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Original Article

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A large case series of travel-related *Mansonella perstans* (vector-borne filarial nematode): a TropNet study in Europe

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Abstract

Background: Infection with *Mansonella perstans* is a neglected filariasis, widely distributed in sub-Saharan Africa, characterized by an elusive clinical picture; treatment for mansonellosis is not standardized. This retrospective study aimed to describe the clinical features, treatment schemes and evolution, of a large cohort of imported cases of *M. perstans* infection seen in four European centres for tropical diseases.

Methods: *Mansonella perstans* infections, diagnosed by identification of blood microfilariae in migrants, expatriates and travellers, collected between 1994 and 2018, were retrospectively analysed. Data concerning demographics, clinical history and laboratory examinations at diagnosis and at follow-up time points were retrieved.

Results: A total of 392 patients were included in the study. Of the 281 patients for whom information on symptoms could be retrieved, 150 (53.4%) reported symptoms, abdominal pain and itching being the most frequent. Positive serology and eosinophilia were present in 84.4% and 66.1%, respectively, of those patients for whom these data were available. Concomitant parasitic infections were reported in 23.5% of patients. Treatment, administered to 325 patients (82.9%), was extremely heterogeneous between and within centres; the most commonly used regimen was mebendazole 100 mg twice a day for 1 month. A total of 256 (65.3%) patients attended a first follow-up, median 3 months (interquartile range 2–12) after the first visit; 83.1% of patients having received treatment based on mebendazole and/or doxycycline, targeting *Wolbachia*, became amicrofilaremic, 41.1–78.4% of whom within 12 months from single treatment.

Conclusions: Lack of specific symptoms, together with the inconstant positivity of parasitological and antibody-based assays in the infected population, makes the clinical suspicion and screening for mansonellosis particularly difficult. Prospective studies evaluating prevalence of infection in migrants from endemic areas, infection-specific morbidity, presence of *Wolbachia* endosymbionts in *M. perstans* populations from different geographical areas and efficacy of treatment regimens are absolutely needed to optimize the clinical management of infection.

Key words: Mansonella perstans, travel, clinical characteristics, treatment, follow-up

Introduction

Mansonella perstans is a filarial parasite of humans that is widely distributed in sub-Saharan Africa, with estimated 100 million people infected and 600 million at risk of infection, while sporadic cases are reported in the Caribbean and in Central and South America.[1,2] Prevalence rates up to 70–100% were reported among people living in rural villages of some endemic areas in African countries such as Cameroon, Ghana and Uganda.[3–5] The prevalence of *M. perstans* infection in migrants is largely unexplored and the infection is most likely often overlooked due to its elusive clinical presentation and low index of suspicion. Martelli *et al*.[6] in Italy reported a seroprevalence of 'filariasis' of 9.25% in migrants from sub-Saharan Africa, but it is unknown what proportion of these cases were actually caused by mansonellosis. In other studies from Spanish tropical diseases hospitals, *M. perstans* was reported in 3.9–10.9% of patients from sub-Saharan Africa having undergone specific parasitological tests to detect blood microfilariae (mf).[7–10]

Infective *M. perstans* larvae are transmitted by biting midges of the genus *Culicoides* during their blood meal.[2] The prepatent period is unknown. Adult worms are rarely recovered in humans; occasionally, they have been retrieved from connective tissues in the serous body cavities during surgery or autopsy.[11] Adult females produce mf, which circulate in the blood without circadian periodicity.[12]

Unlike other filariases, mansonellosis is often asymptomatic and, if symptoms are present, they are usually not associated to a specific clinical picture. Non-specific features such as hypereosinophilia, angioedema, Calabar's swelling-like oedemas, pruritus, fever, headache and pain in synovial/serous cavities are often described in infected patients.[13–18] However, it is often difficult to attribute the clinical manifestations to *M. perstans* infection, due to the high frequency of co-infections with other parasites.

The diagnosis of *M. perstans* relies on the detection of blood circulating mf; however, it is possible that a proportion of infections may be missed in case of infection with very low or absent microfilaremia, similar to what occurs in the case of occult (i.e. amicrofilaremic) loiasis. An antibody-detecting enzyme-linked immunosorbent assay test based on antigens from the related filarial nematode *Acanthocheilonema vitae* is commercially available, but it is not specific for *Mansonella* spp.

The treatment of *M. perstans* infection is not standardized. Prolonged courses of mebendazole, alone or in combination with diethylcarbamazine (DEC) or levamisole (no longer available), seems to be the most effective strategy, while DEC alone has lower efficacy[15,19]; prolonged treatment with albendazole also appears to have some efficacy.[20] However, all these approaches often seem to have only partial efficacy, and multiple treatment courses are often needed to reach mf clearance.[15] The presence of the bacterial endosymbiont *Wolbachia* in *M. perstans* is equivocal;[21] therefore, the efficacy of the anti-*Wolbachia* drug doxycycline for the treatment of infected patients is still not conclusively ascertained.[22–26]

Despite its wide distribution, high prevalence in endemic areas and evident although unspecific clinical manifestations, this infection has so far received very little attention. This study aimed to describe the clinical features, treatment schemes and evolution after treatment of a large cohort of imported cases of *M. perstans* infection seen in four European centres for tropical diseases included in the TropNet network.[27]

Materials and Methods

This is an observational, retrospective study, analysing data collected in four TropNet centres (Hospital del Poniente, Almeria, Spain; Institute of Tropical Medicine, Antwerp, Belgium; Vall d'Hebron University Hospital, Barcelona, Spain and IRCCS Sacro Cuore Don Calabria Hospital, Negrar, Verona, Italy). The study protocol was approved by the Ethics Committee for Clinical Studies of Verona and Rovigo Provinces, Italy (study protocol no. 56014).

Data were retrieved from the databases of each centre of all migrant, expatriate or traveller patients attended between 1994 and 2018 who had been travelling or living in an endemic country and were diagnosed with *M. perstans* infection. A case of *M. perstans* infection was defined, for the purpose of this study, as the demonstration of *M. perstans* mf in the blood by microscopy. For each patient, retrieved data concerned demographic information (sex, age, country of birth and of exposure), clinical history [symptoms (available only for the diagnosis time point), treatments, follow-up length] and laboratory examinations [parasitic co-infections at diagnosis, load of *M. perstans* mf/ml based on analysis of the sediment after modified Knott techniques or blood filtration followed by permanent staining for species identification, serology for filariasis (carried out only at diagnosis), presence of eosinophilia and eosinophils/μl]. Eosinophilia was defined as $\geq$450 eosinophils/μl in peripheral blood. Due to the retrospective and multicentric nature of the study, it was not possible to retrieve details about the methods used (serologic and/or parasitologic and/or molecular) for the diagnosis of parasitic co-infections, which could vary from centre to centre and from period to period within the same centre. De-identified data were collected in an electronic case report form accessible by password only to the investigators of each centre. A descriptive data analysis was performed. Demographic and clinical variables at baseline and at follow-up, as well as percentage change of clinical variables along the follow-up compared to baseline and previous time points, were reported as frequencies and percentages, medians and interquartile range (IQR), or mean and standard deviation (SD), as appropriate.

Results

Baseline cohort characteristics

A total of 392 patients were included in the study: 129 (32.9%) were diagnosed in Almeria, 99 (25.3%) in Negrar, 93 (23.7%) in Antwerp and 71 (18.1%) in Barcelona. Baseline patients' characteristics are summarized in Table 1.

Country of exposure to *M. perstans* was known for 390 (99.5%) cases, while these data were missing for two European expatriates (Figure 1). In migrants, country of exposure coincided with country of birth in all but two patients ($n = 262$, 99.2%). All tourists and the near totality of expatriates ($n = 120$, 97.6%) were from Europe; of the three non-European expatriates, one was from Lebanon, one from the Philippines and one from the Democratic Republic of the Congo. In 7 cases, the

Table 1. Baseline characteristics of patients with *M. perstans* infection

	ALM *N* = 129	NGR *N* = 99	ATW *N* = 93	BCL *N* = 71	All *N* = 392
Demographic data					
Male, *N* (%)	116 (89.9)	74 (74.8)	74 (79.6)	45 (63.4)	309 (78.8)
Age, mean ± SD (years)	29.7 ± 9.5	44.3 ± 17.7	50.3 ± 16.4	39.4 ± 19.6	40 ± 17.5
Type of patient, *N* (%)					
• Migrant	129 (100)	44 (44.4)	22 (23.7)	69 (97.2)	264 (67.3)
• Expatriate	0 (0.0)	54 (54.6)	67 (72.0)	2 (2.8)	123 (31.4)
• Tourist	0 (0.0)	1 (1.0)	4 (4.3)	0 (0.0)	5 (1.3)
Clinical data					
Presence of any symptom, *N* (%)					
• Yes	44 (34.1)	55 (55.5)	31 (33.3)	20 (28.2)	150 (34.4)
• No	85 (65.9)	18 (18.2)	62 (66.7)	51 (71.8)	131 (30.0)
• ND	0 (0.0)	26 (26.3)	0 (0.0)	0 (0.0)	155 (35.6)
Symptoms[a], *N* (% of those with symptoms)					
• Itching	1 (2.3)	24 (43.6)	20 (64.5)	11 (55.0)	56 (37.3)
• Rash	0 (0.0)	9 (16.4)	6 (19.4)	0 (0.0)	15 (10.0)
• Fatigue	0 (0.0)	20 (36.4)	3 (9.7)	1 (5.0)	24 (16.0)
• Asthma-like	0 (0.0)	3 (5.5)	6 (19.4)	0 (0.0)	9 (6.0)
• Abdominal pain	43 (97.7)	18 (32.7)	0 (0.0)	6 (30.0)	67 (44.7)
Laboratory data					
Microfilaremia					
• Quantification done, *N* (%)	8 (6.2)	98 (98.9)	93 (100)	71 (100)	270 (68.9)
• mf/ml, median (IQR)	120 (50–190)	13.5 (5–88)	46 (18–150)	19 (4–69)	26 (7–100)
Eosinophilia					
• Present, *N* (%)	94 (72.9)	77 (77.8)	52 (55.9)	36 (50.7)	259 (66.1)
• Eos/μl if eosinophilia, median (IQR)	815 (640–1287)	1060 (750–1800)	985 (632–1930)	900 (678–1349)	970 (645–1521)
Serology[b]					
• Performed, *N* (%)	76 (58.9)	62 (62.6)	79 (84.9)	1 (1.4)	218 (55.6)
Result if serology performed					
• Positive, *N* (%)	59 (77.6)	59 (95.2)	29 (36.7)	1 (100)	148 (67.9)
• Borderline, *N* (%)	0 (0.0)	0 (0.0)	36 (45.6)	0 (0.0)	36 (16.5)
• Negative, *N* (%)	17 (22.4)	3 (4.8)	14 (17.7)	0 (0.0)	34 (15.6)

ALM, Almeria; NGR, Negrar; ATW, Antwerp; BCL, Barcelona. ND, no data.
[a]Symptoms either present at the time of the visit or reported by the patient as reason for seeking medical advice. [b]Serology was carried out using different assays both between centres and within centres over time; only the final result could be consistently retrieved retrospectively.

country of exposure was not uniquely identifiable since patients resided in two or more endemic countries.

Data on clinical manifestations, either present at the first visit or reported by the patients before the visit, are summarized in Table 1. Of the 281 patients for whom this information could be retrieved, 150 (53.4%) presented one or more symptoms: abdominal pain and itching being the most prevalent. The quantification of mf load was carried out in 270 cases (68.9%) and a median load of 26 mf/ml (IQR 7–100) was observed in these cases. Data on results of serology for filariasis were available for 218 patients (55.6% of the whole cohort; of note Barcelona provided serology results only for 1 patient). Although we did not attempt to retrieve data on the seroassays used in each centre and over time, overall we observed that serology for filariasis was positive or borderline in the majority ($n = 184$, 84.4%) of these patients. Eosinophilia was reported in 259 (66.1%) cases with a median of 970 eosinophils/μl (IQR 645–1521) in patients with this finding. One or more concomitant parasitic infections were reported in 92 (23.5%) patients: $n = 38$ had schistosomiasis (diagnosed parasitologically and/or serologically), $n = 30$ strongyloidiasis (diagnosed parasitologically and/or serologically), $n = 32$ other intestinal helminthiases, $n = 13$ other filarial infections ($n = 10$ loiasis and $n = 3$ onchocercosis) and $n = 15$ malaria.

Treatment and follow-up

Specific treatment for *M. perstans* infection, administered to 325 patients (82.9%), was extremely heterogeneous between and within centres depending on the periods (Table 2) and encompassed the use of albendazole, diethylcarbamazine (DEC), mebendazole, levamisole, thiabendazole and doxycycline, alone or in combination with each other or with ivermectin. The most commonly used regimen was mebendazole 100 mg twice a day for 1 month. Of the treated patients, 107 (32.9%) had also received concomitant treatment for other parasitic infections with one or more drugs among which ivermectin, DEC, albendazole and praziquantel. Of the remaining 67 patients (17.1%), who did not have a record of treatment specifically administered for mansonellosis, 14 (20.9%) had received treatment against other parasites.

Data regarding microfilaremia, eosinophilia and re-treatments along follow-up visits are summarized in Table 3. A total of 136

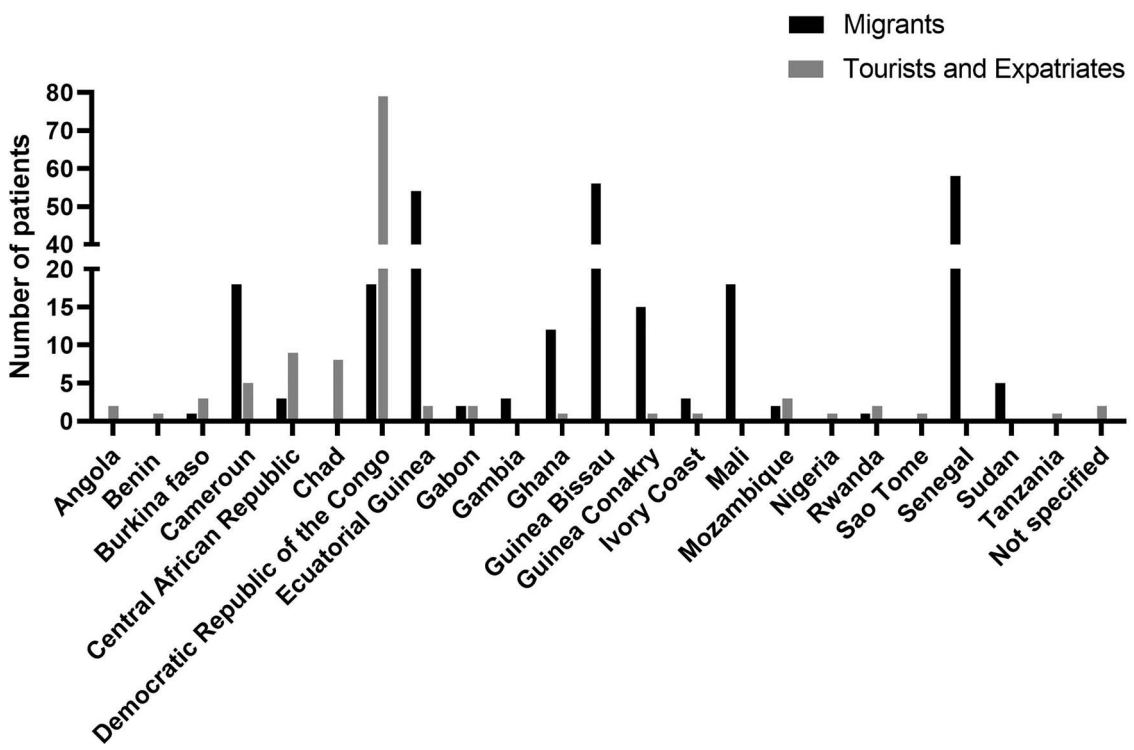

Figure 1. Country of exposure to *M. perstans* infection by patients' category (migrants, expatriates, tourists). In seven cases (3 migrants, 2 expatriates, 2 tourists), the country of exposure could also having been a second one. In these cases, the country reported as the most probable is plotted

Table 2. First treatment regimens for *M. perstans* infection

Drug(s)	Dosage°	Length of administration[a]	N patients treated	Centres having used this regimen
Albendazole	400 mg/12 h	3 days	5	BCL
		7 days	2	BCL, NGR
		10 days	14	ALM, BCL
		14 days	3	ALM, BCL
		21 days	1	ALM
	400 mg/24 h	10 days	1	ALM
		14 days	3	ALM
Diethylcarbamazine	6 mg/kg/24 h	21 days	7	ALM, ATW, NGR
Doxycycline	100 mg/12 h	6 weeks	11	ATW, BCL, NGR
Levamisole	NR	NR	1	NGR
Mebendazole	100 mg/12 h	3 days	5	BCL
		21 days	1	ATW
		30 days	127	ALM, BCL
		NR	2	ATW
	500 mg/8 h	14 days	4	NGR
		30 days	1	NGR
Albendazole + Doxycycline [a]	400 mg/12 h + 100 mg/12 h	14 days +6 weeks	1	NGR
Albendazole + Ivermectin	NR	NR	1	NGR
Diethylcarbamazine + Ivermectin [a]	6 mg/kg/24 h + NR	21 days + NR	1	NGR
Mebendazole + Levamisole	500 mg/8 h + 150 mg	14 days +3 days	110	ATW, NGR
Mebendazole + Doxycycline	500 mg/8 h + 100 mg/12 h	14 days +6 weeks	23	NGR
Diethylcarbamazine + Thiabendazole [a]	6 mg/kg/24 h + NR	NR	1	NGR
No treatment	-	-	67	ALM, ATW, BCL, NGR

ALM, Almeria; NGR, Negrar; ATW, Antwerp; BCL, Barcelona. When drug combination is used, dosage and length of administration are reported for each drug in the same order the drugs are indicated in the first column. NR, not reported.

[a]Drug also possibly administered for another concomitant filarial infection.

Table 3. Clinical data and management of patients along follow-up visits

N who attended (% over those attending the previous time-point)	Months after previous time point – median (IQR)	Clinical status *N* (% of those attending this follow-up)		*N* treated at this follow-up visit per clinical group	*N* treated at this follow-up visit – total (% of those attending this follow-up visit)	No. of patients for whom this follow-up visit was the last attended (% of each clinical group)
First follow-up						
256 (65.3%)	3 (2–12)	Mf + Eos+/−/NR	98 (38.3%)	41	44 (17.19%)	31 (31.6%)
		Mf− Eos+	55 (21.5%)	3		36 (65.5%)
		Mf− Eos−	93 (36.3%)	0		87 (93.6)
		Mf NR Eos+	2 (0.8%)	0		1 (50.0%)
		Mf−/NR Eos NR/−	8 (3.1%)	0		8 (100%)
Second follow-up						
93 (36.3%)	7 (3–18)	Mf + Eos+/−/NR	41 (44.1%)	19	20 (21.51%)	15 (36.6%)
		Mf− Eos+	15 (16.1%)	1		13 (86.7%)
		Mf− Eos−	36 (38.7%)	0		33 (91.7%)
		Mf NR Eos+	0	0		0
		Mf−/NR Eos NR/−	1 (1.1%)	0		1 (100%)
Third follow-up						
31 (33.3%)	5 (3–14.5)	Mf + Eos+/−/NR	15 (48.4%)	8	8 (25.81%)	9 (60.0%)
		Mf− Eos+	1 (3.2%)	0		1 (100%)
		Mf− Eos−	15 (48.4%)	0		14 (93.3%)
		Mf NR Eos+	0	0		0
		Mf−/NR Eos NR/−	0	0		0
≥4th follow-up						
9 (29.0%)	5 (1–7)	Mf + Eos+/−/NR	3 (33.3%)	2	2 (28.57%)	3 (100%)
		Mf− Eos+	0	0		0
		Mf− Eos−	6 (66.7%)	0		6 (100%)
		Mf NR Eos+	0	0		0
		Mf−/NR Eos NR/−	0	0		0

Eos, eosinophilia; Mf, microfilariae; NR, not reported.

(34.7%) patients were lost to follow-up after the first visit, while the remaining 256 (65.3%) attended a further visit between 1 month and 10 years (median 3 months, IQR 2–12). Data on the presence of blood mf at first follow-up were available for 251 of the patients; of these, 153 (60.9%) were amicrofilaremic, while 98 (39%) patients had still circulating mf. The exact circulating mf density at follow-up was recorded for 69 of these patients still microfilaremic, ranging from 1 to 7350 mf/ml (median 12 mf/ml, IQR 3–58), while for 29 patients the only data available were the presence of detectable circulating mf. The changes of mf density from pre-treatment at first follow-up time point are shown in Supplementary Figure 1. Figure 2 in particular shows the changes in mf density from pre-treatment for the patients ($n = 160$) who had their first follow-up time point within 12 months and were either not treated or treated with the most used schemes, deploying mebendazole (100 mg/12 h for 30 days or 500 mg/8 h for 14 days +/− levamisole) and/or doxycycline (100 mg/12 h for 6 weeks).

Of patients who were treated with these regimens described above only once and having at least one follow-up carried out ($n = 160$), 133 (83.1%) reached complete mf clearance within the time span (1–106 months) of follow-up. When focusing only on the first year after treatment, cumulatively between 24.6 and 45.9% patients reached amicrofilaremia within 3 months, between 32.9 and 67.6% within 6 months and between 41.1 and 78.4% within 12 months from treatment. Although no formal comparison between treatments could be made, overall the regime containing mebendazole 100 mg/12 h for 30 days seemed to show the best results, with 78.4% of patients attaining amicrofilaremia within 12 months, followed by doxycycline 100 mg/12 h for 6 weeks (+/− mebendazole 500 mg/8 h for 14 days)-containing schemes (65.4% amicrofilaremic at 12 months), and mebendazole 500 mg/8 h for 14 days (41.1% amicrofilaremic at 12 months). Further 13 (8.1%) patients had ≥90% reduction in mf levels at last follow-up attended (1–30 months), 8 (5%) had less prominent reduction by the last follow-up time attended (1–72 months), 3 (1.9%) had mf counts increased at last follow-up (2–3 months) and 3 (1.9%) still had detectable mf at last follow-up (3–7 months), but estimation of change was not possible because mf counts were not recorded. Of note, also among not treated patients having at least one follow-up record ($n = 19$), 15 (78.9%) reached amicrofilaremia within the time span (2–120 months) of the follow-up [4 (21.1%) within 12 months]. To try evaluating if attained amicrofilaremia was stable or just a result of a temporary fluctuation, we evaluated data on microfilaremia of the 26 patients who were re-evaluated

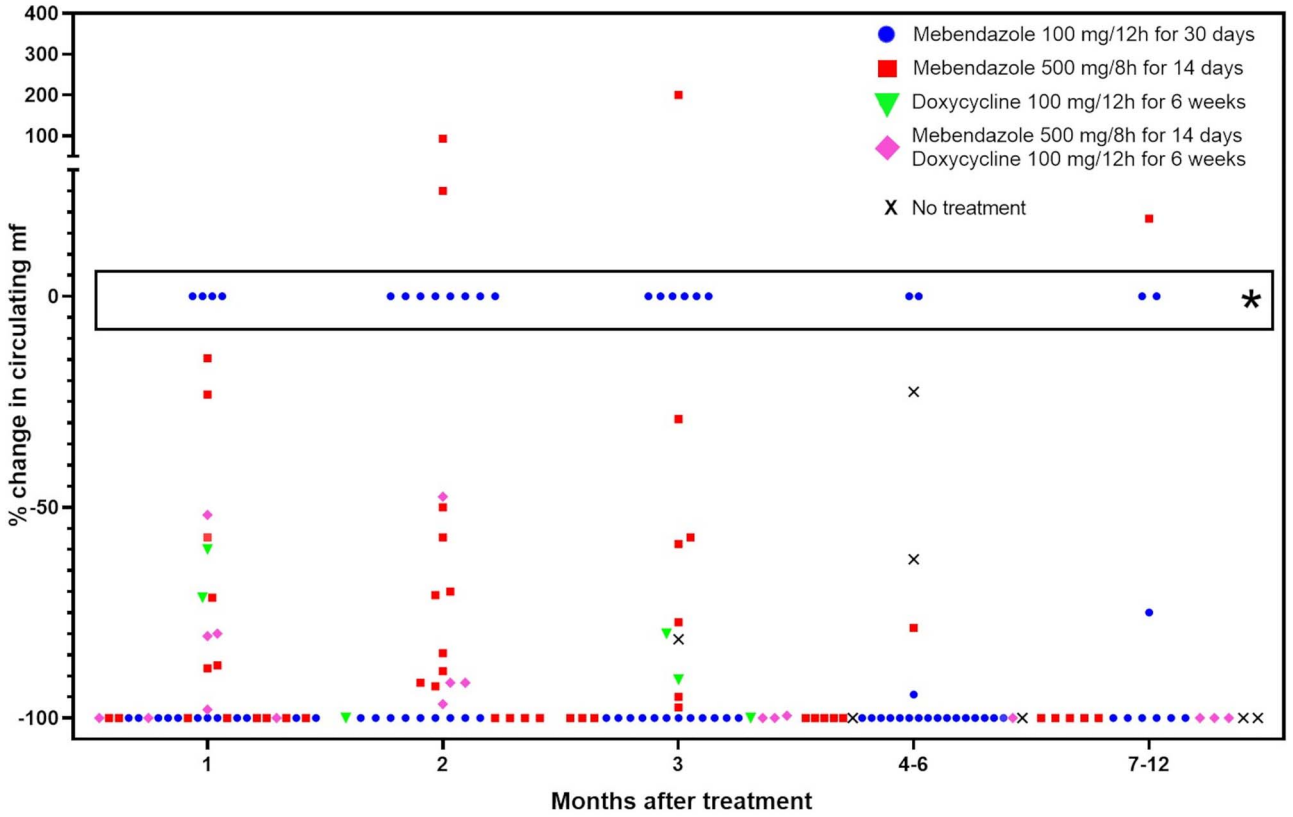

Figure 2. Percentage change in mf/ml blood at first follow-up when performed within 12 months compared to pre-treatment levels in patients having microfilaremia assessed at both time points ($n = 160$) not treated or treated with selected regimes. Each symbol represents an individual patient at his/her first follow-up. First follow-up was performed at variable times (X axis) within the first 12 months for the depicted 160 patients. When mf/ml were not evaluated, but only the presence/absence of circulating mf was reported, persistence presence of mf at follow-up was indicated as 0% change (* box). No mf detectable at follow-up is indicated as −100% change. Blue dots = treatment with mebendazole 100 mg/12 h for 30 days. Red squares = treatment with mebendazole 500 mg/8 h for 14 days +/− levamisole 150 mg for 3 days. Green triangles = treatment with doxycycline 100 mg/12 h for 6 weeks. Pink diamonds = treatment with mebendazole 500 mg/8 h for 14 days followed by doxycycline 100 mg/12 h for 6 weeks. Black cross = no treatment.

at least once after the first time point in which amicrofilaremia was observed (median 15 months after amicrofilaremia was observed, IQR 7.7–16.7). Only in two (7.7%) of these cases, both having attained amicrofilaremia after treatment, blood mf could be detected again at a later time point (6 and 36 months after the previous amicrofilaremic time point).

At first follow-up, eosinophilia was still present in 86 (49.1%) of the 175 patients who had eosinophilia at diagnosis and who had eosinophilia re-assessed; in these patients, eosinophils count had reduced for the majority of them ($n = 57$, 66.3%; reduction between 1.8 and 92%), while eosinophils/μl had increased between 5.2 and 471.1% in the remaining 29 patients (33.7%). Of the 116 patients who had eosinophilia at diagnosis and who attained amicrofilaremia at first follow-up, 52 (44.8%) still had eosinophilia at this time point; of note, 2 of the 37 patients (5.4%) who did not have eosinophilia at diagnosis had developed eosinophilia at first follow-up notwithstanding clearance of microfilaremia. When considering the whole cohort, independently of achievement of amicrofilaremia at first follow-up, of the 133 patients with no eosinophilia at diagnosis, 8 (6%) developed it during the follow-up, 62 remained with eosinophil counts within normal range and for 7 patients these data were not recorded (56 were lost to follow-up).

Further follow-up visits were attended by decreasing number of patients: 93 (23.7% of originally diagnosed patients; 36.3% of those attending a first follow-up) attended a second visit; 31 a third one; 7 a fourth one and 2 even a fifth one. Overall, 163 patients attended only one follow-up visit, 62 attended two follow-up visits, 24 attended three and 9 attended four or more follow-up visits. Between 16 and 42% of patients lost to follow-up at each follow-up visit were still microfilaremic at the last evaluation. After the first follow-up, only 44 patients (17.2% of patients having attended a first follow-up visit) were re-treated due to persistent microfilaremia and/or eosinophilia. Re-treatment was with the same regime as the first one in 22 (50%) of cases.

Discussion

Infection with *M. perstans* is the most neglected filariasis, characterized by an elusive clinical picture. No guidelines are available for its treatment. Outside endemic areas, a number of reference centres for tropical diseases have described the clinical characteristics and management of large cohorts of patients with *M. perstans* infection, in the attempt to better frame its clinical management.[16–18,28]

From the clinical aspect, the results of our study, partly including data presented in[16–18,28], are in line with previous observations. They confirm that (i) infection is largely asymptomatic (at least one-third of clinical records examined in our study reported that the patients did not complain of symptoms); (ii) when symptoms are reported these are non-specific (with abdominal pain and itching being the most frequently reported); (iii) eosinophilia is inconstantly present (in little over half of cases in our study) and, when present, generally is in the mild to moderate range; (iv) microfilaremia is generally high (based on data from patients in whom number of mf/ml was quantified) and (v) serology for filariasis is positive or borderline in the majority, but not the totality of cases. The lack of specific symptoms, together with the frequent but inconstant positivity to serology tests for filariasis (84% of cases in our study, which included only patients with mf in blood), make the clinical suspicion and screening for perstans mansonellosis particularly difficult.

No consensus exists on the treatment of mansonellosis: treatment schemes for *M. perstans* vary from centre to centre and within centres, and some clinicians may even opt not to treat the infection if the patient is completely asymptomatic. The uncertainty on the morbidity caused by mansonellosis is presumably at the basis of this attitude. The presence of *Wolbachia* endosymbionts in *M. perstans*, and therefore the efficacy of the anti-*Wolbachia* drug doxycycline for the treatment of infected patients, is also still uncertain.[21] Initial studies conducted in Gabon and Uganda did not detect *Wolbachia* in *M. perstans*.[22] However, the endosymbiont was detected in *M. perstans* in other studies from Mali,[23,24] Gabon[25] and Ghana.[26] Two trials of doxycycline treatment, carried out in Mali and Ghana,[24,26] showed clearance of microfilaremia in a significant proportion of participants in the months after treatment, as well as depletion of *Wolbachia* bacteria from circulating mf. The recent identification in Gabon of a potentially new species or genotype of *Mansonella*, microscopically undistinguishable from *M. perstans*, called *Mansonella* sp. 'DEUX',[29,30] with similarly inconstant retrieval of *Wolbachia*, adds further complexity to the picture. No clinical trial comparing different treatment schemes has been implemented for this infection. In accordance with previous publications,[16,17] the results of our study show that a high proportion of patients achieved parasitological cure (assessed by attaining amicrofilaremia) after one single treatment and within the first year after treatment, but also, although in apparently lower proportions, spontaneously. Although too few patients had additional follow-up visits after the one where amicrofilaremia was first observed, and at very different intervals, to conclusively evaluate whether amicrofilaremia was permanent or just a result of a temporary fluctuation of blood mf levels, from our data it seems that amicrofilaremia might have been stably achieved in the majority of cases. Overall, the regime containing mebendazole 100 mg/12 h for 30 days seemed to show the best results, followed by doxycycline (+/− mebendazole 500 mg/8 h for 14 days)-containing schemes, and mebendazole 500 mg/8 h for 14 days. However, the heterogeneity in treatment schedules and follow-up time points at which the patients were re-evaluated prevents any conclusion on the comparative efficacy of different treatment schemes. In addition, even outside endemic areas where re-infection cannot occur and confound efficacy results, it is difficult to assess parasitological clearance. Indeed, there are no markers/tests that can detect the adult worms, the presence of which, at present, can only be revealed by the detection of circulating mf. Thus, efficacy evaluations can be only based on the detection (or lack thereof) of circulating mf and ancillary laboratory data (eosinophils, anti-filarial antibodies).[31] In our study, no serology results were available for the follow-up time points and no attempt was made to infer parasitological cure on the basis of presence/absence of eosinophilia in addition to amicrofilaremia. Indeed, data obtained at first follow-up showed that nearly half of patients still had eosinophilia while a small percentage even developed new eosinophilia notwithstanding having cleared blood mf. Treatment efficacy is hence not easily assessed, likely requires follow-up in the absence of treatment to observe changes in laboratory parameters which may occur with some delay, and novel markers of infection are much needed. In this study, achievement of amicrofilaremia spontaneously in a large proportion of untreated patients could reflect spontaneous cure, for example due to natural death of adult worms, or failure to detect persistent infection due to low/fluctuating levels of circulating mf. Similarly, the persistence of circulating mf for months after treatment may not necessarily reflect the concomitant presence of viable fertile adult worms.[1,31] In agreement with the suggestion of Gobbi and colleagues,[31] an observation of 12–15 months after treatment would probably be worth before evaluating the need of re-treatment, to both avoid overtreatment and observe if apparent parasitological cure is a stable condition. However, this is often very difficult to implement since the migrant population, most affected by *M. perstans*, is highly mobile and therefore generally poorly compliant with long-term follow-up. Finally, the relative morbidity caused by parasite adults and mf is not known, which could inform the need to target only adults or also mf with specific treatment.

This study has several limitations which prevent performing a more elaborated analysis of data and driving stronger conclusions, due to its retrospective design, extreme heterogeneity of data (laboratory assays, treatment regimens and their implementation on individual patients, follow-up time points and analyses performed at each time point), presence of gaps in data completeness, non-systematic/inconsistent laboratory follow-up, absence of information regarding re-exposure between visits and high rate of loss to follow-up. This latter finding is not surprising due to the fact that data come from records of routine clinical practice (i.e. with non-standardized procedures in the context of a study protocol) on a migrant population, which is highly mobile and generally complying poorly with follow-up visit for a variety of reasons.

The retrospective design of this and previous studies, together with the high frequency of co-infections with other parasites, hampers a more precise definition of the signs and symptoms caused by mansonellosis, which might be erroneously considered as a relatively benign condition, as it happened with loiasis, for which only recently was demonstrated a relevant impact on morbidity and mortality.[32,33] Prospective studies evaluating infection-specific morbidity, together with systematic, multicentric surveys estimating the prevalence of infection in migrants from endemic areas, are required to quantify the burden of infection and the need of screening and treatment interventions. Likewise, placebo-controlled studies comparing treatment regimens for *M. perstans* (and *Mansonella* spp. 'DEUX') infection are absolutely needed

to rationalize the clinical management (outside transmission areas) and control (in endemic areas) of this infection, since analysis of retrospective data collected during routine clinical activity cannot provide conclusive answers. In this field, the presence of *Wolbachia* in *M. perstans* populations from different geographical origins and long-term efficacy of doxycycline, more or less combined with mebendazole, in international travellers also need to be investigated.

Supplementary data

Supplementary data are available at *JTM* online.

Data availability statement

Data are available at https://zenodo.org/record/6122558

Author contributions

F.G.G. conceived the study. F.G.G., P.R., J.S.-C., E.B., F.S., M.J.S.-P., M.I.C.-B., M.V.E. and B.T. collected the data. F.T. analysed the data. F.T., P.R. and F.G.G. wrote the manuscript. F.G.G., J.S.-C., E.B., F.S., F.T. and D.B. critically revised the manuscript for its scientific content. All authors approved the final version of the manuscript.

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Conflict of interest

None declared.

Ethical statement

The study protocol was approved by the Ethics Committee for Clinical Studies of Verona and Rovigo Provinces, Italy (study protocol no. 56014).

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