Peripheral neuropathy as potential side effect of teriflunomide

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Clinical

YOUNG INVESTIGATOR

Background and Aims

Peripheral neuropathy has been reported as potential but uncommon side effect of teriflunomide. If patients develop symptoms consistent with peripheral neuropathy, the European Medicines Agency recommends to discontinue teriflunomide and performing an accelerated elimination procedure. However, real-world data are scarce, and little is known about the electrophysiological effect on peripheral nerves.

Our aim was to investigate whether neurophysiological abnormalities occur in peripheral nerves of patients with multiple sclerosis (MS) treated with teriflunomide.

Methods

Cross-sectional analysis of 9 patients with relapsing MS treated with teriflunomide:

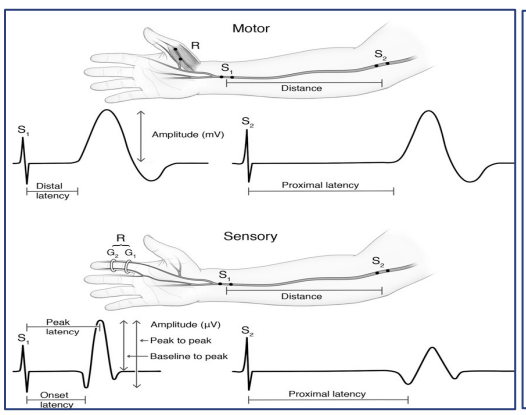
- full **medical history** and **neurological examination**
- peripheral **neuropathy symptom score (NSS):**

1. Burning/numbness/tingling	2
Fatique/cramping/aching	1
No above symptoms	0
2. Symptoms present in feet	2
Symptoms present in calves	1
Symptoms present elsewhere	0
3. Nocturnal exacerbation of symptom	2
Symptoms present day & night	1
Symptoms present at daytime only	0
4. Symptoms wake patient up from sleep	1
5. Manoeuvres to reduce symptoms :	
Walking	2
Standing	1
Sitting/lying	0
Total Score :	

Mild symptoms 3-4, moderate symptoms 5-6, severe symptoms 7-9

Boulton et al, Medical Clinics of North America 1998

- **blood tests** performed within the 3 months previous the study retrospectively analyzed for detection of confounding factors
- **nerve conduction studies (NCS)** testing both upper and lower limbs:



Upper limbs
- DL, amplitude and NCV in motor and sensory ulnar and median nerves, and in sensory radial nerves
- F-wave in motor ulnar and median nerves

Lower limbs
- DL, amplitude and NCV in sural, peroneal and tibial nerves
- F-wave in tibial and peroneal nerves

DL= Distal Latency; NCV= Nerve Conduction Velocity

Results

Patient demographics and clinical characteristics (n = 9)	
Age, y (mean [min-max])	41 [25-66]
Sex, F/M	3/6
Disease duration, y (mean [min-max])	8 [3-37]
Disease course (number of patients and %)	
- RRMS	8 (89)
- SPMS	1 (11)
EDSS score (median [min-max])	1.5 [0-6]
Duration of teriflunomide exposure, mo (mean [min-max])	34 [6-65]
Height, meters (mean [min-max])	1.72 [1.6-1.82]
Previous DMT (0 to 2 per patient) (number of patients and %)	
- none	3 (33)
- glatiramer acetate	1 (11)
- dimethyl fumarate	2 (22)
- beta-interferon	3 (33)

RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; DMT, disease-modifying therapy; NSS, peripheral neuropathy symptom score

4 patients (44%) presented symptoms compatible with a peripheral neuropathy (NSS score ≥ 3)
However, these symptoms were not chronologically related to teriflunomide initiation, not progressive, nor associated with stocking-glove sensory loss and weak reflexes at neurological examination.

At NCS study, only three (33%) patients (two with negative and one with positive NSS, p >0.05) where found with **very mild and isolated abnormalities, not consistent with a drug induced peripheral neuropathy.**

Discussion and conclusions

Main observations:
- the lack of correlation between NCS and symptoms
- the absence of significant NCS abnormalities consistent with a diagnosis of peripheral neuropathy

- Since peripheral neuropathy is a rare side effect of teriflunomide and significant nerve conduction abnormalities are unlikely to be found, there is probably no advantage in carrying out NCS in patients treated with teriflunomide on a routine basis
- However, clinical scales are not specific enough for distinguishing peripheral neuropathy from MS related-symptoms, therefore caution is needed when used for screening of peripheral neuropathy

O'Connor et al. N Engl J Med. 2011, Confavreux et al. Mult Scler 2012, O'Connor et al. Neurology 2016, Confavreux et al. Lancet Neurol. 2014, Vermersch et al. Mult Scler. 2014, Miller et al. Mult Scler Relat Dis 2020, https://www.ema.europa.eu/en/medicines/human/EPAR/aubagio

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