



## Micro article

## Plasma levels of M-CSF are increased in ANCA-associated vasculitides with active nephritis

Giuseppe A. Ramirez<sup>a,b,\*</sup>, Miriam Blasi<sup>a,b</sup>, Clara Sciorati<sup>a</sup>, Patrizia Rovere-Querini<sup>a,b</sup>, Angelo A. Manfredi<sup>a,b</sup>

<sup>a</sup> Unit of Internal Medicine and Immunology, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milano, Italy

<sup>b</sup> Università Vita-Salute San Raffaele, via Olgettina 58, 20132 Milano, Italy

## ARTICLE INFO

## Article history:

Received 9 May 2015

Received in revised form

10 September 2015

Accepted 7 October 2015

Available online 21 October 2015

## Keywords:

M-CSF

ANCA

Vasculitis

Glomerulonephritis

Macrophage

Granulomatosis with polyangiitis

Microscopic polyangiitis

Eosinophilic granulomatosis with polyangiitis

## ABSTRACT

Anti-Neutrophil Cytoplasmic Antibodies (ANCA)-associated vasculitides (AAV) are characterized by small vessel injury and in some cases granulomatous lesions and glomerular inflammation. The pathogenic bases of these clinical phenotypes are incompletely understood, but evidence from patients with AAV and other inflammatory diseases suggest a role for monocyte/macrophages in the perpetuation of tissue injury. Macrophage colony stimulating factor (M-CSF) is a promoter of monocyte recruitment and macrophage proliferation, involved in mesangial cell proliferation and experimental nephritis development. Serum concentrations of M-CSF mark and herald the onset of lupus nephritis. Plasma samples from 29 patients with AAV (18 granulomatosis with polyangiitis, GPA, 6 eosinophilic granulomatosis with polyangiitis, EGPA, and 5 microscopic polyangiitis, MPA) and from 10 healthy controls were collected together with clinical data. Patients with AAV had higher levels of M-CSF when compared to controls. M-CSF levels correlated positively with the BVAS, serum C-reactive protein and erythrocyte sedimentation rate, while haemoglobin correlated inversely with M-CSF. Patients with active renal disease had significantly higher levels of M-CSF when compared to the other subgroups. M-CSF levels did not differ between ANCA subserotypes and were not associated with the involvement of other organs. In conclusion, M-CSF is higher in patients with AAV and active nephritis and could contribute to the pathogenesis of these diseases. In addition, M-CSF could behave as a useful marker of renal involvement in AAV.

© 2015 Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

### 1. Introduction

Renal involvement represents the most severe manifestation of ANCA-associated vasculitides (AAV) and the leading cause of chronic damage accrual [1], despite the lack of specific biomarkers to guide the Clinician's diagnostic and therapeutic decisions [2]. Macrophage colony stimulating factor (M-CSF) is a promoter of monocyte recruitment and macrophage proliferation [3,4]. Circulating levels of M-CSF are increased in patients with chronic renal failure, possibly as a consequence of immune dysregulation during uraemia, since M-CSF metabolism is independent of the renal function [5]. Furthermore, M-CSF is involved in mesangial cell proliferation and acts in synergy with LPS to prompt macrophage recruitment from the bloodstream in experimental nephritis [3,4]. Previous studies also documented increased levels of M-CSF in

sera and renal biopsies of patients with proliferative glomerulonephritis (GN) and in particular lupus nephritis (LN) [6,7]. In addition, recent works showed that serum concentrations of M-CSF marked and heralded the onset of LN in two large lupus cohorts [6]. By contrast, no specific evidence is available to date about a role of M-CSF in AAV, despite pathogenic similarities between AAV and other forms of kidney inflammation, such as LN [8]. In this study, we thus aimed at evaluating a role of M-CSF as a biomarker of disease activity and organ involvement in AAV.

### 2. Methods

Upon informed consent, plasma samples from 29 patients with AAV (18 granulomatosis with polyangiitis, GPA, 6 eosinophilic granulomatosis with polyangiitis, EGPA, and 5 microscopic polyangiitis, MPA) and from 10 healthy controls were collected together with data regarding clinical history, disease activity (as estimated by the Birmingham Vasculitis Activity Score, BVAS) at the time of venepuncture, routine laboratory parameters and markers

\* Corresponding author at: Unit of Internal Medicine and Immunology, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milano, Italy.

E-mail address: [ramirez.giuseppe@hsr.it](mailto:ramirez.giuseppe@hsr.it) (G.A. Ramirez).

of renal involvement such as increased 24 h proteinuria and active urinary sediment. According to the clinical phenotype, AAV patients were divided in patients with active renal disease, patients with active disease without renal involvement, patients in remission with past history of renal involvement, patients in remission with no history of renal involvement. M-CSF plasma concentration was assessed by using a commercial assay (Human M-CSF Quantikine<sup>®</sup> ELISA Kit, R&D Systems, Minneapolis, MN). M-CSF levels were also standardized for GFR by defining a specific variable resulting from the product M-CSF\*ln(GFR). Differences in normally distributed continuous variables (creatinine; glomerular filtration rate, GFR) among groups were measured by employing the ANOVA with Bonferroni's correction, whereas non-normally distributed continuous variables (M-CSF) were analysed by using the Mann–Whitney *U*-test or the Kruskal–Wallis test for multiple comparisons. Correlations between continuous variables were assessed by using the Spearman's test. Data are expressed as median (interquartile range), unless specifically indicated.

### 3. Results

The clinical and serological phenotypes of patients with AAV were equally distributed among disease groups (Table 1).

Patients with AAV had higher levels of M-CSF when compared to controls (Fig. 1). The levels of M-CSF correlated positively with erythrocyte sedimentation rate ( $\rho=0.521$ ;  $p=0.022$ ) and serum C-reactive protein ( $\rho=0.764$ ;  $p<0.001$ ) and negatively with haemoglobin ( $\rho=-0.552$ ;  $p=0.012$ ). Furthermore, M-CSF levels correlated positively with the BVAS ( $\rho=0.472$ ;  $p=0.010$ ).

Patients with active renal disease had significantly higher levels of M-CSF when compared to patients with active disease and no kidney involvement, with patients in remission with or without a history of renal involvement and with healthy controls ( $p=0.014$ ;  $p=0.019$ ;  $p=0.002$ ;  $p<0.001$  respectively; Fig. 1). Patients with renal involvement and in particular those with active renal disease had also higher creatinine levels and lower GFR ( $p<0.05$  towards patients with active disease without renal involvement and patients in remission without history of renal involvement), as expected (Table 1). However, when M-CSF levels were standardized for GFR, the differences among groups were not significantly affected ( $p=0.001$  between AAV patients and controls;  $p=0.064$ ,  $p=0.031$ ,  $p=0.007$ ;  $p<0.001$  when comparing AAV patients with active renal disease and patients with active disease without renal involvement, patients in remission with a history of renal involvement, patients in remission without a history of renal involvement and healthy controls respectively). Patients with active urinary sediment, significant 24 h proteinuria and typical findings

at renal biopsy had also higher M-CSF levels although these findings did not reach statistical significance (Table 2).

M-CSF levels did not discriminate AAV serotype (anti-PR3/MPO positive vasculitis) or phenotype (GPA, EGPA, MPA; Table 2), were similar between genders and did not identify any other type of organ involvement. In particular, circulating M-CSF in patients with vasculitic lung involvement were comparable to those of patients with nodular lesions only (Table 2).

Patients receiving prednisone alone at time of sample collection (all in the induction phase while waiting to start an immune suppressant) had significantly higher M-CSF than those taking prednisone in combination with immune suppressants ( $p=0.033$ ). By contrast, M-CSF levels did not correlate with prednisone dose at venepuncture and were not significantly different among patients taking different immunosuppressive agents either for induction and maintenance of remission. Although the study was not designed for prospective evaluation, we also recorded data about disease activity at 6 months from venepuncture: patients with persistent non-remission or disease flare had slightly higher M-CSF levels, although the datum did not reach statistical significance (Table 3).

### 4. Discussion

In this brief report, we first describe the presence of higher M-CSF levels in patients with AAV. M-CSF correlated with clinical and biochemical markers of systemic inflammation and showed a trend towards a higher expression in patients who eventually experienced a disease flare or who did not reach remission 6 months after sample collection. The highest M-CSF levels were detected in patients with active renal disease. Consistently, we also observed a trend towards a higher M-CSF expression in patients with active urinary sediment, significant 24 h proteinuria and typical histological findings at renal biopsy. Unfortunately, these data did not reach statistical significance, possibly because of the limited sample size. Patients with active renal disease had also signs of impaired renal function, as documented by lower GFR levels. When M-CSF levels were standardized for GFR only minimal differences were observed, which possibly reflect the common influence of renal inflammation on both variables [5]. Previous reports have in fact repeatedly described a general rise in circulating M-CSF in patients with renal disease [5] and a significantly higher local and systemic expression of M-CSF in patients with proliferative GN, class III and IV LN in particular [6,7]. In this latter context, extensive studies, both *in vitro* and *in vivo*, dissected the precise role of M-CSF and its isoforms in prompting the recruitment of circulating monocytes into the glomerulus to cause GN [9].

Unfortunately, less is known about the pathogenic role of M-CSF in AAV. However, evidence from AAV disease models suggest that: (a) M-CSF plays a non-redundant role in experimental

**Table 1**  
Clinical characteristics according to disease activity and renal involvement.

	Active renal disease	Active disease without renal involvement	History of renal involvement	No history of renal involvement	Total AAV
Anti-PR3+	6	1	8	3	18
Anti-MPO+	3	3	1	4	11
GPA (N)	6	1	8	3	18
EGPA (N)	1	2	0	3	6
MPA (N)	2	1	1	1	5
Mean $\pm$ SEM serum creatinine (mg/dl)	2.40 $\pm$ 0.64	0.83 $\pm$ 0.06	1.21 $\pm$ 0.24	0.88 $\pm$ 0.11	1.47 $\pm$ 0.25
Mean $\pm$ SEM glomerular filtration rate (ml/min)	38.55 $\pm$ 7.11*	92.78 $\pm$ 9.85*	72.78 $\pm$ 11.32	90.75 $\pm$ 9.63*	68.49 $\pm$ 6.34

\*  $p<0.05$ .

Download English Version:

<https://daneshyari.com/en/article/2202385>

Download Persian Version:

<https://daneshyari.com/article/2202385>

[Daneshyari.com](https://daneshyari.com)