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Impact of interferon β-1b, interferon β-1a and fingolimod therapies on serum interleukins-22, 32α and 34 concentrations in patients with relapsing-remitting multiple sclerosis

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ABSTRACT

Interleukins (ILs)-22, 32α and 34 were monitored in the sera of relapsing-remitting multiple sclerosis (RRMS) patients at different time intervals with or without interferon β-1b, interferon β-1a and fingolimod treatments. The results showed that sera of untreated RRMS patients were statistically higher in concentration of IL-22 ($P < .001$), but not IL-32α and IL-34, than those of healthy individuals. Interestingly, interferon β-1b, interferon β-1a and fingolimod treatments led to a significant decrease of serum concentrations of ILs-22 and 32α, but not 34, at 6 and 12 months of treatment, compared to their initial concentrations before initiating therapy. The correlation analysis revealed that the changes of serum IL-22 ($r = 0.814$) and, to a lesser extent, IL-32α ($r = 0.381$) concentrations were positively correlated with those of expanded disability status score. In conclusion, serum IL-22 concentration may be a potential marker for MS disease severity and efficacy of treatment.

1. Introduction

Multiple sclerosis (MS) is a chronic demyelinating disorder of the central nervous system. Pro-inflammatory cytokines are major drivers for the development and progression of this debilitating disorder (Pérez-Cerdá et al., 2016). Hence, addressing and characterizing the role of unstudied inflammatory cytokines may efficiently aid in MS monitoring and therapy (Koudriavtseva and Mainero, 2016). Interleukin (IL)-22, a member of the IL-10 cytokine family, is mainly produced by several types of cells, including T helper cell (Th)17, natural killer (NK)22 and Th22 (Yang and Zheng, 2014). Basically, IL-22 has an important role in host immune defense mechanism against infection (Trifari et al., 2009). Because of its critical role in inflammation, chemotaxis and proliferation, IL-22 has been shown to be implicated in several autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and psoriasis (Jia et al., 2011; Kim et al., 2012; Maddur et al., 2012). IL-22 signal transduction initiates upon binding to a heterodimer receptor comprised of IL-10R2 and IL-22R1, leading to activation of signal transducer and activator of transcription (STAT)3 and mitogen-activated protein kinases (MAPKs) pathways (Lejeune et al., 2002). Otherwise, IL-22 may have also an anti-inflammatory role in certain contexts (Yang and Zheng, 2014). Thus, identifying the role of IL-22 in MS disease may provide a better understanding of the disease and novel therapeutic options.

IL-32 is another pro-inflammatory cytokine that was firstly detected in activated NK cells and T lymphocytes (Dahl et al., 1992). IL-32 is also produced by monocytes, endothelial and epithelial cells. Although 6 isoforms (α, β, γ, δ, ε and ζ) of IL-32 have been identified in humans, the actual differences between these isoforms still remain not fully known. Meanwhile, IL-32α and IL-32γ are the mostly expressed isoforms in humans (Nold-Petry et al., 2009). IL-32 is implicated in infectious diseases and autoimmune diseases like myasthenia gravis, rheumatoid arthritis and systemic lupus erythematosus (Gui et al., 2013; Na et al., 2011; Wang et al., 2016). Functionally, IL-32 enhances the production of other pro-inflammatory cytokines like ILs-13, 12, 6, 1β, 8, 21 and tumor necrosis factor (TNF)-α from dendritic, Th1 and Th17 cells (Jung et al., 2011, Pérez-Cerdá, Sánchez-Gómez, 2016). In addition, IL-32 could induce macrophage inflammatory protein-2 expression by activating activator protein-1, nuclear factor-kappa B and p38MAPK dependent signaling pathways (Nold et al., 2008).

IL-34 is a newly discovered cytokine that acts as additional ligand for colony stimulating factor-1 receptor. In the brain, IL-34 is expressed in neural cells, while its receptor is expressed in microglia and capillary endothelial cells (Wang and Colonna, 2014). In the microglia, IL-34 was

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found to enhance the clearance of oligomeric amyloid-β via augmenting the antioxidant enzyme heme oxygenase-1 and transforming growth factor-β1 (Ma et al., 2012; Mizuno et al., 2011). In the capillary endothelial cells, IL-34 was found to maintain blood brain barrier-integrity by restoring the expression levels of tight junction proteins, which were downregulated by pro-inflammatory cytokines (Jin et al., 2014). Otherwise, IL-34 prevented neuroinflammation and neurodegeneration induced in a transgenic mouse model of Alzheimer's disease and by kainic acid (Luo et al., 2013). Despite the previous findings, the complete functions of IL-34 are still not fully resolved in the central nervous system.

Extensive cytokine profiles that provide reliable, rather than conflicting, correlations of MS are still limited. In the current study, we evaluated the extent of correlation between serum ILs-22, 32α and 34 concentrations and the expanded disability status score (EDSS) to see how reliable these parameters are for prediction of the disease activity. Moreover, we assessed the changes of these ILs that occurred during different time intervals in MS-patients that were treated with 3 disease-modifying-drugs (DMDs).

2. Patients and methods

This study comprised 150 Egyptian individuals (Table 1), who were randomly recruited from several centers (Mansoura University Students Hospital, Neurology Department at Mansoura University Hospital and Mansoura New General Hospital) in the period from June 2016 till September 2018. All the participants were asked to sign a written consent prior contribution in the study. The study was approved by the ethical committee at the Faculty of Pharmacy, Mansoura University.

2.1. Inclusion and exclusion criteria

The inclusion criteria were as follows: i) matching with revised McDonald's criteria 2010 for RRMS patients; ii) early diagnosed RRMS or patients who did not receive any treatment at least 3 months prior enrollment in the study; iii) an age ranging from 20 to 60 years old; and iv) an EDSS ranging from 1.5 to 6.5. Meanwhile, the exclusion criteria were as follows: i) contraindication for magnetic resonance imaging (MRI) scanning; ii) failure of matching with McDonald's criteria for RRMS; and iii) falling in any of these categories (pregnancy, autoimmune disorder, malignancy, hypersensitivity to the study drugs, diabetes mellitus, cardiovascular, hepatic and respiratory disorders).

2.2. EDSS, MRI and ELISA assessments

Each patient was clinically assessed with the EDSS alongside MRI to monitor the disease status and clinical response to DMDs at different time intervals (0, 6 and 12 months). Sera were also isolated from blood samples at these time intervals and were stored at −80 °c for later analysis. Serum IL-22, IL-32α and IL-34 concentrations were estimated by ELISA MAX™ Deluxe assay kits (BioLegend, San Diego, CA, USA) according to the manufacturer's instructions.

2.3. Statistical analysis

Normal distribution of data was determined by Shapiro-Wilk test. For the two independent groups (healthy control vs. untreated MS), the statistical significances between the means of non-normally distributed ELISA measurements and EDSS scores were determined non-parametrically by the Mann-Whitney unpaired *t*-test. For the three dependent time point groups (0, 6 and 12 months), the non-normally distributed data of ELISA measurements and EDSS scores were analyzed non-parametrically by Friedman test of repeated measures one-way ANOVA, followed by *Dunn's* post-test. The Spearman's correlation coefficient (r) was used to determine the extent of association between the ELISA measurements and the EDSS scores of MS patients, as well as the ELISA measurements with the ordinal time points for treatment of non-relapsed and relapsed MS patients. The level of significance was set at $P < .05$. Statistical tests were performed with GraphPad Prism software version 7.0 (GraphPad Software Inc., CA, USA).

3. Results

3.1. Clinical features of individuals

Demographic data of healthy individuals ($n = 39$) and untreated/treated MS patients ($n = 111$) illustrated that the means of their age were 38.41 and 33.58 years, respectively. The total percentages of females and males were 56.7% and 44.3%, respectively. MS patients treated with fingolimod demonstrated the longest disease course, because they switched to fingolimod after failure of other DMDs. Demographic and clinical features of participants were summarized in Table 2. MRI evaluation of MS treated patients for the total volume of plaques in fluid-attenuated inversion recovery (FLAIR) was shown Table 3.

Table 1
The clinical design and group assignment for DMDs.

	No. of Patients	Disease	Treatment	Dose Regimen	Study Duration
Group I	39	RRMS	–	–	–
Group II	24	RRMS	Interferon β-1b (Betaferon)	250 μg subcutaneous injection, every other day	12 months
Group III	24	RRMS	Interferon β-1a (Rebif)	44 μg subcutaneous injection, three times per week	12 months
Group IV	24	RRMS	Fingolimod (Gilenya)	0.5 mg oral capsule, once daily	12 months
Group V	39	Healthy controls	–	–	–

RRMS; (relapsing-remitting multiple sclerosis), DMDs; disease-modifying-drugs.

Table 2
Demographic and clinical characteristics of healthy individuals and MS patients.

	Healthy Controls ($n = 39$)	Untreated MS Patients (n = 39)	Interferon β-1b (n = 24)	Interferon β-1a (n = 24)	Fingolimod (n = 24)
Age range (Mean ± SE)	20–60 (38.41 ± 1.84)	17–53 (36.03 ± 1.36)	18–54 (32.33 ± 2.08)	22–46 (34.29 ± 1.59)	20–42 (30.13 ± 1.47)
Female No. (%)	20 (51.3%)	18 (46.2%)	17 (70.8%)	13 (54.2%)	17 (70.8%)
Duration of MS in Months (Mean ± SE)	–	12.00 ± 1.40	13.25 ± 1.22	14.18 ± 0.68	36.33 ± 3.04

Table 3
Total lesion volume of MRI (FLAIR) for MS patients during the treatment with DMDs at the elapsed time points (0, 6 and 12 months)

DMDs	0 Month	6 Months	12 Months
Interferon β-1b	5732 ± 821	5537 ± 838	5874 ± 962
Interferon β-1a	5885 ± 784	5224 ± 624	5371 ± 609
Fingolimod	12,446 ± 2105	11,902 ± 2229	10,736 ± 2186

Magnetic resonance imaging; MRI, fluid-attenuated inversion recovery; FLAIR, MS; multiple sclerosis, DMDs; disease-modifying-drugs.

3.2. Comparison of ILs-22, 32α and 34 concentrations in serum samples alongside EDSS in healthy individuals and untreated RRMS patients

In comparison to healthy individuals, the ELISA data (Fig. 1A–C) indicated that serum IL-22 concentration in untreated RRMS patients was elevated significantly at $P < .001$, respectively. Meanwhile, the increase of serum ILs-32α and 34 concentrations were not statistically significant ($P > .05$) in untreated RRMS patients, compared to healthy individuals. The average of EDSS (2.72) for these untreated RRMS patients was significantly ($P < .001$) higher than those of healthy individuals (Fig. 1D).

3.3. Comparison of ILs-22, 32α and 34 concentrations in serum samples alongside EDSS in RRMS patients treated by interferon β-1b, interferon β-1a and fingolimod

Interferon β-1b, interferon β-1a and fingolimod treatments led to a significant decrease of serum concentration of ILs-22 (Fig. 2A–C) and 32α (Fig. 2D–F), but not 34 (Fig. 2G–I), at 6 and 12 months of treatment, compared to their initial concentrations before initiating therapy. Similarly, these treatments induced the same pattern of decrease in EDSS (Fig. 2J–L) at 6 and 12 months of initiating the therapy. Interferon β-1b and fingolimod-induced decreases in ILs-22 and 32α were partially concordant with decreasing MS severity to some extent in the MRI of the shown patients at 6 months (Fig. 3A–H), despite no significant changes of all DMDs on the means of total volume of plaques at 6 and 12 months (Table 3).

3.4. Correlation analysis of serum ILs concentrations and EDSS values of the participants

Next, Spearman's correlation analysis was made to find the relationship between these ILs concentrations and EDSS values of all participants. The correlation analysis revealed that the elevation of serum IL-22 and, to a lesser extent, IL-32α concentration was consistent

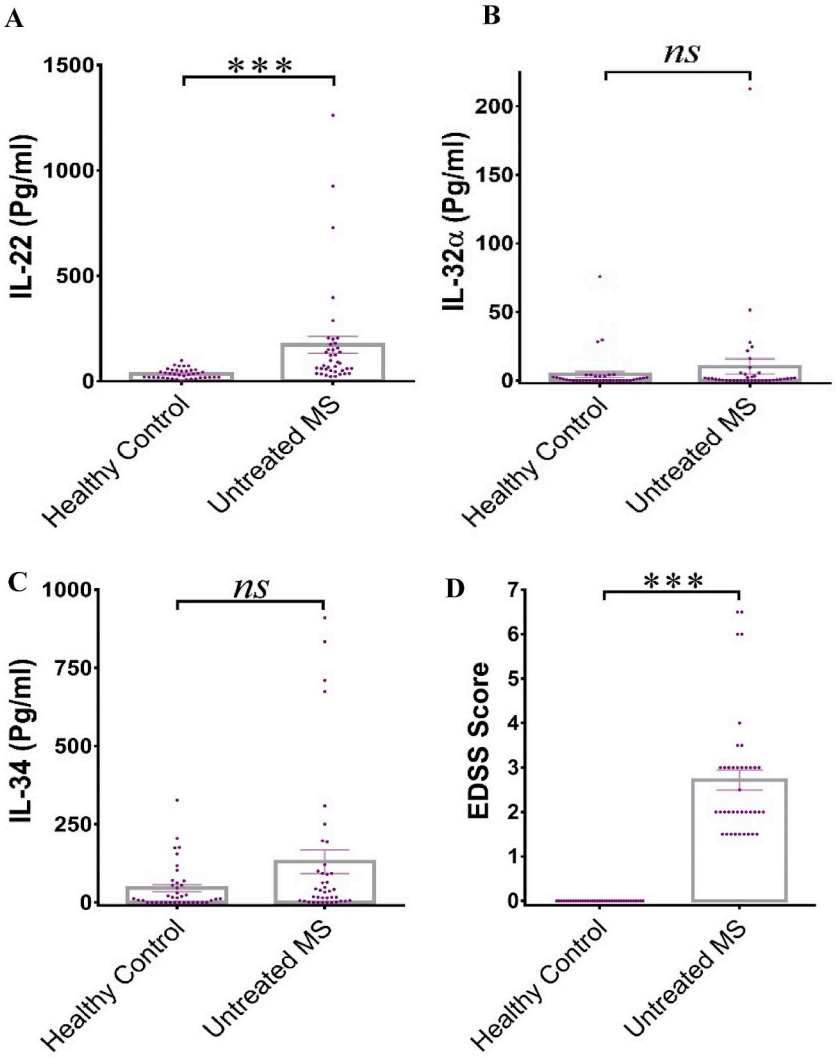

Fig. 1. Comparison of ILs-22 (A), 32α (B), and 34 (C) in healthy individuals and untreated RRMS patients. Bars are means ± SE ($n = 39$/group). Statistical significance was denoted as ***$P < .001$, while non-statistical significance was denoted as ns.

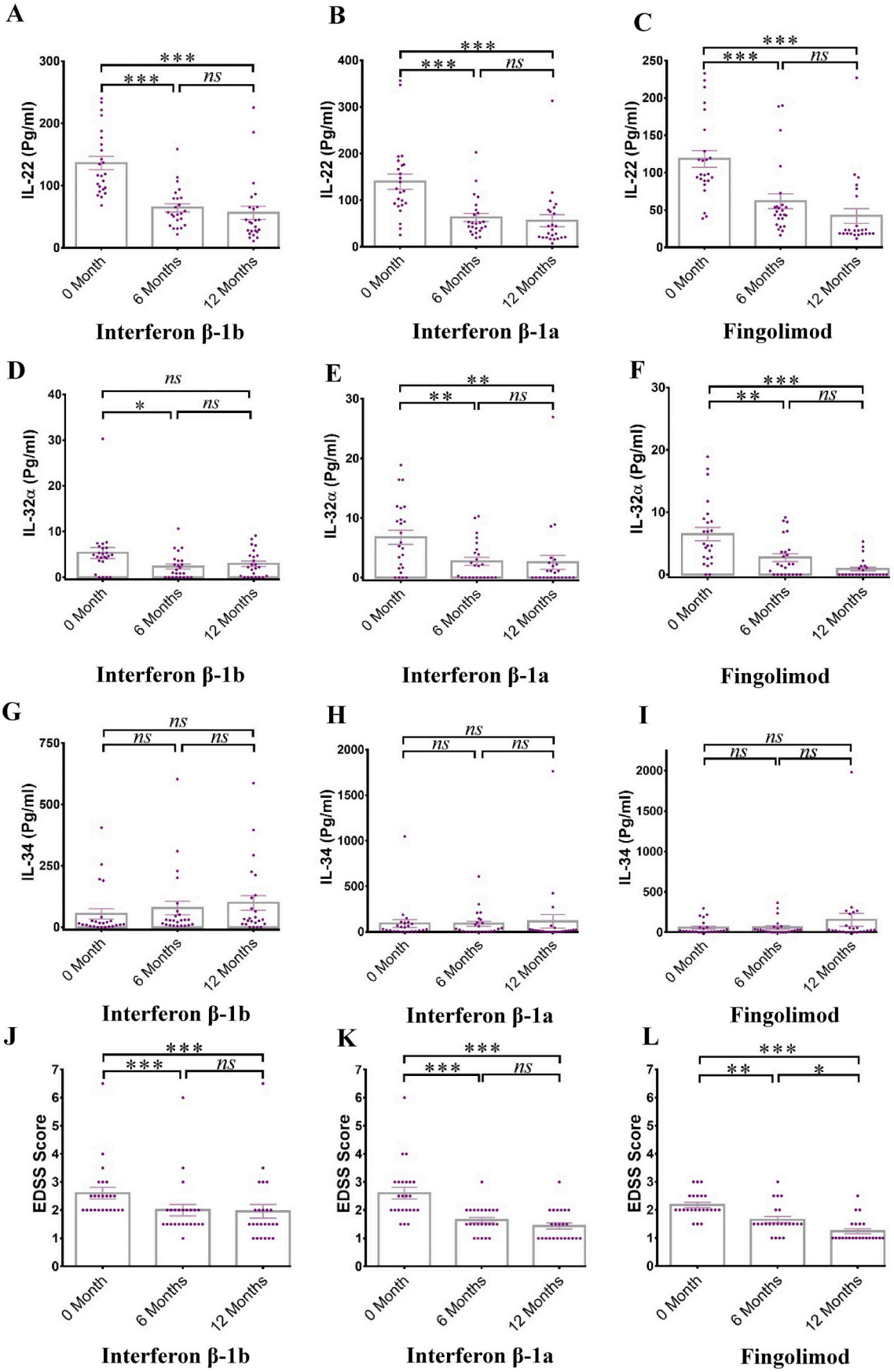

Fig. 2. Effects of interferon β-1b, interferon β-1a and fingolimod treatments on ILs-22 (A-C), 32α (D-F), 34 (G-I) and EDSS (J-L) in RRMS patients at different time intervals. Bars are means ± SE ($n = 24$). Statistical significances were denoted as $^{*}P < .05$, $^{**}P < .01$ and $^{***}P < .001$, while non-statistical significance was denoted as ns.

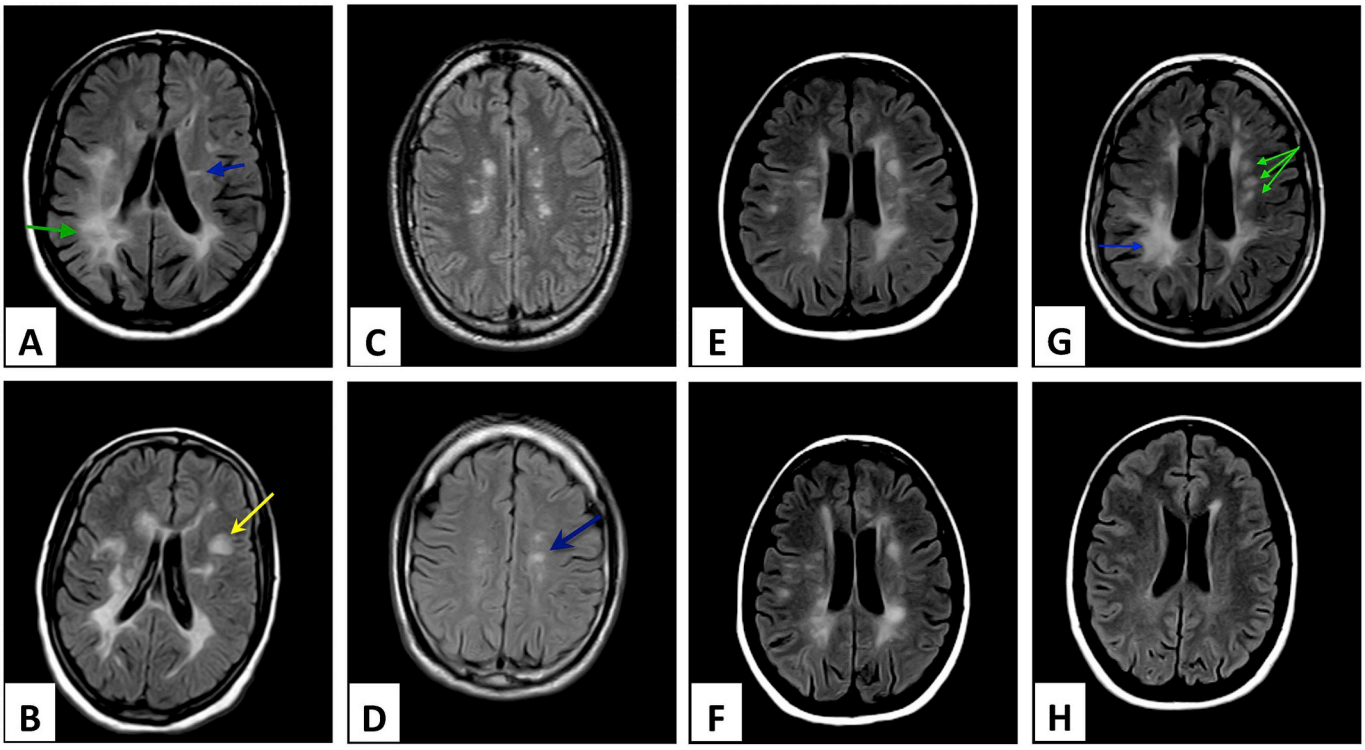

Fig. 3. Representative MRI (FLAIR) of MS patients before and after 6 months of receiving no treatment (A, B), interferon β-1b (C, D), interferon β-1a (E, F) and fingolimod (G, H). A) Periventricular (blue arrow) and high intense juxtacortical (green arrow) plaques; B) Increase in size and intensity of juxtacortical plaques (yellow arrow); C) Parietal variable sized plaques without edema; D) Resolution of the plaques (blue arrow); E) Periventricular and juxtacortical plaques; F) No improvement in the plaques; G) Periventricular, juxtacortical (blue arrow) and 3 adjacent plaques (green arrow); and H) Marked resolution of the plaques. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

with that of EDSS ($r = 0.814$ at $P < .001$ and $r = 0.318$ at $P < .001$, respectively), which in turn means worsening in the patient disability and aggregation of disease severity (Fig. 4A, B). Meanwhile, the elevation of serum IL-34 concentration was in a very weak correlation with that of EDSS ($r = 0.170$ at $P < .01$), which suggests a lack of relationship between both (Fig. 4C).

3.5. Correlation analysis of serum ILs concentrations and EDSS values for each DMD

To further test the applicability of these ILs in monitoring MS therapy, the correlation analysis was then repeated by sorting the study participants according to their respective therapy. The correlation analysis of serum IL-22 concentration and EDSS score showed strong positive relation in patients receiving interferon β-1a and fingolimod ($r = 0.908$ at $P < .001$ and $r = 0.922$ at $P < .001$, respectively), while a medium positive correlation in interferon β-1b-treated patients ($r = 0.691$ at $P < .001$) as shown in Fig. 5A–C. Similarly, serum IL-32α concentration and EDSS score correlated better in interferon β-1a and fingolimod-treated patients than interferon β-1b-treated patients (Fig. 5D–F). However, serum IL-34 concentration and EDSS score were in the very weak range of positive correlation for all DMD-treated patients (Fig. 5G–I).

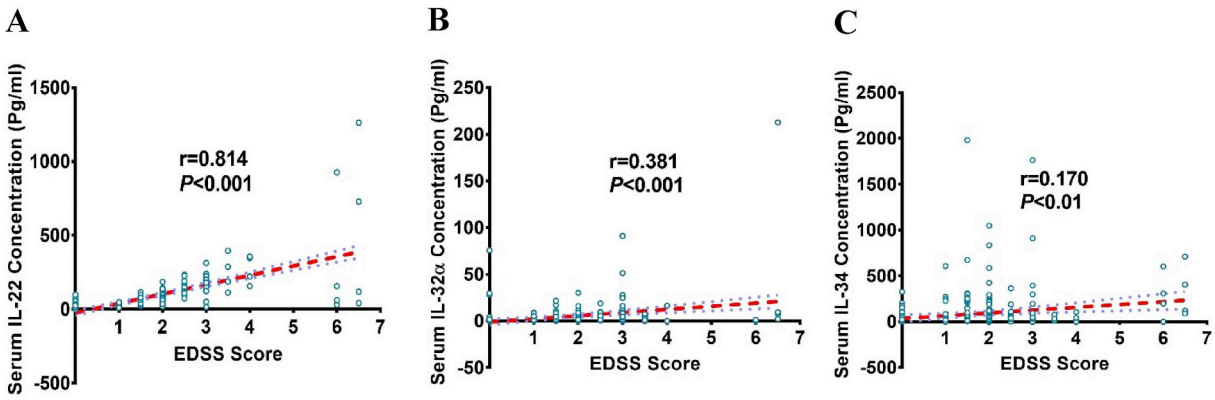

Fig. 4. The extents of correlation between serum interleukins (ILs)-22 (A), 32α (B) and 34 (C) concentrations and EDSS values of RRMS patients (with or without treatment) and healthy individuals. Values are expressed as Spearman's correlation coefficient (r). The positive correlation categories were very weak (> 0 to 0.29); weak (0.3 to 0.49); medium (0.5 to 0.69); and strong (0.7 or more).

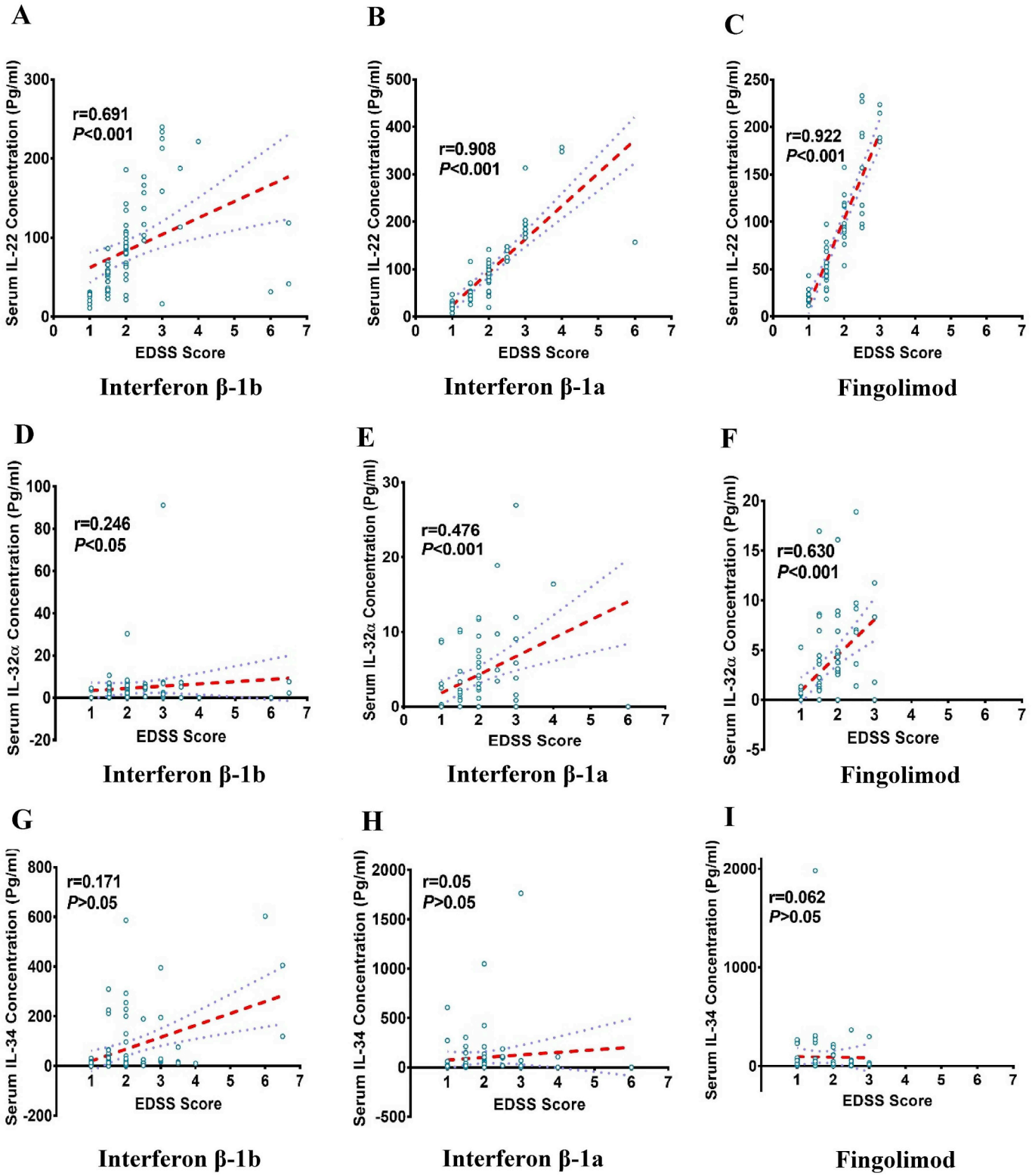

Fig. 5. The extents of correlation between serum interleukins (ILs)-22 (A-C), 32α (D-F) and 34 (G-I) concentrations and EDSS values of RRMS patients with each treatment. Values are expressed as Spearman's correlation coefficient (r). The positive correlation categories were very weak (> 0 to 0.29); weak (0.3 to 0.49); medium (0.5 to 0.69); and strong (0.7 or more).

3.6. Correlation analysis of serum ILs concentrations and the time elapsed during the treatment with DMDs in total, relapsed and non-relapsed MS patients

We observed relapse attacks in some RRMS-patients during the treatment with different DMDs (Table 4). Accordingly, correlation analysis between the ILs concentrations and the elapsed time for treatment of total, relapsed (worsened symptoms occurring over 24 h and separated from a previous attack by at least 30 days) and non-relapsed MS patients was then performed to find out whether these ILs

Table 4
Numbers and percentages of MS patients underwent relapse attacks during treatment with DMDs.

Treatment	Non-Relapsed n (%)	Relapsed n (%)
Interferon β-1b	16 (66.7)	8 (33.3)
Interferon β-1a	21 (87.5)	3 (12.5)
Fingolimod	22 (91.7)	2 (8.3)

MS; multiple sclerosis, DMDs; disease-modifying-drugs.

have different profile in responders and non-responders (Table 5). An intermediate indirect correlation between IL-22 concentration and the elapsed time in interferon β-1b, interferon β-1a and fingolimod-treated RRMS patients (total). Similarly, IL-32α serum concentration negatively correlated with elapsed treatment time in interferon β-1a and fingolimod, but not interferon β-1b, treated patients (total). There were no or weak relationships between serum IL-34 concentration of all participants and the elapsed time for interferon β-1b, interferon β-1a and fingolimod treatments. Noteworthy, stable responder (non-relapsed) patients showed better negative correlation than total patients between ILs-22 and 32α concentrations and the time elapsed, while the reverse for the non-responder relapsed patients who have at least 1 relapse or more over the one year of receiving treatment with a rise of EDSS.

4. Discussion

Herein, we monitored the changes of serum IL-22, IL-32α and IL-34 in the context of MS, because of i) the uncertainty about whether these ILs have pro-inflammatory or anti-inflammatory properties, ii) the limited number or lack of studies dealt with evaluating these ILs in MS, and iii) the potential of intimate relationship between these ILs and disease activity, clinical disability and efficiency/failure of DMDs.

Relevant to the present study outcomes, serum IL-22 serum concentration was found to be greatly elevated in untreated RRMS patients in comparison to healthy individuals. Meanwhile, this elevation of serum IL-22 concentration was reduced when RRMS patients were treated with interferon β-1b, interferon β-1a, or fingolimod. Moreover, our results indicated that serum IL-22 concentration remained elevated in RRMS patient subjected to relapse attacks despite of receiving DMDs. This finding was observed only in non-responders, while clinically stable RRMS patients under targeted DMDs were still having lower IL-22 levels. In this context, monitoring of serum IL-22 changes can predict at early stage of MS whether the MS patient will be responsive or unresponsive, so that treatment can be continued or changed.

Studies dealing with experimental autoimmune encephalomyelitis (EAE), a murine model mimicking the inflammatory characteristics of MS, represent valuable sources for understanding the role of IL-22. For instance, IL-22 was found to be elevated during induction of EAE, while decreased during the recovery (Almolda et al., 2011). Moreover, IL-22 and its expressing cells (Th17 and Th22) were found to be involved in the pathogenesis of EAE (Rolla et al., 2014). More recently, Zhen et al. (2017) showed that IL-22 aggravated EAE by enhancing Fas expression in oligodendrocytes leading to more apoptosis and by reduction of FOXP3-expression in Treg cells.

Several clinical studies were recently done to characterize the actual role of IL-22 in humans. For instance, Xu et al. (2013) demonstrated that serum IL-22 concentration was increased simultaneously with the activation of Th22 cells in MS patients, especially during the relapse attacks, confirming that IL-22 may play a crucial role in MS progression and relapse. Recently, Perriard et al. (2015) reported the same elevation of serum IL-22 in RRMS in comparison to healthy controls. They also showed that astrocytes of the human brain express both subunits of IL-22 receptor, and there is a co-localization of IL-22 with these cells that leads to their pro-survival and worsening of MS disease. IL-22 was implicated in disrupting blood-brain barrier integrity and increasing lymphocyte migration across human brain-derived microvascular endothelial cells and infiltration in MS lesions via increasing monocyte chemoattractant protein-1 (Kebir et al., 2007). More recently, Wing et al. (2016) reported that MS patients were having high circulating levels of IL-17A and IL-22 that were secreted from myelin basic protein-specific CD4 + T cells and positively correlated with the radiological assessment of brain lesions.

The results also indicated statistically insignificant elevation of IL-32α concentration in sera of untreated RRMS patients, compared to those of healthy individuals. Clinical trials that investigated the role of IL-32 in neurodegenerative diseases are scarce. For instance, Wang et al. (2013) reported significant elevation of serum IL-32α concentration in neuromyelitis optica and MS patients. Morsaljahan et al. (2017) reported that total IL-32 serum concentrations were higher in MS patients than healthy controls, but they did not specify which isoform(s) contributed pronouncedly to MS. The authors concluded that total IL-32 serum concentration would be associated with susceptibility to and/or outcomes of MS. Otherwise, IL-32α was shown to play a protective role in MS, because the paralytic severity and neuropathology of EAE in IL-32α transgenic mice were lower than those of the non-transgenic counterparts (Yun et al., 2015). In the fingolimod and interferon β1a-treated groups, serum IL-32α concentration positively correlated with the EDSS (moderate and weak, respectively). Moreover, serum IL-32α concentration showed moderate and weak negative correlations with the time elapsed in non-relapsed MS patients treated with fingolimod and interferon β-1a, respectively. These findings may be applied for the efficient monitoring of the therapy responses of both DMDs in MS patients.

Table 5
The extents of correlation between serum ILs-22, 32α and 34 concentrations and the time elapsed (0, 6 and 12 months) during the treatment with DMDs in total, non-relapsed and relapsed MS patients.

Parameter	Patient Group	Spearman r Value (*P* value)		
		Total	Non-Relapsed Patients	Relapsed Patients
IL-22	Interferon β-1b	−0.664 ($P < .001$)	−0.746 ($P < .001$)	−0.236 ($P > .05$)
	Interferon β-1a	−0.563 ($P < .001$)	−0.691 ($P < .001$)	0.105 ($P > .05$)
	Fingolimod	−0.627 ($P < .001$)	−0.704 ($P < .001$)	0.359 ($P > .05$)
IL-32α	Interferon β-1b	−0.222 ($P > .05$)	−0.390 ($P < .01$)	0.046 ($P > .05$)
	Interferon β-1a	−0.401 ($P < .001$)	−0.480 ($P < .001$)	0.058 ($P > .05$)
	Fingolimod	−0.573 ($P < .001$)	−0.609 ($P < .001$)	−0.258 ($P > .05$)
IL-34	Interferon β-1b	0.232 ($P > .05$)	0.233 ($P > .05$)	0.251 ($P > .05$)
	Interferon β-1a	−0.165 ($P > .05$)	−0.142 ($P > .05$)	−0.105 ($P > .05$)
	Fingolimod	0.025 ($P > .05$)	0.027 ($P > .05$)	−0.120 ($P > .05$)

Values are expressed as Spearman's correlation coefficients (r). The positive correlation categories were very weak (> 0 to 0.29); weak (0.3 to 0.49); medium (0.5 to 0.69); and strong (0.7 or more). The negative correlation categories were very weak (< 0 to −0.29); weak (−0.3 to −0.49); medium (−0.5 to −0.69); and strong (−0.7 or less). MS; multiple sclerosis, DMDs; disease-modifying-drugs.

Finally, we have monitored the changes of IL-34 concentrations in sera of untreated RRMS patients and healthy individuals. There was a non-significant elevation of IL-34 in the blood circulation of RRMS patients, compared to healthy individuals. Also, there were no statistical significant differences in IL-34 concentrations after any treatment at 6 or 12-months in comparison to the initial pretreatment baseline. Despite the limited data, IL-34 was reported to possess reparative properties on microglia (Greter et al., 2012; Mizuno et al., 2011). IL-34 was also reported to maintain the blood-brain barrier integrity by reversing the decrease of tight junction proteins instigated by overproduction of pro-inflammatory cytokines (Jin et al., 2014).

5. Conclusion

IL-22 and, to a lesser extent IL-32α, may be potential marker for MS disease severity and efficacy of DMDs. Meanwhile, there is no relation between the therapeutic mechanism of the used DMDs and the concentration of IL-34 in the blood circulation.

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Nothing to disclose.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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