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1 **JAK Inhibitors for the Treatment of Adult Dermatomyositis:**
2 **a Pilot Study**

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49 **Ethic statement:** Written informed consent from each study patient and approval by local Ethics
50 Committee (CPP Ile De France VI (2013-12-19), CCTIRS (N°14.323) and CNIL (915139)) were
51 obtained to use medical information recorded in the myositis database for scientific purposes.
52 Written informed consent from the patient in Supplemental Figure 2 was obtained for her
53 photographs to be published.

54 **Glossary:** DM: dermatomyositis; IVIg: intravenous immune globulin; JAK: janus kinase;
55 JAKinh: janus kinas inhibitor; ENMC: European NeuroMuscular Center; CDASI: Cutaneous
56 Disease Area and Severity Index; MMT: manual muscle testing; ILD: interstitial lung disease

57 **Keywords:** Dermatomyositis; Myositis; Autoimmune myopathy; JAK inhibitor; interferon;
58 Refractory; Ruxolitinib; Baricitinib

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64 Dermatomyositis (DM) remains difficult to manage and novel therapies to improve DM patients'
65 outcome are needed. Increasing evidence suggests the key role of interferon pathway in DM¹,
66 which may be inhibited *in vitro* by a janus kinase inhibitor (JAKinh)².

67 An open label pilot, single center study was conducted and included adult DM patients defined
68 according to the European NeuroMuscular Center (ENMC) criteria with (i) active cutaneous
69 activity (CDASI ≥ 10), and/or active muscle disease despite ≥ 1 immunosuppressant or (ii) new-
70 onset interstitial lung disease (ILD) with anti-MDA5 positivity. The main outcome was the
71 percentage of patients achieving a clinical cutaneous improvement (decreased CDASI ≥ 5).
72 Secondary outcomes included: (a) clinical muscle improvement (increased Manual Muscle
73 Testing 8 (MMT8) $\geq 20\%$) and/or (b) treatment burden improvement (intravenous
74 immunoglobulin (IVIg) discontinuation and/or decrease of total prednisone dose ≤ 5 mg/day).

75 Sixteen DM patients were treated with JAKinh (Table-1): 14 of 16 (88%) had active cutaneous
76 disease activity, 9 of 16 (56%) had active muscle disease, and 7 of 16 (44%) had both
77 (Supplemental-Figure-1). At baseline, mean \pm SD CDASI was 27 \pm 13 and MMT8 was 120 \pm 31, 13
78 and 5 patients were treated with prednisone >5 mg/day and IVIg, respectively. At 3-months, 90%
79 of patients had a clinical cutaneous improvement and mean \pm SD CDASI was 14 \pm 11 ($p < 0.0001$)
80 (Figure-1, Supplemental-Figure-2). MMT8 was unchanged (Supplemental-Figure-3) and
81 prednisone was decreased to ≤ 5 mg/day in 1 patient (Supplemental-Figure-4). After 1.8 \pm 0.7
82 years of follow-up, 13 patients were still receiving JAKinh therapy. One patient died (anti-
83 MDA5+ with progressive ILD), and 2 patients relapsed (muscle disease). All patients with initial
84 active cutaneous disease activity improved with JAKinh and mean CDASI was 5 \pm 4 (-81%, p
85 < 0.0001). MMT8 was unchanged. Prednisone dose was ≤ 5 mg/day in 10 of 15 (67%) patients
86 and IVIg was discontinued in 4 of 5 patients. One patient developed thromboembolic events and

87 another, treated concomitantly with mycophenolate mofetil, presented with febrile neutropenia
88 both requiring transient hospitalization in the intensive care unit. No patients developed cancer.
89 In this study JAKinh was associated with a beneficial effect in most patients, mainly within the
90 first 3 months of treatment, and was sustained at long-term follow-up. Two other smaller
91 studies^{3,4} reached similar conclusions using tofacitinib on refractory skin disease, with the
92 difference that half of patients included in this study also had active muscle disease at inclusion
93 but no significant effect was observed. However, most cases had mild muscle weakness and we
94 may have lacked power to detect a significant difference. In a recent study⁵, tofacitinib was
95 associated with a higher risk of major adverse cardiovascular events and cancers in patients with
96 rheumatoid arthritis. We did not observe such events in our DM patients, although we used other
97 JAKinh and our follow-up period was shorter. Caution should thus be taken as a class effect is
98 not excluded and whether this risk is encountered in DM remains to be determined.
99 This study supports the efficacy of JAKinh in the management of cutaneous DM. We recently
100 started a randomized controlled trial (NCT04972760) to further assess JAKinh efficacy and long-
101 term safety in DM patients.

102

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121 **TABLE**122 **Table 1. Dermatomyositis patient characteristics at baseline and treatment response to**
123 **JAK inhibitor at 3-month**

| Patients | Age (yrs) | Sex | Disease duration (yrs) | Myositis-specific antibody | Previous treatment | JAKinh Molecule, dose (mg/day) | CDASI activity | | IFN- α (fg/mL) | | MMT8 | | CK level (IU/L) | |
|----------|-----------|-----|------------------------|----------------------------|-----------------------------------|--------------------------------|----------------|----|-----------------------|-------------|----------|-----|-----------------|-----|
| | | | | | | | Baseline | M3 | Baseline | M3 | Baseline | M3 | Baseline | M3 |
| 1 | 59 | F | 5 | Anti-TIF1 γ | CS, HCQ, IVIg, PLEX, MTX, AZA | Ruxolitinib, 30 | 26 | 15 | 68 \pm 19 | 23 \pm 4 | 145 | 145 | 65 | 183 |
| 2 | 79 | F | 4 | Anti-SAE | CS, MTX, IVIg, MMF | Ruxolitinib, 30 | 27 | 7 | 18 \pm 3 | 12 \pm NA | 150 | 148 | 79 | 181 |
| 3 | 84 | F | 1 | Anti-TIF1 γ | CS, MTX, AZA, IVIg | Ruxolitinib, 20 | 44 | 14 | NA | NA | NA | NA | 2559 | 226 |
| 4 | 29 | F | 4 | Anti-TIF1 γ | CS, HCQ, MTX, AZA, MMF, IVIg | Ruxolitinib, 20 | 49 | 30 | 144 \pm 12 | 62 \pm 3 | 131 | 143 | 49 | 40 |
| 5 | 61 | F | 7 | Anti-TIF1 γ | CS, MTX, AZA, MMF, IVIg, RTX, TAC | Baricitinib, 2 | 49 | 39 | 48 \pm 13 | 92 \pm 4 | 146 | 144 | 110 | 219 |
| 6 | 50 | F | 37 | Seronegative | CS, MTX, MMF, IVIg, Cic | Baricitinib, 4 | 30 | 22 | NA | NA | 150 | 146 | 172 | 236 |
| 7 | 75 | F | 14 | Seronegative | CS, HCQ, MTX, AZA, IVIg, RTX | Baricitinib, 2 | 29 | 17 | 221 \pm 15 | 59 \pm NA | 69 | 93 | 110 | 89 |
| 8 | 56 | F | 6 | Anti-SAE | CS, HCQ, MTX, AZA, IVIg, RTX | Baricitinib, 2 | 34 | 11 | 19 \pm 5 | 4 \pm 1 | 131 | 145 | 56 | 67 |
| 9 | 57 | F | 1 | Anti-TIF1 γ | CS, HCQ, MTX, IVIg | Baricitinib, 4 | 10 | 7 | 8 \pm 0 | 3 \pm 3 | 150 | 150 | NA | 97 |
| 10 | 38 | F | 4 | Seronegative | CS, HCQ, AZA, MMF, IVIg | Baricitinib, 4 | 17 | 1 | NA | NA | 150 | 150 | NA | NA |
| 11 | 30 | M | 8 | Seronegative | CS, MTX, AZA, MMF, IVIg, RTX | Baricitinib, 4 | 5 | NA | NA | NA | 144 | NA | 418 | NA |
| 12 | 71 | F | 2 | Anti-MDA5 | CS, HCQ, MMF, IVIg | Baricitinib, 2 | 20 | 7 | 12292 | 10564 | 150 | 150 | 84 | 61 |
| 13 | 74 | F | 0.1 | Anti-MDA5 | None | Baricitinib, 2 | 18 | 7 | NA | NA | 79 | 78 | 83 | 61 |
| 14 | 18 | F | 0.9 | Anti-NXP2 | CS, MTX, IVIg | Baricitinib, 2 | 0 | 0 | NA | NA | 109 | 124 | 221 | 100 |
| 15 | 45 | F | 29 | Anti-NXP2 | CS, MTX, MMF, TAC, IVIg | Baricitinib, 4 | 16 | 6 | NA | NA | 135 | 144 | 341 | NA |
| 16 | 61 | F | 0.5 | Anti-MDA5 | CS, Cic, CYC | Baricitinib, 4 | 10 | 4 | NA | NA | 150 | 150 | 27 | 58 |

124 Yrs: years; CS: corticosteroids; HCQ: hydroxychloroquine; PLEX: Plasma exchange; MTX:
125 methotrexate; AZA: azathioprine; IVIg: intravenous immune globulin; MMF: mycophenolate
126 mofetil; RTX: rituximab; CYC: cyclophosphamide; TAC: tacrolimus; Cic: cyclosporine;
127 JAKinh: JAK inhibitor; CDASI; Cutaneous DM Disease Area and Severity Index; IFN:
128 interferon; M3: 3-month follow-up; MMT8: manual muscle testing 8; CK; creatine kinase; NA:
129 not available

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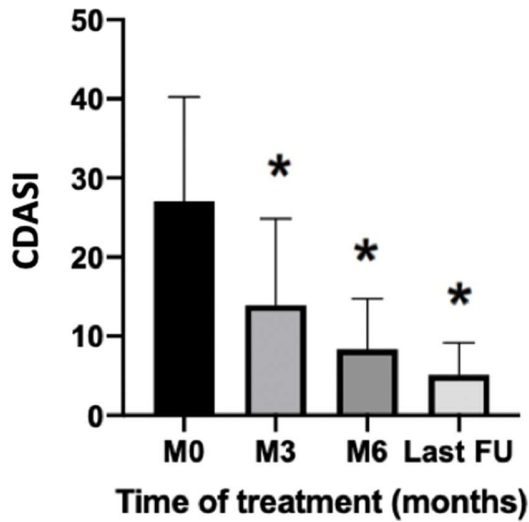
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136 **FIGURE**

137 **Figure 1. Cutaneous disease evolution at follow-up**



138

139 M0: baseline; M3: 3-month; M6: 6-month; FU: follow-up; CDASI: Cutaneous Dermatomyositis
140 Disease Area and Severity Index.

141 Data shown as mean±SD; *p ≤0.05

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143 **Legend**

144 Mean±SD CDASI was 27±13 at baseline (M0) and was significantly decreased to 14±11, 8±6
145 and 5±4 at 3-month, 6-month and last follow-up, respectively.

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