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Teriflunomide in relapsing-remitting multiple sclerosis: outcomes by age and pre-treatment status

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Abstract

Background and aims: To investigate effectiveness and safety of teriflunomide (14 mg once daily) in association with age and pre-treatment in unselected MS patients.

Methods: Prespecified analysis of a non-interventional, prospective, real-world study in Germany.

Results: A total of 558 (49.5%) patients were above 45 years old, and 593 patients (52.6%) had been pre-treated within 6 months prior to teriflunomide. Baseline Expanded Disability Status Scale (EDSS) was higher with older age, with lower number of relapses. Relapse rate decreased in all age groups, and in both treatment-naïve (0.82 ± 0.73 at baseline; 0.25 ± 0.55 under teriflunomide) and pre-treated (from 0.48 ± 0.76; 0.22 ± 0.50) patients after 12 months compared with the year before teriflunomide initiation. EDSS remained stable in patients of all age groups as well as in therapy-naïve and pre-treated patients over 24 months. The percentage of patients with adverse events (AEs) ranged between 29.2% (age group >25–35) and 38.9% (age group >55–65), with an increased discontinuation rate (most commonly due to diarrhoea, alopecia and nausea) in the higher age groups. AE rates were lower in pre-treated compared with treatment-naïve patients.

Conclusion: Overall, patients of all age groups including older patients, and irrespective of pre-treatment, benefit from teriflunomide treatment in routine clinical practice.

Registration: BfArM public study database number 2075.

Keywords: age, immunosenescence, multiple sclerosis, observational, pre-treatment, satisfaction, switch, treatment

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Introduction

Multiple sclerosis (MS) shows highest incidence during young adult age.[1,2] However, due to the chronic character of the disease, an increasing proportion of patients is now elderly.[3] Focal inflammatory activity of the disease as reflected by relapse rates or magnetic resonance imaging (MRI) activity generally is reduced with age.[4,5] On the other hand, elderly patients often have comorbidities such as arterial hypertension or diabetes mellitus, which may complicate MS treatment.[6] In addition, these patients may be affected by a phenomenon named immunosenescence, which comprises aging-associated changes in the innate and adaptive immune response, chronic antigenic stimulation and the occurrence of endogenous macromolecular changes, as well as the presence of senescent cells exhibiting a senescence-associated secretory phenotype.[7]

The effectiveness and safety of drug treatment may depend on patient age (e.g. owing to disease duration, immunosenescence and concomitant disease) and previous treatment.[8] An age-associated loss of relative efficacy has been reported for some MS drugs, including natalizumab[9] and fingolimod,[10]

whereas potentially severe adverse drug reactions have been reported to be overrepresented in older patients.[11]

Teriflunomide is a once-daily oral immunomodulator approved in >80 countries for treating relapsing MS (RMS), including clinically isolated syndrome, relapsing-remitting MS, and active secondary progressive MS, depending on the local label.[12,13] Whereas patients with a relatively broad age range were investigated in the clinical trial programme, the upper age limit was commonly restricted to 55 years. To overcome this restriction, we resorted to the non-interventional TAURUS-MS I study, a large contemporary cohort of real-world MS patients in Germany, where teriflunomide is used commonly for mild to moderate forms of relapsing-remitting MS; under European Medicines Agency approval, teriflunomide should be used with caution in patients aged 65 and above due to insufficient data on safety and efficacy.[14]

We specifically investigated whether age and pre-treatment status have an effect on effectiveness and safety of teriflunomide under routine clinical practice conditions in unselected MS patients.

Methods

Details of the TAURUS-MS I study ('Therapie mit Aubagio® unter Praxisbedingungen: Wirksamkeit, Lebensqualität und Verträglichkeit bei Patienten mit schubförmiger Multipler Sklerose') have been reported previously.[15] In short, this was a non-interventional, prospective, longitudinal study performed by 307 office-based and hospital-based neurologists across Germany from 2014 to 2017. The study was approved locally by the Ethic Committee at the Ruhr-University of Bochum, Faculty of Medicine under number 4874-13, as well as registered in the BfArM public study database under number 2075.

Patients were eligible for documentation if they were aged ⩾18 years (with no upper age limit), had a diagnosis of relapsing-remitting MS, provided written patient informed consent, were capable of completing questionnaires, and had no contraindications to Aubagio® (teriflunomide, approved dose 14 mg once daily). Data were obtained at entry, after 3 months, and 6, 12, 18 and 24 months. Documented parameters included demographics, information on MS (date of onset and diagnosis, type, number of relapses, disability), previous disease modifying therapy (DMT) use, fatigue as measured using the fatigue severity scale (FSS), treatment satisfaction questionnaire of medication (TSQM) and adverse events (AEs).[16]

Statistical analysis

Analyses were done in an exploratory manner using descriptive statistical methods. For continuous variables, the number of patients with non-missing and missing data, mean, standard deviation, minimum, 25% quantile, median, 75% quantile and maximum were calculated. For ordinal and categorical variables, frequencies were calculated. Incomplete data sets were included in the analysis. There was no imputation of missing values for any endpoint. No sensitivity analyses were done.

Subgroups were defined by (a) patient age (18–25 years, 26–35, 36–45, 46–55, 56–65 and 66+ years), and (b) pre-treatment with MS drugs (no pre-treatment, pre-treatment stopped within 6 months before start of teriflunomide). Subgroup analyses were performed independent from each other, and each patient is considered in both analyses.

The safety analysis set (patients with case report form available or AE report from study available) comprised 1139 patients; the effectiveness analysis set (teriflunomide-treated patients who complied with the protocol) comprised 1128 patients.

Clinical results were analysed by visit. For the analysis of relapse rate, the Wilcoxon matched-pairs signed-ranks test was used, because the number of relapses showed a positively skewed distribution. Changes from baseline were analysed by repeated measurement analysis for time trends. Analyses were carried out with the statistical tool SPSS for Windows (version 15.0.0). As an exception, confidence intervals (CI) of categorical variables were calculated with the statistical software BIAS version 10.12.

Results

Data from 1128 patients who fulfilled the inclusion criteria and fully complied with the protocol were analysed.

Information on patients at inclusion is provided in Table 1. Overall, mean age of patients was

Table 1. Demographic data at baseline.

Characteristic	All patients	Stratified by age (years)						Stratified by pre-treatment	
		⩽25	>25–35	>35–45	>45–55	>55–65	>65	No pre-treatment	Pre-treatment stopped ⩽6 months ('switcher')
	N = 1128	*N* = 43	*N* = 168	*N* = 357	*N* = 408	*N* = 131	*N* = 19	*N* = 280	*N* = 593
Sex [*n* (%)]	1128	43	168	357	408	131	19	280	593
Male	367 (32.54)	26 (60.47)	70 (41.67)	113 (31.65)	117 (28.68)	36 (27.48)	5 (26.32)	108 (38.57)	181 (30.52)
Female	761 (67.46)	17 (39.53)	98 (58.33)	244 (68.35)	291 (71.32)	95 (72.52)	14 (73.68)	172 (61.43)	412 (69.48)
Age	1126	43	168	357	408	131	19	279	592
years, mean ± SD	44.85 ± 10.16	22.70 ± 2.11	31.27 ± 2.66	41.20 ± 2.89	50.14 ± 2.79	59.50 ± 2.67	69.05 ± 3.19	44.06 ± 10.77	45.30 ± 10.15
Time since first symptoms	1065	39	163	336	384	125	17	262	565
years, mean ± SD	10.64 ± 8.18	2.00 ± 2.20	5.62 ± 4.57	9.87 ± 6.91	13.15 ± 8.63	13.66 ± 9.08	15.59 ± 10.01	7.25 ± 8.07	11.02 ± 7.83
Time since diagnosis of MS	1075	38	165	338	388	127	18	265	569
years, mean ± SD	8.86 ± 7.55	1.68 ± 2.27	4.78 ± 4.41	8.37 ± 6.50	10.57 ± 8.04	11.74 ± 8.60	13.56 ± 10.29	5.00 ± 7.16	9.44 ± 7.10
EDSS at baseline	947	39	138	294	344	114	17	232	498
Mean ± SD	2.31 ± 1.50	1.13 ± 0.85	1.64 ± 1.22	2.10 ± 1.34	2.67 ± 1.56	2.94 ± 1.59	2.79 ± 1.23	1.83 ± 1.30	2.44 ± 1.54
Number of MS relapses over the past 12 months	1128	43	168	357	408	131	19	280	593
Mean ± SD	0.61 ± 0.78	0.84 ± 0.72	0.85 ± 0.99	0.54 ± 0.70	0.60 ± 0.75	0.50 ± 0.74	0.58 ± 0.77	0.82 ± 0.70	0.49 ± 0.76
Number of MS relapses over the past 24 months	1117	43	167	350	406	130	19	275	589
Mean ± SD	0.95 ± 1.10	1.33 ± 0.71	1.23 ± 1.45	0.88 ± 0.99	0.89 ± 1.00	0.78 ± 1.11	1.11 ± 1.56	1.08 ± 0.91	0.83 ± 1.11
MS associated/induced diseases or symptoms [*n* (%)]	1128	43	168	357	408	131	19	280	593
Fatigue	637 (56.47)	10 (23.26)	81 (48.21)	193 (54.06)	256 (62.75)	84 (64.12)	13 (68.42)	123 (43.93)	353 (59.53)
Depression (major depressive disorder, MDD)	289 (25.62)	5 (11.63)	37 (22.02)	88 (24.65)	118 (28.92)	37 (28.24)	4 (21.05)	47 (16.79)	176 (29.68)
Cognitive deficits	294 (26.06)	3 (6.98)	38 (22.62)	77 (21.57)	118 (28.92)	49 (37.40)	9 (47.37)	56 (20.00)	155 (26.14)
Spasticity	235 (20.83)	2 (4.65)	24 (14.29)	58 (16.25)	108 (26.47)	37 (28.24)	6 (31.58)	33 (11.79)	153 (25.80)
Bladder dysfunction	261 (23.14)	4 (9.30)	23 (13.69)	70 (19.61)	111 (27.21)	46 (35.11)	7 (36.84)	40 (14.29)	154 (25.97)
Other	354 (31.38)	14 (32.56)	49 (29.17)	98 (27.45)	133 (32.60)	51 (38.93)	9 (47.37)	96 (34.29)	184 (31.03)

SD, standard deviation.

44.9 ± 10.2 years, with mean time since MS diagnosis 8.9 ± 7.6 years. Mean Expanded Disability Status Scale (EDSS) was 2.3 ± 1.5 (0.0–7.0). While the mean number of MS relapses was 0.6 ± 0.8 over the past 12-months prior to study entry, a substantial proportion of patients (52.7%) had no relapse during this interval.

Subgroups by age

A total of 558 (49.5%) patients were above 45 years old, with 131 patients in the age group >55–65 and 19 patients being over 65 years old. The proportion of females rose with increasing age (from 39.5% in patients aged 18–25 years to 73.7% in patients aged 66+ years; Table 1). As expected, compared with younger age groups (18–25 and 26–35 years old), older patients had a longer disease duration, more comorbidities, and a higher grade of disability by EDSS; however, they had less active disease with a lower number of relapses. All MS induced symptoms (e.g. depression, fatigue, cognitive deficits) were reported more frequently in patients aged 46+ years. Fatigue was the most common complaint across all age groups (56.5%); however, fatigue clearly increased with age (⩽25 years 23.3%; >65 years 68.4%). In terms of effectiveness, the relapse rate within 1 year under teriflunomide treatment was reduced significantly by more than half in any age group, including the higher age groups of patients above 45 years, compared with the year before teriflunomide initiation (Table 2; Figure 1). Compared with baseline, EDSS remained stable in all age groups during the 24-month observation period (Table 2). Also, FSS scores remained nearly unchanged from baseline to last visit; however, in patients aged 36–45 years it improved slightly ($p \leqslant 0.05$; Table 2).

Subgroups by pre-treatment

Out of the 1128 patients, one quarter ($n = 280$, 24.8%) had not received prior MS treatment and 593 patients (52.6%) had stopped prior treatment in the period from 6 months to 1 day before teriflunomide initiation ('switchers', Table 2). Of the recently pre-treated patients, 253 had received interferon-β (IFN-β), and 119 glatiramer acetate (i.e. injection therapies). Reasons for treatment switches were not reported. Patients without and with pre-treatment were about the same age, but MS disease history (11.0 *versus* 7.3 years since first symptoms), EDSS score at baseline (2.4 *versus* 1.8) and rate of MS-associated symptoms (e.g. fatigue 59.5% *versus* 43.9%) differed in recently pre-treated patients *versus* patients with no pre-treatment. Further, in pre-treated patients, the number of relapses was lower (past 12 months: 0.48 *versus* 0.82 events).

Both treatment-naïve and pre-treated patients experienced a reduction of the relapse rate per year after 12 months of teriflunomide therapy compared with the year before teriflunomide initiation (treatment-naïve: 0.82 ± 0.73 at BL to 0.25 ± 0.55; pre-treated 0.48 ± 0.76–0.22 ± 0.50; both $p \leqslant 0.001$).

The change in the EDSS score in the pre-treated ('switcher') group after 24 months compared with baseline was not significant (+0.08, $p = 0.183$), while the change in the treatment-naïve group was significant (+0.25; $p \leqslant 0.05$). The FSS score was stable in treatment-naïve patients, whereas it improved slightly (−0.19; $p \leqslant 0.05$) in pre-treated patients from baseline to last visit.

Patient satisfaction with treatment

In pre-treated patients all three domains of TSQM improved substantially after 24 months compared with baseline ($p \leqslant 0.001$; Table 2). The majority of pre-treated patients received either IFN-β or glatiramer acetate before initiation of teriflunomide and were therefore analysed separately. In patients pre-treated with injectable therapies, all three domains of TSQM improved substantially after 24 months compared with baseline global satisfaction +15.9 ± 25.4 points ($n = 145$; $p \leqslant 0.001$), effectiveness +7.1 ± 28.6 points ($n = 145$; $p \leqslant 0.01$), convenience + 17.3 ± 27.2 points ($n = 144$; $p \leqslant 0.001$; Figure 2). Effects on the convenience and global satisfaction TSQM scales were numerically smaller in patients aged 46 years and above compared with the younger age groups (Table 2).

Safety

The number of patients with AEs was lowest in patients aged 26–35 years (29.2%), whereas there was no clear difference among the other age strata; this observation also held true for serious AEs [7.7% (26–35 years); 15.0% (46–55 years; Table 3)]. With focus on specific infectious AEs, viral upper respiratory tract infections and influenza did not appear to increase with increasing

Table 2. Effectiveness.

Characteristic	All patients	Stratified by age (years)						Stratified by pre-treatment	
		⩽25	>25–35	>35–45	>45–55	>55–65	>65	No pre-treatment	Pre-treatment stopped ⩽6 months ("switcher")
	N = 1128	*N* = 43	*N* = 168	*N* = 357	*N* = 408	*N* = 131	*N* = 19	*N* = 280	*N* = 593
Relapse rate per year (12 months observation) (mean ± SD)	754	25	105	228	288	92	15	198	406
Relapse rate at baseline last 12 months	0.59 ± 0.76	0.84 ± 0.75	0.90 ± 1.02	0.51 ± 0.69	0.58 ± 0.70	0.43 ± 0.65	0.47 ± 0.74	0.82 ± 0.73	0.48 ± 0.76
Relapses rate after 12 months	0.24 ± 0.53	0.24 ± 0.52	0.34 ± 0.63	0.28 ± 0.57	0.22 ± 0.48	0.15 ± 0.42	0.07 ± 0.26	0.25 ± 0.55	0.22 ± 0.50
	$p \leqslant 0.001$	$p \leqslant 0.01$	$p \leqslant 0.001$	$p \leqslant 0.001$	$p \leqslant 0.001$	$p \leqslant 0.001$	$p < 0.05$	$p \leqslant 0.001$	$p \leqslant 0.001$
EDSS change from BL after 24 months (mean ± SD)	346	7	45	106	135	44	8	88	197
BL	2.28 ± 1.49	0.71 ± 0.57	1.51 ± 1.37	2.06 ± 1.30	2.62 ± 1.53	2.84 ± 1.55	2.31 ± 1.03	1.79 ± 1.20	2.39 ± 1.56
After 24 months change	2.40 ± 1.55	0.64 ± 0.48	1.44 ± 1.39	2.20 ± 1.42	2.70 ± 1.55	3.08 ± 1.46	3.13 ± 1.38	2.04 ± 1.43	2.47 ± 1.61
	+0.11 ± 0.89	−0.07 ± 0.61	−0.07 ± 0.83	+0.14 ± 0.84	+0.08 ± 0.84	+0.24 ± 1.06	+0.81 ± 1.46	+0.25 ± 1.05	+0.08 ± 0.82
		$p = 0.766$	$p = 0.593$	$p = 0.097$	$p = 0.268$	$p = 0.145$	$p = 0.16$	$p \leqslant 0.05$	$p = 0.183$
FSS									
Change from BL *versus* last visit (mean ± SD; *n*)	−0.11 ± 1.60; 724	0.17 ± 1.51; 20	0.04 ± 1.72; 104	−0.21 ± 1.46; 223	−0.17 ± 1.62; 272	0.01 ± 1.66; 88	0.09 ± 2.20; 15	0.15 ± 1.75; 146	−0.19 ± 1.53; 428
	$p = 0.57$	$p = 0.622$	$p = 0.798$	$p \leqslant 0.05$	$p = 0.079$	$p = 0.969$	$p = 0.874$	$p = 0.286$	$p \leqslant 0.05$
TSQM-9 change from BL after 24 months (mean ± SD; *n*)									
Effectiveness scale	7.55 ± 27.90; 338	3.17 ± 28.48; 7	13.06 ± 25.89; 40	8.2 ± 27.62; 102	7.45 ± 27.75; 139	3.59 ± 30.02; 41	−4.17 ± 34.98; 8	0.96 ± 24.89; 49	8.09 ± 27.66; 229
		$p = 0.778$	$p = 0.003$	$p = 0.003$	$p = 0.002$	$p = 0.448$	$p = 0.746$	$p = 0.788$	$p \leqslant 0.001$
Convenience scale	13.95 ± 25.93; 346	1.59 ± 29.17; 7	14.5 ± 31.35; 41	19.71 ± 27.45; 106	12.02 ± 24.43; 146	9.16 ± 19.95; 37	1.39 ± 4.92; 8	−0.43 ± 14.46; 52	17.03 ± 26.58; 231
		$p = 0.890$	$p = 0.005$	$p \leqslant 0.001$	$p \leqslant 0.001$	$p \leqslant 0.01$	$p = 0.451$	$p = 0.832$	$p \leqslant 0.001$
Global satisfaction scale	12.84 ± 26.66; 348	3.57 ± 36.60; 7	11.41 ± 29.55; 41	15.82 ± 26.83; 107	12.87 ± 27.38; 146	8.18 ± 19.84; 38	8.93 ± 14.16; 8	3.92 ± 22.21; 51	15.25 ± 27.36; 232
		$p = 0.805$	$p = 0.18$	$p \leqslant 0.001$	$p \leqslant 0.001$	$p \leqslant 0.05$	$p = 0.118$	$p = 0.213$	$p \leqslant 0.001$

BL, baseline; SD, standard deviation; TSQM, treatment satisfaction questionnaire of medication.

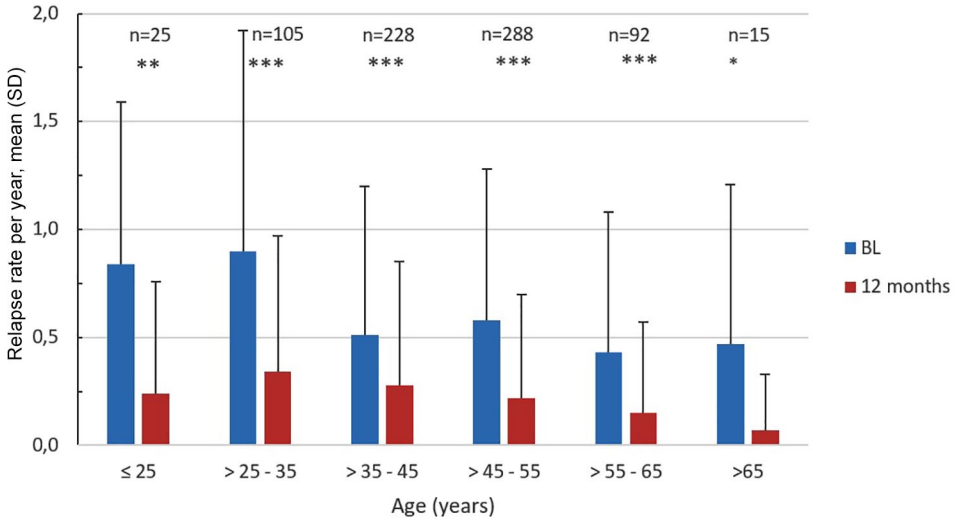

Figure 1. Relapse rate per year after 12 months treatment with teriflunomide versus 12 months before treatment, by age group. Columns display relapse rates per year at baseline, including the 12-month period prior teriflunomide treatment (blue), and after 12-month teriflunomide treatment (red). Whiskers are SD. Comparisons of relapse rates after 12 months versus baseline within each age group were made with two-tailed *t* tests.
*$p < 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.
BL, baseline; SD, standard deviation.

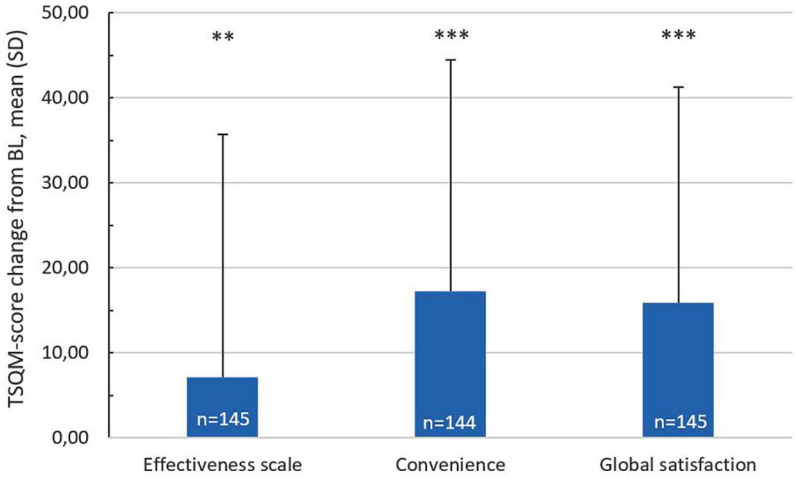

Figure 2. Mean change from baseline in TSQM global satisfaction, effectiveness, and convenience scores to 24 months among 'switchers from injectables.' Analysis based on pre-treated patients who received either IFN-β or glatiramer acetate (i.e. injection therapies) before switch to teriflunomide. Columns display mean changes compared with baseline; whiskers are SD. All changes were statistically significant in two-tailed *t* tests.
**$p \leq 0.01$. ***$p \leq 0.001$.
BL, baseline; IFN-β, interferon beta; SD, standard deviation; TSQM, treatment satisfaction questionnaire of medication.

age (Table 3). The rate of patients with infections (irrespective of severity and type) was very similar in patients aged ⩽45 years and those aged >45 years.

A total of 97 patients (8.6%) discontinued teriflunomide treatment due to AEs, and the rate of discontinuations was higher in patients >45 years (61 cases; 62.9%) compared with the younger age

Table 3. Safety.

Characteristic	All patients	Stratified by age (years)						Stratified by pre-treatment	
		⩽25	>25–35	>35–45	>45–55	>55–65	>65	No pre-treatment	Pre-treatment stopped ⩽6 months ('switcher')
	N = 1128	*N* = 43	*N* = 168	*N* = 357	*N* = 408	*N* = 131	*N* = 19	*N* = 280	*N* = 593
AEs – patient base [*n* (%)]									
Patients with AE	403 (35.73)	16 (37.21)	49 (29.17)	128 (35.85)	152 (37.25)	51 (38.93)	6 (31.58)	112 (40.00)	190 (32.04)
Patients with serious AE	146 (12.94)	6 (13.95)	13 (7.74)	46 (12.89)	61 (14.95)	18 (13.74)	1 (5.26)	43 (15.36)	65 (10.96)
Most common events									
Diarrhoea	54 (4.79)	0 (0.00)	5 (2.98)	19 (5.32)	23 (5.64)	7 (5.34)	0 (0.00)	16 (5.71)	25 (4.22)
MS relapse	48 (4.26)	5 (11.63)	7 (4.17)	14 (3.92)	21 (5.15)	1 (0.76)	0 (0.00)	13 (4.64)	25 (4.22)
Alopecia	38 (3.37)	2 (4.65)	6 (3.57)	8 (2.24)	15 (3.68)	5 (3.82)	2 (10.53)	10 (3.57)	18 (3.04)
Viral upper respiratory tract infection	31 (2.75)	1 (2.33)	5 (2.98)	9 (2.52)	13 (3.19)	2 (1.53)	0 (0.00)	12 (4.29)	11 (1.85)
Influenza	22 (1.95)	1 (2.33)	3 (1.79)	8 (2.24)	9 (2.21)	1 (0.76)	0 (0.00)	6 (2.14)	11 (1.85)
Continuation/discontinuation of treatment [*n* (%)]									
Treatment continued	512 (45.39)	14 (32.56)	62 (36.90)	152 (42.58)	214 (52.45)	59 (45.04)	10 (52.63)	131 (46.79)	283 (47.72)
Treatment discontinued	242 (21.45)	12 (27.91)	34 (20.24)	75 (21.01)	82 (20.10)	36 (27.48)	3 (15.79)	56 (20.00)	111 (18.72)
Thereof: due to AE	97 (8.60)	2 (4.65)	7 (4.17)	27 (7.56)	38 (9.31)	21 (16.03)	2 (10.53)	19 (6.79)	45 (7.59)
Lost to follow up	374 (33.16)	17 (39.53)	72 (42.86)	130 (36.41)	112 (27.45)	36 (27.48)	6 (31.58)	93 (33.21)	199 (33.56)

AE, adverse event.

groups (36 cases; 37.1%; $p \leq 0.01$). The most common AEs leading to discontinuations overall were diarrhoea, alopecia and nausea. In patients aged 46 years and above, for example, hypertension ($n = 4$) and arthralgia ($n = 3$) were reasons for discontinuation that were not noted as reasons in younger patients (Supplemental Table S1).

Comparisons between age groups on blood laboratory values were not feasible due to different standard values of site laboratories.

The number of patients with AEs or serious AEs was lower in the pre-treated compared with the treatment-naïve group (34.2% *versus* 40.0% and 12.2% *versus* 15.4%, respectively). The pattern of events appeared to be similar across groups.

Discussion

The TAURUS-MS I study was one of the first to report experience with teriflunomide under practice conditions in a real-world MS population.[15] Of note, 49.5% of patients were aged 45 years and above, and 24.8% of the observed patients had been treatment-naïve. In this analysis from the TAURUS-MS I study we demonstrate that patients of all age groups and irrespective of pre-treatment status exhibit a decrease of disease activity in terms of relapses under teriflunomide treatment. However, older patients may discontinue treatment more often due to side effects.

Age in randomised clinical trials in MS typically caps at 50–55 years. Data from elderly MS patients are limited and of special interest in view of the fact that an increasing proportion of patients, often after long-term management of their disease, are now in the higher age groups. In addition, the aging process is accompanied by remodelling of the immune system, which may lead to a decline in immune responses as reflected in increased vulnerability to infectious diseases, diminished responses to vaccination and a susceptibility to age-related inflammatory diseases.[17] Immunosenescence-associated changes may also add to the effects produced by immunomodulatory and immunosuppressive medications in MS.[8] Currently approved therapies for MS are effective in preventing relapse but might be less useful in preventing the accumulation of disability associated with aging and disease progression.[18]

The original clinical development plan of teriflunomide comprised 29 clinical studies, of which 12 were phase II and III studies.[14] Across the whole population of studies, there were predominantly female patients (72.3%), with a median age of 39 years. So far, data on teriflunomide from clinical trials on the elderly is limited.[19] The oldest subject in the clinical development program (phase I–III) was aged 65 and none above this age was exposed to teriflunomide, leading to recommendations for cautionary use in patients aged 65 years and above.[14]

The current analysis indicates that teriflunomide is equally effective in patients of younger and older age groups: over time, EDSS was stable, and the reduction of relapse rates compared with the pre-treatment period was not age-dependent.

Fatigue is consistently reported as the most prevalent and persistent symptom in MS, with profound effects on quality of life, work capabilities and activities of daily living.[20] Data on fatigue prevalence are very limited in the elderly MS population. Interferon therapy in MS has been associated with fatigue,[21] and changing from interferon to glatiramer acetate has already been associated with improvement of fatigue and work/activity impairment and quality of life, respectively.[22,23] Indeed, the FSS score in pre-treated patients (many of them previous IFN users) in TAURUS-MS I improved under teriflunomide. Patient satisfaction, as measured with the TSQM, improved efficacy and convenience domains in pre-treated patients, the latter being in line with the general finding that oral medications are more convenient than injectables.[24]

The prescribing information states in the section 'switching to teriflunomide' that there is no waiting period required when teriflunomide is initiated after INF-β or glatiramer acetate, but does not contain information about efficacy when pursuing this approach. The current analysis provides real-world data suggesting that, irrespective of pre-treatment, patients benefit from teriflunomide treatment.

In terms of the effect of pre-treatment MS medication, subgroup analyses of the teriflunomide TEMSO study are of interest.[25] In this randomized, double-blind, placebo-controlled, parallel-group trial, out of 1086 MS patients with relapses, 27.1% had been pre-treated with

previous MS medication in the last 2 years before inclusion. Pre-treated patients had a lower relative risk for MS relapse compared with treatment-naïve patients (each *versus* placebo, 14 mg dose): 0.60 (95% CI 0.43–0.85) *versus* 0.70 (95% CI 0.45–0.92).[25] Given the number of treatment options and the possibility of medication switches in routine clinical treatment of MS patients, it is important to note from our study that pre-treatment does not interfere with effectiveness or safety of later treatment with teriflunomide.

In total, AEs occurred in 35.7% of patients, with 97 patients (8.6%) discontinuing treatment due to AEs. The higher discontinuation rate in the elderly as shown in TAURUS-MS I is a typical finding.[18,26] Against this background, safety results must be interpreted with caution. Teriflunomide treatment appeared not to be associated with increased infections in elderly patients compared with younger patients under real world conditions. Especially for viral respiratory tract infections and influenza there was no clear difference across the age groups.

Further methodological considerations must be taken into consideration when discussing the present results. As limitations, the TAURUS-MS I study used an observational design, which may lead to unquantifiable selection bias of MS patients (e.g. underrepresentation of critically ill individuals).[27] MS patients in the study may be more compliant than non-participating persons.[28] The loss-to-follow-up rate over time was substantial, as in other observational MS studies.[29] Of note, the magnitude of the relapse rate reduction compared with baseline should be considered with caution. Patients who were treatment naïve likely were starting treatment after a new diagnosis of MS accompanied by relapses in the past year. Similarly, patients who switched off IFN-β or glatiramer acetate may have had breakthrough disease activity. Therefore, regression to the mean likely contributed to the decrease in relapses,[30] in particular as this variable has substantial within-subject variability over time.[31]

Strengths of the study comprise the large number of patients, and focus on the ambulatory setting rather than on university or specialist centres, better reflecting real world situations.

In conclusion, in this large real-life cohort, patients of all age groups including older patients (who typically are excluded from older trials of DMTs), and irrespective of pre-treatment, benefit from teriflunomide treatment in routine clinical practice.

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Author contributions

All authors contributed to the design of the study and interpretation of the results. AC and JK wrote the first version of the manuscript, and the other authors provided input into the concept and the interpretation of results. All authors reviewed and approved the final version.

Conflict of interest statement

BAK has received compensation for activities with Bayer, Biogen, Sanofi Genzyme, Merck, Novartis, Roche and Teva.

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Statement on data sharing

Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com/.

Supplemental material

Supplemental material for this article is available online.

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