Alemtuzumab is a budget-saving alternative to fingolimod and natalizumab in the treatment of highly active relapsing-remitting multiple sclerosis

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SUMMARY

Introduction: Alemtuzumab is an efficacious treatment for active and highly active remitting-relapsing multiple sclerosis (RRMS). While beneficial budget impact and cost-effectiveness of alemtuzumab has been demonstrated elsewhere, no published health economic evaluations or technology assessments have examined alemtuzumab in the Finnish setting. We estimated potential net budget impact of alemtuzumab in the treatment of adult Finnish patients with highly active RRMS.

Materials and methods: Budget impact was assessed with a Finnish static cohort model, reported within PICOSTEPS framework. In the base case modelling two identical RRMS patients are assigned to the intervention (alemtuzumab) or comparator (fingolimod, natalizumab – most relevant and widely used treatment alternatives) and are followed for the modelled 5-year time period (2019–23). Treatment switching, drop-out or mortality were not considered. The primary outcomes were the total cumulative budgets and net budget impact (differences in cumulative budgets) per patient. One- and multi-way deterministic sensitivity analyses were carried out. To examine whether net budget-impacts are associated with differences in the clinical outcomes, number of relapses experienced and proportion of patients remaining free of disease worsening were modelled as secondary clinical outcomes, based on published clinical trial data and network meta-analysis.

Results: Alemtuzumab was budget-saving on the fourth and on the second year compared to fingolimod and natalizumab, respectively. Modelled cumulative 5-year budget savings were €26,294 and €100,789 per patient, respectively. Treatment with alemtuzumab also resulted in better modelled clinical outcomes than either comparator, implying the budget-savings are not associated with poorer clinical outcomes.

Conclusions: The present study, with support of previous findings from foreign settings, indicate that alemtuzumab is budget-saving alternative to fingolimod and natalizumab in treatment of highly active RRMS in Finland.

Keywords: affordability, budget impact analysis, multiple sclerosis, health economics, health technology assessment, outcomes assessment

INTRODUCTION

Multiple sclerosis (MS) is a progressive, chronic inflammatory auto-immune disease in which immune cells destroy central nervous system myelin (Browne *et al.* 2014). MS is the most common neurological disorder to cause disability in young adults, affecting more than two million people worldwide (Atlas of MS 2013).

The epidemiology of MS varies considerably between regions and populations. In Europe, estimates vary from less than 20 to more than 200 per 100,000, Finland being among the countries with the highest prevalence and incidence rates (Kingwell *et al.* 2013, Browne *et al.* 2014, Pirttisalo *et al.* 2019). Generally, MS is reported up to 3-fold more prevalent and incident among women compared to men and locations further from the equator, such as the Nordic countries (Koch–Henriksen & Sørensen 2010, Simpson *et al.* 2011, Kingwell *et al.* 2013, Browne *et al.* 2014, Pirttisalo *et al.* 2019). Interestingly, the MS epidemiology also varies regionally in Finland, being more prevalent and incident in western than in eastern Finland (Pirttisalo *et al.* 2019).

MS is typically diagnosed as relapsing-remitting (RRMS; patient achieves remission, but experiences repeated relapses with varying frequency), but becomes progressive over time (Tremlett *et al.* 2008). There is no cure for MS. The treatment with disease-modifying therapies (DMT) is aimed at decreasing inflammatory activity leading to relapses, slowing the progression of disability and delaying the eventual progression to the secondary progressive phase (Cree at al. 2016). MS is associated with significant direct and indirect costs and disease burden (Ernstsson *et al.* 2016, Ruutiainen *et al.* 2016). Nevertheless, the hospitalizations and annual cost of MS inpatient care in Finland have declined substantially from 2.5 to 1.2 million euros between 2004 and 2014, concurrently with the rise of DMTs available (Pirttisalo *et al.* 2018).

Alemtuzumab is an intravenously administered humanized monoclonal antibody causing depletion of circulating lymphocytes and a distinct pattern of lymphocyte repopulation, producing a durable and long-lasting efficacy without continuous treatment in the first (CARE-MS I: Cohen *et al.* 2012, Havrdova *et al.* 2017) and later treatment lines (CARE-MS II: Coles *et al.* 2012, 2017) of active and highly active RRMS. In addition to clinical efficacy and safety, alemtuzumab has been demonstrated to yield significant improvements in physical, mental and emotional quality of life, regardless of the patient's treatment history (Arroyo *et al.* 2017). Alemtuzumab is administered as courses in minimum dosing intervals of 12-months, with most patients requiring only two treatment courses (Alemtuzumab Summary of Product Characteristics (SPC); Coles *et al.* 2017, Havrdova *et al.* 2017), potentially reducing the drug costs associated with the MS medication.

We evaluated the net budget impact and health outcomes of using alemtuzumab in the treatment of Finnish adult patients with highly active RRMS. Alemtuzumab was compared to the two most relevant and widely sold treatment alternatives, fingolimod and natalizumab (IMS 2019), which alemtuzumab is most likely to substitute, if used more widely. Based on a 30-year cohort of incident Finnish MS patients, the proportionate survival benefit associated with DMT was over two-fold (hazard ratio 2.3, 95% confidence interval 1.4–3.7) compared to the untreated group (Murtonen *et al.* 2016), indicating the need to assess potential costs and clinical outcomes simultaneously.

While the cost-effectiveness of first-line RRMS treatments has been evaluated in the Finnish setting (Soini *et al.* 2017), the cost-effectiveness or budget impact of highly active, active or second-line RRMS treatments have not been published from the Finnish setting. Moreover, while the budget impact and cost-effectiveness of alemtuzumab have been evaluated and demonstrated elsewhere (NICE 2014, Couto *et al.* 2016, ICER 2017, Montgomery *et al.* 2017, Hamidi *et al.* 2018, Piena *et al.* 2018, Zimmermann *et al.* 2018, Chirikov *et al.* 2019, Taheri *et al.* 2019, Walter *et al.* 2019), no Finnish evaluation of alemtuzumab has been published previously.

MATERIALS AND METHODS

In the present analyses, the budget impact was assessed with a Finnish static cohort model Setting implemented in Microsoft Excel and developed specifically for the Finnish evaluation. PICOSTEPS principle, which describes the essential components of evidence-based health economic and outcomes research framework in the order of importance (**Table 1**; Soini 2017, Soini *et al.* 2017, 2018), was applied. The model and the analyses were informed by the pivotal alemtuzumab, fingolimod, and natalizumab trials (Polman *et al.* 2006, Calabresi *et al.* 2013, Fox *et al.* 2016, Coles *et al.* 2016, LaGanke *et al.* 2016, Wiendl *et al.* 2016, Coles *et al.* 2017, Havrdova *et al.* 2017), a published network meta-analysis (NMA, Siddiqui *et al.* 2018), Finnish clinical practice and treatment guidelines

Table 1. The budget impact analysis in the PICOSTEPS* framework.

PICOSTEPS	Description
P: Patients	Finnish adult patients with highly active RRMS
I: Intervention	Alemtuzumab 12 mg; at least two and up to five treatment courses administered in minimum of 12-month intervals (**Table 2**)
C: Comparators	The two most prevalent current relevant DMTs: fingolimod and natalizumab.
O: Outcomes	Primary outcomes of interest: • Total cumulative budgets per patient • Net budget impact per patient (differences in the cumulative budgets) Secondarily, clinical outcomes over the modelled time horizon to examine whether the potential budget impacts are associated with differences in the clinical outcomes: • Number of relapses • Freedom from 6-month confirmed disease worsening (CDW)
S: Setting	Static cohort budget impact modelling examining second-line treatment of highly active RRMS (CARE-MS II trial setting) in Finland
T: Time horizon	Five-year time horizon. No discounting or corrections over time applied
E: Effects	**Direct cost driver effects based on Finnish clinical practice and treatment guidelines (Tables 4 and 5) and Finnish unit costs (Table 3) and other data from Finland and elsewhere (Table 5):** *Cost effect* — *Sources* Drug acquisition — Drug prices: FMT 05 / 2019 Drug administration (for intravenous medications) — Unit costs: Soini *et al.* 2013 Routine monitoring — Resource utilization: Soilu-Hänninen M, unpublished observations 2019; Multiple Sclerosis 2019; Unit costs: HDSWF 2019 Relapses — Alemtuzumab: Coles *et al.* 2017; Comparators relative to alemtuzumab: Siddiqui *et al.* 2018; Unit costs: O'Connor *et al.* 2013; Soini *et al.* 2017 Adverse events — Rates: Polman *et al.* 2006; Calabresi *et al.* 2013; Coles *et al.* 2017; Kartau *et al.* 2019; Management: Soilu-Hänninen M, unpublished observations 2019; Unit costs: Kapiainen *et al.* 2014; HDSWF 2019 Serious infusion site reactions (for alemtuzumab only) — Rates: Coles *et al.* 2018; Unit costs: Pirttisalo *et al.* 2018; HDWSF 2019 Travelling expenses — Unit costs: Hujanen *et al.* 2008 Patient fees — Unit costs: HDSWF 2019 **Clinical effects based on alemtuzumab trial and NMA (Table 2):** *Clinical effect* — *Sources* Annualized relapse rate (ARR) — Alemtuzumab: Coles *et al.* 2017; Comparators relative to alemtuzumab: Siddiqui *et al.* 2018 Freedom from 6-month confirmed disease worsening (CDW) — Alemtuzumab: Fox *et al.* 2016; LaGanke *et al.* 2016; Comparators relative to alemtuzumab: Siddiqui *et al.* 2018
P: Perspective	Finnish health care payer perspective
S: Sensitivity	Deterministic sensitivity analyses were conducted, examining: • Patient population, safety and efficacy based on first-line treatment (CARE-MS I trial population, **Appendix Table 1**) • Only two alemtuzumab courses administered (instead of up to five) • Proportion of patients receiving alemtuzumab (7.6 %, Coles *et al.* 2017), modelled to receive other DMT on years 3 to 5 (here fingolimod or natalizumab) • Fingolimod and natalizumab discontinuation considered (Polman *et al.* 2006, Kappos *et al.* 2010, 2015), with and without accounting for the subsequent treatments and their costs • Travel expenses and patient fees excluded • Decreasing or increasing all costs by 20 % • Alemtuzumab administration cost equal to natalizumab's and vice versa • Assumed alemtuzumab rate of serious infusion reactions for natalizumab (vs. no infusion reactions considered for natalizumab) • Longer 10-year time horizon

** Soini 2017, Soini et al. 2017, 2018. FMT = Finnish Medicines Tariff; DMT = disease-modifying therapy; MS = multiple sclerosis; NMA = network meta-analysis; RRMS = relapsing–remitting multiple sclerosis.*

(Soilu-Hänninen M, unpublished observations 2019, Multiple sclerosis 2019) as well as Finnish unit costs (Hujanen *et al.* 2008, Soini *et al.* 2013, Kapiainen *et al.* 2014, Soini *et al.* 2017, Pirttisalo *et al.* 2018, HDSWF 2019) and other data from Finland (Kartau *et al.* 2018) and elsewhere (O'Connor *et al.* 2013).

In the model, two identical Patients with highly active RRMS are assigned to Intervention (intravenous alemtuzumab) and Comparator (oral fingolimod or intravenous natalizumab) and are followed for the modelled period, assuming no treatment switching, drop-out or mortality. The base case considered a five-year Time horizon (2019-23). This was deemed optimal for two main reasons. First, alemtuzumab trial follow-ups extend to five years (longer than available for fingolimod or natalizumab; CARE-MS II, Coles *et al.* 2017 and CARE-MS I, Havrdova *et al.* 2017 – both considered in the analyses), allowing comprehensive evaluation of additional alemtuzumab treatment courses potentially required after the first two treatment courses. Consequently, shorter time frame would not capture all relevant alemtuzumab Effects, while longer time horizon would add more uncertainty, due to lack of longer-term data and need for extrapolation. Second, five-year time horizon has been utilized in the previous assessments of alemtuzumab's health economic aspects (Couto *et al.* 2016, ICER 2017, Hamidi *et al.* 2017, Piena *et al.* 2018). Time horizons of 1 to 5 years are also common in the budget impact analyses in general. In line with the good common practices, costs were not discounted, or half-cycle corrected in the analyses (Sullivan *et al.* 2014).

At the end of the five-year time period, the modelled budgets and clinical outcomes were aggregated. The primary Outcome of interest were the total cumulative budgets and the net budget impact (the differences in the cumulative budgets) per patient from the health care payer Perspective. One- and multiway deterministic Sensitivity analyses were carried out.

As differences in net budgets can come at the cost of clinical effectiveness, we also examined two relevant clinical Outcomes (annualized relapse rate, ARR, and 6-month confirmed disease worsening, CDW). ARR and CDW were reported in most randomized clinical DMT trials and were assessed here as the secondary Outcomes to examine whether the expected clinical effects differ between the examined DMTs.

First, the five-year alemtuzumab efficacy data were extracted from the published pivotal alemtuzumab clinical trials (Coles *et al.* 2017, Havrdova *et al.* 2017; **Table 2 and Appendix Table 1**). Second, relative effects (rate ratios for ARR and hazard ratios for CDW) of fingolimod and natalizumab were extracted from a published NMA (Siddiqui *et al.* 2018; **Table 2**). These relative effects were then applied to alemtuzumab efficacy parameters to estimate the five-year clinical Outcomes for fingolimod and natalizumab. In order to put the modelled clinical Outcomes into more practical perspective, they were also reported using a hypothetical cohort of 100 patients.

HEALTH CARE RESOURCES AND COSTS

Drug acquisition and health care resource unit costs, as well as the resource use for the routine monitoring, relapses, and management of the most relevant adverse events (AE) were based on Finnish practices (**Tables 3, 4 and 5**). The costs of administering alemtuzumab and natalizumab infusions were considered, in addition to the travelling expenses and patient fees associated with the visits to primary and secondary care, as well as visits to pharmacy.

Drug prices represent those applicable in Finland in May 2019. For the medications administered in the outpatient setting, the retail price excluding value added tax was used, whereas for treatment administered in hospital, official wholesale prices were used (PPB 2018). In the base case analysis, the patients treated with fingolimod and natalizumab were modelled as fully adherent and compliant to treatment during the modelled time horizon; the patients were modelled to receive 365 daily doses of fingolimod (0.5 mg per day) and 13 four-weekly doses of natalizumab (300 mg) annually, based on SPCs. Sensitivity analyses considered scenarios where fingolimod and natalizumab discontinuation was modelled based on the trial discontinuation rates (Polman *et al.* 2006, Kappos *et al.* 2010, Kappos *et al.* 2015). Total of 81.2 % and 68.2 % continued fingolimod at two and four years in FREEDOMS trial (Kappos *et al.* 2010, 2015). In total 87.9 % were still on natalizumab treatment at 2 years in AFFIRM trial (Polman *et al.* 2006). These proportions were converted to 6-month probabilities assuming an exponential function. The estimated proportion of patients remaining on treatment in the middle of the year was used in the model. Overall 94.9, 85.5, 77.7, 71.3, and 65.3 % of the patients receiving fingolimod were modelled to receive fingolimod for year 1 to 5 in sensitivity analysis, respectively. Correspondingly, 96.8, 90.8, 85.1, 79.8, and 74.8 % of the patients receiving natalizumab were modelled to re-

Table 2. Alemtuzumab dosing and clinical outcomes, base case analysis examining the second-line patient population (CARE-MS II).

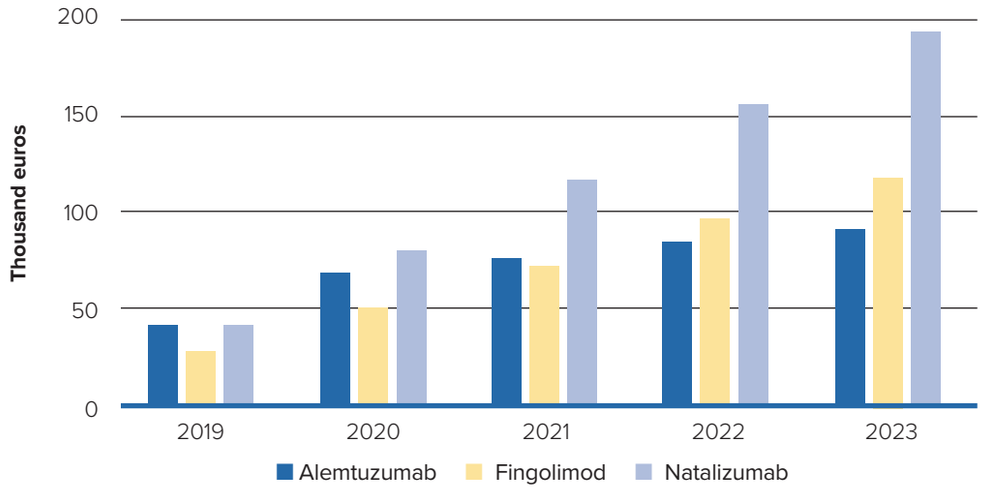
Input / Year	Year 1	Year 2	Year 3	Year 4	Year 5	Source
Receive alemtuzumab treatment[a]	100.0 %	100.0 %	18.4 %	16.8 %	12.9 %	Adapted from Coles et al. 2017 [a]
Course 1 (five 12 mg infusions)	100.0 %	-	-	-	-	
Course 2 (three 12 mg infusions)	-	100.0 %	-	-	-	
Course 3 (three 12 mg infusions)	-	-	18.4 %	10.1 %	7.8 %	
Course 4 (three 12 mg infusions)	-	-	-	6.7 %	3.7 %	
Course 5 (three 12 mg infusions)	-	-	-	-	1.4 %	
Infusion site reactions (of alemtuzumab courses received) [b]						
Any Serious	83.7 % 1.4 %	71.3 % 1.4 %	63.9 % 1.3 %	65.9 % 0.8 %	63.8 % 0.8 %	Coles et al. 2017
CLINICAL OUTCOMES, BASED ON THE PUBLISHED CLINICAL TRIAL DATA Annualized Relapse Rate (ARR)						
Alemtuzumab	0.28	0.28	0.22	0.23	0.18	Coles et al. 2017
Relative effects (Rate ratios) compared to alemtuzumab based on network meta-analysis						
Fingolimod Natalizumab			1.43 1.07			Siddiqui et al. 2018 [c]
6-month Confirmed Disease Worsening (CDW)						
Alemtuzumab: No CDW during year	94.3 %	91.9 %	91.9 %	91.7 %	94.8 %	LaGanke et al. 2016
Alemtuzumab: Free of CDW, cumulatively	94.3 %	89.0 %	82.0 %	77.0 %	75.0 %	Fox et al. 2016
Relative effects (Hazard ratios) compared to alemtuzumab based on network meta-analysis						
Fingolimod Natalizumab			1.73 1.13			Siddiqui et al. 2018 [c]

a) Calculated based on the number of patients initiating alemtuzumab in CARE-MS II trial (n=435), assuming conservatively that all (100 %) patients are compliant to the 2nd administration at the beginning of the 2nd year, although less than 100 % (96.8 %, n=421/435) of the patients initiating alemtuzumab actually received the 2nd administration in the second year. The number of patients receiving the third to fifth alemtuzumab dose each year (on the third, fourth and fifth year, respectively Course 3: 80, 44, 34; Course 4: 29, 16 and Course 5: 6) was conservatively divided by the total number of patients initiating alemtuzumab in the CARE-MS II trial (Coles et al. 2017; n=435). All patients were conservatively assumed to receive full courses of five or three infusions. After the first two courses alemtuzumab dosing interval may be increased from the initial 12 months. b) Accounts for the distribution of courses each year and the fact that the later courses are associated with fewer infusion site reactions. Most infusion site reactions associated with alemtuzumab are minor and were not expected to incur substantial impact to the budget; only serious infusion site reactions were considered relevant for the analysis. Conservatively, infusion site reactions associated with natalizumab were not considered in the base case analyses even though AFFIRM trial reported 24 % of natalizumab receiving patients experiencing infusion reactions during trial (Polman et al. 2006). For sensitivity analysis with 10-year time horizon, average observed data was used to extrapolate the clinical outcomes for years 6 to 10. c) As Siddiqui et al. (2018, Figure 2) report the relative effects for cladribine vs. other DMT, the effects were first converted to ratios compared to alemtuzumab. ARR: 1.30 / 0.91 = 1.43 and 1.30 / 1.22 = 1.07 for fingolimod and natalizumab, respectively. CDW: 1.37 / 0.79 = 1.73 and 1.37 / 1.21 = 1.13 for fingolimod and natalizumab, respectively.

ceive natalizumab for year 1 to 5 in sensitivity analysis, respectively. In the first scenario, discontinuing patients were modelled to receive no further treatments and incur no additional drug costs (a very conservative approach). In the second scenario, discontinuing patients were modelled to receive the other comparator for the rest of the model duration (realistic approach).

Alemtuzumab patients were modelled to receive 12 mg per day on five consecutive days at the treatment initiation (total 60 mg) and at 12 mg per day on three consecutive (36 mg) days with minimum dosing intervals of 12 months thereafter. Thus, all patients were modelled to receive at least two alemtuzumab treatment courses, as described in the alemtuzumab SPC, and up to five courses based on the second-line clinical trial (CARE-MS II, Coles *et al.* 2017; **Table 2**) although only up to four doses are recommended in the SPC. The patients receiving alemtuzumab were modelled to be fully adherent to each treatment course, i.e. no partial courses with less than five or

A: Cumulative total budgets



B: Cumulative net budget impact

vs fingolimod	**2019**	**2020**	**2021**	**2022**	**2023**
Total	**14 320 €**	**18 412 €**	**4 041 €**	**-10 706 €**	**-26 294 €**
Drug acquisition	13 111 €	12 441 €	-5 097 €	-22 968 €	-41 646 €
Administration	3 324 €	5 318 €	5 685 €	6 020 €	6 276 €
Monitoring	-1 936 €	1 009 €	3 954 €	6 899 €	9 843 €
Adverse Events	68 €	136 €	185 €	232 €	279 €
Relapses	-246 €	-493 €	-686 €	-889 €	-1 047 €
vs natalizumab	**2019**	**2020**	**2021**	**2022**	**2023**
Total	**1 355 €**	**-9 896 €**	**-39 655 €**	**-69 782 €**	**-100 789 €**
Drug acquisition	5 200 €	-3 380 €	-28 829 €	-54 610 €	-81 199 €
Administration	-2 126 €	-5 582 €	-10 665 €	-15 781 €	-20 974 €
Monitoring	-1 723 €	-943 €	-164 €	616 €	1 396 €
Adverse Events	42 €	84 €	107 €	128 €	149 €
Relapses	-38 €	-75 €	-105 €	-136 €	-160 €

Figure 1. Potential per-patient budgets over the five years. A: Cumulative total budgets over the modelled 5-year time horizon. B: Differences in cumulative budgets: alemtuzumab vs fingolimod and natalizumab; negative values denote budget savings with alemtuzumab.

Table 3. Unit costs of the health care resources included in the analyses.

Procedure	Unit cost*	References
Medications for treatment of RRMS		
Alemtuzumab	6,890 € per dose	Drug prices based on FMT 5/2019. For fingolimod, retail price excluding VAT (pack of 28 capsules), for alemtuzumab and natalizumab official wholesale price per administered dose.
Fingolimod	1,637 € per pack	
Natalizumab	2,250 € per dose	
Administration costs		
Alemtuzumab	615.58 €	Alemtuzumab and natalizumab are administered over 4-hour and 1-hour IV-infusions, respectively. Administration costs were based on average administration costs of treatments with similar infusion times (Soini et al. 2013); rituximab for alemtuzumab and weighted average of other reported costs for natalizumab. The utilized infusion administration unit costs were expected to include the cost of all relevant pre-treatment medications.
Natalizumab	370.04 €	
Monitoring (see Table 4)		
Clinical evaluation	205.00 €	HDSWF 2019
MRI	1,954.00 €	HDSWF 2019
Heart monitoring	440.00 €	HDSWF 2019
Eye examination	200.00 €	HDSWF 2019
Laboratory tests		
Basic fee	8.50 €	HDSWF 2019
Complete blood count	6.20 €	HDSWF 2019
MxA- protein	80.00 €	HDSWF 2019
Creatinine	0.80 €	HDSWF 2019
Liver function	1.60 €	HDSWF 2019
Urinalysis	50.80 €	HDSWF 2019
Thyroid function, TSH	2.50 €	HDSWF 2019
Bilirubin	0.80 €	HDSWF 2019
Tuberculosis screening	42.53 €	HDSWF 2019
VZV antibodies	20.00 €	HDSWF 2019
HPV test	91.50 €	HDSWF 2019
JCV antibodies	70.00 €	HDSWF 2019
Hepatitis test	16.20 €	HDSWF 2019
Immunoglobulin	3.90 €	HDSWF 2019
Drug antibodies	215.00 €	HDSWF 2019
Costs associated with relapses		
Without hospitalization	1,303.13 €	Costs based on Soini et al. 2017. Proportion of relapses requiring hospitalization was modelled at 17.6 % for all DMT (O'Connor et al. 2013).
With hospitalization	5,561.97 €	
Other outpatient and inpatient care		
Call or visit	120.00 €	HDSWF 2019 (used for AEs: Liver anomaly, ITP, nephropathies, herpes, serious infection, pulmonary infection, pneumonia)
Ophthalmologist visit	140.00 €	HDSWF 2019 (used for AEs: macular edema)
Eye examination	60.00 €	HDSWF 2019 (used for AEs: macular edema)
Splenectomy	2,570.00 €	HDSWF 2019 (used for AEs ITP)
Lab test: Thrombocyte follow-up	10.10 €	HDSWF 2019 (used for AEs: ITP)
Inpatient care day	440.00 €	HDSWF 2019 (used for AEs: PML, serious infection)
Institutional rehabilitation (day)	139.43 €	Kapiainen et al. 2014 (used for AEs: PML)
Thyroidectomy	2,050.00 €	HDSWF 2019 (used for AEs: thyroid disorders)
Lab test: CRP follow-up	9.30 €	HDSWF 2019 (used for AEs: pulmonary infection)
Acute Chest X-ray	87.00 €	HDSWF 2019 (used for AEs: pneumonia)
Chest X-ray	58.00 €	HDSWF 2019 (used for AEs: pneumonia)
Serious infusion site reaction (requiring hospitalization)	1,672.00 €	Modelled based on the average length-of-stay of 3.8 days (Pirttisalo et al. 2018) and average cost of inpatient care day (440 €).

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Patient fees		
Outpatient visit	41.20 €	HDSWF patient fees 2019
Inpatient care day	48.90 €	HDSWF patient fees 2019
Serie treatment visit	11.40 €	HDSWF patient fees 2019
Pharmacy; dispensing surcharge	2.17 €	Without VAT, added to each prescription dispensed.
Travelling expenses		
Visit to secondary care	37.80 €	Hujanen et al. 2008
Visit to primary care / Pharmacy	7.40 €	Hujanen et al. 2008

*AE: Adverse Event; FMT: Finnish Medicines Tariff; HPV = Human papilloma virus; ITP: immune thrombocytopenic purpura; JCV = John Cunningham virus; MxA protein: Myxovirus resistance protein; PML Progressive multifocal leukoencephalopathy; VAT: Value added tax; VZV = Varicella zoster virus. *Unit costs based on Southwest Finland hospital district tariffs 2019 (HDSWF 2019), wherever available. Other than travel costs and costs sourced from HDSWF 2019, were inflated to 2018 values using latest full year price index for public expenditure (OSF 2019a). Travelling costs were inflated using the transport section of the Finnish Consumer Price Index (OSF 2019b). Unit costs reported without travelling expenses of patient fees.*

Table 4. Health care resources associated with routine monitoring.

	Alemtuzumab		Fingolimod		Natalizumab	
Monitoring resource	**1st year**	**Years after**	**1st year**	**Years after**	**1st year**	**Years after**
Clinical evaluation, outpatient visit	3	1	3	1	3	1
MRI	1	1	2	0	2	1
Heart monitoring	0	0	1[a]	0	0	0
Eye examination	0	0	1	0	0	0
Laboratory tests						
Basic fee	13	12	6	2	4	1
Complete blood count	13	12	6	2	4	1
MxA- protein	0	0	0	0	0	0
Creatinine	13	12	1	0	0	0
Liver function	6	4	6	2	4	1
Urinalysis	13	12	0	0	0	0
Thyroid function, TSH	5	4	1	1	0	1
Bilirubin	0	0	1	0	0	0
Tuberculosis screening	1	0	1	0	0	0
VZV antibodies	1	0	1	0	0	0
HPV antibodies	0.67[b]	0.67[b]	0	0	0	0
JCV antibodies	1	0	1	0	2	2
Hepatitis test	1	0	1	0	0	0
Drug antibodies	0	0	0	0	3	0

MRI = Magnetic Resonance Imaging; MxA protein: Myxovirus resistance protein; VZV = Varicella zoster virus; HPV = Human papilloma virus; JCV = John Cunningham virus. a) Fingolimod initiation is associated with heart monitoring at hospital b) HPV test administered only to women once annually; proportion of women (67 %) based on CARE-MS II trial baseline data (Coles et al. 2012). The alemtuzumab safety monitoring was modelled to be extended to four years after the last administration. Modelled resource use based on clinical practices in hospital district of Southwest Finland (Soilu-Hänninen M, unpublished observations) and Finnish Current Care Guidelines (Multiple sclerosis 2019).

Table 5. Incidence rate (per patient year), health care resource utilization and total costs per event, for the key adverse events included in the analyses.

Adverse event	Alemtuzumab	Fingolimod	Natalizumab	Treatment / management	Total cost per event
Liver anomaly	0.0000	0.0405	0.0250	2-3 additional laboratory follow-ups (liver function)	163.74 €
Macular edema	0.0000	0.0042	0.0000	Topical steroids, 2 additional ophthalmologist follow-ups (with eye examinations)	586.27 €
ITP	0.0070	0.0000	0.0000	All oral prednisone (3 weeks starting from 300 mg/day) and thrombocyte laboratory follow-up (modelled up to 7-weeks; first week daily, second week every second day, and then weekly for 5 weeks) , 13 % receive rituximab (total average 4 vials weekly for 4 weeks), 3 % receive splenectomy	697.11 €
PML	0.0000	0.0000	0.0012	Hospitalization (modelled 6.6 days, Pirttisalo et al. 2018) and long institutional rehabilitation (modelled duration the expected lifetime of 233.9 days, Kartau et al. 2019)	35,876.28 €
Thyroid disorder	0.1130	0.0000	0.0000	79 % require treatment (modelled half receiving medication for hyperthyroidism, half for hypothyroidism for 5 years), 8.5 % thyroidectomy	316.39 €
Nephropathies	0.0010	0.0000	0.0000	Oral ACE inhibitors (modelled ramipril 10 mg for 5 year), steroids (modelled 1-year treatment with methylprednisolone)	680.46 €
Herpes	0.0580	0.0419	0.0499	Antiviral medication, typically for 5 days	214.97 €
Serious infection	0.0170	0.0154	0.0100	Hospitalization (6.6. days; Pirttisalo et al. 2018), antibiotics (modelled for 10 days)	3,456.25 €
Pulmonary infection	0.0710	0.0531	0.0850	Antibiotic, typically for 7 days. Laboratory follow-up (CRP)	253.62 €
Pneumonia	0.0050	0.0070	0.0000	Antibiotic, typically for 10 days. 2 chest X-rays (one acute, one follow-up)	541.10 €

ITP: immune thrombocytopenic purpura; PML Progressive multifocal leukoencephalopathy. Probabilities based on respective clinical trials: alemtuzumab, exact rates reported in Coles et al. 2017; fingolimod and natalizumab, approximated based on number of patients experiencing adverse events, study duration and number of patients in Calabresi et al. 2014 and Polman et al. 2006, respectively): Natalizumab PML incidence was based on Finnish data published by Kartau et al. (2019) and natalizumab incidence herpes was modelled as average between alemtuzumab and fingolimod. Adverse event management based on Finnish Clinical Practice from hospital district of Southwest Finland (Soilu-Hänninen M, unpublished observation 2019) and Finnish Current Care Criteria. In addition, liver anomaly and nephropathies, were modelled to be associated with one additional call, and ITP, herpes, serious infection, pulmonary infection, and pneumonia were modelled to be associated with one additional visit based on the clinical practices in hospital district of Southwest Finland (Soilu-Hänninen M, unpublished observation 2019). Total costs (reported including travelling costs and patient fees) per event were modelled as one-off costs at the time of occurrence.

three infusions were considered. As 7.6 % of the patients were reported to have received other DMTs in CARE-MS II (Coles *et al.* 2017), sensitivity analyses considered two scenarios where proportion of patients receiving alemtuzumab were treated with fingolimod or natalizumab for three years (years 3 to 5). In these scenario analyses, the total annual costs associated with fingolimod and natalizumab treatments were based on the modelled base case results.

The relevant figures applied in the sensitivity analysis examining alemtuzumab as first-line treatment based on CARE-MS I (Havrdova *et al.* 2017) are presented in the **Appendix Table 1**. As with CARE-MS II data, CARE-MS I data was available up to five years (Coles *et al.* 2017, Havrdova *et al.* 2017). Medications for the treatment of AEs are described in the **Appendix Table 2**.

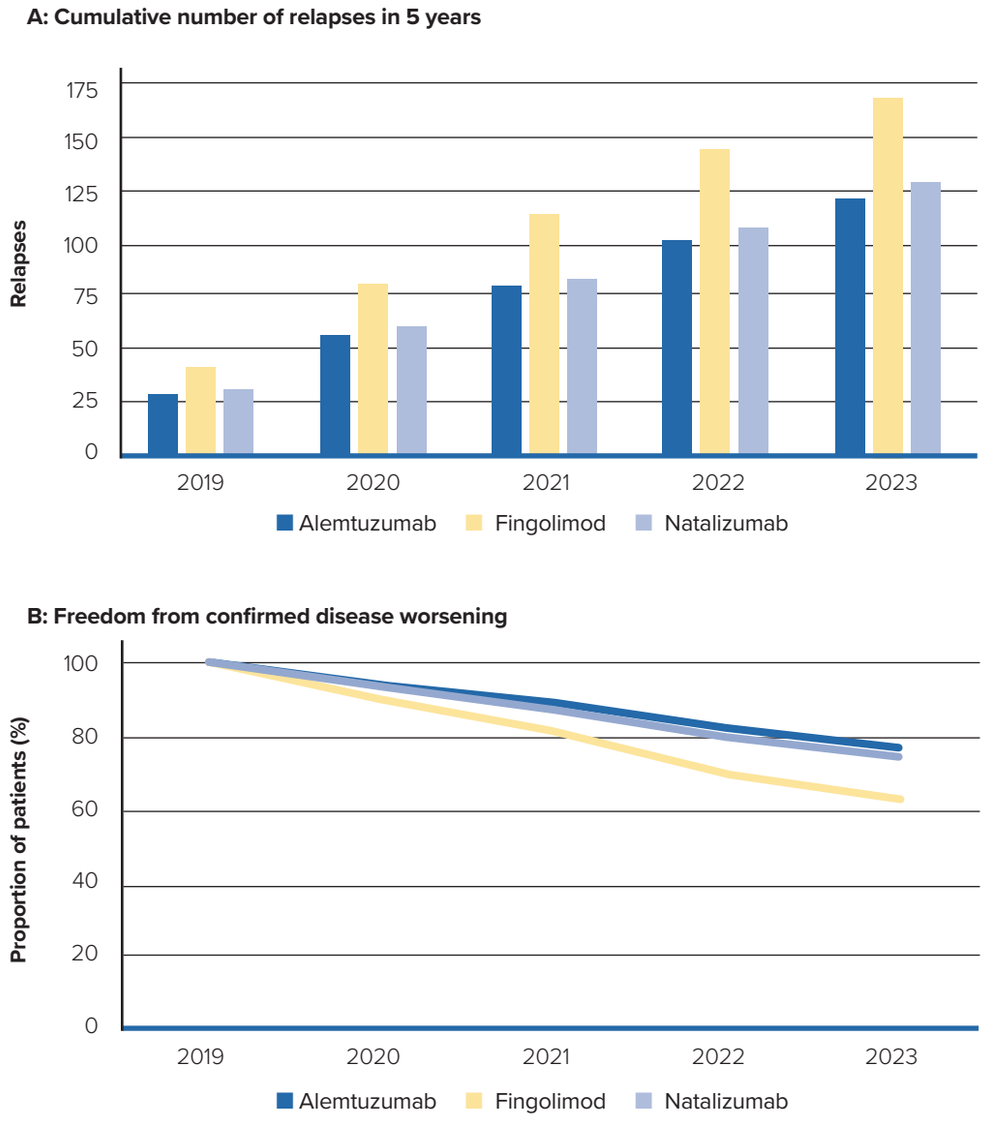

Figure 2. Clinical outcomes over the five years, modelled based on CARE-MS II trial and published network meta-analysis. A: Cumulative number of relapses. B: Cumulative freedom from confirmed disease worsening (CDW).

Table 6. Results of the sensitivity analyses.

Scenario: Patient population, safety and efficacy based on first-line treatment (CARE-MS I trial vs. CARE-MS II trial)

Cumulative total budgets	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab	42,368 €	68,793 €	76,374 €	82,584 €	88,858 €
Fingolimod	27,967 €	50,256 €	72,575 €	94,748 €	116,949 €
Natalizumab	41,004 €	78,710 €	116,437 €	154,055 €	191,695 €
Net cumulative budget impact	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab vs Fingolimod	14,401 €	18,537 €	3,799 €	-12,164 €	-28,091 €
Alemtuzumab vs Natalizumab	1,364 €	-9,916 €	-40,063 €	-71,472 €	-102,837 €

Scenario: Only two alemtuzumab courses administered (vs. up to five)

Cumulative total budgets	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab	42,580 €	69,255 €	73,118 €	77,002 €	80,784 €
Fingolimod	28,260 €	50,843 €	73,250 €	95,686 €	117,976 €
Natalizumab	41,225 €	79,151 €	116,946 €	154,762 €	192,470 €
Net cumulative budget impact	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab vs Fingolimod	14,320 €	18,412 €	-131 €	-18,684 €	-37,192 €
Alemtuzumab vs Natalizumab	1,355 €	-9,896 €	-43,827 €	-77,760 €	-111,686 €

Scenario: 7.6 % of the alemtuzumab patients modelled to use Fingolimod for years 3 to 5

Cumulative total budgets	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab	42,580 €	69,255 €	82,857 €	92,252 €	100,647 €
Fingolimod	28,260 €	50,843 €	73,250 €	95,686 €	117,976 €
Natalizumab	41,225 €	79,151 €	116,946 €	154,762 €	192,470 €
Net cumulative budget impact	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab vs Fingolimod	14,320 €	18,412 €	9,608 €	-3,434 €	-17,328 €
Alemtuzumab vs Natalizumab	1,355 €	-9,896 €	-34,088 €	-62,510 €	-91,822 €

Scenario: 7.6 % of the alemtuzumab patients modelled to use Natalizumab for years 3 to 5

Cumulative total budgets	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab	42,580 €	69,255 €	86,178 €	96,742 €	106,309 €
Fingolimod	28,260 €	50,843 €	73,250 €	95,686 €	117,976 €
Natalizumab	41,225 €	79,151 €	116,946 €	154,762 €	192,470 €
Net cumulative budget impact	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab vs Fingolimod	14,320 €	18,412 €	12,929 €	1,056 €	-11,667 €
Alemtuzumab vs Natalizumab	1,355 €	-9,896 €	-30,767 €	-58,020 €	-86,161 €

Scenario: Fingolimod and Natalizumab discontinuation considered – no further treatments or costs modelled

Cumulative total budgets	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab	42,580 €	69,255 €	77,290 €	84,980 €	91,681 €
Fingolimod	26,871 €	46,315 €	63,857 €	80,031 €	95,403 €
Natalizumab	39,937 €	74,428 €	106,478 €	136,582 €	164,733 €
Net cumulative budget impact	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab vs Fingolimod	15,710 €	22,939 €	13,433 €	4,949 €	-3,722 €
Alemtuzumab vs Natalizumab	2,643 €	-5,173 €	-29,188 €	-51,602 €	-73,051 €

Scenario: Fingolimod and Natalizumab discontinuation considered – discontinuing patients receive the other comparator

Cumulative total budgets	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab	42,580 €	69,255 €	77,290 €	84,980 €	91,681 €
Fingolimod	28,965 €	54,211 €	80,451 €	107,718 €	134,214 €
Natalizumab	40,836 €	77,756 €	113,491 €	148,452 €	182,555 €
Net cumulative budget impact	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab vs Fingolimod	13,615 €	15,044 €	-3,160 €	-22,738 €	-42,533 €
Alemtuzumab vs Natalizumab	1,744 €	-8,501 €	-36,201 €	-63,472 €	-90,874 €

Scenario: Travel expenses and patient fees excluded (vs. included)

Cumulative total budgets	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab	41,887 €	68,132 €	75,859 €	83,243 €	89,643 €
Fingolimod	27,644 €	50,114 €	72,408 €	94,732 €	116,909 €
Natalizumab	40,142 €	77,238 €	114,202 €	151,188 €	188,065 €
Net cumulative budget impact	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab vs Fingolimod	14,243 €	18,018 €	3,451 €	-11,490 €	-27,266 €
Alemtuzumab vs Natalizumab	1,745 €	-9,106 €	-38,343 €	-67,946 €	-98,422 €

Scenario: All costs –20 %

Cumulative total budgets	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab	40,954 €	66,428 €	73,617 €	80,462 €	86,355 €
Fingolimod	26,876 €	49,210 €	71,403 €	93,620 €	115,720 €
Natalizumab	38,830 €	75,021 €	111,107 €	147,210 €	183,226 €
Net cumulative budget impact	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab vs Fingolimod	14,078 €	17,218 €	2,213 €	-13,158 €	-29,365 €
Alemtuzumab vs Natalizumab	2,124 €	-8,593 €	-37,490 €	-66,748 €	-96,871 €

Scenario: All costs +20 %

Cumulative total budgets	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab	44,206 €	72,082 €	80,964 €	89,498 €	97,007 €
Fingolimod	29,644 €	52,476 €	75,096 €	97,752 €	120,231 €
Natalizumab	43,620 €	83,281 €	122,785 €	162,315 €	201,714 €
Net cumulative budget impact	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab vs Fingolimod	14,562 €	19,606 €	5,868 €	-8,253 €	-23,224 €
Alemtuzumab vs Natalizumab	587 €	-11,199 €	-41,820 €	-72,817 €	-104,706 €

Scenario: Alemtuzumab administration same as Natalizumab's (419.23 €)

Cumulative total budgets	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab	41,352 €	67,290 €	75,191 €	82,757 €	89,363 €
Fingolimod	28,260 €	50,843 €	73,250 €	95,686 €	117,976 €
Natalizumab	41,225 €	79,151 €	116,946 €	154,762 €	192,470 €
Net cumulative budget impact	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab vs Fingolimod	13,093 €	16,448 €	1,941 €	-12,929 €	-28,613 €
Alemtuzumab vs Natalizumab	128 €	-11,860 €	-41,755 €	-72,006 €	-103,107 €

Scenario: Natalizumab administration same as alemtuzumab's (664.78 €)

Cumulative total budgets	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab	42,580 €	69,255 €	77,290 €	84,980 €	91,681 €
Natalizumab	44,417 €	85,535 €	126,522 €	167,531 €	208,430 €
Net cumulative budget impact	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab vs Natalizumab	-1,837 €	-16,280 €	-49,231 €	-82,550 €	-116,749 €

Scenario: Assumed alemtuzumab rate of serious infection reactions for Natalizumab (vs. none)

Cumulative total budgets	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab	42,580 €	69,255 €	77,290 €	84,980 €	91,681 €
Natalizumab	41,248 €	79,198 €	117,014 €	154,844 €	192,565 €
Net cumulative budget impact	*2019*	*2020*	*2021*	*2022*	*2023*
Alemtuzumab vs Natalizumab	1,332 €	-9,943 €	-39,724 €	-69,864 €	-100,883 €

RESULTS

Budgets

Total estimated cumulative five-year budgets per patient with highly active RRMS were €91,681 for alemtuzumab, €117,976 for fingolimod and €192,470 for natalizumab (**Figure 1A**). The 5-year potential budget savings associated with alemtuzumab were €26,294 (-22 %) and €100,789 (-52 %) per patient compared to fingolimod and natalizumab, respectively. Drug acquisition was the largest driver of the budget, contributing €65,051 (71 %), €106,697 (90 %) and €146,250 (76 %) to the budget of alemtuzumab, fingolimod and natalizumab, respectively (**Figure 1B**). The total 5-year costs related to AEs and monitoring were modelled to be minor-to-moderately higher with alemtuzumab compared to fingolimod and natalizumab. Overall, compared to treatment with fingolimod and natalizumab, alemtuzumab was budget-saving starting from the fourth and second year, respectively.

Budget impacts were similar in the sensitivity analyses (**Table 6**). In the analysis based on first-line CARE-MS I data, the modelled five-year budget savings increased by €1,796 and €2,047 per patient compared to base case. Administering only two alemtuzumab courses increased the budget savings by €10,897 per patient. When fingolimod and natalizumab discontinuations were modelled, but subsequent treatments were not considered, the alemtuzumab's budget savings decreased to €3,772 (decrease of €22,572 compared to base case) and €73,051 (€27,737) compared to fingolimod and natalizumab, respectively. When the subsequent treatments and their costs were also included, the budget savings increased to €42,533 (increase of €16,238) compared to fingolimod and decreased to €98,422 (decrease of €9,915) compared to natalizumab. Using the base case natalizumab administration cost (€419.23) also for alemtuzumab increased the alemtuzumab's budget savings by €2,318 compared to both comparators. When the base case alemtuzumab administration (€664.8) cost was assumed for natalizumab, the budget savings increased by €15,960 compared to natalizumab. When time horizon was extended to 10 years, cumulative budgets were €96,365, €230,274 and €381,641 per patient with alemtuzumab, fingolimod and natalizumab, respectively. Respective modelled 10-year budget savings were €133,909 and €285,275. In other scenarios modelled budget impact was smaller and/or mixed.

Clinical outcomes

Based on the efficacy outcomes of the CARE-MS II trial and NMA, the treatment with alemtuzumab was modelled to be associated with 30 % and 6 % less relapses than the treatment with fingolimod or natalizumab (**Figure 2A**), respectively. In a modelled cohort of 100 patients, the patients treated with alemtuzumab were modelled to experience 119 relapses over five-years, or 51 and 8 relapses less than the 100 modelled patients treated with fingolimod and natalizumab, respectively. In total, 25 % and 4 % more patients were modelled to remain free of confirmed disease worsening (CDW) for the five years, compared to fingolimod and natalizumab (**Figure 2B**). In a modelled cohort of 100 patients, the treatment with fingolimod and natalizumab were modelled to result in 15 and 3 less patients free of CDW at five-years compared to 75 CDW free patients with alemtuzumab, respectively.

In the scenario examining the first-line alemtuzumab treatment modelled based on CARE-MS I trial data, fewer relapses were modelled to occur (84, 120 and 90 relapses among the modelled cohorts of 100 patients with alemtuzumab, fingolimod and natalizumab, respectively), and more patients were modelled to remain free of CDW (79, 66 and 77 out of modelled cohorts of 100 patients with alemtuzumab, fingolimod and natalizumab, respectively) than in the base case analysis.

DISCUSSION

In the present modelled budget impact analyses, alemtuzumab was budget-saving starting from the fourth and the second year compared to fingolimod and natalizumab, respectively. Total modelled potential 5-year budget-savings were €26,294 and €100,780 per patient compared to fingolimod and natalizumab, respectively. Furthermore, based on CARE-MS I and II clinical trials and NMA, alemtuzumab was modelled with fewer relapses and higher proportion of patients remaining free of disease worsening than either comparator, implying that the budget-savings are not associated with poorer clinical outcomes. Although no real-world data was applied for the estimation of the clinical parameters in the present modelling analyses, the clinical experience of the MS-patients treated with alemtuzumab in Turku University Hospital in Finland since 2014 is in line with the CARE-MS I and CARE-MS II trials results (Soilu-Hänninen M, unpublished observation 2019).

Our findings are in line with the previous findings (NICE 2014, Couto *et al.* 2016, ICER 2017, Montgomery *et al.* 2017, Hamidi *et al.* 2018, Piena *et al.* 2018, Zimmermann *et al.* 2018, Chirikov *et al.* 2019, Taheri *et al.* 2019, Walter *et al.* 2019). In the United Kingdom, National Institute of Clinical Excellence (NICE 2014) committee concluded that alemtuzumab was at least as effective as fingolimod and natalizumab for patients with highly active RRMS despite beta interferon treatment and rapidly evolving severe RRMS, respectively: alemtuzumab was found to be more effective and cost-saving (dominant) compared to natalizumab and fingolimod, when patient-access scheme was not applied.

Both Institute for Clinical and Economic Review (ICER 2017) in the United States and Norwegian Institute of Public Health (Couto *et al.* 2016, Hamidi *et al.* 2018) concluded that alemtuzumab was dominant compared to all other active treatments available for RRMS over the examined 5-year time horizon. Alemtuzumab has also been found to be dominant in Austria (Walter *et al.* 2019), Iran (Taheri *et al.* 2019), the United Kingdom (Montgomery *et al.* 2017), and the United States (Zimmermann *et al.* 2018, Chirikov *et al.* 2019). Piena *et al.* (2018) reported that treatment with alemtuzumab would save 30,327 € and 45,522 € per patient compared to fingolimod and natalizumab in the Netherlands in a five-year time horizon, respectively.

In the present analysis, the alemtuzumab's efficacy, safety, and drug use patterns were modelled based on the published five-year randomized controlled trials (Coles *et al.* 2017, Havrdova *et al.* 2017), covering the full duration of evaluated base case time horizon, and reducing uncertainty associated with inputs related to alemtuzumab. The five-year time horizon was considered sufficient to capture all relevant costs associated with the alemtuzumab's budget. Five-year time horizon has also been utilized in several previous health economic evaluations examining alemtuzumab (Couto *et al.* 2016, ICER 2017, Hamidi *et al.* 2017, Piena *et al.* 2018). However, 36 % of the alemtuzumab patients were modelled to receive three or more alemtuzumab courses, while none of the patients have needed a third course of alemtuzumab in Turku University Hospital between 2014 and May 2019 (Soilu-Hänninen M, unpublished observation 2019), meaning that the present analysis might be conservative for alemtuzumab. When only two alemtuzumab courses were modelled, the total alemtuzumab costs decreased by €10,897 per patient. Correspondingly, the modelled budget savings compared to fingolimod and natalizumab increased with the same amount.

Moreover, we compared alemtuzumab (intravenous medication) to prevalent current practice, including another intravenous medication (natalizumab) as well as to a reimbursed oral medication (fingolimod). The distinction between intravenous and oral medications is important, because the costs of intravenous medications are subject to hospital district budgets at wholesale drug prices or potentially tendered prices, whereas the costs of reimbursed oral medications are subject to state budget through social insurance reimbursements at retail price (without VAT), where pharmaceutical pricing scheme impacts the prices of reimbursed products (e.g. Hallinen & Soini 2011). Because the price rationale and immediate payer varies depending on the administration route, there is a risk for sub-optimization. Thus, the budget impact was modelled from the perspective of the actual end payer.

However, the present analyses do also have limitations. First, the most prominent limitation is the fact that the base case analysis did not consider switching or stopping the DMT. While this confounds the absolute budgets associated with the modelled treatments to some degree, the bias arising from this modelling setting is limited by the facts that alemtuzumab drug use patterns were well established in the relevant trial (Coles *et al.* 2017) and that the most likely switch alternative for each comparator medication was also evaluated in the present analysis (for natalizumab that would be fingolimod and vice versa). However, the total budget associated with alemtuzumab was possibly underestimated due to the fact that some patients may receive other medications during the five-year period after the alemtuzumab treatment initiation; in CARE-MS II trial, 7.6 % of the patients received other DMT in years 3-5 (Coles *et al.* 2017). When 7.6 % of the patients receiving alemtuzumab were considered to receive fingolimod or natalizumab continuously for three years on years 3 to 5 in sensitivity analyses, alemtuzumab was still a budget saving alternative to both comparators, although the modelled budget savings were decreased. Budget savings also persisted when fingolimod and natalizumab discontinuation were modelled, even when discontinuing patients were modelled to be left without treatment for the rest of the model duration.

Second, mortality was not considered in the analysis – although the impact of this is substantially diminished by the fact that the typical RRMS patients

are rather young, usually in their 30s, and that the modelled time horizon was only five-years (Cohen *et al.* 2012, Pirttisalo *et al.* 2019). Third, the analysis only included direct medical costs, as typical for budget impact assessments, and did not consider substantial non-healthcare costs such as social services, informal care, sick leaves or productivity losses and early retirement due to MS (Ernstsson *et al.* 2016, Ruutiainen *et al.* 2016). However, excluding these cost drivers is more likely to favor the examined comparators than alemtuzumab.

Fourth, whereas alemtuzumab's clinical outcomes as the intervention were based on data from 5-year clinical trials (Coles *et al.* 2017, Havrdova *et al.* 2017), clinical outcomes associated with the comparators were based on relative effects extracted and calculated from a published NMA (Siddiqui *et al.* 2018), because five-year data were not available for the comparators. Consequently, the five-year clinical outcomes for the comparators could be better or worse than predicted here based on the indirect comparison and alemtuzumab's five-year data. Overall, more uncertainty is associated with the modelled clinical outcomes associated with the two comparators than those modelled for alemtuzumab.

Moreover, although we examined two relevant clinical outcomes as secondary outcomes, our primary focus was on the budget impact analysis. Therefore, in the future analyses alemtuzumab's cost-effectiveness should be formally evaluated in a sequential setting, i.e., in terms of incremental cost per QALY gained, fully accounting for treatment switching and sequential use of multiple treatments. Additionally, it would be beneficial to incorporate Finnish real-world evidence to validate the findings based on the clinical trial data and NMA.

Finally, European Medicines Agency (EMA) issued a restriction on alemtuzumab use in April 2019, when EMA initiated a safety review due to reports of rare, but serious side effects. Based on this review EMA's safety committee (PRAC) and Committee for Medicinal Products for Human use (CMPH) opinioned in November 2019 that alemtuzumab should only be used to treat patients with highly active RRMS despite at least one DMT or with rapidly worsening disease. It was also recommended that alemtuzumab should only be given in a hospital with ready access to intensive care facilities and specialists who can manage adverse reactions. This restricted indication was confirmed by the European Commission in their final decision issued on January 16th, 2020.

Of note, the present analyses are in line with the restricted indication; all three medications examined in the present analyses have the same indication. In addition, the alemtuzumab administration in a hospital with access to intensive care facilities was also considered in the present analyses.

However, it was not feasible to estimate the impact of these newly observed adverse events in the present analysis, given that their incidence is unknown. Overall, these adverse reactions are so rare at they are expected to have only a negligible impact on the results of the present analyses. For instance, natalizumab is associated with rare but very serious adverse event, PML, which was modelled to occur at the rate of 0.0012 per patient-year and cost approximately 35,876.28 € per case. If we assumed that the incidence rate and cost of the newly observed alemtuzumab adverse events were the same as with PML associated with natalizumab, the budget savings associated with alemtuzumab would be diminished by approximately 218 € compared with both fingolimod and natalizumab (0.83 % and 0.22 %, respectively). This is well in line with the PRAC and CMPH endorsement that alemtuzumab's benefit-risk balance remains favorable subject to the agreed amendments to the product information and indication.

CONCLUSIONS

The present study, with the support of previous findings from foreign settings, indicate that alemtuzumab is a budget-saving alternative to fingolimod and natalizumab for highly active RRMS in Finland. Moreover, the data from the clinical trials and published NMA imply that these budget-savings are not associated with poorer clinical outcomes.

TIIVISTELMÄ

Alemtutsumabi on kustannuksia säästävä vaihtoehto fingolimodille ja natalitsumabille erittäin aktiivisen aaltomaisen MS-taudin hoidossa

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Johdanto: Alemtutsumabi on tehokas suonensisäisesti annosteltava lääke aktiivisen ja erittäin aktiivisen aaltomaisen multippeliskleroosin (MS-taudin) hoitoon. Vaikka alemtutsumabin on todettu olevan kustannusvaikuttava ja kustannuksia säästävä muissa maissa, ei alemtutsumabin terveystalous- tai terveydenhuollon menetelmäarviota ole aiemmin julkaistu Suomesta. Arvioimme alemtutsumabin mahdollista nettomääräistä budjettivaikutusta suomalaisten erittäin aktiivista aaltomaista MS-tautia sairastavien potilaiden hoidossa.

Aineisto ja menetelmät: Budjettivaikutusta arvioitiin suomalaisella staattisen kohortin mallilla, jonka menetelmät ja tulokset raportoitiin PICOSTEPS-viitekehystä käyttäen. Mallissa kahdelle identtiselle MS-potilaalle annetaan joko tarkasteltavaa hoitoa (alemtutsumabi) tai verrokkihoitoa (fingolimodi, natalitsumabi). Mallinnettavaa potilasta seurattiin perusskenaariossa viiden vuoden ajan (2019–23) sillä oletuksella, ettei potilas vaihda tai lopeta lääkitystä tai kuole seurannan aikana. Arvioinnin ensisijaiset päätemuuttujat olivat kumulatiiviset kokonaisbudjetit ja erot suorissa kumulatiivisissa budjeteissa vertailuvalmisteiden välillä terveydenhuollon maksajan näkökulmasta (nettobudjettivaikutus). Mallin ja tulosten herkkyyttä testattiin yksi- ja moniulotteisin deterministisin herkkyysanalyysein. Toissijaisena tavoitteena tarkasteltiin mallintamalla kahta kliinistä päätemuuttujaa, relapsien kokonaismäärää ja taudin etenemisestä vapaiden potilaiden määrää, kliinisiin tutkimuksiin ja verkostometa-analyysiin perustuen.

Tulokset: Alemtutsumabi oli kustannuksia säästävä fingolimodiin verrattuna neljäntenä vuonna ja natalitsumabiin verrattuna toisena vuonna. Fingolimodiin ja natalitsumabiin verrattuna alemtutsumabi säästi 26 294 ja 100 789 euroa kustannuksia potilasta kohden mallinnetun viiden vuoden aikana. Kliinisiin tutkimuksiin ja verkostometa-analyysiin perustuvassa mallinnuksessa alemtutsumabilla saavutettiin fingolimodia ja natalitsumabia paremmat kliiniset lopputulokset, mikä viittaa siihen, etteivät kustannussäästöt tule hoitotulosten kustannuksella.

Johtopäätökset: Alemtutsumabi on aiempien julkaistujen tutkimusten ja tämän budjettivaikutusarvioinnin valossa kustannuksia säästävä vaihtoehto fingolimodille ja natalitsumabille erittäin aktiivisen aaltomaisen MS-taudin hoitoon.

Avainsanat: budjettivaikutusanalyysi, hoitotuloksen mittaaminen, kustannukset, multippeliskleroosi, terveydenhuollon menetelmäarvio, terveystaloustiede

CONFLICTS OF INTEREST

ESiOR has received financial support from Sanofi Oy for the conduct of this study. ESiOR Oy provides consulting as well as analytical and educational services to companies, organizations and projects in pharmaceutical, health, food and research industries, including pharmaceutical companies marketing MS medications. SV and ES declare no personal conflicts of interest. LL declares no personal conflicts of interest. MSH has received congress fee covering, investigator fees and honoraria for lectures or advisory boards from Biogen, Merck, Novartis, Roche, Teva, Sanofi Genzyme.

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Appendix Table 1. Alemtuzumab dosing and clinical outcomes, sensitivity analysis based on first-line patient population (CARE-MS I).

Input / Year	Year 1	Year 2	Year 3	Year 4	Year 5	Source
Receive alemtuzumab treatment [a]	100.0 %	100.0 %	16.8 %	11.2 %	11.4 %	Adapted from
Course 1 (five 12 mg infusions)	100.0 %	-	-	-	-	Havrdova *et al.*
Course 2 (three 12 mg infusions)	-	100.0 %	-	-	-	2017 [a]
Course 3 (three 12 mg infusions)	-	-	16.8 %	6.9 %	5.6 %	
Course 4 (three 12 mg infusions)	-	-	-	4.3 %	4.5 %	
Course 5 (three 12 mg infusions)	-	-	-	-	1.3 %	
Infusion site reactions (of courses received) [b]						
Any	85.9 %	65.7 %	65.5 %	61.3 %	58.2 %	Havrdova
Serious	2.7 %	0.5 %	0.0 %	0.0 %	0.0 %	*et al.* 2017
CLINICAL OUTCOMES, BASED ON THE PUBLISHED CLINICAL TRIAL DATA Annualized Relapse Rate (ARR)						
Alemtuzumab	0.18	0.18	0.19	0.14	0.15	Havrdova *et al.* 2017
6-month Confirmed Disease Worsening (CDW)						
Alemtuzumab: No CDW during year	95.9 %	93.6 %	95.2 %	93.9 %	94.4 %	Wiendl *et al.* 2016
Alemtuzumab: Free of CDW, cumulatively	95.9 %	92.0 %	88.0 %	83.0 %	79.0 %	Coles *et al.* 2016

a) Calculated based on the number of patients initiating alemtuzumab in CARE-MS I trial (n=376), assuming conservatively that all (100 %) patients are compliant to 2nd administration at the beginning of the 2nd year, although less than 100 % (98.4 %, n=370/376) of the patients initiating alemtuzumab actually received 2nd administration at the second year. Number of patients receiving the third to fifth alemtuzumab dose each year (on third, fourth and fifth year, respectively: Course 3: 63, 26, 33; Course 4: 16, 17 and Course 5: 5) was conservatively divided by the total number of patients initiating alemtuzumab in the CARE-MS I trial (Havrdova et al. 2017; n=376). All patients were conservatively assumed to receive full courses of five or three infusions. After first two courses alemtuzumab dosing interval may be increased from the initial 12 months. b) Accounts for the distribution of courses each year and the fact that the later courses are associated with fewer infusion site reactions. Conservatively, infusion site reactions associated with natalizumab were not considered in the analysis. In CARE-MS I, the incidence of key adverse events included in the analyses were as followed: ITP 0.2; Thyroid disorder 13.2; Nephropathies 0.1; Herpes 4.1; Serious infection 0.9 and pulmonary infection 8.2 per 100 patient years (Havrdova et al. 2017).

Appendix Table 2. Acquisition cost of medications for the treatment of Adverse Events (Finnish Medicines Tariff 5/2019).

Medication	Cost	Adverse event, modelled use
Oftan Dexa, 1 mg / ml, 5 ml	9.28 €	For macular edema, modelled on average 1.5 packs.
Prednisolone 40 mg, 100 tablets Prednisolone 5 mg, 100 tablets	46.15 € 5.16 €	For ITP; modelled 3 weeks treatment starting with 300 mg/day and down titrated. 1 pack 40 mg and 1 pack 5 mg.
Mabthera (Rituximab), 10 mg / ml, 2x10 ml	552.02 €	For ITP; 4 packs weekly for 4 weeks, based on average estimated average BSA of 1.89 m2 and dose of 375 mg/m2.
Tyrazol, 100 tablets Thyroxin, 100 tablets	27.79 € 5.73 €	For thyroid disorders; modelled half receiving Tyrazol, half receiving Thyroxin for 5 years.
Ramipril Hexal 10 mg, 100 tablets	11.60 €	For nephropathies, modelled continuous daily use for 5 year.
Medrol 32 mg, 20 tablets Medrol 16 mg, 50 tablets Medrol 4 mg, 100 tablets	17.86 € 27.68 € 17.17 €	For nephropathies, modelled 1-year treatment with monthly down titration from 80 mg every other day to 4 mg every other day. 3 packs 32 mg, 2 packs 16 mg and 2 packs 4 mg.
Aciclovir Sandoz 200 mg 25 tablets	6.41 €	For herpes, 1 pack.
Levofloxacin 500 mg 10 tablets	20.95 €	For serious infection, 1 pack.
Amoxin 750 mg 20 tablets	11.66 €	For pulmonary infection, 1 pack.
Amoxin 750 mg, 14 tablets	9.99 €	For pneumonia, 2 packs.

BSA: Body surface area; ITP: immune thrombocytopenic purpura. Retail prices without value added tax where applied to all medications except rituximab, which is administered in hospital setting and where wholesale price is applied.