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**CASE REPORT** **OPEN ACCESS**

# Treatment of Systemic Lupus Erythematosus with Macrophage-Activating Factor GcMAF$^{anti}$: Case Report

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**Abstract:**

***Introduction:*** GcMAF$^{anti}$ is a Gc protein-derived macrophage-activating factor that enhances macrophage phagocytic activity and stimulates the production of anti-inflammatory cytokines. The aim of this study was to describe the clinical picture of monotherapy in the treatment of systemic lupus erythematosus.

***Case Presentation:*** The patient (female, 37 years old) was diagnosed with systemic lupus erythematosus according to the EULAR/ACR 2019 diagnostic criteria. The patient had elevated titers of antinuclear antibodies, recurrent episodes of fever, a low C4 level, and a high level of anti-dsDNA antibodies. The activity of systemic lupus erythematosus was low, 5 points on the SLEDAI-2K scale. The patient was transitioned to GcMAF$^{anti}$ monotherapy after two years of standard therapy with hydroxychloroquine and prednisolone. A total of four courses of subcutaneous GcMAF$^{anti}$ injections were administered, each consisting of 12 injections over 24–36 days (a single 2–5 μg injection every 2–3 days), with 2–4-month intervals between treatment courses. GcMAF$^{anti}$ monotherapy did not reverse the positive clinical changes in the patient achieved by standard therapy with hydroxychloroquine and prednisolone. No febrile episodes were observed during therapy and for 2–3 months following treatment; neither patient-reported complaints nor adverse events were reported during the same period. The result of GcMAF$^{anti}$ monotherapy was 2-4 points on the SLEDAI-2K scale. Indicators of immunobiological markers of systemic lupus erythematosus indicated stabilization of the disease with GcMAF$^{anti}$ monotherapy.

***Conclusion:*** The results obtained in this case report of systemic lupus erythematosus treatment using the novel agent GcMAF$^{anti}$ suggest that clinical studies are required to further analyze the effect of GcMAF$^{anti}$ on systemic lupus erythematosus.

**Keywords:** Systemic lupus erythematosus, Antigen-presenting cell, Macrophage, Interleukin-10, Transforming growth factor beta, Vitamin D-binding protein.

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## 1. INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic multisystem autoimmune disease characterized by loss of immunological tolerance to self-antigens, production of a broad spectrum of autoantibodies, and damage to virtually any organ and system [1]. SLE predominantly affects women of childbearing age (female-to-male ratio of approximately 9:1), and its prevalence ranges from 20 to 150 cases per 100,000 individuals [2]. The disease is characterized by high clinical heterogeneity in terms of severity, disease course, and organ involvement [3, 4]. This clinical heterogeneity arises due to dysregulation of multiple interconnected immune and signaling pathways underlying disease pathogenesis. The clinical course of SLE is typically characterized by frequent relapsing episodes alternating with remission periods. The disease duration and organ involvement are often unpredictable. SLE pathogenesis is highly complex, and a primary disease driver is impairment of mechanisms responsible for elimination of autoreactive T cells [5, 6]. Immune complexes formed by autoantibodies and circulating self-antigens represent key effector elements in SLE. These autoimmune complexes are simultaneously generated at high levels in the body to activate the complement system, resulting in widespread non-specific lysis of random cells in any part of the body and sustained inflammation.

Vitamin D-Binding Protein (DBP) is a multifunctional polymorphic protein of the albumin family present in humans and other vertebrates [7]. DBP is synthesized by hepatic parenchyma cells and secreted into the bloodstream as a mature monomeric protein with a molecular weight of 51.2 kDa [8]. DBP is believed to be converted into Gc protein-derived Macrophage-Activating Factor (GcMAF) through partial deglycosylation, resulting in exposure of a terminal N-acetylgalactosamine residue, which is thought to be critical for macrophage-activating activity [7, 9-13]. The factor is attributed with various properties, and the experiments conducted indicate the contradictory nature of the described therapeutic potential of GcMAF [11, 14-17].

The preparation GcMAF$^{anti}$ was developed at the Laboratory of Induced Cell Processes at the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences [18, 19]. Our studies have demonstrated that modulation of deglycosylation regimens enables the generation of agents with either pro- or anti-inflammatory properties [19]. The anti-inflammatory form, GcMAF$^{anti}$, has demonstrated a series of therapeutic effects. It has been shown to ameliorate experimentally induced arthritis and cystitis [19] and attenuate COVID-19 progression both through targeting the virus and by neutralizing the inflammatory response of alveolar macrophages [20]. GcMAF$^{anti}$ also inhibits the development of stress-induced depression and reduces depressive-like behavioral patterns in experimental mice (manuscript in preparation). In ongoing clinical trials, GcMAF$^{anti}$ has been reported to improve clinical manifestations of arthritis. Available data suggest that GcMAF$^{anti}$ has an active component affecting Antigen-Presenting Cells (APCs), dendritic cells and macrophages, promoting their differentiation towards either a tolerogenic state or a phenotype characterized by enhanced anti-inflammatory function. It has been hypothesized that the response to the preparation is systemic, associated with a local effect on naive T lymphocytes and the generation of T-regulatory lymphocytes, and that any systemic inflammatory disease associated with dysregulation of innate immune responses may represent a potential therapeutic target for GcMAF$^{anti}$.

GcMAF$^{anti}$ (Immutalon®) was provided by ACTIVATOR MAF LLC (Novosibirsk, Russia). It is an injection solution, 2 or 5 μg/ml GcMAF. GcMAF$^{anti}$ enhances the phagocytic activity of murine peritoneal macrophages and exhibits anti-inflammatory properties. It also induces the production of anti-inflammatory cytokines TGF-β and IL-10 without stimulating the synthesis of pro-inflammatory cytokines IL-1β and TNF-α in murine peritoneal macrophages [18, 19].

In this case report, we evaluated for the first time the effect of GcMAF$^{anti}$ on SLE symptoms.

## 2. CASE PRESENTATION

A female patient first manifested clinical symptoms at the age of 36 years, which included intermittent febrile episodes (fever up to 39 ± 0.5°C) and generalized body aches. Each febrile episode persisted for 10–14 h and resolved spontaneously without the use of any medication. The episodes initially occurred 1–2 times per month, then progressed to 3–4 times per month. Myalgia, weight loss, and fatigue were also reported. Finger joint pain was infrequent and mild.

One year after the onset of symptoms, the patient was diagnosed with low-activity SLE according to the EULAR/ACR 2019 diagnostic criteria with a SLEDAI-2K score of 5 [21]. Comprehensive blood biochemistry testing revealed elevated levels of antinuclear antibodies and anti-dsDNA antibodies, along with a low level of complement component C4 (Table **1**). Standard treatment was prescribed immediately. For one and a half years, the patient received daily 200 mg of hydroxychloroquine as a specific agent suppressing autoreactive T cell production and 5 mg of prednisolone as a systemic anti-inflammatory modulator, followed by monotherapy with 200 mg of hydroxychloroquine daily for 6 months. The treatment was effective, and febrile episodes were completely resolved; the SLEDAI-2K score was 2-4 (Tables **1** and **2**). However, adverse effects (weight gain, enhanced sweating, nervousness, *etc.*) were observed.

**Table 1. Hematological parameters and parameters related to disease severity before treatment (0 months), during standard therapy (1-24 months), and during GcMAF$^{anti}$ administration (25-36 months) compared with the normal range.**

| Indicator | Normal Range | Time, Months | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 4 | 18 | 24 | 25 | 27 | 30 | 31 | 33 | 36 |
| | | Before Treatment | Standard Therapy | | | | GcMAF | | | | | |
| Hematocrit | 35-45, % | **34.6** | 39.0 | 37.1 | 39.0 | 35.3 | **34.9** | **32.7** | 36.7 | **34.8** | 36.9 | 39.1 |
| Hemoglobin | 117-155 g/l | **115** | 132 | 123 | 129 | **116** | **111** | **105** | 124 | 119 | 124 | 125 |
| Erythrocytes | 3.8-5.1, $\times10^6$/µl | 3.80 | 4.33 | 4.02 | 4.40 | 4.19 | 4.18 | 4.00 | 4.16 | 3.93 | 4.17 | 4.40 |
| Leukocytes | 4.5-11, $\times10^3$/µl | 8.72 | 6.49 | 5.90 | 5.67 | 9.09 | **4.06** | **4.23** | 6.74 | 5.07 | 7.20 | 5.88 |
| Neutrophils | 48-78, % | 69.8 | **47.9** | **41.5** | 50.1 | 69.7 | **46.7** | **47.6** | 60.8 | 51.2 | 66.8 | 53.8 |
| Lymphocytes | 19-37, % | 23.4 | **42.1** | **51.7** | **41.9** | 23.5 | **43.9** | **43.2** | 32.3 | **41.0** | 27.3 | **38.6** |
| Monocytes | 3-11, % | 3.9 | 7.2 | 5.0 | 5.3 | 4.5 | 6.4 | 6.4 | 5.5 | 5.4 | 4.4 | 5.9 |
| Neutrophils abs. | 1.56-6.13, $\times10^3$/µl | 6.08 | 3.11 | 2.44 | 2.84 | **6.33** | 1.90 | 2.00 | 4.10 | 1.90 | 4.80 | 3.17 |
| Alanine aminotransferase | 0-35, U/l | 6.5 | 9.8 | 6.0 | 8.7 | 8.4 | 9.3 | 3.2 | 9.5 | 8.8 | 7.6 | 8.0 |
| Aspartate aminotransferase | 0-35, U/l | 11.7 | 15.0 | 12.7 | 16.9 | 16.9 | 18.4 | 13.4 | 17.5 | 15.9 | 14.5 | 16.0 |
| Urea | 2.8-7.2 mmol/l | 3.54 | 3.26 | 3.48 | 3.67 | 4.01 | 4.19 | 4.41 | 4.17 | 4.76 | 4.07 | - |
| Creatinine | 58-96 µmol/l | 80.27 | 88.15 | 82.42 | 90.80 | 90.18 | 82.78 | 80.16 | 91.28 | 80.52 | 87.07 | 77.00 |
| Total bilirubin | 5-21 µmol/l | 5.98 | 9.25 | 6.29 | 8.78 | 5.74 | 6.04 | 5.30 | 9.21 | 9.05 | 7.15 | - |
| Fibrinogen | 2.0-4.0, g/l | - | **1.75** | **1.77** | 2.30 | 3.03 | 2.35 | 2.16 | 2.67 | 2.22 | 2.73 | - |
| C-reactive protein | 0.0-5.0, mg/l | - | 0.7 | 1.9 | 1.5 | **6.4** | 3.6 | **6.8** | **5.2** | 4.2 | 5.0 | 3.0 |
| Rheumatoid factor | 0-14 IU/ml | - | **-** | **-** | 4.32 | 3.28 | 6.07 | 6.12 | 6.43 | 4.83 | 4.58 | - |
| Complement C3 | 0.83-1.93, g/l | 1.34 | 1.14 | 1.28 | 1.35 | 1.34 | 1.22 | 1.13 | 1.22 | 1.17 | 1.24 | 1.20 |
| Complement C4 | 0.15-0.57, g/l | **0.14** | **0.12** | **0.12** | **0.12** | 0.16 | **0.13** | **0.13** | **0.14** | **0.14** | **0.13** | **0.12** |
| ANA by IFA (on HEp-2 cells) | <1:160 | **1:640 F, C** | **1:160 F, C** | **1:640 F, C** | **1:160 F, C** | **1:160 C** | <1:160 | **1:160 F, C** | **1:160 F** | **1:160 F, H** | **1:160 H** | <1:160 |
| ANCA IgG by IFA | <1:40 | **1:40 P** | <1:40 | **1:40 P** | <1:40 | <1:40 | <1:40 | <1:40 | **1:40 P** | <1:40 | <1:40 | <1:40 |
| Anti-dsDNA IgG | <25, IU/ml | **155** | **104** | **107** | **42** | **32** | **45** | 23 | **93** | **69** | **57** | **114** |

**Note:** Black font indicates abnormal values. F – Fine-grained type, C – Cytoplasmic type, H – Homogeneous type, P – Perinuclear type.

**Table 2. SLEDAI-2K scores during SLE therapy.**

| Time, Months | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 1 | 4 | 18 | 24 | 25 | 27 | 30 | 31 | 33 | 36 |
| Before treatment | Standard therapy | | | | GcMAF | | | | | |
| | | | | | After the 1st course | 2 months after the 1st course | 2 months after the 2nd course | After the 3rd course | 2 months after the 3rd course | After the 4th course |
| 5 | 4 | 4 | 4 | 2 | 4 | 2 | 4 | 4 | 4 | 4 |

The patient was the developer of the preparation and made an independent decision to initiate therapy with the experimental compound GcMAF$^{anti}$ due to side effects of standard therapy. The patient signed informed consent for participation in experimental therapy with a complete change in treatment regimen by discontinuing standard therapy and transitioning to GcMAF$^{anti}$ monotherapy. The authors acknowledge that the self-administration of an experimental therapeutic agent by a patient-researcher is outside the scope of standard clinical research protocols. However, this action is ethically consistent with Section 5 of the Nuremberg Code (1947), which permits potentially risky experiments in cases where researchers themselves serve as test subjects. Other sections of the Nuremberg Code (1947) 1-10 may also be cited as arguments for the permissibility of conducting the study.

The preparation was administered under the supervision of a rheumatologist, who monitored vital functions and recorded side effects throughout the treatment and to this day, and who conducts clinical work within the framework of regulatory documents for conducting clinical trials for the treatment of autoimmune diseases.

Three courses of GcMAF$^{anti}$ were administered: the patient received subcutaneous abdominal injections at 2-month intervals. No other medications were used during this period.

Course 1: GcMAF$^{anti}$ 2 μg administered 12 times with 1-day intervals.

Course 2: GcMAF$^{anti}$ 5 μg administered 12 times with 2-day intervals.

Course 3: GcMAF$^{anti}$ 5 μg administered 12 times with 1-day intervals.

GcMAF$^{anti}$ monotherapy did not reverse the positive clinical changes in the patient achieved by standard therapy with hydroxychloroquine and prednisolone (Tables **1** and **2**). No febrile episodes were observed during therapy and for 2 months following treatment; neither patient-reported complaints nor adverse events were reported during the same period.

After this, in order to determine the duration of the therapeutic effect of GcMAF$^{anti}$, the patient stopped the treatment on his own. Four months after the third GcMAF$^{anti}$ course, in the absence of therapy, the patient developed clinical symptoms manifested as fever, and a fourth course of GcMAF$^{anti}$ was immediately initiated. After resumption of GcMAF$^{anti}$ administration, clinical symptoms of the disease disappeared.

Course 4: GcMAF$^{anti}$ 5 μg administered 12 times with 2-day intervals.

The important fact is that after the 1st and 4th courses, the ANA indicator temporarily normalized (<1:160).

The patient is currently taking a one-month course of GcMAF$^{anti}$, followed by a two-month break. No clinical symptoms have been observed during this time period. A combined assessment of molecular and biochemical parameters indicates low SLE activity according to the SLEDAI-2K scale (2-4) and no disease progression (Tables **1** and **2**).

## 3. DISCUSSION

The cellular events that initiate and propagate disease pathology can be summarized as follows. Antibodies are produced by plasma B cells that have received activation signals from autoreactive T helper cells carrying T cell receptors, which recognize various self-antigens presented by B cells as part of the major histocompatibility complex. Autoreactive T helper cells arise as a result of defective negative selection in the thymus. Their further differentiation into autoreactive T cells is mediated by expression of costimulatory molecules on APCs, including dendritic cells and macrophages. Under physiological conditions, the interaction between autoreactive T helper cells and self-antigens does not trigger expression of costimulatory molecules. However, during inflammation or under conditions of increased hormonal stress, dendritic cell and macrophage function is disrupted, and costimulatory proteins are expressed on the APC surface, thereby providing the second signal required to trigger T cell proliferation. Once the autoreactive T helper cell has received this dual signal from APCs and has been activated (primed) against self-antigens presented to it, the cell proliferates. Subsequently, autoreactive T cells disseminate throughout the body in search of their cognate antigens presented on the surface of B cells. Following binding to T helper cells, B cells are activated, initiating autoantibody production and thereby driving the pathological process. The autoreactive DNA-antibody complex is marked by complement factors, precipitates on the membranes of nearby cells, and forms a membrane-attack complex, which results in cell lysis. This activation leads to the development of systemic inflammation and the development of SLE symptoms [5, 22, 23].

GcMAF$^{anti}$ is a partially deglycosylated DBP precursor. The performed site-specific enzymatic processing yielded a factor that, upon interaction with macrophages of different tissue localization (peritoneal macrophages, alveolar macrophages, and microglia), induces either a tolerogenic M0-like or an anti-inflammatory phenotype. This is accompanied by enhanced macrophage phagocytic activity and increased secretion of anti-inflammatory cytokines IL-10 and TGF-β, whereas key pro-inflammatory cytokines IL-1β and TNF-α are either not expressed or maintained at basal levels [18, 19]. The transition of macrophages into different states (M1, M0, and M2), which characterize their inflammatory phenotype, is regulated by the interaction of GcMAF with different deglycosylation modes and two C-type lectin domain family 10 member A (CLEC10A) derivatives, 63 and 65 kDa, activated in the presence of $Ca^{2+}$ ions. The pro-inflammatory, specifically deglycosylated form GcMAF$^{pro}$ interacts with the 65 kDa CLEC10A-associated derivative, promoting a pro-inflammatory phagocyte phenotype. In contrast, the anti-inflammatory form GcMAF$^{anti}$ interacts with the 63 kDa CLEC10A-associated variant, supporting either an anti-inflammatory or neutral macrophage profile [18, 19]. GcMAF$^{anti}$ may act on macrophages, which, along with dendritic cells, are the primary activators of naive T helper cells, thereby partially or completely suppressing the production of autoreactive T cells.

Having analyzed possible pathways underlying therapeutic effects of GcMAF$^{anti}$ in SLE, we considered two mechanisms based on the experimentally identified properties of the preparation.

The first mechanism involves clearance of excessive apoptotic debris from the circulation. This mechanism is associated with a significant increase in macrophage phagocytic activity across various tissue compartments [24].

The second mechanism is modulation of dendritic cell and macrophage states *via* interaction with the 63 kDa CLEC10A-associated receptor variant in a $Ca^{2+}$-dependent manner. There are several possible pathways that could have contributed to the positive clinical outcomes with GcMAF.

Activation of CLEC10A by the ligand enhances its interaction with CD45 phosphatase on the surface of autoreactive T cells, disrupting its phosphatase activity. This leads to the blocking of the activity of key signaling proteins of the T cell receptor cascade, which “turns off” the autoreactive cell, preventing its proliferation.

Increased absorption of calcium ions by APCs, which occurs as a result of CLEC10A and GcMAF$^{anti}$ engagement, is accompanied by activation of the calcineurin pathway. The high ion concentration in the cytosol, which occurs after the internalization of the complex into an APC, activates the NFAT transcription factor through the calmodulin-calcineurin pathway, which, under the described conditions, triggers the programmed death (apoptosis) of autoreactive T helper cells in contact with APCs through the T cell receptor [25, 26].

By binding to CLEC10A receptors on APCs, GcMAF$^{anti}$ stimulates the production of anti-inflammatory cytokines IL-10 and TGF-β, thereby establishing a tolerogenic microenvironment that suppresses the activity of autoreactive clones. Ligand–receptor interactions can activate signaling pathways in APCs that may favor T cell transformation into regulatory T cells over terminal activation of effector T helper cells [27-29]. Regulatory lymphocytes actively suppress inflammation at autoimmune inflammation sites. We believe that this mechanism is dominant and determines the positive processes associated with the action of GcMAF. Local injections of GcMAF alone, due to the minimal amount of active protein, are apparently unable to cover the entire body. However, M2 cells activated for anti-inflammatory activity migrate to local lymph nodes, where they encounter antigens, products of SLE activity. Primed phagocytes, secreting anti-inflammatory TGF-β and IL-10, initiate the generation of T-regulatory lymphocytes, shaping a systemic anti-inflammatory response with a specific focus. This mechanism represents *in situ* anti-inflammatory vaccination and is discussed in the scientific literature [30-33].

In general, the interaction of GcMAF$^{anti}$ with CLEC10A, depending on the molecular context, leads either to immunosuppression (*via* IL-10, TGF-β) or to apoptosis of autoreactive cells.

## 4. STUDY LIMITATIONS

The main limitation of this study is that it is a case report and describes the treatment experience of only one patient. In addition, the patient initially had low SLE activity, which may have contributed to the effect of GcMAF$^{anti}$. The results cannot be extrapolated to the general SLE patient population without conducting full-scale randomized controlled trials.

## CONCLUSION

The results obtained in this case report of SLE treatment using the novel agent GcMAF$^{anti}$ suggest that this preparation is of significant potential interest. However, clinical trials are required to further confirm its efficacy and safety. Nevertheless, the present findings provide a rationale for further investigation and support further advancement to clinical development.

## AUTHORS' CONTRIBUTION

The authors confirm their contributions to the paper as follows: A.S.P.: Performed research, collected and analyzed data, and wrote the paper; S.S.K., N.A.I., E.V.L., and G.S.R.: Performed research and contributed important reagents; V.S.R. and E.V.D.: Collected and analyzed data; E.R.C. and N.A.K.: Designed research and analyzed data; S.S.B.: Designed research, analyzed data, and wrote the paper. All authors read and approved the final manuscript.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| APC | = | antigen-presenting cell |
| CLEC10A | = | C-type lectin domain family 10 member A, CD301 |
| DBP | = | vitamin D-binding protein |
| GcMAF | = | Gc protein-derived macrophage-activating factor |
| SLE | = | systemic lupus erythematosus |

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Local Ethics Committee of the Research Institute of Fundamental and Clinical Immunology, Russia (Protocol No.1 of February 09, 2021).

## HUMAN AND ANIMAL RIGHTS

All procedures involving human participants were conducted in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

## CONSENT FOR PUBLICATION

Consent for publication was obtained from the participant.

## AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the article.

## STANDARDS OF REPORTING

CARE guidelines were followed.

## FUNDING

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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