ABSTRACT

Introduction: Treatment of idiopathic inflammatory myopathies (IIMs) is challenging due to a lack of safe and efficacious medication. Low-dose interleukin-2 (IL-2) treatment emerges as a new option in active IIMs. This study aims to explore the clinical and immunological effects of low-dose IL-2 in patients with active IIMs.

Methods: Eighteen patients with active IIMs were enrolled and received $1 \times 10^6$ IU of IL-2 subcutaneously every other day for 12 weeks on top of standard care. The primary endpoint for the trial was change in percentage of regulatory T (Treg) cells in total CD4$^+$ T cells at week 12. The secondary endpoints included the International Myositis Assessment and Clinical Studies (IMACS) definition of improvement (DOI), the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) myositis response criteria, safety, and steroid-sparing effect at weeks 12 and 24.

Results: With low-dose IL-2 treatment, 77.78% (14/18) patients achieved IMACS DOI and 83.33% (15/18) patients met the 2016 ACR/EULAR myositis response criteria at week 12. All individual core set measures (CSMs) including PhGA, PGA and HAQ-DI, muscle enzymes, MMT-8 and extramuscular activity were improved at week 12. The cutaneous dermatomyositis disease area and severity index activity score (CDASI-a) decreased significantly from 7 (4.5, 13) to 2 (0, 7) after IL-2 administration ($P < 0.001$). Proportion of Treg cells significantly increased with low-dose IL-2 treatment at week 12 (8.97% [5.77, 9.89%] vs. 15.2% [10.4, 17.3%], $P = 0.009$). There were no serious adverse events.

Conclusions: Low-dose IL-2 was effective in active IIMs and well tolerated. The amelioration
of disease activity may associate with promo-
tion of Tregs.

**Trial Registration**: ClinicalTrials.gov identifier, NCT04062019.

**Keywords**: Low-dose interleukin-2; Idiopathic inflammatory myopathies; Regulatory T cell

### Key Summary Points

**Why carry out this study?**

Treg deficiency plays a crucial role in the pathogenesis of idiopathic inflammatory myopathies (IIMs).

Low-dose IL-2 is known to promote expansion of Treg cells and might be potentially therapeutic for patients with IIMs.

**What was learned from the study?**

Low-dose IL-2 was effective in treatment of active IIMs and well tolerated.

Low-dose IL-2 promoted the expansion of functional Treg cells in patients with active IIMs.

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**INTRODUCTION**

The idiopathic inflammatory myopathies (IIMs) are acquired autoimmune disorders characterized by immune-mediated skeletal muscle inflammation and damage, which include dermatomyositis (DM), inclusion body myositis (IBM), immune-mediated necrotizing myopathy (IMNM), and antisynthetase syndrome (ASS) [1]. The standard treatment of IIMs includes glucocorticoids and immunosuppressive agents, which are associated with severe side effects. A proportion of patients are refractory to these treatments, leading to flares and organ damage [2, 3].

The pathogenesis of IIMs is not well understood at present, and immunological imbalance is considered to be a key promoter to the disease progress [2]. Regulatory T (Treg) cells are essential to the maintenance of peripheral tolerance by suppressing the activation and expansion of auto-reactive T cells and other pathogenic immune cells. It was indicated that Treg cells were impaired in both number and function in multiple autoimmune diseases including IIMs [4, 5].

Multiple studies have demonstrated effectiveness of low-dose IL-2 in autoimmune diseases, especially systemic lupus erythematosus [6–9]. However, the effect of IL-2 in IIMs has not been well studied. Immunological and laboratory effects of low-dose IL-2 have been shown in IIMs in previous studies [4] and clinical effects in case report [10]. In this study, we explored clinical and immunological effects, safety and steroid-sparing effect of low-dose IL-2 in patients with active IIMs.

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**METHODS**

**Study Design and Participants**

This was a pilot prospective study in the Department of Rheumatology and Immunology at Peking University People’s Hospital (Beijing, China). The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation guidelines on good clinical practice. Peking University People’s Hospital Ethics Committee approved the trial. All patients provided written informed consent before enrollment. The trial is registered at https://clinicaltrials.gov (NCT04062019).

Eligible patients were aged 18–70 years, had a confirmed diagnosis of IIMs according to the 1975 Bohan/Peter criteria [11, 12], or ASS proposed by Solomon et al. [13], IMNM criteria...
proposed by ENMC [14]. All patients had active
disease, defined as cutaneous visual analogue
scale (VAS) score on Myositis Disease Activity
Assessment Tool (MDAAT) ≥ 3 cm and at least
three additional abnormal core set measures
(CSMs), or manual muscle test 8 (MMT-
8) ≤ 125/150 and at least two additional
abnormal CSMs [15]. Concomitant use of glu-
cocorticoids and immunosuppressants were
permitted before and during the study at
stable doses. Glucocorticoid should be ≤ 1 mg/
kg/day prednisone or other hormones with
equivalent dose and at a stable dose for at least
4 weeks before enrollment. Immunosuppressant
drugs (e.g., cyclosporine or methotrexate)
should be stable for at least 12 weeks before
enrollment. Detailed information about inclu-
sion and exclusion criteria were provided in
online supplementary text.

Procedures

Low-dose interleukin-2 was injected subcuta-
enously at a dose of 1 × 10^6 IU once every other
day for 12 weeks. Patients were then followed
up for another 12 weeks. Dose of immuno-
suppressive drug remained stable throughout the
24-week trial period. Tapering of prednisone
was permitted from baseline to week 20. No
changes in dose of prednisone were permitted
between weeks 20 and 24.

Study visits took place on week 0 and every
4 weeks for 24 weeks (Figure S1). Disease activity
score included cutaneous dermatomyositis dis-
ease area and severity index (CDASI), patient
and physician global activity assessment (PGA
and PhGA), MMT-8, myositis disease activity
assessment tool (MDAAT), extramuscular global
and health assessment questionnaire disability
index (HAQ-DI). Laboratory parameters includ-
ing muscle enzymes, erythrocyte sedimentation
rate (ESR), C-reactive protein (CRP), comple-
ments, and complete blood count were also
evaluated at each visit. Safety was assessed at
every study visit during the whole study period.
Foxp3+ Treg cells and other immune cells were
detected by flow cytometry (Table S1) at each
visit. Fasting venous blood in the morning was
collected for laboratory examination. High-
resolution computed tomography (HRCT) was
performed at week 0 and week 24. An overall
HRCT score was obtained by quantifying the
extent of each abnormality in three lung zones
in each lung [16].

In vitro regulatory T cell suppression assays
were performed as described using
CD4+CD25hiCD127lo Treg cells isolated from
peripheral blood of patients before and after IL-
2 treatment and effector T cells (CD4+CD25− T
cell) from healthy controls. Peripheral
CD4+CD25hiCD127lo Treg cells from patients
and Teff cells from healthy controls were sorted
using MoFlo Astrios EQ (Beckman Coulter). In
each experiment, Teff cells were stained using
Cell Trace CFSE (Thermo Fisher) according to
the manufacturer’s instructions. Treg and Teff
cells were then mixed at the ratio of 1:1 per
well, then stimulated with anti-CD2/CD3/CD28
beads (Treg Suppression Inspector, Miltenyi
Biotec) at a 1:1 Teff + Treg: beads ratio in
complete RPMI media for 4 days. In this assay, T
cell proliferation is indicated by dilution of Cell
Trace CFSE.

Outcomes

The primary endpoint for the trial was change
in percentage of regulatory T cells in total
CD4+ T cells at week 12. The secondary end-
point for the trial included the International
Myositis Assessment and Clinical Studies
(IMACS) definition of improvement (DOI), the
2016 American College of Rheumatology
(ACR)/European League Against Rheumatism
(EULAR) myositis response criteria [16], safety,
and steroid-sparing effect. IMACS DOI includes
three of any of the six CSMs improved by
≥ 20%, with no more than two CSMs worsening
by ≥ 25% (worsening measure cannot include the
MMT-8) [17, 18]. 2016 ACR/EULAR myositis
response criteria definite that a total score
improvement (a metric derived from the 2016
ACR-EULAR myositis response criteria, which
corresponds to the magnitude of improvement)
of ≥ 20 represents minimal improvement, a
score of ≥ 40 represents moderate improve-
ment and a score of ≥ 60 represents major
improvement [19].
Statistical Analysis

Descriptive statistics were evaluated for baseline demographic, clinical, and laboratory variables, and frequency of patients meeting DOI. Wilcoxon signed-rank test was used for continuous variable and Chi-squared test for categorical variables within each of the treatment cycles (baseline vs. weeks 4, 8, 12, 24; week 12 vs. week 24). Pearson correlation analysis was performed between total improvement score and change of T cell subsets or baseline characters. Endpoints were assessed in all patients who completed at least 1 month of treatment. All patients who had ever received at least one dose of IL-2 were included in the safety assessment population. Differences were considered to be significant if P values were less than 0.05. Statistical analysis for all endpoints was performed using SPSS v.22.0. Figures were prepared using Adobe Illustrator CS6 and GraphPad Prism (version 8).

RESULTS

Patient Characteristics

Between September 19, 2019, and April 24, 2020, 18 patients with IIMs fulfilled the eligibility criteria and were enrolled. All of the treated patients completed the 12-week treatment period and 17 completed the 12-week follow-up period. One withdrew at week 12 due to poor response. Table S2 and S3 summarized the patients’ baseline characteristics, demographic data, and details of previous and current treatment. In this study, there were ten patients with DM, six patients with ASS, and two patients with IMNM (Table S2, S3).

Proximal muscle weakness was present in 44.44% (8/18), rash in 83.33% (15/18), arthritis in 22.22% (4/18), and myositis-associated interstitial lung disease (ILD) in 55.56% (10/18) of all IIMs patients. Mechanic’s hands, heliotrope rash, Gottron’s sign/papules, V sign, and Shawl sign accounted for 22.22%, 50, 22.22, and 5.56% of all patients, respectively (Table S2, S3).

Antibodies were represented, with 61% of the cohort possessing at least one myositis-associated autoantibody as determined by Western blot. This included anti-synthetase antibodies (n = 6, 33.33%), anti-melanoma differentiation-associated protein 5 (MDA5) (n = 2, 11.11%), anti-Mi-2α (n = 1, 5.56%), anti-SRP (n = 1, 16.67%), and anti-HMGCR (1, 5.56%). No patient was positive for anti-PM/Scl 100, anti-NXP2, anti-TIF-1γ or anti-Mi-2β (Table S2, S3).

Efficacy

After 3 months of treatment with low-dose IL-2, 14 out of 18 (77.78%) patients were responders and reached the IMACS DOI (Fig. 1a, b). The responders included nine DM patients and five ASS patients. Non-responders included two IMNM patients, one DM patient, and one ASS patient. Two of four non-responders at week 12 responded at week 24; 15/18 (83.33%) met the 2016 ACR/EULAR myositis response criteria. The total improvement score was 23.8 (8.1–37.5) at week 12 and 22.5 (2–37.5) at week 24, the end of follow-up, with eight (44.44%), six (33.33%) and one (5.56%) of patients achieving minimal, moderate, and major improvement, respectively (Fig. 1b). MMT-8 was increased from 129 (120, 141) at baseline to 135 (126, 143) (P = 0.017) at week 12 and 140 (128, 145) (P = 0.043) at week 24. Details of improvements in other CSMs including PhGA, PGA and HAQ-DI, muscle enzymes, and extramuscular activity were summarized in Table 1 and Table S4.

The extramuscular global, primarily driven by skin rash in our study, showed a median of 50% improvement in all patients. The cutaneous dermatomyositis disease area and severity index activity score (CDASI-a) was decreased significantly from 7 (4.5, 13) to 2 (0, 7) after IL-2 administration (P < 0.001). The improvement of skin rash included mechanic’s hands (in four of the five patients with this manifestation), heliotrope rash (nine of ten patients), Gottron’s sign/papules (six of nine patients), V sign (all of four patients with this manifestation), Shawl sign (in the one patient with this manifestation), and periungual erythema (four of five patients) (Table 1).
Daily dose of prednisone decreased from 12.25 (5, 15) mg at baseline to 10 (4.37, 15) mg ($P = 0.016$) at week 12 and 10 (2.5, 12.5) mg ($P = 0.013$) at week 24 (Table 1). There was a trend that total HRCT score was improved at week 24 (82 [25, 397.5] vs. 53 [10, 360], $P = 0.125$) (Table 1), although there was no statistic difference. Besides, there was no obvious improvement of lung function (Table S5).

**Safety**

Low-dose IL-2 therapy was well tolerated at a daily dose of $1 \times 10^6$ IU. Safety data during the treatment period were shown in Table S6. No serious adverse events were observed. The most common adverse events were injection-site reactions, manifested as injection-site pain, redness, and swelling, which were observed in five of 18 (27.78%) patients. Transient influenza-like symptoms and transient fever occurred in two (11.11%) patients. These symptoms were resolved without intervention. There were no significant changes in routine laboratory examinations including white blood cell count, hemoglobin, platelet count, kidney function, or blood glucose over the 24-week trial period.

![Fig. 1 Clinical response to low-dose IL-2 treatment. International Myositis Assessment and Clinical Studies (IMACS) definition of improvement (DOI) (a) and 2016 American College of Rheumatology-European League Against Rheumatism myositis response criteria (b)](image-url)
Table 1  Response of IIMs patients to low-dose IL-2 treatment (n = 18)

| Characteristics                           | Baseline (week 0) | Week 12 | Week 24                          | P value (week 12 vs. 0) | P value (week 24 vs. 0) |
|-------------------------------------------|-------------------|---------|----------------------------------|-------------------------|-------------------------|
| Core set measures                         |                   |         |                                  |                         |                         |
| PhGA-VAS, median (range)                  | 5 (4, 5.5)        | 2.5 (2, 4) | 2.25 (1.25, 3.75)                | < 0.001                 | 0.002                   |
| PGA-VAS, median (range)                   | 5 (3.5, 7)        | 3 (2, 4) | 2 (1, 3.5)                       | < 0.001                 | 0.002                   |
| MMT-8 (0–150), median (range)             | 129 (120, 141)    | 135 (126, 143) | 140 (128, 145)                  | 0.017                   | 0.043                   |
| HAQ-DI (1–3), median (range)              | 2 (0.4, 5)        | 2 (0.15, 3.15) | 2 (0.15, 3.15)                  | 0.007                   | 0.277                   |
| Extramuscular disease, VAS (0–10)         | 5 (4, 6)          | 3 (2, 4) | 2 (1, 3.5)                       | 0.001                   | 0.008                   |
| ALT, median (range)                       | 15 (11, 23.5)     | 14 (10, 18) | 13.5 (11, 22.5)                 | 0.209                   | 0.609                   |
| AST, median (range)                       | 23 (18, 31)       | 18 (14, 23) | 20.5 (17, 26.5)                 | 0.004                   | 0.35                    |
| LDH, median (range)                       | 228 (162.5, 256)  | 188 (149, 251) | 205 (181, 245)                  | 0.023                   | 0.638                   |
| CK, median (range)                        | 125 (51.5, 331)   | 67 (49.5, 208) | 102 (10.1, 168)                | 0.005                   | 0.875                   |
| CDASI-a (0–100), median (range)           | 7 (4.5, 13)       | 2 (0, 7) | 1 (0, 3)                         | < 0.001                 | 0.006                   |
| CDASI-d (0–32), median (range)            | 1 (0, 8.5)        | 0 (0, 8.5) | 0 (0, 8.5)                      | 0.180                   | 0.972                   |
| Fatigue-VAS, median (range)               | 2 (1, 4.5)        | 2 (0.5, 3.5) | 1 (0.5, 2.5)                   | 0.015                   | 0.167                   |
| Mechanic’s hands, n (%)                   | 5 (27.78)         | 1 (5.56) | 2 (11.11)                       | 0.125                   | 0.206                   |
| Heliotrope rash, n (%)                    | 10 (55.56)        | 1 (5.56) | 2 (11.11)                       | 0.004                   | 0.017                   |
| Gottron’s sign/papules, n (%)             | 9 (50)            | 3 (16.67) | 3 (16.67)                       | 0.031                   | 0.031                   |
| V sign, n (%)                             | 4 (22.22)         | 0 (0)   | 1 (5.56)                        | 0.125                   | 0.148                   |
| Shawl sign, n (%)                         | 1 (5.56)          | 0 (0)   | 0 (0)                           | > 0.99                  | > 0.99                  |
| Periungual erythema, n (%)                | 5 (27.78)         | 1 (5.56) | 1 (5.56)                        | 0.125                   | 0.125                   |
| Arthritis, n (%)                          | 4 (22.22)         | 2 (11.11) | 4 (22.22)                       | 0.500                   | > 0.99                  |
| ILD, n (%)                                | 10 (55.56)        | 10 (55.56) | 10 (55.56)                      | > 0.99                  | > 0.99                  |
| Malignancy, n (%)                         | 0 (0)             | 0 (0)   | 0 (0)                           | > 0.99                  | > 0.99                  |
| ESR, median (range)                       | 14 (6.25, 22.25)  | 23 (7.5, 29.5) | 13.5 (7.25, 23)                 | 0.398                   | 0.9                     |

△ Adis
**Immunological Analysis**

The proportion of Treg cells in CD4\(^+\) T cells was increased at week 12 compared with that at baseline (8.97% [5.77, 9.89%] vs. 15.2% [10.4, 17.3%], \(P = 0.009\)). Similarly, the absolute number of Treg cells were increased from 49.2 (39.3, 79.14) to 57.61 (36.68, 84.16) at week 4 (\(P = 0.047\)) (Fig. 2a). Elevated number of Treg cells was correlated with increased total improvement score (\(r = 0.688, P = 0.002\), Fig. 3a, b). The proportion and absolute number of Teff cells were significantly decreased by week 12. At the same time, Treg/Teff were also significantly elevated (0.1 [0.06, 0.11] vs. 0.18 [0.12, 0.21], \(P = 0.046\)) (Fig. 2b). Neither proportion nor absolute number of Th17 cells significantly changed (Fig. S2).

Significant decreases of CD3\(^-\)CD56\(^-\)CD19\(^+\) B cells and follicular helper T (Tfh) cells were noted in both proportion and number at week 4, 8, 12 (Fig. 4a, b). The absolute number and proportion of CD3\(^-\)CD56\(^+\)CD16\(^+\)NK cells were obviously increased in IIMs patients at week 4, 8, 12. However, the number of Tfh cells, B cells and NK cells reverted to baseline levels after 24 weeks (Fig. 4c).

We next evaluated the function of Treg cells. There was an increased suppressive function of Treg cell after IL-2 treatment. The relative proportion of proliferation and division index of Teff cells were obviously decreased after IL-2 treatment compared to that at baseline (\(P = 0.004\) and \(P = 0.022\), respectively) (Fig. 5).

In addition, we analyzed three subsets of Treg cells, including active-Treg (aTreg) and resting-Treg (rTreg) and non-functional Treg (non-Treg) cells (Figure S3). There were decrease of aTreg and rTreg cells in IIMs, while an increase of aTreg and an increase of CD25 levels on aTreg were observed after IL-2 therapy (\(P = 0.028\), \(P = 0.028\), respectively, Figure S3, S4).

**DISCUSSION**

This was a prospective pilot study to explore the clinical and immunological effects, safety, and tolerability of low-dose IL-2 treatment in patients with active IIMs. After 3 months of treatment, 77.78% of patients were responders.
Fig. 2 Changes of percentage and absolute number of Foxp3⁺Treg, Teff and Treg/Teff in peripheral blood of IIMs patients after the treatment of low-dose IL-2. Treg, regulatory T cells. Teff, effector T cells. IIMs, idiopathic inflammatory myopathies. *P < 0.05; **P < 0.01; compared to week 0. a P < 0.05 compared to week 4.

b P < 0.05 compared to week 8. c P < 0.05; cc, P < 0.01 compared to week 12.

Fig. 3 The correlation between change of Treg cell and total improvement score
according to the IMACS DOI, and 15/18 (83.33%) met the 2016 ACR/EULAR myositis response criteria. The CDASI was decreased. The mean daily dose of prednisone was also decreased. Treg cells were significantly increased with low-dose IL-2 treatment. There were no serious adverse events.

Clinical response intensity varied, mainly relative to response of Treg cells. We found that change of Treg cell number was correlated with increased total improvement score, which might be a biomarker of clinical response. A beneficial effect of IL-2 on patients could be explained by increased Treg cells in circulation after therapy. Pandya et al. proved decreased Foxp3 in muscle after immunosuppressive treatment [20]. It was suggested that tissue-resident Foxp3+ Treg cells have been implicated in muscle repair and regeneration. In an 8-month study, patients received 1 million IU/day of IL-2 from day 1 to day 5 (the induction period), and then every 2 weeks from day 15 to day 180 (the maintenance period). Treg was significantly upregulated on day 8 versus baseline as well as at day 180 versus baseline, indicating that low-dose IL-2 effects on Tregs were maintained over time across diseases [9]. Treg proportion was at a relatively lower level with the dose of 1 million IU every 2 weeks compared to the level in the induction period [9]. We assume that 1 million IU/week is probably the dose to maintain the level of Treg, but further studies are still needed. Although treatment-related increases in Treg cells were transient, total improvement score were maintained in most of patients (77.78%) in our study. In addition, we found further increased improvements in some of the patients (27.78%) after withdrawal of Low-dose IL-2.
appears that the effects of low-dose IL-2 lasted in the 3-month follow-up period even though Treg cells decreased during this period.

Clinical response intensity also associated with subtypes of IIMs. Despite limitation of sample size, we found poor response to low-dose IL-2 in IMNM patients and good response in DM (including anti-MDA5-positive dermatomyositis). It seems like that low-dose IL-2 was more efficacious in rash than in muscle. The potential mechanisms remain unclear, which might relate to different characters of different disease subtypes.

Absolute number and proportion of B cells and Tfh cells were decreased, which suggest that low-dose IL-2 therapy suppress immune responses in the germinal centers of lymphatic tissues. Absolute number and proportion of NK cells were increased. The results are in agreement with those of previous studies of low-dose IL-2 in a variety of autoimmune diseases [9,21–25].
Limitations of this trial include the small sample size and the lack of control group. Background treatment was not changed except tapering of GCs in this trial, indicating that the outcomes of the patients were contributed mainly by low-dose IL-2. The results are encouraging, but randomized placebo-controlled trials with a larger cohort are needed in future.

CONCLUSIONS

Low-dose IL-2 treatment was clinically efficacious in patients with active IIMs, with improvement of Treg cell deficiency.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authors’ Contributions. Zhanguo Li, Jing He, Xiaolin Sun, Yuhui Li and Miao Miao contributed to study conception and design. Yuhui Li, Miao Miao, Bo Huang, Jiali Chen, Yuebo Jin, Miao Shao and Xia Zhang performed data acquisition and analysis. Zhanguo Li, Jing He, Xiaolin Sun, Yuhui Li and Miao Miao were involved in data interpretation. All authors participated in the drafting, critical revision, and approval of the final version of the manuscript.

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Disclosures. All of the authors (Miao Miao, Yuhui Li, Bo Huang, Jiali Chen, Yuebo Jin, Miao Shao, Xia Zhang, Xiaolin Sun, Jing He, Zhanguo Li) have nothing to disclose.

Compliance with Ethics Guidelines. The approval (Reference Number: 2019PHB089) was obtained from the Peking University People’s Hospital Ethics Committee prior to initiation of the study. Written informed consent (for participation and publication) was acquired from all patients involved. The study was performed in accordance with the Helsinki Declaration of 1975 and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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