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Research Article

TNF-α and IL-6 levels in Multiple Sclerosis on Dimethyl Fumarate: A Retrospective Study

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Abstract

This 6-year retrospective study evaluated correlations between TNF-α, IL-6, EDSS, vitamin D levels, age, duration of disease, or number of MRI lesions in in attack-free MS patients on dimethyl fumarate. TNF-α levels were affected by the duration of dimethyl fumarate therapy, patient age, and CRP levels. IL-6 levels were affected by the duration of dimethyl fumarate therapy, patient age, and vitamin D levels. We maintain that TNF-α is a more promising serum biomarker than IL-6 in monitoring dimethyl fumarate therapy in MS NEDA patients.

Keywords: *TNF-α; IL-6; Multiple Sclerosis; Biomarker; Dimethyl Fumarate*

1. Introduction

Multiple sclerosis (MS) is an acquired demyelinating disease of the CNS (Lucchinetti et al., 2000, Wingerchuk et al., 2001). MS affects more than 2.3 million worldwide; most have relapsing-remitting multiple sclerosis (RRMS) (Lublin et al., 2014). Because it is difficult to predict responses to disease-modifying therapies (DMTs), there is growing interest in studying biomarkers to individualize treatment (Harris and Sadiq, 2014).

One is tumor necrosis factor-alpha (TNF-α), a pro-inflammatory cytokine produced by activated macrophages. TNF-α negatively correlates with Expanded Disability Status Scale (EDSS) scores (Uysal et al., 2014). Interleukin-6 (IL-6) is both a pro- and anti-inflammatory cytokine that inhibits TNF-α (Scheller et al., 2011, Rodriguez et al., 1994). Hautecoeur et al. have shown that both TNF-α and IL-6 are increased ($p < 0.007$) during relapses, concluding that TNF-α could be a relapse marker while IL-6 might reflect the global immune activity in MS (Hautecoeur et al., 1997). Polachini et al. also found that TNF-α and IL-6 were elevated compared with controls in RRMS (Polachini et al., 2014). Moreover, interferon β-1b decreases TNF-α and increases IL-6 in MS (Brod et al., 1996).

DMF(Tecfidera®) has been FDA-approved for RRMS since 2013. DMF decreases TNF- α and IL-6 in activated microglia and astrocytes in vitro (Wilms et al., 2010) and down-regulates TNF-α-induced IL-6 secretion in lung fibroblasts (Seidel et al., 2010). However, little is known about how DMF works in vivo, especially with no evidence of disease activity (NEDA).

Hence, we conducted a retrospective study on patients receiving DMF, with TNF-α and IL-6 assessed as part of routine care.

Our objectives were:

A. To investigate TNF-α and IL-6 in MS NEDA patients on DMF

B. To see if any correlation between TNF-α, IL-6, EDSS, vitamin D, age, duration of DMF therapy, or the number of MRI lesions exists

2. Methods

2.1 Patients

This was a six-year retrospective study of patients seen by a single neurologist (WSB) from January 1, 2014, to October 31, 2019. WSB confirmed participants' diagnosis of MS, or a clinically isolated syndrome (CIS) based on the 2017 McDonald diagnostic criteria. After we applied the inclusion and exclusion criteria, we collected the final data from a total of 11 study participants, with participants having six visit-points during this six-year retrospective study.

2.2 Inclusion criteria

1. Patients aged 18 or above with a new or pre-existing diagnosis of either MS or CIS

2. Patients with laboratory data performed at baseline and every 3-4 months afterwards (at least three times), and MRI prior to starting DMF and afterwards (at least twice)

3. Patients who were naïve to MS medications or had been off treatment for at least one year prior to starting DMF

2.3 Exclusion criteria

1. Those still on multiple sclerosis disease-modifying therapy at the time of the initial visit

2. Those who missed their follow up visits, lab tests, MRIs or discontinued DMF

3. Patients with concurrent infectious or inflammatory/autoimmune conditions

4. Patients who relapsed or developed new MS lesions on MRI during the study period

2.4 Study Design

If a patient had visited the clinic several times in one year, we calculated the mean number of clinical records among these visits and used them in the subsequent analysis. Occasional laboratory values were missing as the laboratories had failed to perform the correct tests. We used Multiple Imputation by Chained Equations (MICE) to replace the missing values (Azur et al., 2011, White et al., 2011).

2.5 Statistical Analysis

We performed longitudinal data analysis using linear mixed-effects models (Laird and Ware, 1982). Specifically, we treated TNF-α and IL-6 as separate quantitative endpoints. For the fixed effects model used to describe how the mean values change within this population, we included within the full model the duration of DMF therapy, the patient's age, CRP levels, absolute lymphocyte count(ALC), vitamin D levels, baseline number of T1 black holes, baseline number of T2 lesions, and baseline EDSS scores, as well as the interactions between the duration of DMF therapy and the other variables. To account for heterogeneity of participants' baseline levels of TNF- and IL-6, we also included random, subject-specific intercepts and slopes. While constructing the prediction model for the within-subjects analysis, we considered different variance-covariance structures among the six visit-points including compound symmetry, first-order autoregression and spatial power, then selected the optimal model according to the Akaike information criterion (AIC) (Sakamoto et al., 1986).

1.6 Standard Protocol Approval

This study was approved by the Institutional Review Board of the University of California at Riverside.

3. Results

A total of 84 study participants were started on DMF either as de novo or second-line therapy. After we applied exclusion criteria, we included 11 participants in the data analysis. Ten were female and one was male, with a mean age was 46.9 years. The mean age of MS symptom onset was 33.3 years, with a mean time from symptom onset to diagnosis of 6.6 years. The mean baseline EDSS score was 2.5. On baseline brain MRI, participants had a mean of 21.6 T2-FLAIR lesions and 6.4 T1-hypointense lesions. Mean values for baseline laboratory studies included CRP of 1.78 mg/ml (SD 2.57 mg/ml), ALC of 1542/μL (SD 513/μL), and vitamin D level of 35.64 ng/ml (SD 21.97 ng/ml). Figure 1 illustrates the interaction between the duration of DMF therapy and the other factors affecting TNF-α levels. Figure 2 shows the TNF-α levels from all 11 subjects on DMF during the six-year study. Figure 3 shows how the interaction between the duration of DMF therapy and other factors affect IL-6 levels. Figure 4 shows the IL-6 levels from all 11 subjects on DMF during the six-year study.

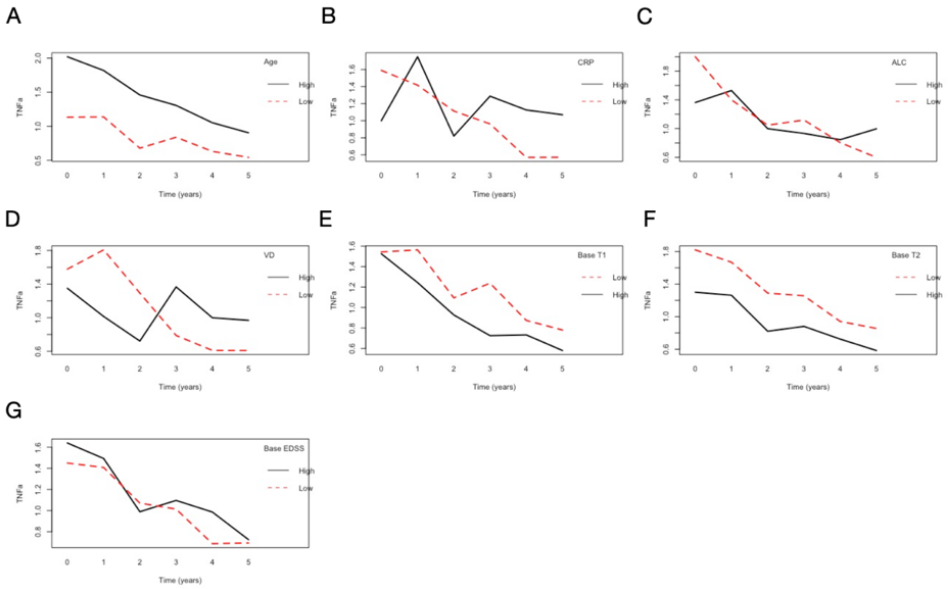

Figure 1: Graphs depicting how the interaction between variables affect TNF- levels. TNF- levels are affected by the interaction between the duration of DMF therapy and A. age, B. CRP levels, C. ALC, D. vitamin D levels, E. baseline T1 black holes, F. baseline T2 lesions, and G. baseline EDSS score. The terms high and low here refer to higher or lower than the population mean.

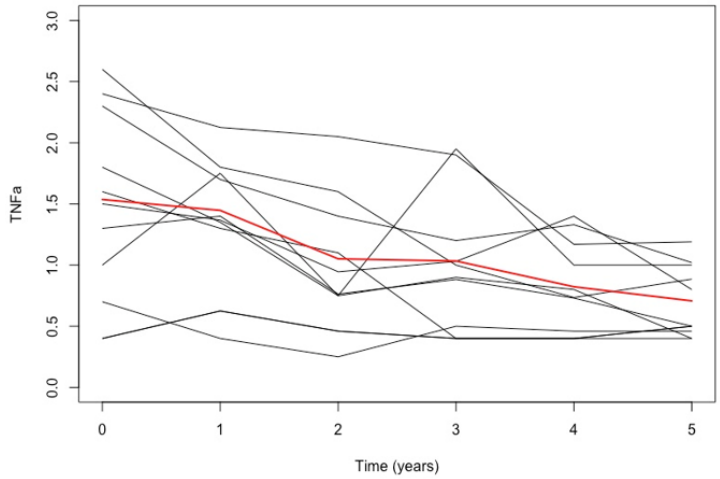

Figure 2. Graph of TNF- levels from all patients while on DMF therapy. The population mean at each time point is shown in red.

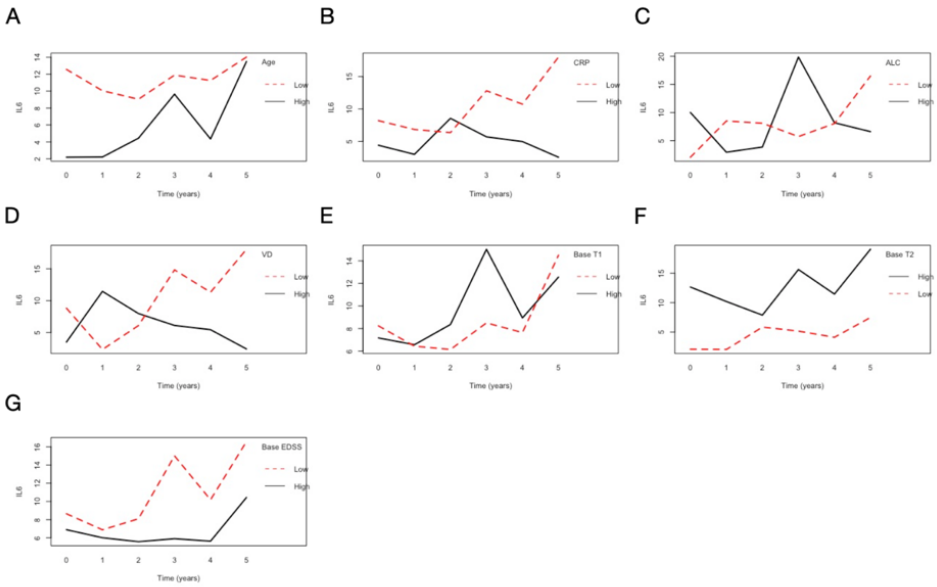

Figure 3. Graphs depicting how the interaction between variables affect IL-6 levels. IL-6 levels are affected by the interaction between the duration of DMF therapy and A. age, B. CRP levels, C. ALC, D. vitamin D levels, E. baseline T1 black holes, F. baseline T2 lesions, and G. baseline EDSS score. The terms high and low here refer to higher or lower than the population mean.

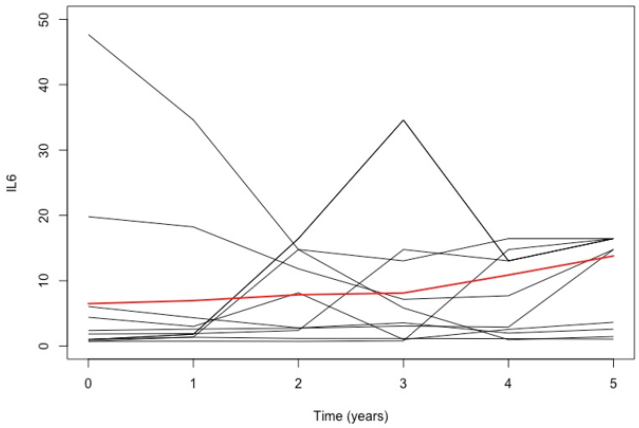

Figure 4. Graph of IL-6 levels from all patients while on DMF therapy. The population mean at each time point is shown in red.

3.1. TNF-α levels are affected by the duration of DMF therapy, patient age, and CRP levels.

Taking TNF-α as a quantitative endpoint, and AIC as the model selection criteria, the optimal model would include the duration of DMF therapy, patient age, CRP levels, the interaction between the duration of DMF therapy and CRP levels, as well as the random intercept and slope (Table 1).

Table 1. Linear mixed-effects model, taking TNF- as the endpoint.

Fixed Effects					
	Value			*p* value*	
Intercept	1.18			< 0.00	
Duration of DMF therapy (years)	-0.22			< 0.00	
Patient age (years)	0.01			0.10	
CRP levels (mg/ml)	-0.08			0.07	
Duration of DMF therapy CRP levels	0.03			0.02	
Random Effects					
Patient ID	Time	Patient ID	Time	Patient	Time
1	-0.03	2	-0.07	3	-0.03
4	-0.07	5	0.14	6	-0.12
7	-0.02	8	-0.01	9	-0.01
10	0.04	11	0.16		

*significance level = 0.10

The variance-covariance structure within each patient is formulated as the first-order autoregressive structure, which assumes that the further away between two visit-points the less correlation there will be.

The following mathematical formulas that are derived from Table 1 numerically characterize the relationship between TNF- levels and the duration of DMF therapy, age, and CRP levels.

- TNF- 0.01 age

Age affects TNF- levels regardless of the duration of DMF therapy: the older the subject was, the higher the TNF- levels were. In other words, when age increases by 1 year, TNF- levels increase by 0.01pg/ml.

- TNF- (- 0.08 + 0.03 duration of DMF therapy) CRP levels

The effect of CRP levels on TNF- levels depends on the duration of DMF therapy. That is, during the first 3 years of DMF therapy, a higher CRP level implies a lower TNF- level; however, when beyond 3 years of DMF therapy, a higher CRP level implies a higher TNF- level.

- TNF- (- 0.22 + 0.03 CRP levels) duration of DMF therapy

TNF- levels decreased significantly according to the duration of DMF therapy: the longer the duration of DMF therapy, the lower the TNF-α levels were. However, the rate of decrease depended on the CRP levels; a higher CRP level implied a lower rate of decrease.

In summary, the duration of DMF therapy, age, and CRP all significantly affected TNF- levels at a significance level of 0.10, whereas baseline T1 black holes, baseline T2 lesions, baseline EDSS scores, ALC, or vitamin D levels did not. As shown in Table 1, TNF- levels decreased significantly during the DMF therapy as a whole ($p < 0.00$). Furthermore, a likelihood ratio test demonstrated that random effects were significant within this model ($p = 0.01$), which means that the rates of decrease in TNF- levels among different patients deviated significantly from the population-averaged rate of decrease.

3.2. IL-6 levels are affected by the duration of DMF therapy, patient age, and vitamin D levels.

Taking IL-6 as a quantitative endpoint, and AIC as the model selection criteria, the optimal model would include the duration of DMF therapy, age, and the interaction between time and vitamin D levels, as well as the random intercept and slope (Table 2).

Table 2. Linear mixed-effects model, taking IL-6 as the endpoint.

Fixed Effects		
	Value	*p* value*
Intercept	19.67	0.01
Duration of DMF therapy (years)	2.21	0.08
Age (years)	-0.27	0.09
Duration of DMF therapy Vitamin D levels (ng/ml)	-0.04	0.07

Random Effects					
Patient ID	Time	Patient ID	Time	Patient	Time
1	5.57	2	-0.50	3	-0.26
4	-0.54	5	1.66	6	-0.86
7	1.22	8	-6.02	9	-2.37
10	0.32	11	1.25		

*significance level = 0.10

The variance-covariance structure within each patient is formulated as the first-order autoregressive structure.

The following mathematical formulas derived from Table 2 numerically characterize the relationship between IL-6 levels and the duration of DMF therapy, age, and vitamin D levels:

- IL-6 ∝ - 0.27 × age

Age affects IL-6 levels regardless of the duration of DMF therapy: the older the subject was, the lower the IL-6 levels were. In other words, when age increases by 1 year, IL-6 levels decrease by 0.27 pg/ml.

- IL-6 ∝ (- 0.04 × duration of DMF therapy) × vitamin D levels

IL-6 level decreases when vitamin D levels increase. In addition, this rate increases with the duration of DMF therapy.

- IL-6 ∝ (2.21 – 0.04 × vitamin D) × duration of DMF therapy

IL-6 levels increased significantly according to the duration of DMF therapy: the longer the duration of DMF therapy, the higher the IL-6 levels were. However, the rate of increase depended on the vitamin D levels; higher vitamin D levels implied a lower rate of increase.

In summary, the duration of DMF therapy, age, and vitamin D level all significantly affected IL-6 levels at a significance level of 0.10, whereas baseline T1 black holes, baseline T2 lesions, baseline EDSS scores, CRP, or ALC did not. Of note, although IL-6 levels increased significantly during the DMF therapy as a whole (p = 0.08 < 0.10), this was not as significant as the decrease in TNF- levels (p < 0.00). Furthermore, a likelihood ratio test implied that random effects were not significant within this model (p = 0.12). In other words, the rates of increase in IL-6 levels among different patients during DMF therapy did not deviate significantly from each other.

4. Discussion

In this six-year retrospective study we found that levels of both TNF-α levels and IL-6 were affected by the duration of DMF therapy and patient age. TNF-α levels were also affected by CRP levels, while IL-6 levels were affected by vitamin D levels. DMF appeared to decrease TNF-α levels while increasing IL-6 levels. We created mathematical formulas to calculate these values based on several variables, a process which to our knowledge has not previously been reported in the published literature.

Medina et al. have reported that only MS patients with NEDA showed a significant decrease in TNF-α levels (Medina et al., 2018). However, our results indicate that the rate of decrease depends on the CRP levels, which has not been previously reported. This might have been due to fact that CRP cutoff values differ among laboratories and are reported solely as less than such values (without providing an exact number), which might have skewed the data.

The fact that TNF-α levels increase with age has been previously reported (Bruunsgaard et al., 2000), which was confirmed again in our study. Previous reports on how age affects IL-6 levels have been somewhat conflicting, with some studies showing that IL-6 levels increase with age (Bruunsgaard et al., 2000, Ashtari et al., 2019), and others demonstrating no increase at all (Beharka et al., 2001). In our study cohort, IL-6 levels decreased with age. We also discovered that CRP levels significantly affected TNF levels, whereas baseline T2 lesions, T1 lesions, baseline EDSS scores, ALC, or vitamin D levels did not. As a pro-inflammatory cytokine, TNF-α is known to stimulate the release of CRP. The duration of DMF therapy, patient age, and vitamin D levels all significantly affected IL-6 levels, whereas baseline T1 lesions, baseline T2 lesions, baseline EDSS scores, or ALC did not. Our findings were consistent with the results shown by Taşdemir et al., who reported no correlation between the number of baselines T2 lesions and IL-6 levels (Taşdemir et al., 2010). Our data showing that IL-6 levels decreased with an increase in vitamin D levels were consistent with previous reports (Hashemi et al., 2018). Moreover, this rate increases with the duration of DMF therapy, which has not been previously reported. We also discovered that IL-6 levels increased significantly according to the duration of DMF therapy: the longer the duration of DMF therapy, the higher the IL-6 levels were. An increase in IL-6 levels produced by classically stimulated monocytes in RRMS patients on DMF therapy has been previously reported (Fiedler et al., 2017, Chuluundorj et al., 2014, Sarchielli et al., 1997).

It has been suggested that DMF-induced IL-6 has the potential to act in an anti-inflammatory/protective manner on the mixed phenotype cells present in MS lesions(Fiedler et al., 2017) The role of IL-6 in multiple sclerosis remains somewhat controversial, with some investigators suggesting that IL-6 signaling may increase MS disease activity(Schneider et al., 2013),while others characterizing IL-6's dual role as both a pro- and anti-inflammatory cytokine as not entirely detrimental in MS(Fuster and Walsh, 2014, Göbel et al., 2018).In this study, we found that the decrease in TNF-α levels correlated more strongly with the duration of DMF therapy than the increase in IL-6 levels. For this reason, TNF-α may be a more promising biomarker than IL-6 for monitoring MS patients who are on DMF therapy. The substantial variation in the rates of decrease in TNF- levels among different patients suggests an opportunity for future studies to identify which subgroup of patients will have greater rates of decrease in TNF- levels. We believe TNF-α has the potential to become a clinically valuable serum biomarker that could allow a more individualized approach to enhancing the efficacy of DMF therapy.

This was a retrospective study which was not without its own intrinsic limitations. We were unable to establish cause and effect between TNF-α and CRP levels, and IL-6 and vitamin D levels. Another limitation of our study is that the final sample size was small with only 11 patients, hence we chose a relatively flexible significance level 0.1 instead of 0.05(Fisher, 1960, Perezgonzalez, 2015). Furthermore, our linear mixed-effects model implies that IL-6 levels decrease with age in MS, which is inconsistent with the previous studies (Bruunsgaard et al., 2000, Ashtari et al., 2019, Beharka et al., 2001), which also might also be due to sample size. Lastly, there was no age-matched untreated group as a control.

We created mathematical formulas to calculate these values based on several variables, which to our knowledge has not previously reported.

Although the field of neuroimmunology has rapidly evolved in the past two decades, even now in the 21st century we are still unable to predict how individual patients will respond to DMF and other DMTs. Even in the quiescence of NEDA, DMF affects TNF-α and IL-6 levels to promote a more favorable balance between pro-inflammatory and anti-inflammatory mediators, decreasing the number of MS lesions and relapses. Our data suggest that TNF-α is a more promising serum biomarker than IL-6 in monitoring DMF therapy in MS NEDA patients.

Declaration of Competing Interests

Dr Baek has received speakers' honoraria from Allergan.

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