Benefit-Risk Assessment of Cladribine Tablets using Multi-Criteria Decision Analysis (MCDA) for Patients with Relapsing Multiple Sclerosis Demonstrating High Disease Activity

Patrick Vermersch[1], Vittorio Martinelli[2], Claudia Pfleger[3], Peter Rieckmann[4], Andrew Galazka[5], Fernando Dangond[6], Lawrence Phillips[7]

[1]Université de Lille, Department of Neurosurgery, CHU Lille, LIRIC-INSERM U995, FHU Imminent, F-59000 Lille, France, [2]San Raffaele Hospital, Milan, Italy, [3]Aalborg Universitets Hospital, Hobrvej 18-22, 9000 Aalborg. Denmark, [4]Department of Neurology, Medical Park Loipl and University of Erlangen, Erlangen, Germany; [5]Merck, Aubonne, Switzerland, [6]EMD Serono, Inc., Billerica, MA, USA, [7]FACILITATIONS Limited, London, UK

INTRODUCTION

- Patients with relapsing multiple sclerosis (RMS) experiencing frequent relapses can be described as having high disease activity (HDA).
- Disease modifying drugs (DMDs) available as treatment options for patients with HDA have distinct efficacy and safety profiles. Consequently, benefit-risk balance is a key consideration for physicians when selecting effective treatments for these patients.
- Increasingly, structured decision making and treatment choice from alternatives offering different potential benefits or risks employs Multi-Criteria Decision Analysis (MCDA) methods.

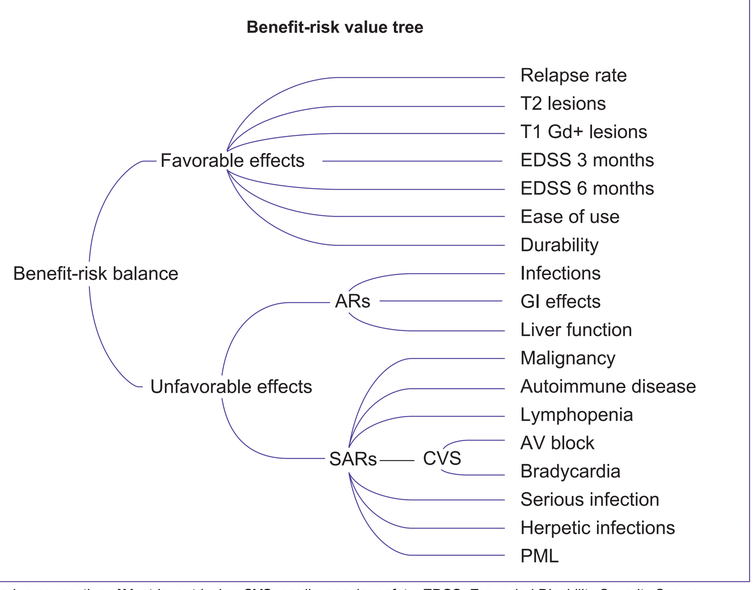
OBJECTIVES

- To apply MCDA to a structured, blinded, benefit-risk assessment of cladribine tablets and newer approved DMDs for patients with HDA.

METHODS

- Decision conferencing with expert clinical neurologists as the decision makers was used to create an MCDA model incorporating available evidence and clinical judgements about the relevance of that evidence.
- This followed a group workshop approach, guided by the PrOACT-URL (**P**roblem formulation, **O**bjectives, **A**lternatives, **C**onsequences, **T**rade-offs, **U**ncertainties, **R**isk attitude, and **L**inked decisions) framework.[1]
- Benefit-risk assessments were conducted for DMDs in patients with RMS and HDA (defined as ≥ 2 relapses in the previous year – also described as high relapse activity [HRA]).
- Treatments options included in the model were cladribine tablets and recently approved DMDs available in the EU countries at the time of assessment (December 2015): alemtuzumab, dimethyl fumarate, fingolimod, natalizumab, and teriflunomide.
- Experts independently agreed on 7 favorable effects and 11 unfavorable effects based on study endpoints, posology, and established or potential risks of DMDs (**Figure 1**).

Figure 1. Favorable and Unfavorable Effects Used for Determining Relative Benefit-Risk Balance in the MCDA Model



AR, adverse reaction; **AV**, atrioventricular; **CVS**, cardiovascular safety; **EDSS**, Expanded Disability Severity Score; **Gd+**, gadolinium enhanced; **GI**, gastrointestinal; **PML**, progressive multifocal leukoencephalopathy; **SAR**, serious adverse reaction.

Data Identification for the MCDA Model

- A hierarchical search strategy was used to obtain treatment effect data for the model as follows:
  1. EU regulatory approval documents
  2. US regulatory approval documents
  3. Post-marketing surveillance data
  4. Peer-reviewed publications
  5. Congress presentations
- If the relevant data were not found in the first data source, then the second data source was searched and so on down the hierarchy until the relevant data were identified. Only one set of data were reported for each parameter for each drug.
- Only trials where the DMD was given as monotherapy were chosen and the highest values for favorable effects attained in any trials were included in the model (ie the highest efficacy result). For alemtuzumab, in which the clinical programme did not include placebo as a comparator, arbitrary high values were assigned by independent clinicians on MRI and clinical efficacy measures.
- Treatment effects data used in the model are shown in **Table 1**.

Scoring the DMDs

- Experts established a measurement scale for each treatment effect criterion which included the relative importance of each effect.
- Based on this scale, preference values were assigned for each DMD using hypothetical treatment effect data.

Weighting the Treatment Effects Criteria

- Preference values were weighted to ensure that the scales judged to be more important by the experts carried more weight in the final benefit-risk calculation.
  - — Weightings represent the trade-off between the most beneficial favorable effect and the most risky unfavorable effect.
  - — The final cumulative weights showed that four effects in the model were the most important discriminators between DMDs: progressive multifocal leukoencephalopathy (PML), relapse rate, 6-month confirmed Expanded Disability Severity Score (EDSS), and T2 lesions.
  - — AV block and bradycardia showed the smallest cumulative weights.
- Experts made their judgements of the weightings solely on the basis of the ranges of preference values and were blinded to the specific DMDs.

Table 1. The Effects Table for the HDA Population with Values Assigned to Each Favorable or Unfavorable Effect Used in the MCDA Model

Criteria	Description	Metric	Alemtuzumab	Cladribine tablets	Dimethyl fumarate	Fingolimod	Natalizumab	Teriflunomide
Favorable effects								
Relapse rate	RR, compared to the control, in ARR at 2 years	%	71	68	60	63	81	19
T2 lesions	RR in mean number of active T2 lesions per patient per scan over 2 years	%	92	73	85	74	83	53
T1 Gd+ lesions	RR in mean number of T1 Gd+ lesions per patient per scan over 2 years	%	97	86	94	82	92	80
EDSS 3 months	RR in time to 3-month confirmed EDSS progression over 2 years	%	71	72	21	33	53	35
EDSS 6 months	RR in the time to 6-month confirmed EDSS progression over 2 years	%	71	82	21	33	64	35
Ease of use	Ranking based on 4 sub-criteria*	1–3.5	1.0	3.5	2.5	2.0	1.5	3.0
Durability	Number of months of remaining efficacy after stopping the drug	Months	12	12	1	1	2	1
Unfavorable effects								
AR infections	% patients with any infections	%	70.9	51.8	60.0	65.1	73.7	61.7
AR GI effects	% patients with any GI disorder	%	49.0	31.6	44.0	43.0	0.0	45.3
Liver function	% patients experiencing elevated liver enzymes	%	0.0	1.5	6.0	10.1	0.0	15.0
Malignancy	Number of new cases per 100 patient-years	No/100	0.370	0.370	0.375	0.400	0.320	0.200
Autoimmune disease	% patients with any autoimmune disease	%	47.0	2.0	0.0	0.0	0.0	0.0
Lymphopenia	% patients experiencing lymphopenia Grade 4	%	52.1	0.7	0.13	18.0	0.0	0.0
AV block	% patients with first degree AV block	%	0.0	0.0	0.0	4.7	0.0	0.0
Bradycardia	% patients with bradycardia	%	0.3	0.2	0.0	4.1	0.0	0.0
Serious infections	% patients with any serious infection	%	2.7	2.5	2.0	1.6	2.4	2.2
Herpetic infections	% of herpetic infections	%	15.7	7.9	0.0	9.0	8.0	0.5
PML	Number of cases of PML per 1,000 patients	No/1000	0.000	0.000	0.029	0.104	2.100	0.000

(1) oral vs iv, (2) few or many doses, (3) monitoring during administration (Y or N), and (4) co-administration of other drugs (Y or N).
AR, adverse reaction; **ARR**, annualized relapse rate, **AV**, atrioventricular; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium enhanced; **GI**, gastrointestinal; **HDA**, high disease activity; **iv**, intravenous; **PML**, progressive multifocal leukoencephalopathy; **RR**, relative reduction

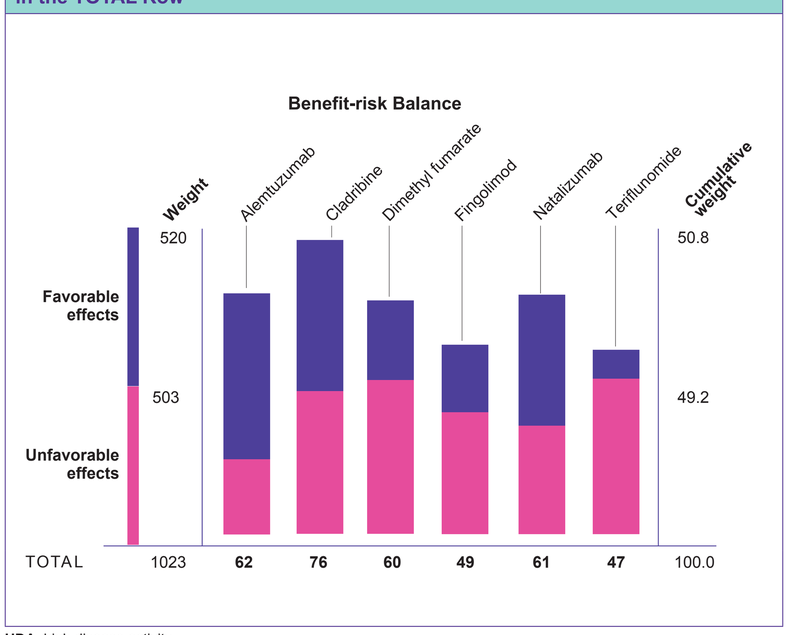
Exploring the Model

- Based on scoring and weighting of preference values, overall weighted preference values were calculated for each DMD (the basic output of the MCDA model).
- Sensitivity analyses were conducted by changing the cumulative weighting assigned to the unfavorable treatment effects.
- The benefit-risk profiles of cladribine tablets and other DMDs were also compared, following the established priorities for favorable and unfavorable effects and reflecting the treatment effects data for the DMDs in the model.

RESULTS

- Cladribine tablets had the highest overall weighted preference value for patients with HDA (indicating that it was the most preferred option in the model) followed by alemtuzumab and natalizumab, (**Figure 2**).

Figure 2. The Overall Weighted Preference Values in the HDA Population, Shown in the TOTAL Row



HDA, high disease activity.
The overall weighted preference values for the six drugs in the HDA population, shown in the TOTAL row. More purple means more benefit; more pink indicates more safety. Weights shown in the left column are the sums of the non-normalized cumulative weights, and the normalized values are given in the right column.

- — Sensitivity analyses showed no change in results over large ranges of the weighted preference values for unfavorable effects (not shown).
- Comparisons of risk-benefit profiles with weighted differences favored cladribine tablets for severe lymphopenia, autoimmune disease, herpetic infections, infections, gastrointestinal effects, and ease of use, and favored alemtuzumab for T2 lesions and T1 Gd+ lesions (**Table 2**).

Table 2. Differences in Weighted Preference Values Between Cladribine Tablets and Alemtuzumab

	Model order	Cumulative weight	Difference	Weighted difference	Sum	**Purple:** Weighted difference favors cladribine tablets **Pink:** Weighted difference favors alemtuzumab
SARs	Lymphopenia	6.5	93	6.1	6.1	
SARs	Autoimmune disease	6.0	90	5.4	11.6	
Favorable effects	Ease of use	4.0	83	3.4	14.9	
SARs	Herpetic infections	5.0	49	2.5	17.4	
ARs	Infections	2.8	76	2.2	19.5	
ARs	GI effects	3.0	35	1.1	20.6	
SARs	Serious infection	7.0	13	0.9	21.5	
CVS	Bradycardia	1.5	3	0.0	21.6	
Favorable effects	Durability	2.5	0	0.0	21.6	
SARs	PML	10.1	0	0.0	21.6	
SARs	Malignancy	4.0	0	0.0	21.6	
CVS	AV block	2.0	0	0.0	21.6	
ARs	Liver function	2.5	-8	-0.2	21.4	
Favorable effects	T1 Gd+ lesions	7.0	-30	-2.1	19.2	
Favorable effects	EDSS 6 months	10.1	-23	-2.3	16.9	
Favorable effects	T2 lesions	8.1	-31	-2.5	14.4	
Favorable effects	Relapse rate	9.1	-28	-2.6	11.8	
Favorable effects	EDSS 3 months	8.6	-58	-5.0	6.9	
		100.0		6.9		

ARs, adverse reactions; **CVS**, cardiovascular safety; **HDA**, high disease activity; **SARs**, serious adverse reactions.

- Differences favored cladribine tablets for PML, durability of effect, and 3-month and 6-month confirmed EDSS progression, and favored natalizumab for relapse rate, T2 lesions, and T1 Gd+ lesions (**Table 3**).

Table 3. Differences in Weighted Preference Values Between Cladribine Tablets and Natalizumab

	Model order	Cumulative weight	Difference	Weighted difference	Sum	**Purple:** Weighted difference favors cladribine tablets **Pink:** Weighted difference favors natalizumab
SARs	PML	9.8	105	10.3	10.3	
Favorable effects	Durability	3.9	91	3.6	13.8	
Favorable effects	EDSS 3 months	8.3	38	3.2	17.0	
Favorable effects	EDSS 6 months	9.8	28	2.7	19.7	
ARs	Infections	2.7	88	2.4	22.1	
Favorable effects	Ease of use	2.9	67	2.0	24.0	
SARs	Herpetic infections	4.9	1	0.0	24.1	
CVS	AV block	2.0	0	0.0	24.1	
CVS	Bradycardia	1.5	-5	-0.1	24.0	
SARs	Lymphopenia	6.4	-1	-0.1	23.9	
ARs	Liver function	2.4	-8	-0.2	23.7	
SARs	Autoimmune disease	5.9	-4	-0.2	23.5	
SARs	Serious infection	6.8	-7	-0.5	23.0	
SARs	Malignancy	3.9	-20	-0.8	22.3	
ARs	GI effects	2.9	-63	-1.9	20.4	
Favorable effects	T2 lesions	8.8	-22	-2.0	18.4	
Favorable effects	Relapse rate	9.3	-22	-2.0	16.4	
Favorable effects	T1 Gd+ lesions	7.8	-30	-2.3	14.1	
		100.0		14.1		

ARs, adverse reactions; **CVS**, cardiovascular safety; **HDA**, high disease activity; **SARs**, serious adverse reactions.

CONCLUSIONS

- **Using MCDA with decisions from blinded expert physicians, the benefit-risk profile of cladribine tablets in HDA patients (≥ 2 relapses in the previous year; HRA) was favorable compared to the other DMDs included in the model.**

REFERENCES

1. Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (www.protectbenefitrisk.eu/PrOACT-URL.html accessed 17 October 2017).

ACKNOWLEDGMENTS

This study was sponsored by EMD Serono, Inc., a business of Merck KGaA, Darmstadt, Germany (in the USA), and Merck Serono SA – Geneva, an affiliate of Merck KGaA Darmstadt, Germany (ROW). Medical writing assistance was provided by Mark O'Connor of inScience Communications, Springer Healthcare, Chester, UK, and was funded by Merck KGaA, Darmstadt, Germany. The expert decision makers in the structured MCDA benefit-risk assessment served as authors, and wish to thank Lucia Alonso-Magdalena, Skåne University Hospital, Neurologiska Kliniken, Sweden, who also served as a decision maker.

DISCLOSURES

PV has received honoraria or consulting fees from Biogen, Sanofi-Genzyme, Bayer, Novartis, Merck, Celgen, Roche and Almirall; and research support from Biogen, Sanofi-Genzyme, Bayer, and Merck. **VM** received honoraria for speaking and/or for consultancy and support for travel expenses and participation in Congresses from Bayer, Biogen, Merck-Serono, Novartis, Genzyme and Teva. **CP** has received honoraria for advisory council meetings from Novartis and travel expenses for attending meetings from Novartis, Biogen Idec, Roche, Genzyme and Merck Serono. The Department of Neurology, Aalborg Hospital has received compensation for participation in industry sponsored clinical trials from Merck Serono, Roche, Novartis, Genzyme and Biogen Idec. **PR** has received honoraria for lectures/steering committee meetings from Merck, Biogen Idec, Bayer Schering Pharma, Boehringer-Ingelheim, Sanofi-Aventis, Genzyme, Novartis, Teva Pharmaceutical Industries, and Serono Symposia International Foundation. **AG** is an employee of Merck, Aubonne, Switzerland, a division of Merck KGaA, Darmstadt, Germany. **FD** is an employee of EMD Serono, Inc., a business of Merck KGaA, Darmstadt, Germany. **LP** has received consultancy fees from Amgen, GE Healthcare, Merck KGaA, Pfizer, Sanofi, and, indirectly, Reckitt Benckiser.

GET POSTER PDF

Presented at European Charcot Foundation (ECF) 2017; 30 November - 2 December; Baveno, Italy