Supplementary Material 1 for

**The Method and Results of a Treatment Targeting SARS-CoV-2-Activated Inflammasomes**

The Ethics and Administrative Committee of Hunt Regional Hospital in Greenville, TX, approved this clinical treatment based on the World Medical Association’s Declaration of Helsinki. All patients (or their parents or guardians) provided written informed consent.

The criterion for ARDS onset was the requirement of FIO2 via simple nasal cannulation of up to 15 L/min. The criteria for aggravated cases of ARDS were FiO2 administered via an HFNC (high-flow nasal cannula) of 95-100% and/or bilevel positive airway pressure (BiPAP). The criterion for severe ARDS was the need for mechanical ventilation.

Protocol for administration: Written informed consent should be obtained, and potential side effects should be explained. The common side effects are haemolytic anaemia (in patients with G6PD deficiency)10, methemoglobinemia, and allergic reaction. The patients should also be informed that currently, G6PD is a send-out test and can take up to 5-7 days. Cimetidine 400 mg orally TID will now be administered to counter dapsone methemoglobinemia side effects11. The venous methemoglobin level should be checked every day, and a mild methemoglobin level of 2-10%12 is well tolerated. Dapsone should be discontinued if the level reaches 15 or above.

**Patient management report**

1. A total of 22 patients were treated with standard COVID-19 therapy (with dapsone)

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| --- | --- | --- | --- |
| **Categories** | **Decrease in FIO2** | **Progression of hypoxia** | **No further progression of hypoxia** |
| Onset  (FIO2 requirement  via simple nasal  cannulation of up to  15 L/min)  Aggravated  (FIO2 administered  via an HFNC of 95-100%  and/or BiPAP)  Severe  (requiring mechanical ventilation) | 7/22    6/22    0/22 | 0/22 (no deaths)    3/22 (all deaths)    2/22 (both deaths) | 1/22    3/22    0/22 |
| **Total** | **13** | **5** | **4** |

2. A total of 22 patients treated with standard COVID-19 therapy (without dapsone)

|  |  |  |  |
| --- | --- | --- | --- |
| **Categories** | **Decrease in FIO2** | **Progression of hypoxia** | **No further progression of hypoxia** |
| Onset  (FIO2 requirement  via simple nasal  cannulation of up to  15 L/min)  Aggravated  (FIO2 administered  via an HFNC of 95-100%  and/or BiPAP)  Severe  (requiring mechanical  ventilation) | 8/22    1/22    0/22 | 8/22 (all deaths)    1/22    0/22 | 4/22    0/22    0/22 |
| **Total** | **9** | **9** | **4** |

**Statistics 1. The chi-square statistics**

1.1. The comparison was made assuming that only the case of decreased FIO2 was influential in the entire dapsone (+) group and dapsone (-) group.

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|  | | | | | | | |
| Study 1 | dec FIO2 | others |  | |  |  | ***Row Totals*** |
| Dapsone (+) | 13  (11.00)  [0.36] | 9  (11.00)  [0.36] | |  |  |  | 22 |
| Dapsone (-) | 9  (11.00)  [0.36] | 13  (11.00)  [0.36] |  | |  |  | 22 |
|  |  |  |  | |  |  |  |
| ***Column Totals*** | 22 | 22 |  | |  |  | **44 (Total)** |

The chi-square statistic is 1.4545. The p-value is .2278. The result is not significant at  p < .05

1.2. The comparison was made assuming that cases of decreased FIO2 and no further progression were influential in the dapsone (+) group and the dapsone (-) group as evidence of improvement.

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| Study 2 | dec FIO2+No progress | progression |  |  |  | ***Row Totals*** |
| Dapsone (+) | 17  (15.00)  [0.27] | 5  (7.00)  [0.57] |  |  |  | 22 |
| Dapsone (-) | 13  (15.00)  [0.27] | 9  (7.00)  [0.57] |  |  |  | 22 |
|  |  |  |  |  |  |  |
| ***Column Totals*** | 30 | 14 |  |  |  | **44 (Total)** |

The chi-square statistic is 1.6762. The p-value is .195431. The result is not significant at p < .05.

1.3. The comparison was made assuming that only the case of decreased FIO2 was influential in the entire dapsone (+) group and dapsone (-) group, which was applicable to only the ARDS onset stage.

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| Study 3 | dec FIO2 | others |  |  |  | ***Row Totals*** |
| Dapsone (+) onset | 7  (4.29)  [1.72] | 1  (3.71)  [1.98] |  |  |  | 8 |
| Dapsone (-) onset | 8  (10.71)  [0.69] | 12  (9.29)  [0.79] |  |  |  | 20 |
|  |  |  |  |  |  |  |
| ***Column Totals*** | 15 | 13 |  |  |  | **28 (Total)** |

The chi-square statistic is 5.1836. The p-value is .022801. The result is significant at p < .05.

1.4. The comparison was made assuming that only the case of decreased FIO2 was influential in the ARDS onset and aggravated stage dapsone (+) group and ARDS onset and aggravated stage dapsone (-) group.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study 4 | dec FIO2 | others |  |  |  | ***Row Totals*** |
| Dapsone (+) onset + aggravated | 13  (10.48)  [0.61] | 7  (9.52)  [0.67] |  |  |  | 20 |
| Dapsone (-) onset + aggravated | 9  (11.52)  [0.55] | 13  (10.48)  [0.61] |  |  |  | 22 |
|  |  |  |  |  |  |  |
| ***Column Totals*** | 22 | 20 |  |  |  | **42 (Total)** |

The chi-square statistic is 2.4376. The p-value is .11846. The result is not significant at p < .05.

1.5. The comparison was made assuming that the dapsone (+) group and the dapsone (-) group in the ARDS onset stage were influential in the case of decreased FIO2 and no further progression.

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| Study 5 | dec FIO2 + no progress | progression |  |  |  | ***Row Totals*** |
| Dapsone (+) onset | 8  (6.21)  [0.52] | 1  (2.79)  [1.15] |  |  |  | 9 |
| Dapsone (-) onset | 12  (13.79)  [0.23] | 8  (6.21)  [0.52] |  |  |  | 20 |
|  |  |  |  |  |  |  |
| ***Column Totals*** | 20 | 9 |  |  |  | **29 (Total)** |

The chi-square statistic is 2.4202. The p-value is .119776. The result is not significant at p < .05.

1.6. The comparison was made assuming that the dapsone (+) group and the dapsone (-) group in the ARDS onset and aggravated stages were influential in the case of decreased FIO2 and no further progression.

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| Study 6 | dec FIO2 + no progress | progression |  |  |  | ***Row Totals*** |
| Dapsone (+) onset + aggrav | 17  (14.29)  [0.52] | 3  (5.71)  [1.29] |  |  |  | 20 |
| Dapsone (-) onset + aggrav | 13  (15.71)  [0.47] | 9  (6.29)  [1.17] |  |  |  | 22 |
|  |  |  |  |  |  |  |
| ***Column Totals*** | 30 | 12 |  |  |  | **42 (Total)** |

The chi-square statistic is 3.4459. The p-value is .063409. The result is not significant at p < .05.

**Statistics 2. Fischer's exact test**

When using the chi-square test, there were cases where 0 was entered into the cell, so this was replaced with 1. Fisher’s test was again conducted to compensate Statistics 1.

|  |  |  |  |
| --- | --- | --- | --- |
| Study 2-1 | dec FIO2 | others | Marginal Row Totals |
| Dapone (+) onset | 7 | 1 | 8 |
| w dap agg + severe | 6 | 8 | 14 |
|  | 13 | 9 | 22    (Grand Total) |

The Fisher exact test statistic value is 0.0743. The result is not significant at p < .05.

|  |  |  |  |
| --- | --- | --- | --- |
| Study 2-2 | decFIO2+no progress | progression | Marginal Row Totals |
| Dapone (+) onset | 8 | 0 | 8 |
| Dapone (+) agg + severe | 9 | 5 | 14 |
|  | 17 | 5 | 22   (Grand Total) |

The Fisher exact test statistic value is 0.1154. The result is not significant at p < .05.

|  |  |  |  |
| --- | --- | --- | --- |
| Study 2-3 | dec FIO2 | others | Marginal Row Totals |
| Dapone (+) onset + aggrav | 13 | 7 | 20 |
| Dapone (+) severe | 0 | 2 | 2 |
|  | 13 | 9 | 22    (Grand Total) |

The Fisher exact test statistic value is 0.1558. The result is not significant at p < .05.

|  |  |  |  |
| --- | --- | --- | --- |
| Study 2-4 | decFIO2+no progress | progression | Marginal Row Totals |
| Dapone (+) onset + aggrav | 17 | 3 | 20 |
| Dapone (+) severe | 0 | 2 | 2 |
|  | 17 | 5 | 22    (Grand Total) |

The Fisher exact test statistic value is 0.0433. The result is significant at p < .05

With the chi-square test (Studies 2-4), on the basis of decreased FIO2 and no further progression of hypoxia, the addition of dapsone to standard COVID-19 treatment was more effective in ARDS-onset cases than in severe cases.

The 22 patients who received dapsone were divided into onset and aggravated (onset + aggravated) and severe (severe) groups. With Fisher’s exact test, on the basis of decreased FIO2 and no further progression of hypoxia, dapsone was useful, and the results were statistically significant.

Additionally, when the dapsone-treated group was compared with the ARDS onset group and the other groups, there was no meaningful result regardless of whether the criterion for determining the effect was only decreased FIO2 or included no further progression of hypoxia.

Finally, to judge whether the effects of this dapsone treatment (name: **Soon-Joe treatment**) are meaningful, it is more appropriate to conduct Fischer’s exact test than the chi-square test. Of course, the statistic results were the same.