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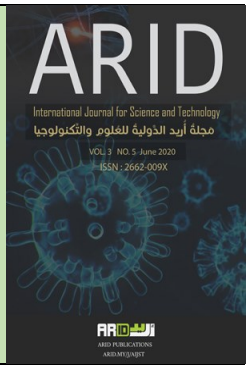

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Dapsone and Doxycycline trial a therapeutic modality in mild and moderate cases of COVID-19 associated with dermatological manifestations

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استخدام عقاري الديوكسي سيكلين والدابسون في علاج الحالات البسيطة والمتوسطة من فايروس كورونا والمرتبطة بحدوث الطفح الجلدي

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Abstract

Doxycycline and Dapsone was been used in the treatment of mild and moderate cases of covid19 in adjusted doses 75 ,50 mg, which could be the hinder of cytokines and interleukins action associated with dermatological signs, Dyspnea, cough fever, aches, and abdominal , the joint pains and pulmonary embolism associated with covid19, two drugs were used on 150 patients of covid19, no background of chronic illness diseases in mild and moderate cases of covid-19 results of healing appeared after 72 hours where is the signs and symptoms of cough , Dyspnea and joint pain plus dermatological signs complains started to improve after 72 hours , noting that the cases initially show symptoms of the disease and the middle stage, the condition worsens and the rash spreads more.

keywords: Doxycycline, Dapsone, interleukins, cytokines, anti-inflammatory

ملخص البحث

استخدام عقاري ال ديوكسسيكلين والدابسون بجرعات محددة 50- 75 مجم للديوكسيسيكلين و50 مجم للدابسون يوميا في علاج مرضى كورونا التي ظهرت عليهم الأعراض في بداية الإصابة بالفيروس، وكذلك في المرحلة المتوسطة وذلك للحد من آثار الفيروس وتأثيره على تنشيط الستوكينيز والانترلوكينز، ومايسببه من أعرض مثل الطفح الجلدي وضيق التنفس والكحة وارتفاع الحرارة وآلام المفاصل والجلطات الرئوية التي تؤدي بدورها للوفاة، ومقارنة النتائج في جداول ليسع الاستفادة منها وتقييم أثر العقاريين المستخدمين على عينة متكونة من 150 مريض في العزل الطبي بالمستشفى لايعانون في الأساس من أمراض مزمنة في المرحلة المتوسطة، ومن ثم أجريت تجارب جديدة على المرضى في المرحلة المتوسطة بعد المرحلة الأولى وكانت النتائج متطابقة في نهاية فترة الاختبار مع نتائج المرحلة الأولى حيث تم تجريب نفس الجرعات على المرضى في الحالات المتوسطة، وقد أظهرت تحسن حقيقي في أول 72 ساعة للمرضى مع ملاحظة أن الحالات في البداية تظهر عليها أعراض المرض وفي المرحلة المتوسطة تزداد الحالة سوءا ويصبح الطفح الجلدى أكثر انتشارا.

كلمات افتتاحية: ديوكسي سيكلين، دابسون، انترلوكينز، سيتوكينز، مضادات الالتهاب

ملاحظة: تمت أخذ موافقة المرضى على إجراء البحث عليهم وتم البحث تحت إشراف مستشفى العزل.

I. Introduction

COVID-19 is an emerging pandemic caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) and presented mainly by fever, cough, sore throat, breathlessness, fatigue, malaise and may be complicated by pneumonia, acute respiratory distress syndrome (ARDS). Dermatological manifestations of COVID-19 could be presented by erythematic of acral areas with vesicles or pustules (Pseudo-chilblain), other vesicular eruptions, urticaria lesions, maculopapular eruptions, and livedo or necrosis [**1**]. Skin lesions associated with COVID-19 and dynamic changes of lymphocyte subsets and cytokines profiles of patients with COVID-19 and their correlation with the disease detected in mild and moderate cases. Some of the sever COVID-19 cases showed significant and sustained decreases in lymphocyte counts (lymphopenia) while increases in neutrophils counts than moderated cases. Further analysis demonstrated significant decreases in the counts of T cells, especially CD8 + T cells, as well as increases in IL1, IL1B IL-6, IL-10, IL-2, IL-8 and IFN-γ, INF alpha, with increase amount of complement C3 levels in the peripheral blood in the moderate cases. C3 activates chemo taxis actions like neutrophils which lead to inflammation reaction and vasculitis in some cases [**2**]. These Cytokines environment activates inflammatory monocytes and flourishes the inflammation. These aberrant pathogenic Th1 cells and inflammatory monocytes may cause damage to the lungs and accelerate the mortality. Dapsone and Doxycycline were showing effectiveness with this regards.

In blocking inflammatory storms and, therefore, could be a promising treatment of severe COVID-19 patients. Dapsone could inhibit production of specific cytokine signatures as IL1α, IL8, IL1β, IL6 and tumor necrosis factor-α [**3**]. Doxycycline, a tetracycline antibiotic, is used for its antibiotic, anti-inflammatory properties and good safety profile and may impair neutrophils aggregation which had been used two drugs Doxycycline50- 75mg daily with Dapsone 50 mg daily to control the actions of cytokines and overcome the induction of skin rashes, fever, cough,

Dyspnea and clotting in lung. The sample consists of 150 patients infected by the virus with no chronic diseases and have signs and symptoms of covid-19 infected in moderate stage and the results were excellent in the end of the period of the experiment, by notice, that mild cases a 1ry stage of disease fever, aches Skin rashes, cough with or without diarrhea, moderate cases patients suffered from Dyspnea, skin rash more spreads on the skin and the fever was in a dangerous stage as many patients exposed to death by clotting inductions in lung [**4**].

In the crisis of COVID-19 pandemic many drugs were tried but shown to be unhelpful in the treatment or decreasing mortality. During this trial medication and doses were added using the Egyptian protocol of the Ministry of Health whether the treatment ware administered as outpatient or in hospital. Doses adjusted to decrease the side effects of two drugs and got the good results in hindering induction of lug embolism and any induction of thrombosis in the body due to cytokines action and c3 complement action [**5**]. It has been found, during pharmacological researches, that interleukins 6,2,8 act on half factor 8 to induce coagulopathy action and this action stopped by using adjusted doses of two drugs Doxycycline and Dapsone.

II. Method and procedures

150 patients were randomly chosen with moderate cases with no background of chronic illnesses and classified as moderate COVID cases aged from 30 up to 45 years' women and men with symptoms like diarrhea headache, mild fever, skin rashes, vasculitis, dry cough, dyspnea, tests required to detect the neutrophils and interleukins amounts in their blood, examined other signs can be appeared related to virus, two groups had been chosen for clinical trial.

Numerically two groups were prepared (1 to 75) group one and (76 to 150) group two where group one assigned to adjusted medications (Doxycycline and Dapsone adjusted doses), while group two was following the original regiment of Egyptian protocol medications (50- 75mg) Doxycycline,

Dapsone 50 mg per day for 3 days. Samples had been collected from the patients to detect the neutrophils and interleukins with observation of fading skin rash and decrease complains of urticaria compared with other group were under administration of Egyptian protocol of Ministry of Health. The 1st group, after 3 days of administration medication improved. The collected samples showed clearly decrease in neutrophils and interleukins compared to the second group (not administrated Doxycycline and Dapsone), medications as in Ministry of Health protocol). When samples had been collected after 72 hrs. from the 2nd group, observed no change, became worsen lesions than the first group (administrated Doxycycline and Dapsone). In group administrated adjusted dose medications (administration Doxycycline and Dapsone) skin lesions became fading and complains of skin rash Dyspnea and headache decreased, completely improved in 5 days after applied Doxycycline with Dapsone with adjusted dose, 2nd group started to take Doxycycline and Dapsone adjusted dose medications after 72 hours with Doxycycline 50-75mg with Dapsone 50mg , sample of results of 18 patients had been taken with adjusted dose medications(Doxycycline and Dapsone) and whose taken protocol medications of ministry of health in Egypt for 1st 3 days. After 5 days of taken drugs, complains deceased and improvement had been clearly observed and within 7 days no skin rashes and no signs and symptoms of covid19 remained, with no side effect had been reordered of Doxycycline with Dapsone in adjusted dose

When samples had been collected, neutrophils and interleukins became in normal range.

III. Results and discussion

Doxycycline with Dapsone in adjusted doses could be effective in treatment of covid19 cases in mild and moderate cases with none background of chronic diseases and might be of protective value against lung thrombosis. Adjusted dose of Doxycycline with Dapsone important to lessen the side effects of two drugs in its original doses as it played an essential role to lessen the skin lesions appeared on covid19 patients like urticaria, skin rash, erythematosus and vasculitis in 5

days. As this trial showed to be relatively safer than other drugs used in Egyptian protocol like azithromycin Doxycycline and Dapsone in adjusted dose recommended for patients with mild-moderate cases with NO chronic diseases. During clotting occurrence, IL1B; IL6; IL8 activate half factor 8 and factor10 with presence factor 4 and factor 3 leading to activation of conversion prothrombin factor 2 to thrombin which activates conversion fibrinogen factor 1 to fibrin factor 13 and it causes thrombosis. C3 is crucial for platelet and tissue factor (TF) pro-coagulant activation dependent on protein disulfide isomerase (PDI) [6]. Furthermore, C5 selectively contributes to the exposure of leukocyte pro-coagulant phosphatidyl serine (PS), which is a prerequisite for rapid activation of monocyte TF and fibrin formation in thrombosis. This study shows that monoclonal cofactor-independent antiphospholipid antibodies (aPLs) rapidly activate TF on myelomonocytic cells. TF activation is blocked by PDI inhibitor and an anti-TF antibody interfering with PDI binding to TF and requires C3 but unexpectedly not C5[7]. Other prothrombotic, complement-fixing antibodies, for example, antithymocyte globulin, typically induce TF activation dependent on C5b-7–mediated, APS exposure on the outer membrane. This trial showed that combination use in protocol Doxycycline with Dapsone in Treatment leads to inhibit phosphodiesterase leading to inhibition of chemotactic effect of C3 and interfering with tissue cofactor led to hinder thrombosis inflammatory conditions. Hyper-coagulability is an important hallmark of inflammation, and these cytokines are critically involved in abnormal clot formation, erythrocyte pathology and platelet hyper-activation, and these three cytokines have known receptors on platelets. Although these cytokines are always unregulated in inflammation. It was discovered how the individual cytokines act upon the structure of erythrocytes and platelets, and which of the viscoelastic clot parameters are changed. IL1B; IL6; IL8 responsible for coagulation action by activating half factor8, cascade coagulator process. Microscopy and thrombo-elastography. All three interleukins caused the viscoelastic properties to display an increased hyper-coagulability of whole blood and pathology of both erythrocytes and platelets [8]. The most pronounced changes

were noted where all three cytokines caused platelet hyper-activation and spreading. Erythrocyte structure was notably affected in the presence of IL-8, where the morphological changes platelets are particularly sensitive to cytokine presence, and that they are excellent health indicators. Complex interactions exist between cytokines and inflammation, and specifically the interleukin family plays a fundamental role in systemic inflammation. Particularly IL-1β, IL-6 and IL-8 are present in whole blood [9], and on research had used two drugs in combination Doxycycline, 50-75mg with Dapsone 50 mg per day to overcome side effects of two drugs. with Pro-inflammatory cytokines

that can activate the coagulation system and play an important role in the downregulation of important physiological anticoagulant pathways. Also, Plasma levels of several inflammation markers have been found to be associated with future cardiovascular risk in a variety of clinical settings. By combination two drugs in treatment patients of COVID-19 in mild and moderate cases unregulated The coagulation system is primarily triggered in response to damage to the endothelium, which allows induction of blood clotting factors to extra vascular tissue. In healthy individuals, homeostasis is closely regulated by several anticoagulant mechanisms that balance the pro-coagulant forces and thus preventing untimely vascular clotting. Pro-inflammatory cytokines and chemo-kines can affect all coagulation intricate relationship between the We applied our research on presence of cytokines resulting in inflammation and could lead to hyper-coagulation, interested in the effects of two drugs combinations circulating IL-1β, IL-6 and IL-8 -Interleukin 1 Receptor 1 (IL1R1) and its legend, IL1β, are unregulated in cardiovascular disease and infection. IL-1β is also known to be present in autoimmune conditions and contributes to IL-1β in inflammation. Bursts of IL-1β are involved in acute attacks of systemic or local inflammation with interleukins 6 and8 lead to mature thrombi [10] that had been hindered by using two combination drugs with adjusted dose. When comparing different medications of Egyptian protocol, a

conclusion reached to the result of superiority of Doxycycline with Dapsone in first three days that showed promising results overcoming signs and symptoms by decreasing interleukins as was mentioned before.

Vasculitis on toe of foot

Figure (1): Before drug administration

Erythematouses on dorsal side of big toe

Figure (2): Fading erythematosus after medications administration

Erythematouses on dorsal fingers of foot

Figure (3): Before medications administration

Erythematouses on finger of hand

Figure (4): After drug administration

Erythematouses on dorsal finger of hand

Figure (5): Before drug administration

Table (1): Randome sample of patients //not taking dcoxyaycline and Dapsone.

NO of patients	IL6 pg/ml	IL1 pg/ml	IL2 pg/ml	IL8 NG	NEUTROPHIL PRECENTAGE
1	25	20	20	25	21
2	20	20	20	30	25
3	20	20	15	25	21
4	20	20	15	25	31
5	20	20	15	25	31
6	25	20	15	25	31
7	20	20	15	25	22
8	20	20	20	25	25
9	25	15	20	30	25
10	22	17	20	26	25
11	20	19	20	30	23
12	20	20	20	30	25
13	20	20	20	30	25
14	21	16	20	30	25
15	25	15	20	25	25
16	25	15	15	25	25
17	21	16	18	30	25
18	20	15	18	25	25

Moderate cases are seen to be more severe.

Table (2): showing results after Doxycycline and Dapsone

They are taking the ministry protocol medications. in 1st 72 hr

AFTER ONE WEAK OF ADMINSTRATIONS OUR MEDICATIONS

COLLECT 29 SAMPLES RONDOMLY FROM TWO GPS

NUMBER OF PATIENTS	IL6 PG/ML	IL1 PG/ML	IL2 PG/ML	IL8 NG	NEUTROPHIL PRECENTAGE
1	5	0.5	0.5	6.5	3
2	4.5	0.5	0.6	5.7	2.9
3	4.5	0.5	0.6	5.8	3
4	4.5	0.5	0.6	5.8	5
5	4.5	0.5	0.6	5.7	3
6	4.5	0.5	0.6	5.7	1.8
7	5	0.5	0.5	5.7	2.8
8	4.5	0.4	0.5	5.7	3.5
9	4.5	0.4	0.33	5.7	1.8
10	4.5	0.36	0.33	5.7	2.1
11	4.5	0.49	0.33	5.7	3.5
12	4.5	0.9	0.3	5.7	3.5
13	4.5	0.5	0.3	5.7	3.5
14	4.5	0.5	0.3	5	1.5
15	4.5	0.6	0.3	5.8	2.8
16	4.5	0.5	0.3	5.2	3.5
17	4.5	0.5	0.3	5.3	3.5
18	4.5	0.5	0.3	5.2	3.5
19	4.5	0.5	0.3	5.4	5
20	4.5	0.5	0.5	5.4	3.6
21	4.3	0.5	0.3	5.4	3.5
22	3.9	0.5	0.3	5.5	3.5
23	4.6	0.5	0.3	5.4	3.8
24	4.5	0.5	0.5	5.4	3.5
25	6.1	0.5	0.5	5.4	1.5
26	3.9	0.5	0.5	5.4	3.5
27	6.8	0.5	0.5	5.4	3.4
28	4.5	0.5	0.5	5.4	1.5
29	4.5	0.5	0.5	5.4	1.5

Moderate cases not seen to be worsened.

Table (3): moderate cases seen to be worse, severe in 72 hours

Table for patient's results administration azithromycin for 25 patients in moderate case

Number of patients	TNF PG/ML	IL6 PG/ML	IL1 PG/ML	IL2 PG/ML	IL8 NG	NEUTROPHILS %
1	15	25	18.5	15.8	15.8	19.5
2	14	20	17.5	15	19.7	19.5
3	12	20	18	17	20	20.5
4	13	15.8	17.5	3	17.5	19.5
5	15	20	17.5	15	16.1	23
6	14.3	18	20	17.5	18.9	21
7	15.1	16	15	18	17.9	20.8
8	14	15.8	18.0	17	15.2	20.2
9	17	15.3	19.5	18.8	15.5	22.6
10	20	17	19.5	17	18.2	22
11	15.2	15.7	18	15.3	19.7	21
12	18	15	15.5	12.8	19.4	21
13	16	14.8	15.9	22.0	21.1	25
14	17	15.9	18.5	15	21.2	21
15	15	14.9	16.9	22.5	18.0	21
16	18	15.3	18.5	15	17.2	20
17	17.3	15.6	18.5	15.9	15.3	25
18	15.9	15.1	19.8	16.9	11.00	22
19	15.5	15.3	19.9	17.5	15.8	20.9
20	15.1	14.6	16.2	17.5	12.00	23.5
21	15.6	15.8	15.6	15	18.8	23.5
22	16.4	15.00	17.5	14.8	18.2	20.5
23	15.4	15.00	15.9	12.8	15.2	21.3
24	15.8	17	18.8	15	17.00	20.5
25	15.9	15.8	22	14.7	18.5	22.3

The result obtained is contrary to what the Egyptian protocol indicated that the situation is not improving but in fact, it is getting worse.

IV. Conclusion

This trial showed that the two drugs in their adjusted doses promising results with less side effects.

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Abbreviations:

ARDS: acute respiratory distress syndrome.

apL : antiphospholipid antibody

APS: antiphospholipid syndrome

C: complement

IL: interleukin

Ng: nanogram

Pg.: picogram

PDI: protein disulfide isomerase

TF: trans-necrosis factor

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