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# Abnormalities on structural MRI associate with faster disease progression in multiple system atrophy

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ABSTRACT

*Background:* The rate of clinical progression in patients with multiple system atrophy (MSA) varies between individuals and predictors for disease progression remain undefined. While the MSA-rasagiline study found no difference in the rates of clinical progression for patients treated with rasagiline versus placebo, it included a large, prospective magnetic resonance imaging (MRI) substudy that can provide new information on the underlying disease progression in patients with early MSA.

*Methods:* This *post-hoc* analysis compared the rate of clinical progression in patients with MSA-specific structural changes at baseline (MRI-positive group) versus the rate of progression in patients without evidence of such changes at baseline (MRI-negative group) using a repeated measures ANCOVA. Clinical progression was assessed using the Unified MSA Rating Scale (UMSARS) and Clinical Global Impression of Improvement (CGI-I).

*Results:* Twenty-eight patients with early MSA of the parkinsonian subtype (MRI-positive n = 13; MRI-negative n = 15) who had complete baseline and follow-up UMSARS data were included in this analysis. Patients in the MRI-positive group had faster clinical progression from baseline to the end of the 48-week study compared with those in the MR-negative group as assessed by the UMSARS total ($p = 0.028$) and UMSARS motor ($p = 0.008$) scales. At week 48, MRI-positive patients also had a significantly worse health status vs. MRI-negative patients ($p = 0.015$).

*Conclusions:* This is the first study to demonstrate that MSA-specific abnormalities on structural MRI might represent a variant of MSA-P that is associated with more rapid progression and an overall worse prognosis.

## 1. Introduction

Multiple system atrophy (MSA) is a sporadic, progressive, adult-onset, neurodegenerative disease characterized by a combination of parkinsonian, cerebellar, autonomic and pyramidal symptoms and by cell loss, gliosis and glial cytoplasmic inclusions in multiple brain areas and spinal cord [1,2]. Disease progression in MSA is fast, with mean survival ranging between 7 and 9 years after initial clinical presentation. Almost 80% of patients are disabled within 5 years of onset of the motor symptoms, and only 20% survive past 12 years [3,4]. The parkinsonian variant of MSA (MSA-P) was associated with a more rapid decline when compared with patients with predominantly cerebellar symptoms (MSA-C) in some studies [4–6]. Nevertheless, the rate of progression and speed of decline may vary widely between individuals and predictors for disease progression remain largely undefined, although factors such as symptomatic autonomic failure at diagnosis [7] and absence of levodopa response [8] have been associated with faster progression and worse prognosis in natural history studies.

Structural magnetic resonance imaging (MRI) in patients with MSA frequently shows characteristic abnormalities in putamen and infratentorial regions. Findings detected by MRI at 1.5 T generally demonstrate high specificity for distinguishing MSA from PD and healthy controls [9]. However, the sensitivity of the characteristic findings can be inconsistent, especially in early disease, and one study found that about 60% of patients with MSA-P had neither putaminal nor infratentorial changes within the first 2 years from disease onset [3] More

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recently, serial imaging studies have shown that abnormalities in diffusion-weighted MRI of the putamen of patients with MSA-P correlate with disease severity [10] suggesting that this MRI measure may be a more suitable marker for monitoring disease progression in MSA-P in an objective and quantitative manner.

The recent rasagiline for MSA (MSA-RAS) trial was the largest randomised controlled trial in a cohort of patients with early MSA-P and included a prospective MRI substudy to compare rates of progression of putaminal MRI abnormalities in subjects treated with rasagiline versus placebo [11]. After 52 weeks of follow-up, putaminal diffusivity increased significantly in both treatment groups, without significant difference between the placebo and rasagiline treated groups, which was in line with the lack of significant treatment effect on any clinical outcome in this study [11]. The current *post-hoc* analysis was performed to assess whether clinically diagnosed patients with MSA-P showing MSA-specific structural changes on MRI at baseline differed in their rates of clinical progression from patients without such MRI changes at baseline.

## 2. Methods

The MSA-Ras study was a multi-centre, randomised, double-blind, placebo-controlled study (NCT00977665) that has been described in detail in its primary publication [11]. The MRI substudy was performed at 10 of the 40 study sites, dependent on site ability to meet technical criteria (e.g. correct equipment and adequate training). The study was undertaken in accordance with Good Clinical Practice and the provisions of the International Conference on Harmonization, with all patients providing informed and written consent for both the overall study and the substudy.

### 2.1. Rasagiline for MSA study design

In brief, patients with a diagnosis of possible or probable MSA-P according to Gilman criteria [12] were randomised in a 1:1 ratio to rasagiline (1 mg/day) or matching placebo and were followed for 48 weeks. Patients were eligible for this study if they had 'early' disease (< 3 years from the time of documented MSA diagnosis) and an anticipated survival of at least 3 years. Patients demonstrating signs of severe disease (i.e. severe orthostatic symptoms, speech impairment, swallowing impairment, impairment in ambulation and/or falling ≥1 per week) were excluded from the study. All anti-parkinsonian medications and allowed treatments of orthostatic hypotension (fludrocortisone, pyridostigmine or vasopressin) were kept unchanged from the baseline visit until at least the week 24 visit.

Clinical progression was assessed at baseline and Weeks 12, 24, 36, and 48 using the Unified Multiple System Atrophy Rating Scale (UMSARS) total, motor and activity of daily living (ADL) scores, and the Clinical Global Impression of Improvement (CGI-I) (7-point scale assessed by the investigator as: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; or 7 = very much worse).

### 2.2. Imaging substudy

All patients enrolled into the MRI substudy with complete baseline and follow-up UMSARS data were included in this *post-hoc* analysis. Patients enrolled into this substudy were imaged at baseline visit and at the end of the study (i.e. at week 48 or termination visit) using identical magnetic resonance scanners at all participating sites (1·5 T Siemens Avanto) according to the common standard protocol described by Scherfler et al. [13] Centralised image analysis was performed at Medical University Innsbruck by two independent investigators, blinded to treatment allocation and scan order [11].

### 2.3. Analyses

This *post-hoc* subgroup analysis compared the rate of clinical progression in patients with features on structural MRI consistent with MSA present at baseline (designated the MR-positive group) versus the rate of progression in patients without evidence of MSA-specific structural MRI changes at baseline (MR-negative group). The following MRI abnormalities were considered MSA-specific: putaminal atrophy, pontine atrophy, cerebellar atrophy and middle cerebellar peduncle atrophy, presence of a putaminal hyperintense rim, putaminal signal hypointensity, and the hot cross bun sign [11].

Images were assessed for abnormalities which were first rated either as MSA-specific or non-specific by two experienced investigators. Each MSA-specific abnormality was then individually graded on a 4-point Likert scale with increasing severity (no, mild, moderate, severe abnormality) as published previously [10,14–17]. The MCP width was measured on sagittal T1-weighted images with the left and right MCPs being identified on the parasagittal view that best expose the MCP between the pons and the cerebellum. The linear distance between the superior and inferior borders of the MCP delimited by the perpendicular cerebrospinal fluid spaces of the pontocerebellar cisterns was measured [18]. Reduced MCP width was assigned to the different severity grades according to the following scheme: > 9 mm no, 8–9 mm mild, 7–8 mm moderate, < 7 mm severe abnormality. Patients were allocated to the MR-positive group if at least one of the seven possible MSA-specific MRI abnormalities was graded as moderate or severe or more than two MRI abnormalities were graded as mild on the baseline scan. There was good consistency between raters for the initial rating of MSA-specificity and the classification of patients by graded abnormalities.

For the analysis of UMSARS progression rate, a repeated measures analysis of variance (RM-ANOVA) including age, disease duration, gender and treatment allocation as co-variates was applied. Sphericity was assessed using Mauchly's sphericity test, and the F-ratio was adjusted using the Greenhouse-Geisser correction for UMSARS total scores ($\varepsilon < 0.75$) and the Huynh-Feldt correction for UMSARS motor and ADL scores ($\varepsilon > 0.75$). Differences in CGI-I were analysed using a generalized linear model with age, disease duration, gender and treatment allocation included as co-variates.

## 3. Results

### 3.1. Patient disposition and baseline characteristics

Of the 40 patients with early MSA disease enrolled into the substudy; 28 had complete baseline and follow-up UMSARS data and were included in this *post-hoc* analysis. A total of 12 patients could not be evaluated due to early termination (n = 7) or incomplete UMSARS data (n = 5). Baseline characteristics of patients in this study showed a mean ± SD age of 65.1 ± 8.6 years, and a time from first symptom of 2.9 ± 1.8 years (Table 1).

Based on imaging analysis, 13 patients had clear imaging signs consistent with MSA and were categorised as MRI-positive, and 15 patients were categorised as being MR-negative (Supplementary appendix). Supplementary Fig. 1 shows examples of images from patients with MRI-positive and MRI-negative features. Despite having a similar or non-significantly shorter disease duration (MRI-positive: 2.5 ± 1.4 vs. MRI-negative: 3.2 ± 2.1 years; p = 0.323), patients in the MRI-positive group already had significantly worse disease severity compared to patients in the MRI-negative group based on a higher UMSARS score (37.9 ± 7.4 vs. 27.7 ± 7.4, respectively). Patient demographics were well balanced in all other respects, and patients in both subgroups were evenly distributed in the two original study arms (rasagiline and placebo).

**Table 1**
Patient characteristics.

| | Overall (n = 28) | MRI-positive (n = 13) | MRI-negative (n = 15) | P value (MRI-positive vs. MRI negative) |
|---|---|---|---|---|
| Gender; | | | | 0.718[a] |
| Male | 16 | 8 | 8 | |
| Female | 12 | 5 | 7 | |
| Treatment; | | | | 0.137[a] |
| Placebo | 17 | 10 | 7 | |
| Rasagiline | 11 | 3 | 8 | |
| Age; (mean ± SD) | 65.1 ± 8.6 | 64.8 ± 8.3 | 65.3 ± 9.2 | 0.881[b] |
| Disease duration; (mean ± SD) | 2.9 ± 1.8 | 2.5 ± 1.4 | 3.2 ± 2.1 | 0.323 |
| UMSARS Total; (baseline, mean ± SD) | 32.4 ± 8.9 | 37.9 ± 7.4 | 27.7 ± 7.4 | 0.001 |
| UMSARS I; (baseline, mean ± SD) | 15.1 ± 5.4 | 18.2 ± 4.4 | 12.5 ± 4.9 | 0.003 |
| UMSARS II; (baseline, mean ± SD) | 17.3 ± 4.2 | 19.8 ± 3.3 | 15.2 ± 3.8 | 0.002 |

[a] Fisher exact test.
[b] Student's T Test.

**Table 2**
UMSARS progression by MR subtype at different weeks.

| | Group | Baseline | Week 12 | Week 24 | Week 36 | Week 48 | P value |
|---|---|---|---|---|---|---|---|
| UMSARS total | MRI-negative | 27.7 ± 7.4 | 28.8 ± 9.7 | 30.1 ± 0.6 | 30.4 ± 1.1 | 30.5 ± 2.3 | 0.028[a] |
| | MRI-positive | 37.9 ± 7.4 | 39.0 ± 9.8 | 42.9 ± 9.0 | 48.6 ± 0.4 | 48.2 ± 0.2 | |
| UMSARS I (activities of daily living) | MRI-negative | 12.5 ± 4.9 | 13.4 ± 6.3 | 13.7 ± 6.6 | 14.1 ± 7.6 | 13.9 ± 8.4 | 0.051[a] |
| | MRI-positive | 18.2 ± 4.4 | 18.7 ± 5.3 | 20.1 ± 5.0 | 23.7 ± 5.4 | 23.1 ± 5.7 | |
| UMSARS II (motor) | MRI-negative | 15.2 ± 3.8 | 15.4 ± 4.1 | 16.3 ± 4.6 | 16.3 ± 4.2 | 16.6 ± 4.6 | 0.008[a] |
| | MRI-positive | 19.8 ± 3.3 | 20.3 ± 4.9 | 22.9 ± 4.9 | 24.9 ± 5.2 | 25.1 ± 5.1 | |

[a] RM-ANOVA. p value for time*MRI-subtype interaction.

### 3.2. UMSARS progression over time

As shown in Table 2, patients in both groups showed disease progression (i.e. increasing scores at each subsequent visit). When assessed using repeated measures ANCOVA adjusted for sphericity; patients in the MRI-positive group were found to have faster disease progression from baseline to the end of the 48-week study than patients in the MRI-negative group on the UMSARS total (p = 0.028) and UMSARS motor (p = 0.008) scales (Fig. 1). A strong trend towards more rapid progression in MRI-positive patients was also observed when patients were assessed with the UMSARS ADL scale (p = 0.051). This more rapid rate of clinical progression was reflected in the change in CGI-I scores at week 48, where patients with MRI-positive abnormalities were rated as significantly worse (p = 0.015) than those in the MRI-negative group (Fig. 2). In our models, treatment allocation to either placebo or rasagiline had no significant impact on UMSARS progression (p = 0.646) or CGI-I scores at week 48 (p = 0.267).

## 4. Discussion

Epidemiological studies have shown significant variability in progression rates for patients with MSA [8]. This is the first study to demonstrate that the presence of structural MRI features consistent with MSA at baseline is associated with more rapid clinical progression compared to patients lacking these abnormalities.

Rates of progression of UMSARS scores in other clinical trials have ranged from 11 to 17 units per year [19–22]. This variability poses significant problems in designing disease modification trials in MSA as exemplified by data from two recent natural history studies: a European study reported a progression rate of 15 UMSARS units per year [8], whereas a similar series from an US study found a considerably lower rate of 8 units per year [7]. The latter is consistent with data from the MSA-Ras study, which also reported a rate of progression of approximately 8 units per year [11]. The reason for this variance is unclear although it is conceivable that there are subtypes of MSA with different rates of progression as has been observed in PD [23,24]. Indeed, MSA patients presenting with autonomic failure have shown more rapid decline [7,8]. Our data suggest that MSA-specific abnormalities on structural MRI might represent a variant of MSA-P that is associated with more rapid progression and an overall worse prognosis.

In the absence of post-mortem confirmation, we cannot exclude a possibility of misdiagnosis as a contributor to the differences observed

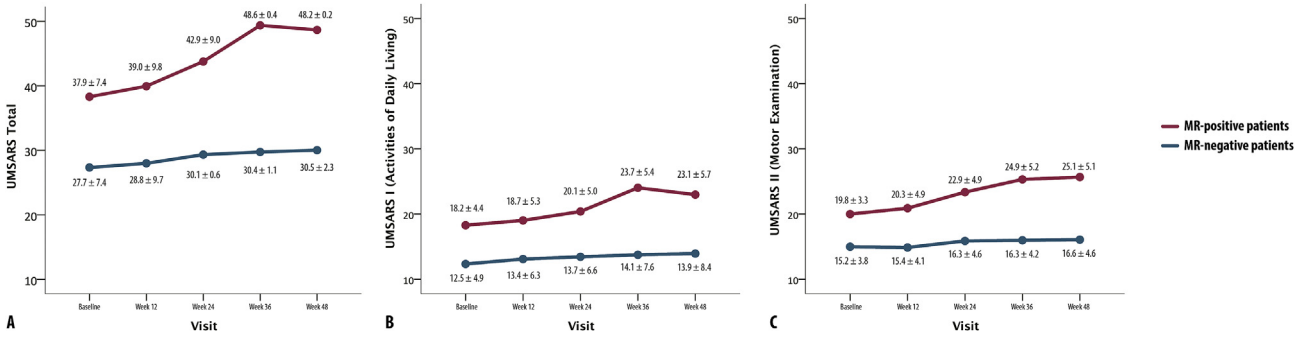


**Fig. 1.** UMSARS progression by MR subtype (a) Total, (b) activities of daily living (c) motor scores.
Legend: Repeated measures ANCOVA using the Greenhouse-Geisser correction for UMSARS total scores and the Huynh-Feldt correction for UMSARS motor and ADL scores.

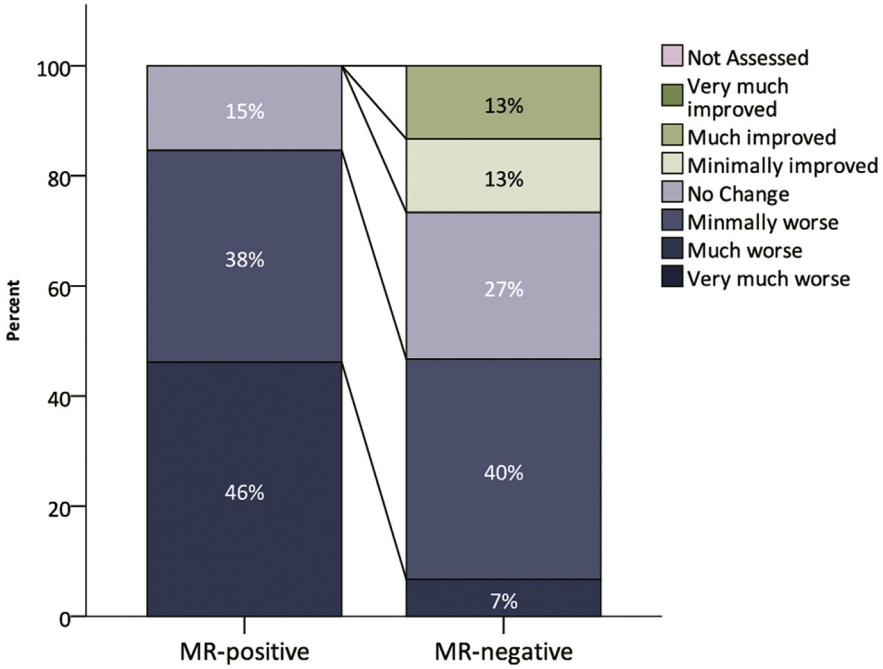


**Fig. 2.** CGI-I at week 48 by MR subtype.

in this analysis. Indeed, none of the 15 subjects with normal scans at baseline shifted from 'possible' to 'probable' MSA, and none of these patients developed MSA specific signs during MR follow-up over the 12 months' duration of this trial. While misclassification is always a serious possibility particularly in early MSA, we nevertheless consider it unlikely to account for our results. This substudy was performed in highly experienced clinical centres applying validated diagnostic criteria [12] and an error rate of 15 out of 28 patients (i.e. more than 50%) would be far beyond what has been observed in previous clinical series with *post mortem* confirmation [25,26]. Furthermore, a retrospective assessment of 31 patients followed long-term at our own centre (Innsbruck, Austria) with a classical presentation and disease-course of MSA revealed that 10 (32.2%) of these would have been classified as MR-negative at baseline [27].

Although this is the first study assessing the association of specific structural changes on structural MRI on the clinical progression of the disease, other than the lack of post-mortem verification, the small sample size is a further limitation of this study. Future studies in a larger sample of MSA-P patients as well as quantitative assessment of MR abnormalities would be highly warranted (1) to study the relationship between changes in clinical scales (UMSARS and its subitems) and brain volume changes and (2) to refine MRI predictors of more rapid progression and worse prognosis Moreover, the trial had only included patients with the parkinsonian variant of MSA, hence, our findings cannot be generalized to patients with MSA-C.

The present results seem to suggest that the presence of MRI features indicate a more aggressive or more advanced pathology, thus greater severity and faster progression. Such findings have obvious implications for trial design and future MSA studies may need to consider stratification by MRI signs at baseline. Patients with a faster rate of progression will reach milestones earlier – facilitating shorter trial periods, but with the added risks of early discontinuation. Using the 12-month UMSARS total decline rates from this study, we have estimated the required sample sizes for interventional trials with 1-year follow-up (Supplementary Appendix). Our estimations demonstrate that recruiting MRI-positive patients could reduce the number of patients per group by around 9-fold compared to MRI-negative patients. For example, 70–93 patients with MRI-positive signs would be required to detect 50% effect size with 80% and 90% power, respectively, compared to an estimated 607–812 patients with MRI-negative signs.

In conclusion, the results of this *post-hoc* analysis should have immediate impact on the future planning of clinical trials in MSA. The full study already demonstrated the feasibility of recruiting adequate patient numbers for this orphan disease and the potential utility of MRI imaging as a quantitative measure of disease progression [11]. It now appears that incorporating MR imaging into trial design, will not only offer a quantitative measure to show an effect on underlying disease, but will also reduce the numbers of patients required to show an effect. In terms of clinical practice, an understanding of the differing rates of progression will aid in the planning of long-term care.

## Competing interests

FK reports grants from MSA Coalition, the International Parkinson's Disease and Movement Disorder Society, and the Austrian Parkinson's Disease Society, and non-financial support from Fight MSA. K.S. reports grants from Oesterreichische Nationalbank, FWF Austrian Science Fund, Michael J. Fox Foundation, and International Parkinson and Movement Disorder Society and personal fees from International Parkinson and Movement Disorder Society, Boehringer Ingelheim, UCB, Lundbeck, Teva, Abbvie and AOP Orphan Pharmaceuticals AG. GW reports receiving consulting and/or lecture fees from Affiris, Astra Zeneca, Boehringer Ingelheim, Ever Pharma, Lundbeck, Neuropore, Orion and UCB as well as grant support from Medical University of Innsbruck, Oesterreichische Nationalbank, FWF Austrian Science Fund, US MSA Coalition, Affiris, Astra Zeneca and Boehringer Ingelheim. VA and SP are employed by Teva Pharmaceutical Industries. WP reports receiving consulting fees from Teva, Boehringer Ingelheim, Genzyme, Solvay, and Novartis, lecture fees from Teva, Boehringer Ingelheim, Novartis, UCB, and Orion and grant support from the Michael J Fox Foundation, EU FP7 and Horizon 2020 programmes.

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## Documentation of author roles

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

FK: 2A, 2B, 3A
KS: 1A, 1C, 2A, 2B, 3A
GKW: 1C, 2C, 3B
VA: 1C, 2C, 3B
SP: 1C, 2C, 3B
GG: 1C, 2A, 2C, 3B
MS: 1C, 2C, 3B
WP: 1A, 1B, 1C, 2A, 2C, 3A

## Financial disclosures

KS, GKW, WP report fees for consultancy and speaker fees from Teva Pharmaceuticals, and participated in the MSA-Ras trial. VA and SP are employed by Teva Pharmaceuticals. FK, GG, MS have nothing to report in relation to this study.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.08.004.

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