The Viral Respiratory Diseases of Sorok Island at Pandemic

Jong-Hoon Lee (science@research.re.kr)
Seoul National University College of Medicine
Chul Joong Lee
Zein Pain Clinic Seongbuk
So Jeong Lee
Rice University
Su-Hee Choi
Seoul National University Hospital
Sang-Suk Oh
Ewha Womans University
Jungwuk Park
Chungdam Hospital
Consolato Sergi
Chungdam Hospital
Michael D. Coleman
Aston University

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Abstract

Background: Dapsone is helpful in the molecular regulation of Nod-like receptor family pyrin domain-containing 3 (NLRP3).

Objective: To study the targeting of NLRP3 itself or up-/downstream factors of the NLRP3 inflammasome by Dapsone should be responsible for its observed preventive treatment effects, functioning as a competitor against Pandemic viral inflammasome.

Methods: We compared Hansen's disease (HD) patients with viral respiratory diseases (VRD) after prescribing Dapsone to standard treatment from 2005 to 2020.

Results: The 3022 VRD participants who received the dapsone intervention (M = 201, SD = 34) compared to the 3961 VRD participants in the control group (M = 264, SD = 84) demonstrated significantly better peak flow scores, t(28) = -2.7, p = .01. It demonstrated significantly more prevalences of VRD in the DDS unprescribed group.

Conclusion: This study is theoretical clinical data to warrant a pilot study with Dapsone for deteriorating leprosy patients at Pandemic.

One-sentence Summary:

We analyzed 9649 participants with Hansen's disease starting in the Sorokdo National Hospital. The 3022 participants who received the dapsone intervention (M = 201, SD = 34) compared to the 3961 participants in the control group (M = 264, SD = 84) demonstrated significantly better peak flow scores, t(28) = -2.7, p = .01. Clinicians should be aware of the inflammasome competitor: Dapsone for more potent uses for Hansen's disease patients at Pandemic.

Introduction

The Sorok island as a Japanese leper colony was established in May 1916 to quarantine leprosy patients. During the colonial period, the notorious expansion project for the Sorok Leprosarium was supposed from 1933 to 1941 because of its supposed competition with the Culion Leprosarium in the American –Occupied Philippines. The public health report filed on June 4, 1946, succinctly stated that they would increase the capacity of Sorokdo Leper Colony to 8,000 – 9,000 and make it the largest leprosarium in the world[1,2]. They self-administer a prescribed medication steadily. The missionaries went to Sorok Island to care for the leprosy patients. We analyzed the medical records of Sorokdo National Hospital from 2005 to 2020. Sister M. Stoeger and Sister M. Pissarek cared for the patients for forty years[3]. So we regarded those as a kind of standard-cared group initiated from 1962 to 2005.

The antibiotic Dapsone (4,4'-diaminodiphenyl sulfone, DDS) is predominantly associated with the treatment of leprosy[4], and it is both an antibiotic and an anti-inflammatory agent. Dapsone has been

used for leprosy, malaria, toxoplasmosis and Pneumocystis pneumonia in persons with human immunodeficiency virus infection. Moreover, Dapsone is prescribed for dermatitis herpetiformis, linear IgA dermatosis, bullous pemphigoid, subcorneal pustular dermatosis, erythema elevatum diutinum, bullous systemic lupus erythematosus and other chronic inflammatory diseases characterized by the infiltration of neutrophils or eosinophils[5]. Dapsone may be helpful as an alternative therapy in some, especially colchicine resistant patients with Familial Mediterranean Fever (FMF)[6]. FMF is caused by homozygous or compounded heterozygous gain-of-function mutations in the Mediterranean fever gene, which encodes pyrin, an inflammasome protein[7], which has a role in activating the proinflammatory cytokine interleukin (IL)-1β[8]. In the preliminary cross-sectional study, the Covid-19 acute respiratory distress syndrome (ARDS) standard treatment plus Dapsone resulted in clinical improvement within 24-48 hours at ARDS onset. The chi-square is 5.1836. The p-value is 0.022801. (significant at $p < .05$.)[9].

The dapsone hypersensitivity syndrome is a severe idiosyncratic drug reaction characterized by the clinical triad of fever, rash, and systemic involvement. HLA-B*13:01 was described with a 99.8% negative predictive value and a 7.8% positive predictive value as a risk factor among Chinese patients for dapsone hypersensitivity in 2013[10]. HLA-B*13:01 is comparatively absent among Europeans and Africans[11]. The affinity of dapsone binding to HLA-B*13:01 is greater than that of HLA-B*13:02 and binds to the HLA-B*13:01 greater[12,13]. CD8+ clones displayed an HLA-B*13:01-restricted pattern of activation. Dapsone activates specific T cells from hypersensitive patients expressing the risk allele HLA-B* 13: 01. HLA-B*13:01-CD8+ T-cells (also called cytotoxic T lymphocytes) induce a dapsone-responsive immune response[14]. Covid-19 induces an immune response in CD8+ T-cells [15,16], and it may be in a pathway similar to that of Dapsone. CD8+ T-cell feedback activates the NLRP3 inflammasome in antigen-presenting cells in an antigen-dependent manner to promote IL-1β maturation[17]. They might be originated from T-cell activation caused by HLA polymorphism[18,19].

Targeting Nod-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome may be essential for Covid-19 treatment, and its activation is implicated in Alzheimer's disease, prion diseases, type 2 diabetes, and numerous infectious diseases. SARS-CoV-2 activates inflammasomes, which are large multiprotein assemblies that are broadly responsive to pathogen-associated and stress-associated cellular insults. Inflammasomes lead to the secretion of the IL-1β and IL-18 pleiotropic IL-1 family cytokines [20]. The activation of cytokines or pathogen-associated molecular patterns leads to the transcriptional upregulation of canonical and noncanonical inflammasome components. Therefore, we investigated the Hansen' disease (HD) patients that have been prescribed with an inflammasome competitor, Dapsone, following the Dementia Management Act (DMA) in Sorokdo National Hospital. Dapsone has been the treatment and prevention drug for mild cognitive impairment, Alzheimer's disease, and Covid-19 ARDS as an inflammasome competitor[9,21-23]. Therefore, it is necessary to compare viral respiratory diseases (VRD) in Sorok Island, established in May 1916. Until now, clinicians prescribed Dapsone as an adjuvant, alternative, augmentation or active ingredient for patients' treatment[24].

Methods

Ethics

The Korea National Institute for Bioethics Policy (KoNIBP) approved this study to manage life-sustaining treatment properly (approval number P01-202007-22-006). The KoNIBP approved the observational study of patients ethically based on FDA guidelines following the World Medical Association Declaration of Helsinki. Informed consent was obtained from all subjects and/or their legal guardians.

Study Design

Medical data on the correlation between DDS and respiratory diseases were then analyzed by the International Classification of Diseases (ICD) codes of respiratory infectious diseases (RIS). However, severe acute respiratory syndrome coronavirus (SARS-CoV) (2002), Influenza A virus subtype H1N1 (2009), MERS (2015), and SARS-CoV-2 (2020) have not occurred at Sorokdo National Hospital. There is no significant change and no statistical correlation[23]. So, we connected to the EMR database of the Sorokdo National Hospital, archived from January 2005 to June 2019, and searched the ICS-10 codes of viral respiratory diseases (VRD) with Dapsone. This cohort study is the first study to be validated by RCT methodology because the intervention was performed for the dementia treatment according to the Dementia Management Act.

Population Demography

HD patients have lived in Sorok Island for a lifetime. According to the request for disclosure of health checkup information from 2005 to 2020 on October 27, 2020, a total of 1321 people (694 males, 627 females) reside there, and the average age is 84.3 years (M 84.3, SD 17.1, 95% CI: 83.6 – 85.0).

Eligibility Criteria

According to the Infectious Disease Control and Prevention Act, all Hansen subjects in Sorok Island are registered and treated at Sorokdo National Hospital. Therefore, we analyzed all HD patients who could study the relationship between viral respiratory diseases and Dapsone for this study. The cohort was consisted of HD patients, Dapsone, and viral respiratory diseases in all Hansen subjects according to South Korea's Official Information Disclosure Act. We searched all medical records of the Sorokdo National Hospital with ICD 9 and -10 codes in South Korea from 2005, when the Korean government computerized the ICD and EDI codes. With the ICD-9 and -10 codes, we then analyzed medical data on the correlation between Dapsone and viral respiratory diseases.

Study Setting for ICD Code of Korean Diseases and Medicines (ICD-10 Version:2019)

J00 Acute nasopharyngitis [common cold]

J02 Acute pharyngitis

J02.9 Acute pharyngitis, unspecified

J03 Acute tonsillitis

J03.9 Acute tonsillitis, unspecified

J04.0 Acute laryngitis

J06.0 Acute laryngopharyngitis

J06.9 Acute upper respiratory infection, unspecified

J09 Influenza due to identified zoonotic or pandemic influenza virus

J10.8 Influenza with other manifestations, seasonal influenza virus identified

J12.9 Viral pneumonia, unspecified

J20.9 Acute bronchitis, unspecified

Complete Blinded Study & Randomization

South Korea declared war against dementia in 2008 and prepared a National Dementia Plan every five years. The Korean National Assembly unanimously passed the DMA in 2011 and diagnosed and treated all Hansen subjects for Alzheimer's disease without exception[25]. However, medical staff treated HD patients with VRD, while no one knew about dapson's relationship with viral inflammasomes. Therefore, all were in complete-blinded states. Participants were randomized in a 1:1 ratio to DDS prescribed (+) group or matching DDS unprescribed (-) control group. Randomization was unrestricted (no blocking or stratification), and the study's data team analyzed the ICD codes in EMR databases of Sorokdo National Hospital.

Interventions

According to the DMA, the medical staff of Sorokdo National Hospital started a full investigation in 2011 for the treatment of dementia for all HD patients in Sorok Island. As a result, an anti-Alzheimer's disease drug was prescribed for Hansen subjects diagnosed with dementia, and doctors stopped prescribing Dapsone for inactive HD patients. They have followed up for all HD patients from 2011. DMA administered Dapsone to the trial group if we classified Dapsone unprescribed subjects as the control group.

Outcomes

From 2005 to 2019, significance was evaluated based on a p-value of 0.05 in the DDS prescribed (+) subgroup and the DDS unprescribed (-) subgroup of the VRD diagnosed (+) subgroup and VRD

undiagnosed (-) subgroup. It was reported to conduct an effects analysis from 2005 to 2019. (Supplement S3. Study of DDS group)

Statistical Analysis

We used the software programs Object-Relational DBMS, Google spreadsheet with SPSS. T-Test, the Mann-Whitney U Test, One-Way Repeated Measures ANOVA Calculator and Post Hoc Tukey honestly significant difference (HSD) were applied. A significant T-test was performed among the each group of T1: DDS(+)/VRD(+), T2: DDS(-)/VRD(+), T3: DDS(+)/VRD(-), T4: DDS(-)/VRD(-).

Results

A total of 9649 participants were enrolled, of whom 4685 were randomized to Dapsone and 4964 to control, from 2005 to 2020 in Sorok Island. (Figure 1)

According to the DMA, the medical staff of Sorokdo National Hospital started the diagnosis and treatment of Alzheimer's disease for Hansen subject in Sorokdo National Hospital. Medical doctors stopped prescribing Dapsone for inactive leprosy subjects. Thus, the dapsone prescription separated two groups, and we classified VRD diagnosed patients. (Table 1)

Because the DMA was enacted in 2011 after the declaration of dementia policy in 2008, it became clear whether DDS was prescribed or not because HD patients at Sorok Island should visit Sorokdo National Hospital to examine the cognitive function and receive treatment. Significant changes were apparent in the disease patterns from 2010. The proportion of T2 (M = 264, SD = 84) increased significantly. T2:T3 (M = 111, SD = 104) shows that HD patients with prescribed dapsone have a very low prevalence of VRD, $t(28) = 4.5$, $p = .0001$. (Supplement S4. Table S9-S10, Fig. S3 for T2:T3)

However, HD patients with prescribed dapsone have the prevalence of VRD at a rate between 31-42% since 2010 in the T1 (M = 201, SD = 34): T4 (M = 67, SD = 66), $t(28) = 7.0$, $p = < .00001$. Therefore, we can assume that Dapsone does not affect the inflammasome of all viruses. (Supplement S4. Table S7-S8, Fig. S2 for T1:T4)

Nonetheless, T2:T3 might explain the no prevalence of SARS-CoV (2002), Influenza A virus subtype H1N1 (2009), MERS (2015), and SARS-CoV-2 (2020) at Sorok Island. (Figure 2)

Treatment Study (T1:T2)

One is DDS (+) with VRD (+) subgroup, and the other is DDS (-) VRD (+). (Table 2) The 3022 participants who received the dapsone intervention (M = 201, SD = 34) compared to the 3961 participants in the control group (M = 264, SD = 84) demonstrated significantly better peak flow scores, $t(28) = -2.7$, $p = .01$. (Figure 3) The same results were obtained in the Mann-Whitney U Test. (Supplement S4. Table S11-S14, Fig. S4)

Safety

Dapsone's adverse reactions are well documented. Consequently, all HD patients and medical staff in Sorok Island already avoided the known side effects of Dapsone very carefully. The adverse reactions associated with this drug include the clinical triad of fever, rash, and systemic involvement, which can cause severe organ dysfunction (most commonly of the liver and the hematologic system). Dapsone hypersensitivity can also lead to leukocytosis and eosinophilia, resembling a mononucleosis infection. The drug is also associated with haematological effects, such as hemolytic anaemia and methemoglobinemia: hepatitis/liver toxicity, cholangitis, colitis, thyroiditis, pancreatitis and pleural effusion: acute renal failure: myocarditis, dapsone-induced hypersensitivity syndrome-associated complete atrioventricular block, myocardial injury: pneumonitis, pneumonia or multiple organ failure.

Limitations

The limitation is that this study was conducted in an island area and to the HD patients. So, more studies are required to compare the COVID 19 survival rates later. Furthermore, since Dapsone's maximal allowance price in South Korea was very low in 2016, pharmaceutics, which produced it in Korea, stopped the production of Dapsone except for the supply for HD patients[26]. So we could not examine the full pharmacological efficacy of Dapsone. Nonetheless, we trusted the Korean FDA.

Discussion

The application of Dapsone and the introduction of multi-drug therapy containing rifampin and Clofazimine were decisive for eradicating leprosy[27]. Clofazimine inhibits cell fusion mediated by the viral spike glycoprotein, as well as the activity of the viral helicase[28]. However, all leprosy patients were cured, and only 0-4 people per year in South Korea were using multi-drug therapy[29]. Some people took Dapsone for more than 50 years from our survey[30]. When we studied the longevity index, leprosy-affected males showed higher longevity values than their male counterparts in the comparison groups[31].

Dapsone as a supplement can be used for the optimum second-line treatment of immune thrombocytopenia[32]. Dapsone reduced the local expression of mRNA transcripts encoding inflammation-related molecules, including endothelin-1, macrophage inflammatory protein-1-alpha, and transforming growth factor-beta. Dapsone decreased the paraquat-induced generation of superoxide anions in mouse lung fibroblasts[33]. The administration of Dapsone reversed the alterations induced by doxorubicin in serum levels of creatine kinase-MB fraction (CK-MB), electrocardiographic parameters, papillary muscle contractility, and excitation: the measurement of malondialdehyde, superoxide dismutase, and TNF-α levels in tissue indicated that Dapsone significantly reduced oxidative stress, consistent with histopathological analysis[23]. Dapsone prevents ischemic injury, inhibits apoptosis and shows functional improvement post-ischemia. It repressed pro-apoptotic proteins c-Jun N-Terminal Kinases (JNK), Phosphatase and Tensin Homologue (PTEN), Calpain, Caspase-3 of cerebral ischemia along with activation of pro-survival protein Brain-derived Neurotrophic Factor (BDNF)[34]. Dapsone protects

microvascular integrity from high-fat diet-induced low-density lipoprotein (LDL) oxidation[35]. Dapsone on acetic acid-induced colitis in rats reduced acetic acid-induced inflammatory response in rat colon tissue through inhibition of NF-kB signalling pathway[36].

Dapsone binds to myeloperoxidase and regulates the production of hypochlorite. It reduces the inflammatory response of cells. DDS has a structure that can competitively reduce the positively charged sulfur radical production rate because it is similar to methionine sulfoxide[23]. The reversibility of ubiquitination by deubiquitinating enzymes (DUBs) serves as a significant regulatory layer within the ubiquitin system. The human genome encodes approximately 100 DUBs, and DUBs have implicated pathologies, including neurodegeneration and cancer[37]. The conjugation of ubiquitin can be reversed by DUBs, which reflect additional regulation of ubiquitin[38]. The nucleophilic properties of Dapsone compete with Ub, similar to DUBs. Before loading Ub onto the substrate, the Ub-activating (E1)/Ub-conjugating (E2)/E3 ligase acts at each stage of the ubiquitination process. The identical mechanism can potentially ubiquitinate cysteine thiols and hydroxyls on serines, threonines, leucines, and tyrosines[37 39]. Dapsone noncovalently binds/interacts with the minor groove of DNA. Docking analysis revealed that Dapsone preferentially binds to the AT-rich region of DNA. The nucleophilic properties of DDS also compete with NLRP3. ORF8b activates NLRP3 through the interaction of the AT-rich repeat domain of NLRP3. The redox properties of DDS dependent on amine and sulfone moieties explain the oxidation mechanism of DDS by electron transfer[23]. (Figure 4)

BNT162b2 is a lipid nanoparticle–formulated and nucleoside-modified RNA vaccine expressing the full-length prefusion spike glycoprotein (S) of SARS-CoV-2[40]. BNT162b2 and mRNA-1273 produce cross-neutralizing antibodies against B.1.351 and P.1, as well as against other variants, suggesting that they can protect against them. However, cross-neutralization efficacies have been significantly lower compared with the ancestral variant[41,42]. Thus, we need to develop broadly protective T-cell-based vaccines because the emergence of SARS-CoV-2 variants escapes convalescent and vaccine-induced antibody responses[43]. Adverse events of special interest (AESI) include vaccine-associated enhanced disease[44,45]. In addition, mRNA vaccine is associated with an elevated risk of myocarditis, lymphadenopathy, appendicitis, herpes zoster infection[46-48]. Therefore, we studied a supplement that might reduce the future risk of AESI or others induced by the various inflammasome after vaccination. Early indications of supplement care with vaccination may potentially alleviate the course of Covid-19 prevention.

Conclusion

This study is theoretical clinical data to warrant a pilot study with Dapsone for deteriorating leprosy patients at Pandemic.

Declarations

Acknowledgments: After graduating from the University of Innsbruck Nursing School in Tyrol, Western Austria, Sister Marianne Stoeger, who worked at a hospital in Innsbruck, joined Sorok Island in February 1962. Sister Margaritha Pissarek entered Sorok Island in October 1967. They left Sorok island on November 21, 2005. Their dedication to medical service made this study possible.

Statement of Ethics

This study was based on FDA guidelines in accordance with the World Medical Association Declaration of Helsinki. Informed consent was obtained from all subjects and/or their legal guardians. We administered medicines in compliance with medical and pharmacy laws with the informed consent of the patient. The National Agency approved this study for Management of Life-sustaining Treatment, which certified that the life-sustaining treatments were managed properly (Korea National Institute for Bioethics Policy (KoNIBP) approval number P01-202007-22-006). The KoNIBP approved the observational study of patients ethically based on FDA guidelines following the World Medical Association Declaration of Helsinki. Therefore, we carried out all methods following relevant ethical guidelines, regulations and reported the study results. Sorokdo National Hospital provided the necessary information in accordance with Article 13 of Act on Information Disclosure of Public Institutions. Sorokdo National Hospital obtained informed consent from all participants or if participants are under 18, from a parent and/or legal guardian.

Conflicts of Interest

The author has no conflicts of interest to declare.

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Author contributions: JL did conceptualization, methodology, investigation, and writing the original draft. CJL, CS, JP, SO, SJL, SC, MDC examined, reviewed, updated and discussed the study and result of the manuscript.

Competing interests: "Authors declare that they have no competing interests."

Data and materials availability: "All data are available in the main text or the supplementary materials." Additional data that support the findings of this study are available from the corresponding author upon reasonable request. In addition, the complete detailed survey is provided as a separate file. https://osf.io/3js4u/. The stable DOI for the repository is DOI 10.17605/OSF.IO/3JS4U.

Supplementary Materials

Materials and Methods

Supplementary Text Section 1. ~ 4.

Figs. S1 to S4

Tables S1 to S14

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Tables

Table 1. T1:T2:T3:T4 study for the retrospective cohort study at Sorok Island.

Year	T1	T2	T3	T4	Sum	Mean	SD	95% CI	[CI	CI]	X^2	p value
2005	148	126	233	237	744	235	2.83	0.20	234.80	237.83	1.3658	0.242538
2006	166	147	237	172	722	204.5	45.96	3.36	201.14	250.46	1.734	0.187895
2007	170	150	252	150	722	201	72.12	5.27	195.73	273.12	6.7071	0.009603
2008	207	198	219	78	744	148.5	99.70	895.79	-747.29	248.20	36.7668	< 0.00001
2009	222	206	196	44	722	110	107.48	965.67	-855.67	217.48	58.3009	< 0.00001
2010	202	241	186	34	722	104	93.34	838.61	-734.61	197.34	91.8606	< 0.00001
2011	205	243	170	38	702	78.5	93.34	838.61	-760.11	171.84	75.0642	< 0.00001
2012	237	259	103	54	668	78.5	34.65	311.30	-232.80	113.15	15.1784	0.000098
2013	269	357	8	15	663	11.5	4.95	44.47	-32.97	16.45	0.6081	0.435519
2014	236	362	6	19	656	12.5	9.19	82.59	-70.09	21.69	2.4159	0.120108
2015	227	348	7	21	653	14	9.90	88.94	-74.94	23.90	2.3569	0.124733
2016	207	343	4	37	649	20.5	23.33	209.65	-189.15	43.83	12.92	0.000325
2017	193	328	14	28	623	21	9.90	88.94	-67.94	30.90	0.2302	0.631373
2018	178	328	15	35	603	25	14.14	127.06	-102.06	39.14	0.5383	0.463134
2019	155	325	13	41	591	27	19.80	177.89	-150.89	46.80	1.5201	0.217603
Sum	3022	3961	1663	1003								
Mean	201	264	111	67								
SD	34	84	104	66								
95% CI	1	3	5	4								
[	200	261	106	63								
]	203	267	116	71								
The chi-square is 281.826.												
The p value is < 0.00001. I t is significant at p < .05.												

*Four groups were classified: T1 group is DDS-prescribed (+) with VRD-diagnosed (+) subjects, and T2 group is DDS-unprescribed (-) with VRD-diagnosed (+) subjects, and T3 group is DDS-prescribed (+) with VRD-undiagnosed (-) subjects, and T4 group is DDS-unprescribed (-) with VRD-undiagnosed (-) subjects. VRD: Viral Respiratory Disease

Table 2. The viral respiratory disease (VRD) prevalence in the dapsone (DDS) prescription group.

Year	DDS TOTAL (+)	DDS TOTAL (-)	ALL	DDS(+)-VRD(+)	DDS(-)-VRD(+)	Sum	Mean	SD	95% CI	[CI	CI]
2005	381	363	744	148	126	274	137	15.56	1.85	135.15	152.56
2006	403	319	722	166	147	313	156.5	13.44	1.49	155.01	169.94
2007	422	300	722	170	150	320	160	14.14	1.56	158.44	174.14
2008	426	276	702	207	198	405	202.5	6.36	0.62	201.88	208.86
2009	418	250	668	222	206	428	214	11.31	1.07	212.93	225.31
2010	388	275	663	202	241	443	221.5	27.58	2.58	218.92	249.08
2011	375	281	656	205	243	448	224	26.87	2.49	221.51	250.87
2012	340	313	653	237	259	496	248	15.56	1.37	246.63	263.56
2013	277	372	649	269	357	626	313	62.23	4.88	308.12	375.23
2014	242	381	623	236	362	598	299	89.10	7.16	291.84	388.10
2015	234	369	603	227	348	575	287.5	85.56	7.01	280.49	373.06
2016	211	380	591	207	343	550	275	96.17	8.05	266.95	371.17
2017	207	356	563	193	328	521	260.5	95.46	8.22	252.28	355.96
2018	193	363	556	178	328	506	253	106.07	9.26	243.74	359.07
2019	168	366	534	155	325	480	240	120.21	10.78	229.22	360.21
Sum	4685	4964	9649	3022	3961	6983					
Mean	312.33	330.93	643.27	201.47	264.07	436.44					
SD	95.71	45.18	64.39	33.86	83.63	154.59					
95% CI	2.74	1.26	1.28	1.21	2.61	3.63					
[CI	309.59	329.68	641.98	200.26	261.46	432.81					
CI]	315.07	332.19	644.55	202.67	266.67	440.06					

Figures

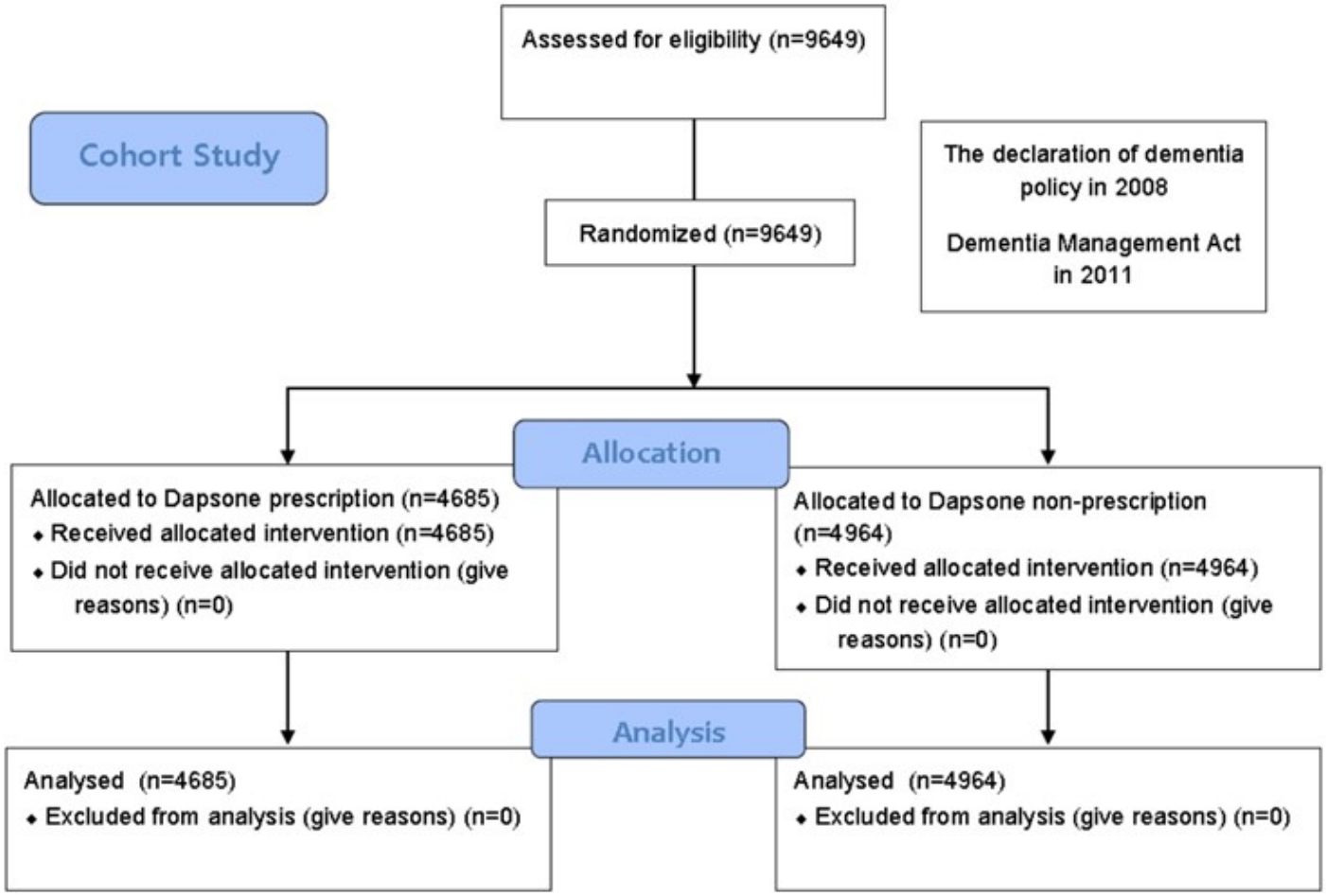

Figure 1

The flow of Participants of Dapsone for Viral Respiratory Disease Infection in Sorok Island

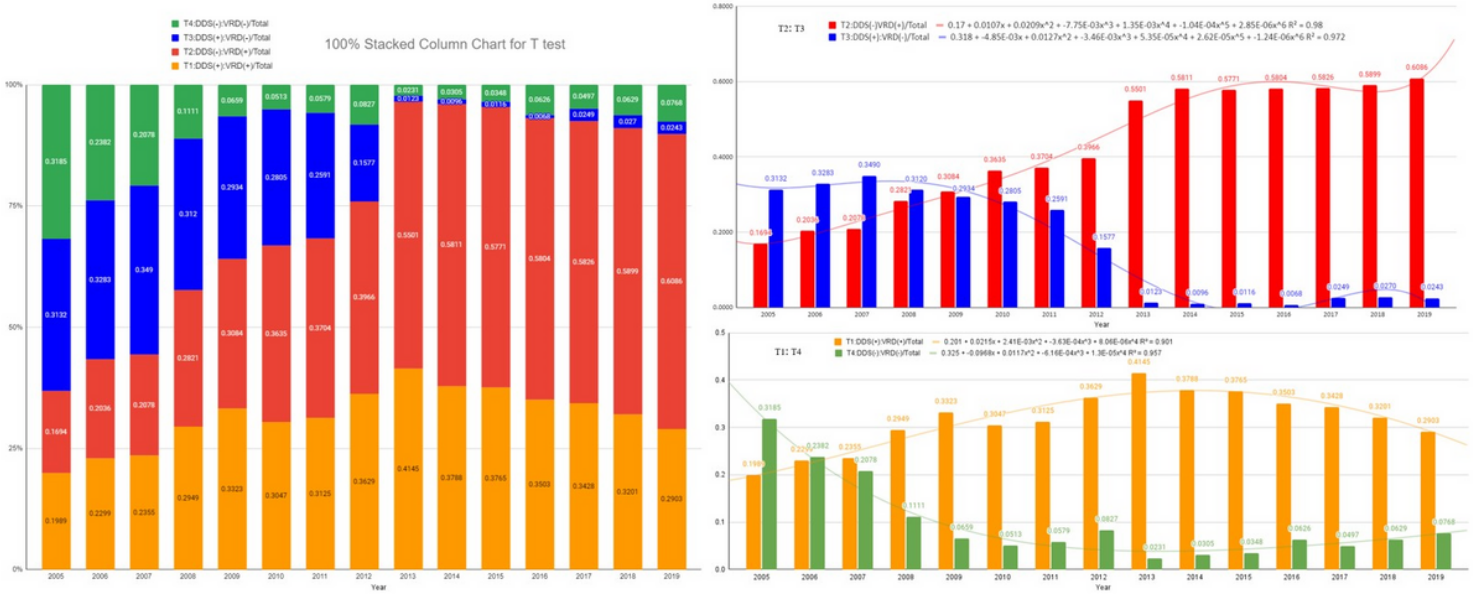

Figure 2

The retrospective cohort study at Sorok Island from 2005 to 2019. T1 group is DDS-prescribed with VRD-diagnosed subjects, and T2 group is DDS-unprescribed with VRD-diagnosed subjects, and T3 group is DDS-prescribed with VRD-undiagnosed subjects, and T4 group is DDS-unprescribed with VRD-undiagnosed subjects. After Dementia Management Act was enacted in 2010, it became clear whether DDS was prescribed or not because HD patients at Sorok Island should visit Sorokdo National Hospital to receive treatment. (1) 100% Stacked Column Chart for T-test - Changes started in 2007 and were apparent in the disease pattern of T2, T3, and T4 except for T1 from 2010. The proportion of T2 without Dapsone and with VRD increased significantly. (2) T2: T3 – The graph shows that HD patients with prescribed Dapsone have a very low prevalence of VRD and vice versa. (3) T1: T4 – HD patients with prescribed Dapsone have the prevalence of VRD at a rate between 31-42% since 2010. Therefore, we can assume that Dapsone does not affect the inflammasome of all viruses.

Figure 3

Treatment Study Treatment one is DDS (+) with VRD (+) subgroup, and the other is DDS (-) VRD (+). The 3022 participants who took the Dapsone was compared to the 3961 participants who did not prescribe. Two trend lines demonstrated significantly more prevalences of viral respiratory disease in the DDS (-) group.

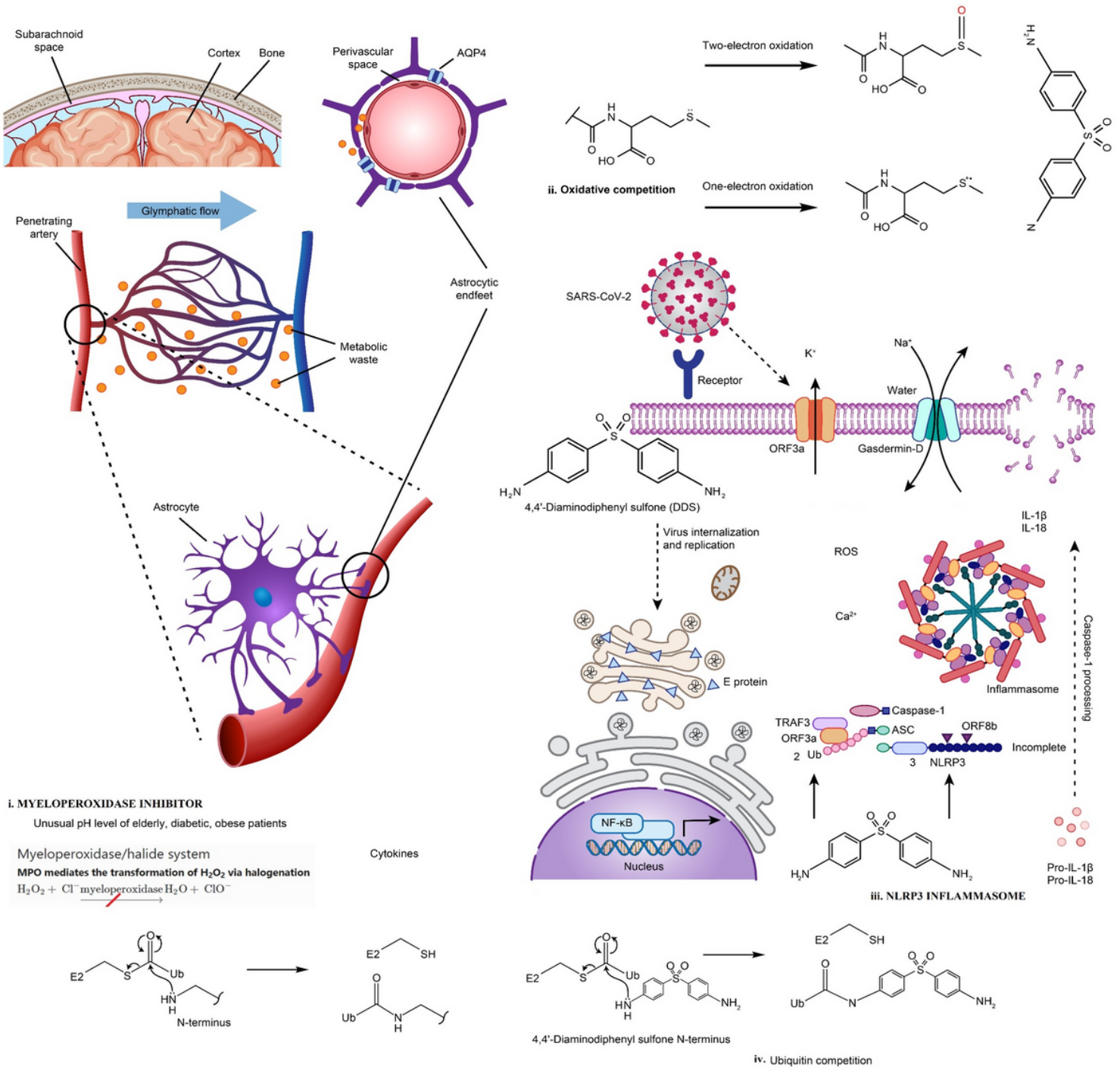

Figure 4

Nucleophilic properties of DDS compete with NLRP3. The initial step in the cellular entry of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is binding SARS-CoV-2 spike protein to cell surface angiotensin-converting enzyme (ACE) 2. This allows the fusion of the virus to the cell surface through cellular proteases such as TMPRSS2 and furin to be involved in priming of the S protein, which involves cleavage at the S1/S2 domains. Virions are taken up into endosomes, where SARS-CoV-2-S is cleaved and possibly activated by the pH-dependent cysteine protease cathepsin L. ACE catalyzes the conversion of angiotensin (Ang) I to the octapeptide AngII, whereas ACE2 converts AngII to Ang1–7. SARS-CoV-2 uses the endogenous cellular machinery to replicate itself inside the cell49. I. Though COVID-

19 patients exhibit neurological signs and symptoms, the histopathological examination of brain specimens shows hypoxic changes. Pathogen-associated molecular patterns (PAMP) or danger-associated molecular patterns (DAMP) induced by SARS-CoV-2 may affect neurological symptoms. Dapsone binds to myeloperoxidase and regulates the production of hypochlorite, thereby reducing the cellular circumstance. DDS blocks bicarbonate to promote two-electron oxidation, as mediated by hydrogen peroxide after the generation of peroxymonocarbonate (HCO4−). II. The bicarbonate/carbon dioxide pair stimulates one-electron oxidation mediated by the carbonate radical anion (CO3●−), which efficiently oxidizes the thioether sulfur of the methionine residue to sulfoxide, so bicarbonate cannot promote two-electron oxidations mediated by hydrogen peroxide after the generation of peroxymonocarbonate (HCO4−). The topological properties of Dapsone, such as electron density and its Laplacian delocalization index, the negative potential of the vicinity of O and O atoms is susceptible to severe electrophilic attack. The nucleophilic/electrophilic region of Dapsone interacts with amino acids by molecular bonding. Dapsone has a structure that can reduce the sulfur radical production rate by electron charge transfer. III. Nucleophilic properties of Dapsone compete with NLRP3 in the mode of DDS–DNA complex can be understood through the nucleophilic properties of DDS for ubiquitination. IV. Proteins contain many nucleophilic sites capable of attacking a ubiquitin (Ub)-conjugating enzyme (E2)–Ub thioester linkage and undergoing ubiquitination. The best-described sites are the amine-containing internal lysine residues and the free amine of the polypeptide backbone's N-terminus. Ub is activated by a Ub-activating (E1) enzyme, using energy from ATP hydrolysis, and passes to a Ub-conjugating (E2) enzyme. Ub can then be passed to a substrate protein, specified by the distinct E3 ligase that binds both the substrate and the E2. Thus, Dapsone can compete with the ubiquitination cascade23.

Supplementary Files

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- SupplementaryMaterials.docx