Autoimmunity Reviews 18 (2019) 102387

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

# Intravenous immunoglobulin efficacy for primary Sjögren's Syndrome associated small fiber neuropathy

*Dear Editor,*

Primary Sjögren's Syndrome (pSS) is a chronic systemic autoimmune disease which might be complicated with peripheral neuropathies, in up to 20% of patients [1]. Among peripheral neuropathies, small fiber neuropathies (SFN) are the most frequent, occurring in 3% to 9% of pSS-patients and representing 25% to 35% of all types of pSS-associated polyneuropathies [2]. Usual analgesic drugs including anticonvulsant and depressive treatments are inconsistently efficient and have no effect on the underlying immune process. In previous reports, intravenous immunoglobulin (IVIG) therapy was proposed in the context of pSS-SFN with successful outcome in at least 16 patients [3–8]. Herein, we report the retrospective analysis of a monocenter series of 11 pSS-patients (AECG-2002) with definite SFN and pain insufficiently controlled by optimized analgesic treatments (11-point pain intensity numeric rating scale [NRS] ≥5/10) who received 6 monthly IVIG infusions (0.4 g/kg/day for 5 days). All patients gave a written informed consent prior to investigation and they were also informed of the off-labeled use of IVIG. Main features of the study population are listed on Table 1. Patients were evaluated for: 1) pain intensity, rated on NRS before IVIG treatment (M0) and one month after the third (M3) and sixth (M6) infusions; 2) for quality of life scores, assessed on the SF-36 scale, including its Physical and Mental Component Summaries (PCS, MCS) at M0 and M6; 3) quantitative sensory testing at the four extremities with measurement of the average warm detection threshold (WDT). Our results showed that the pain intensity NRS scores significantly decreased between M0 [median (95% CI) 7 (5.5–8)] and both M3 [4 (3–6); $P < .00001$)] and M6 [3 (1.8–5); $P < .00001$)] (Fig. 1). Compared to baseline, the median percentage of pain intensity reduction was 40% (22–57%) at M3, and 50% (28%–72%) at M6. Using the IMMPACT (Initiative on Methods, Measurements and Pain Assessment in Clinical Trials) recommendations [9], 9 patients (82%) at M3 and M6 were considered responders with a meaningful pain intensity-NRS decrease ≥2 points. Moreover, five patients (45%) at M0 and six patients (54%) at M6 were very much improved with a pain intensity-NRS decrease ≥4 points. The analysis of the ten available SF-36 questionnaires showed a significant improvement of the PCS subscore between M0 [median (95% CI) 23.5 (15–32)] and M6 [48.5 (26–65); $P = .003$] (Fig. 1). Finally, average WDT at the four limbs also improved with a significant reduction between M0 [median (95% CI) 5.5 °C (4.6–8.1)] and M6 [4.6 °C (4–7.2); $P = .01$]. In summary, our results show that pain intensity (NRS) was reduced by ≥2 points and ≥ 4 points in 82% and 54% of patients, respectively, after six monthly IVIG infusions, along with a significant improvement of the SF-36 PCS subscore and average WDT. They confirmed the data previously reported in 16 pSS-SFN patients who benefitted from IVIG treatment [3–8,10]. Similar results were also reported in other inflammatory or dysimmune clinical conditions associated with SFN, such as sarcoidosis [11,12], coeliac disease, or even in idiopathic SFN [7].

This study presents various limitations and weaknesses (small sample size, retrospective and open-labeled design) and its results should be considered with caution, even though they are consistent with previous reports. The cost of IVIG treatment should be also emphasized, although counterbalanced by the major alteration of the quality of life due to pSS-SFN with its consequences on drug and healthcare consumption, and social and professional activities [14]. In conclusion, our results support the efficacy of IVIG treatment for pain relief in pSS-SFN with a surrogate improvement of quality of life and sensory testing. They support the rationale and pave the way for placebo-controlled studies of IVIG treatment of pSS-SFN or 'apparently autoimmune' SFN (aaSFN) as recently proposed by Oaklander et al. [13] and also ambitioned by our team for pSS-SFN and others for "idiopathic" SFN [15]. In the meantime, we do believe that IVIG treatment should be considered for pSS-SFN patients with severe pain having insufficient improvement by conventional analgesic treatment.

**Table 1**
Demographic, clinical, and paraclinical characteristics of SFN-pSS patients.

| Parameters | *N* = 11 |
|---|---|
| Age at SFN diagnosis, median (95%IC) (years) | 51 (41–62) |
| Time between SFN symptoms and treatment onset median (95%IC) (years) | 6.5 (3 − 11) |
| Female, n (%) | 10 (91%) |
| Xerostomia n (%) | 11 (100%) |
| Xerophthalmia n (%) | 9 (81%) |
| Focal lymphocytic sialadenitis with a focus score ≥ 1 focus/ 4 mm2), n (%) | 10/10 (100%) |
| Antinuclear antibodies, n (%) | 4 (36%) |
| Anti-SSA (Ro)/ Anti-SSB (La), n (%) | 3 (27%)/ 0% |
| Hypergammaglobulinemia, n (%) | 0/10 (0%) |
| Rheumatoid Factor +, n (%) | 3/10 (30%) |
| Cryoglobulin, n (%) | 0 (0%) |
| Normal EMG | 11 (100%) |
| Normal MRI cerebral and medullar (*n* = 9/8) | 9/9 and 8/8 (100%) |
| Extra-glandular symptoms | |
| Lymphoma, n (%) | 0 (0%) |
| Arthralgia, n (%) | 6 (54%) |
| Purpura, n (%) | 0 (0%) |
| Treatment | |
| Paracetamol | 5 (45%) |
| Opioids | 7 (64%) |
| Pregabalin | 6 (55%) |
| Gabapentin | 1 (9%) |
| Selective Serotonin Reuptake Inhibitors | 1 (9%) |
| Lidocaine patch | 4 (36%) |

pSS = primary Sjogren Syndrome; SFN = small fiber neuropathy; EMG = electromyogram; MRI = Magnetic Resoning Imaging.

https://doi.org/10.1016/j.autrev.2019.102387
Received 14 June 2019; Accepted 18 June 2019
Available online 11 September 2019

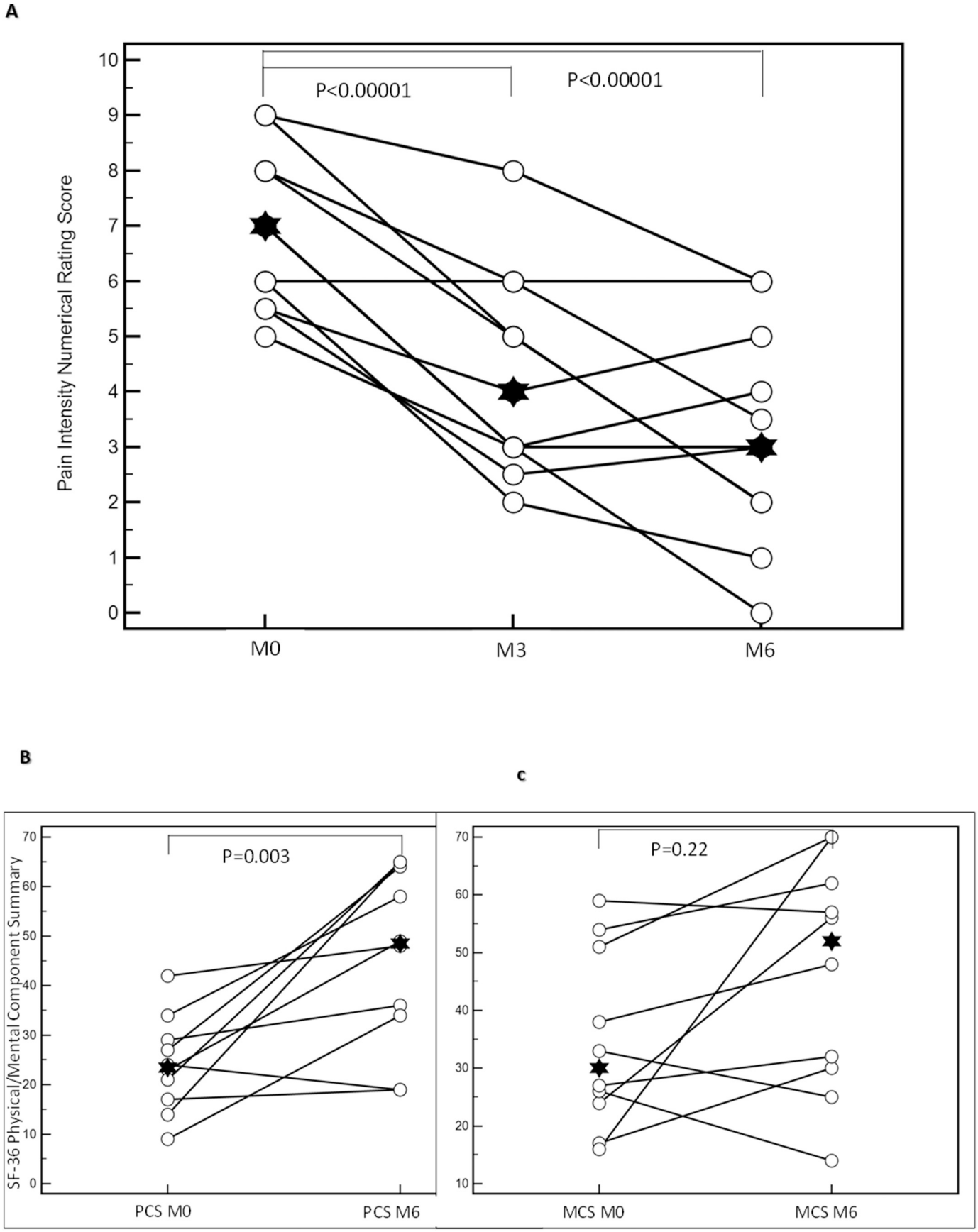


**Fig. 1.** Evolution of pain intensity scored on 11-point Numeric Rating Scale (A), SF-36 physical component summary (PCS) (B) and mental component summary (MCS) (C) in 11 patients treated by intravenous immunoglobulin infusions (M0 = before treatment; M3 = after the 3rd infusion; M6 = after the 6th infusion): individual data (open circles) and median results (black stars) are presented.

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