Interferon-β therapy and risk of thrombocytopenia in multiple sclerosis patients

R Renna[1], D Plantone[1], C Mandoj[2], D Giannarelli[3], C Mainero[4,5], T Koudriavtseva[1]

[1]Neurology Unit, [2]Clinical Pathology, [3] Scientific Direction, Regina Elena National Cancer Institute, Rome, Italy

[4]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital

[5]Harvard Medical School, Boston, MA, United States

Introduction

Multiple sclerosis (MS) prevalence in patients with immune thrombotic thrombocytopenia was reported 25 times higher than in the general population.[1] At the same time, thrombocytopenia is an adverse event during several MS disease-modifying therapies (DMT) such as IFN-β[2], cladribrine[3], alemtuzumab and fingolimod. It is uncommon in patients on teriflunomide and rare in those on natalizumab or Glatiramer acetate. The aims of this retrospective cross-sectional case-control study, based on MS database of Regina Elena National Cancer Institute were:

to compare thrombocytopenia prevalence in MS patients and controls;

to evaluate the relationship between thrombocytopenia and patients' demographic and clinical characteristics;

to evaluate the risk for thrombocytopenia in relation to DMT.

Methods

187 consecutive MS patients and 200 age and sex matched controls were enrolled. MS patients were characterized as the following: a) no-therapy (untreated patients), b) on therapy (all treated patients), c) IFN-β therapy (patients treated with Betaferon, Extavia, Rebif 44 mcg, Avonex, Rebif 22 mcg), d) high-dose IFN-β, e) low-dose IFN-β, f) other therapies (patients treated with Copaxone, Tysabri, Gilenya). A multivariate logistic regression analysis was used to estimate drug-related risk of thrombocytopenia.

Results

187 MS patients (51 M, mean age 44.5±10.7 y) and 200 controls (56 M, mean age 45.5±12 y) were enrolled. Patients' disease duration was 132.2±92.6 months, EDSS was 3.1±2.2. There were 156 relapsing-remitting (RR), 27 secondary-progressive (SP) and 4 primary-progressive (PP) MS patients.

Table 1. Type of treatment in MS patients and thrombocytopenia %

Treatment	Patients	Thrombocytopenia %
High-dose INF-β (Betaferon, Extavia, Rebif 44)	50	16%
Low-dose INF-β (Avonex, Rebif 22)	32	3.1%
Copaxone	25	4%
Tysabri	22	9.1%
Gylenia	13	0%
Untreated	45	2.2%

Treated patients had lower EDSS compared to the untreated ones (2.9±2.1 vs 3.7±2.5, p=0.05), but they did not differ in age, gender, disease duration, and platelet (PLT) count. Treated patients differed from untreated patients for disease type: the majority of RRMS (81.4%) and SPMS (55.6%) patients were treated, while all PPMS patients were untreated (p=0.001). 13 of 187 MS patients (7%) and 5 of 200 controls (2.5%) were thrombocytopenic, with thrombocytopenia prevalence significantly higher in patients (p=0.04).

Thrombocytopenia was mild (PLT count 100-130x109/L) in 17 subjects and moderate-severe in 1 MS patient (45 x109/L), and was not associated with any clinically relevant event.

Thrombocytopenia was found only in RRMS patients and was more frequent in patients on high-dose than those on low-dose IFN-β, other therapies or no therapy (p=0.02). It was also significantly associated with lower EDSS (p=0.002) and with a trend for shorter disease duration (p=0.06). There were no significant associations between thrombocytopenia and type of disease, gender or age.

Table 2. Relationships between PLT count and MS patients' demographical and clinical characteristics

Variable	Platelet count		p-value
	Normal (n 174)	Lower than normal (n 13)	
Age (years)	44.8±10.7	40.6±9	0.17*
Disease duration (months)	135.5±93.2	86.7±77.5	0.06*
EDSS	3.1±2.2	2±1	0.002*
Sex, n (%)			
Male	46 (90.2)	5 (9.8)	0.35**
Female	128 (94.1)	8 (5.9)	
Type of disease, n (%)			
Relapsing-remitting	143 (91.7)	13 (8.3)	
Secondary progressive	27 (100)	0 (0)	0.25**
Primary progressive	4 (100)	0 (0)	
Therapy, n (%)			
High-dose IFN-β	42 (84.0)	8 (16.0)	
Low-dose IFN-β	31 (96.9)	1 (3.1)	0.02**
Other therapies	57 (95.0)	3 (5.0)	
No therapy	44 (97.8)	1 (2.2)	

At multivariate logistic regression analysis, high-dose IFN-β was associated with more than 8-fold increase in the risk for thrombocytopenia when comparing untreated patients with those treated with high-dose IFN-β, low-dose IFN-β and other drugs as well as when comparing untreated patients with those treated with high-dose IFN-β and other therapies+low-dose IFN-β.

Conclusions

IFN-β therapy is the variable most strongly associated with thrombocytopenia in our MS cohort. Since the rate of thrombocytopenia in untreated patients (2.2%) was similar to that in controls (2.5%), it is reasonable to assume that its prevalence may depend prevalently on DMT, especially on high-dose IFN-β. A possible explanation for this association is the increased PLT consumption due to activation of inflammatory-thrombotic processes since the physiological production of type I IFNs and inflammatory cytokines starts the innate immune response.[4] PLT are among the main effector cells in coagulation, but also in inflammation and in the continuum between innate and adaptive immunity. It can be hypothesized that as far both IFN-β and pathophysiological MS processes contribute to induce thrombocytopenia in MS patients, the drug effect is prevalent through the increased activation of innate immunity. Our work suggests the importance of a closer PLT count monitoring especially during high-dose IFN-β therapy to prevent the symptomatic thrombotic cases, strengthening EMA recommendations on thrombocytopenia control in MS.

References

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