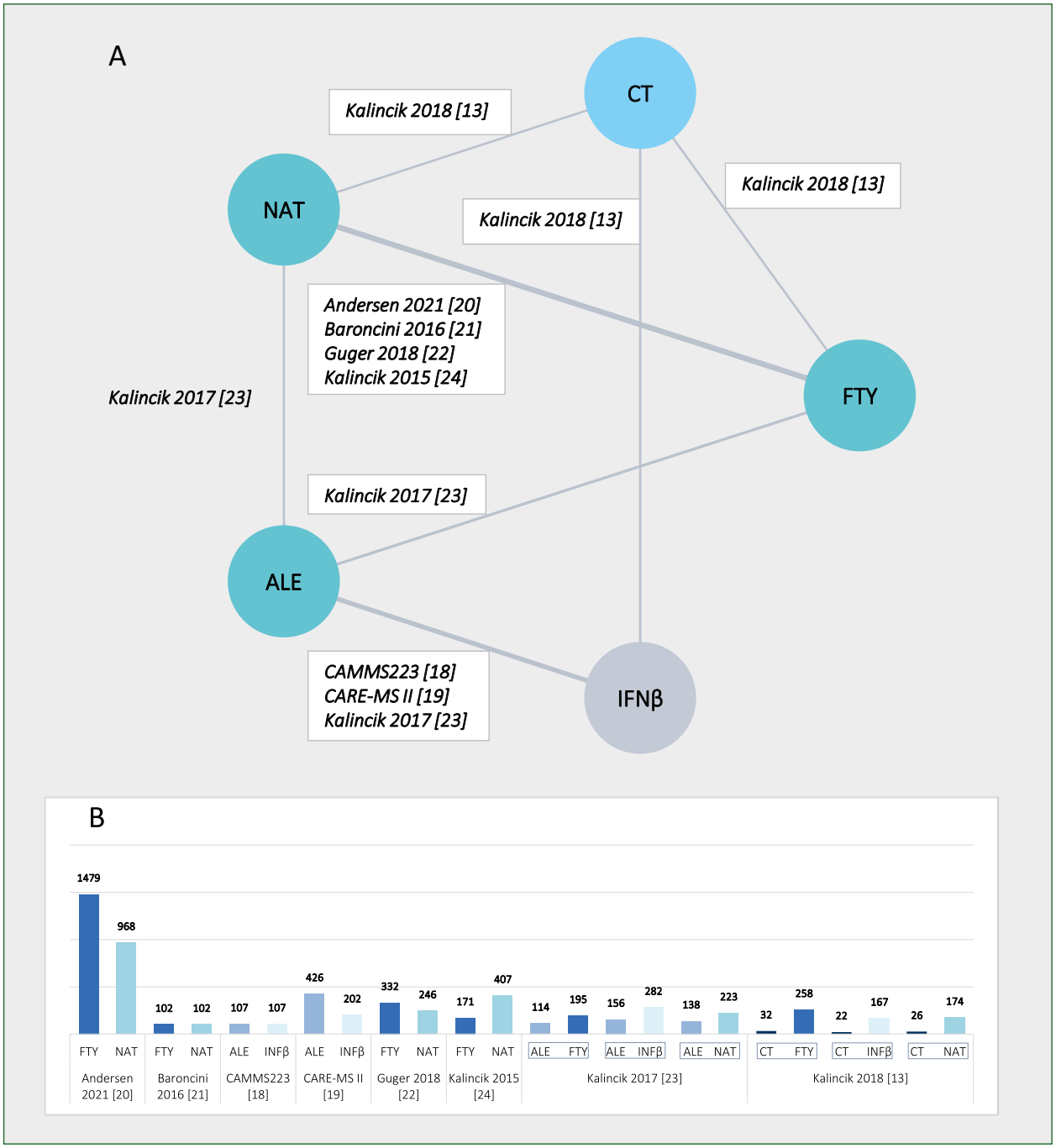

Figure 2. Evidence network for network meta-analysis (NMA) of achieving sustained disability improvement (SDI) — main analysis **(A)**. Number of subjects included in main analysis **(B)**. ALE — alemtuzumab; CT — cladribine tablets; FTY — fingolimod; INFβ — interferon β; NAT — natalizumab

Table 1. Direct comparison of achieving sustained disability improvement (SDI) [13]

Comparison	HR (95% CI)
CT *vs.* FTY	3.90 (1.60–9.60), p = 0.0025
CT *vs.* NAT	4.00 (1.80–9.20), p = 0.00099
CT *vs.* INFβ	15.00 (3.60–59.00), p = 0.00017

CI — confidence interval; CT — cladribine tablets; FTY — fingolimod; HR — hazard ratio; INFβ — interferon β; NAT — natalizumab

times higher: HR = 9.29 (95% CrI: 3.40; 25, 21). When compared to FTY, CT increased that probability over four times: HR = 4.98 (95% CrI: 2.11; 11.79); and compared to NAT — more than three times: HR = 3.12 (95% CrI: 1.31; 7.27). All these results were statistically significant. The conclusions of the main analysis were also confirmed in conducted sensitivity analyses (Fig. 3A). The results of the preferred model, characterised by the lower value of the DIC parameter, were

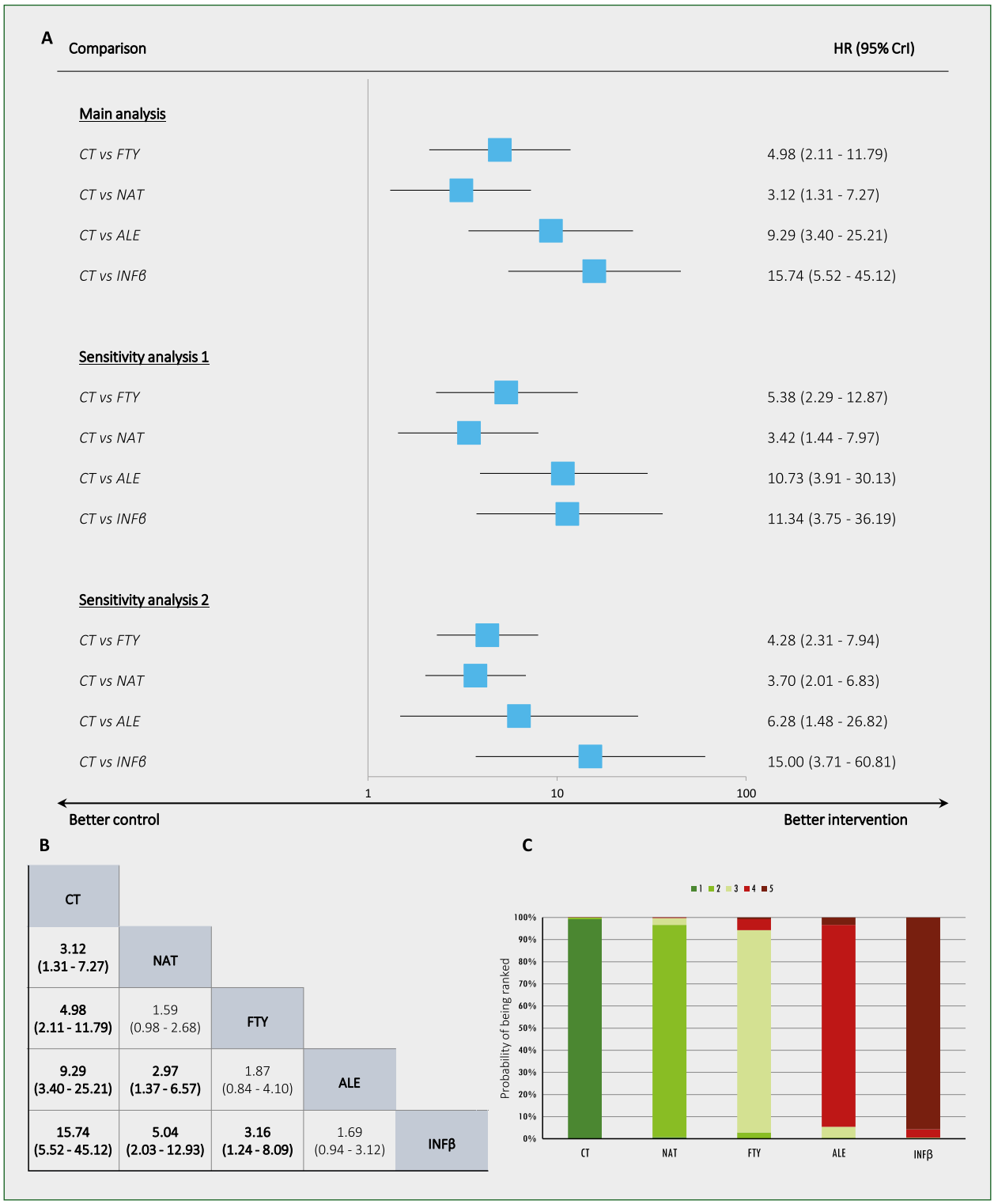

Figure 3. Forest plot of NMA results of achieving sustained disability improvement (SDI); main and sensitivity analyses (model with lower DIC value is presented) **(A)**. League table showing results of NMA comparing effects of all drugs including hazard ratios (HR) and 95% credible intervals (95% CrI) **(B)**. Rankogram for treatment efficacy of achieving sustained disability improvement (SDI) in NMA, main analysis (random model) **(C)**. HR — hazard ratio; CrI — credible intervals; CT — cladribine tablets; FTY — fingolimod; NAT — natalizumab; ALE — alemtuzumab; INFβ — interferon β. Sensitivity analysis 1: excluded randomised trials CARE-MS II [19] and CAMMS223 [18], which differed in methodology from others; Sensitivity analysis 2: excluded trials other than Kalincik 2018 [13], which assessed subjects' data from MS Base registry to avoid multiple subjects participation (in Andersen 2021 study [20], instead of presenting total results, which also included the MS Base registry, only results from two other registries were used — DMSTR and OFSEP)

presented — all results, as well as the input data used in the intermediate comparison, are shown in Tables S5 and S6 in Supplementary Materials.

Efficacy results of all treatments included in the indirect comparison are also summarised in the form of a league table. The results are to be interpreted as the comparison of intervention in a given column versus interventions from subsequent rows, and the order of the columns reflects the ranking of those interventions, starting with the best from the left. The effectiveness estimate is located at the intersection of the treatment-defining column and the treatment-defining row. Statistically significant results are shown in bold text (Fig. 3B). League tables for sensitivity analyses are presented in Supplementary Materials — Figure S.3 and S.4.

According to the performed ranking of individual drugs in the main analysis (random model), CT was very likely (99.2%) to be the most effective therapy in terms of the considered endpoint (Fig. 3C, rankograms for both sensitivity analyses are presented in Fig. S.5 and S.6 in Supplementary Materials). This was confirmed by the SUCRA score (99.8%). Detailed ranking probabilities of each treatment effect and SUCRA value are presented in Table S.7 in Supplementary Materials.

Discussion

One of the main consequences of MS relapses is persistent disability presenting during the relapse period assessed using the Expanded Disability Status Scale. The core goal of treatment in MS is to reduce the accumulation of irreversible disability, which may not be straightforward in elderly patients where diagnostic delay is a common problem [25] or under unusual conditions, as in the case of COVID-19 infection [26, 27]. Typically, studies assess the occurrence of a sustained deterioration on the EDSS, confirmed over a specific period (e.g. 3 or 6 months). However, disease-modifying therapies may help restore function over time in MS patients. One measure of restoration of function is sustained disability improvement, defined by a specific decrease in EDSS score confirmed over a specific period (e.g. 3 or 6 months). This endpoint is especially important, as it may lead to improvement in patient-reported QoL measures of physical and mental function, as well as overall wellbeing [6]. Achieving sustained disability improvement on the EDSS has rarely been explored as an outcome in MS clinical studies, mostly as post-hoc analyses from randomised trials or as retrospective analyses based on patient registry records. The research question of the publication, therefore, focuses on the less frequently evaluated but interesting outcome concerning confirmed in a defined time interval improvement of disability and is based on systematically retrieved all available best evidence. However, of course, one should bear in mind the general limitations associated with the indirect comparison methodology.

To the best of our knowledge, this study is the first systematic review evaluating cladribine tablets compared to other DMTs for achieving sustained disability improvement on the EDSS scale (SDI). There have been systematic reviews with network meta-analyses comparing CT to other DMTs, but most of them assessed classic MS endpoints such as relapses or sustained disability progression. In general, based on RCT studies, they showed that CT are similarly or significantly more effective than the comparators analysed in this review and have an acceptable safety profile [28-30]. There were no significant differences between CT and FTY, ALE and NAT in the assessment of ARR (RR = 0.91, RR = 1.30, and RR =1.22; respectively), 3mCDP (HR = 0.78, HR = 2.25, and HR = 1.10; respectively), 6mCDP (HR = 0.79, HR = 1.37, and HR = 1.21; respectively) and any AEs (OR = 1.31, OR = 0.27, and OR = 2.70; respectively) [30]. Significant differences in favour of CT *vs.* FTY were shown in the MRI NEDA assessment (OR = 1.58) [28].

The results of our systematic review confirmed the limited number of available published studies, which provided information on the SDI. Only two RCT trials were found [18, 19], and for this reason, we decided to include non-randomised controlled studies with lower reliability, according to the hierarchy of evidence. The six remaining included studies were conducted based on registry data, and groups for comparison were created under the propensity score matching method, based on many potential confounding factors, including age, sex, duration of illness, baseline EDSS, number of relapses in the past, or previous DMTs used [13, 20–24]. This technique minimises the differences between the groups in terms of known confounders as much as possible and is intended to bring the study as close as possible to an RCT trial [31, 32]. As a result, participants were chosen from the hundreds of patients in the registry to create secondary matching groups, which were less numerous than the total number of patients in the registry.

The systematic search allowed for the identification of just one study [13] presenting a direct comparison of cladribine tablets with fingolimod, natalizumab, and interferon β, within cohorts matched by the propensity score matching method, although in this study, adequate methods were applied to match the analysed groups in order to minimise the differences resulting from the characteristics of patients.

The methodology of Kalincik 2018 [13] and the way of presenting the results basically determined the possibility of comparison with other comparators. In total, nearly 700 patients were included in the study, but the number of patients receiving cladribine tablets was relatively low, amounting to just 37, and similarly, the matched cohorts comprised no more than 32 patients. The authors also pointed to this as a limitation, but at the same time emphasised that while the power of the study is thus limited, it demonstrated a number of statistically significant differences between cladribine and the three comparators [13]. These numbers for CT were very low compared to other interventions already included in the indirect comparison; after summing up the numbers of

individual groups (ignoring the possible double counting of patients from the same registry enrolled in several studies), the total of analysed patients reached 6,436, of whom only 80 (1.2%) were those treated with cladribine tablets. It should also be noted that in Kalincik 2018 [13], all the matched cohorts consisted of patients drawn from the same pool. These cohorts in the indirect comparison are treated as separate, independent groups, but the impact of double-counted patients on the possible correlation is not taken into account. At the same time, this study cannot be treated as a multi-arm comparison, where the correlation between comparators is assumed in advance, and therefore the performed NMA may be at risk of some overestimation of the cladribine tablets efficacy. The same applies to Kalincik 2017 [23], where alemtuzumab was assessed.

Another limitation of Kalincik 2018 [13] was only a one-year follow-up period, when in most other trials it was about two years. However, taking into account the advanced stage of the patients in this study (depending on the group, the median duration of disease ranged from 10 to 14.1 years, the median EDSS score ranged from 3.5 to 4.5, and the median prior treatments ranged from 1 to 2), it was concluded as being sufficient. Additionally, it should also be noted that cladribine tablets are administered for only 20 days in total, during two short courses at the beginning of the first and second year of treatment, which provides treatment benefit up to four years, as proven in the extension trial of the CLARITY study [33]. Moreover, the latest results of the CLASSIC-MS study indicate that the effect of CT therapy may last even longer — over 60% of patients did not require further treatment for 8-14 years [34]. Thus it can be expected that the incidence of SDI will increase in the following years, as it is noticeable in other analysed trials — e.g. Baroncini 2016 [21] and Guger 2018 [22] — and then limiting the observation to one year for CT is conservative.

Importantly, Kalincik 2018 [13] did not present the percentage of patients who achieved SDI6 and it could not be deduced from the Kaplan-Meier curves presented in the publication, so only the results presented in the form of hazard ratio values became the basic input for the indirect comparison network, which consequently significantly reduced the number of adequate studies. The systematic review identified many more studies that evaluated chosen comparators (fingolimod, natalizumab, alemtuzumab, ocrelizumab) in the context of SDI6 measure. Most of them were single-arm trials, reporting only percentages of patients achieving SDI6 or presenting the results in a way that made it impossible to compare them to cladribine tablets' results. Finally, only eight clinical studies comprised relevant comparisons of interventions that could be used in forming a network with CT. However, no studies enabling the inclusion of ocrelizumab in the network were found.

The main considered endpoint itself is rarely presented in clinical trials and appears mostly only in recently published studies. Sustained disability improvement can be measured over a 3-, 6-, or 12-month period, and the choice of a 6-month period in this analysis was dictated by the methodology used in the only study for CT. Possible limitations resulting from slight differences in the very definition of the assessed endpoint in individual studies should also be considered. In Kalincik 2018 [13], SDI6 was broadly defined as a reduction in EDSS of ≥ 1 point sustained for at least six months. Additional criteria were applied to correlate this endpoint with the baseline EDSS value: for patients with a low EDSS value — 1.5 points at baseline (a change from 1 EDSS point to 0 was not considered an improvement in disability), the response criterion was extended to the reduction of at least 1.5 EDSS points, yet in patients with greater disability at baseline (EDSS > 6), the criterion was relaxed - a reduction in EDSS of ≥ 0.5 point was sufficient. The same definition was applied in the Andersen [20] and Kalincik 2017 [23] studies, while in other studies the definitions slightly differed (Table S2 in Supplementary Materials). The required reduction in the EDSS score in Kalincik 2018 [13] was increased to ≥ 1.5 points for patients who had an EDSS of 1.5 points at baseline, while Guger [22] reported that in patients with high (≥ 5.5 points) EDSS, the criterion was decreased to ≥ 0.5 points. In the CARE-MS II [19] and CAMMS223 [18] studies, disability improvement was defined as a reduction in EDSS score of ≥ 1 point over six months among patients with a baseline EDSS score of ≥ 2 points (in the second trial, patients with a baseline EDSS of 0 were not assessed). It's not entirely clear to what extent these differences may translate into the heterogeneity of studies included in the NMA, as it was not specified what percentage of patients with sustained disability improvement was enrolled by stricter or relaxed criteria.

Taking into account the direct comparison of interventions under assessment conducted in Kalincik 2018 [13], it has been shown that cladribine significantly increases the probability of achieving a sustained disability improvement over ≥ 6 months, compared to interferon β, fingolimod, and also natalizumab. In the case of the NMA, in every sub-analysis, parallels with the direct comparison were observed — cladribine in tablets significantly increased the probability of obtaining SDI6 when compared to every considered comparator and interferon β as well. The indirect comparison results were similar in value to those observed in Kalincik 2018 [13] — cladribine increased the likelihood of achieving SDI6 approximately by three-fold compared to natalizumab and by approximately five-fold compared to fingolimod. Therefore, the NMA supported the results of the direct comparison and additionally allowed for a comparative assessment with alemtuzumab.

The indirect comparison itself was difficult to perform due to the necessity of simultaneous inclusion of studies that differed methodologically, i.e. observational and randomised trials. Another limitation is the fact that Andersen [20], Kalincik 2018 [13], Kalincik 2017 [23], and Kalincik 2015 [24] enrolled patients from the same MS Base register, which carries the risk of double-counting the same patient in the compared

groups. However, the impact of both limitations on obtaining the results was addressed in the sensitivity analyses, which led to results not diverging far from the main variant of the indirect analysis.

Nevertheless, the limitations of indirect comparison should be kept in mind, and to confirm the publication conclusions, further analyses of data from MS patients registers and preferably head-to-head RCTs are necessary.

Considering the capability of increasing the probability of achieving sustained disability improvement, both the results of the direct comparison and those resulting from the extensive network of indirect comparisons consistently indicate that cladribine tablets are more effective than other highly-active MS drugs (alemtuzumab, natalizumab, fingolimod). This endpoint reflects the extension of the primary goals of MS treatment, being not just the control of the clinical (relapses) and radiological (no new/active MRI lesions) activity or claiming no proven EDSS progression by disease-modifying therapy, but also leads to sustained disability improvement, which can also affect the patient's quality of life. The authors tried to perform analysis in the best methodological approach using the best available evidence to obtain the most reliable results on comparing CT to other DMTs in the context of outcome that seems to be of increasing importance in the treatment of MS. However, the methodological limitations of the conducted indirect comparison and the small size of the population receiving cladribine in tablet form may weaken the final conclusions from this work. Hence, further inferencing will be possible if credible further analyses of observations collected in registers of MS patients, or even head-to-head trials, become available.

Future directions

Measuring sustained disability improvement allows for a comprehensive assessment of multiple sclerosis therapies, because it refers to not only disability progression but also its reversion. Therefore, it's likely that this endpoint in the near future will gain importance in clinical trials conducted in multiple sclerosis patients, as well as in clinical practice. This may be of particular importance in Poland, where there is still room for improvement in terms of patient access to effective MS therapies [35].

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