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ORIGINAL ARTICLE

Tetracyclines in COVID-19 patients quarantined at home: Literature evidence supporting real-world data from a multicenter observational study targeting inflammatory and infectious dermatoses

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Abstract

Tetracyclines (TetraC) are widely used in dermatology for both inflammatory and infectious dermatoses; recently both in vivo and in vitro studies started to suggest also a potential antiviral effect. During COVID-19 outbreak, several dermatological patients contracted SARS-CoV-2 experiencing only mild symptoms, but no protocol were approved. A multicenter prospective observational study that enrolled COVID-19 patients visited with teledermatology and undergoing TetraC was performed. About 38 adult outpatients (M/F: 20/18, age 42.6 years [21-67]) were enrolled. During the TetraC treatment, symptoms resolved in all patients within 10 days. Remarkably, ageusia and anosmia disappeared in the first week of TetraC treatment. TetraC seem a promising drug to treat COVID-19 outpatients with mild symptoms.

KEYWORDS
COVID-19, doxycycline, drug re-proposal, inflammatory dermatoses, minocycline, SARS-Cov-2, tetracyclines

1 | INTRODUCTION

The rapid pandemic spread overwhelmed healthcare systems capacity worldwide, forcing physicians to quarantine at home both confirmed and suspected COVID-19 patients with mild respiratory symptoms.[1] At the same time, no treatment protocols were approved for these patients, consequently only a symptomatologic therapy was delivered. Furthermore, several antivirals and immunomodulators which seem to have shown anti-COVID-19 effects (ie, lopinavir/ritonavir, tofacitinib etcetera) are currently recommended by the World Health Organization (OMS) only in the context of clinical trials.[2] Thus, drug re-proposal and drug discovery are magnetizing both physician and scientists' efforts for their potential; in silico evaluation and pharmacoepidemiology play a pivotal role in scanning the possible candidate against COVID-19.[3,4] In this scenario dermatology offers a wide *armamentarium* of immunomodulatory and immunosuppressant drugs that may contrast or even prevent the cytokines storm due to COVID-19 hyperinflammatory phase.[5-8]

Remarkably, tetracyclines (TetraC) were candidate as promising drugs to fight against COVID-19 pandemics due to their potential antiviral effect.[9] TetraC represent a wide spectrum polyketide antibiotic that show a bacteriostatic effect on bacteria, that act through inhibition of translation and, consequently, the bacterial growth. The first members of the TetraC group to be discovered were chlortetracycline and oxytetracycline in the 1940s.

In the following years, the TetraC family has expanded a lot; currently, it includes more than a dozen molecules. In the dermatological field, TetraC have been widely used for several decades to treat both

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infectious and noninfectious diseases (Table 1). As a matter of fact, TetraC are largely used in dermatology also for their additional properties, such as antioxidative, immunomodulatory, antiapoptotic, proproliferation, and proangiogenetic ones, to treat several inflammatory and immunemediated skin disorders summarized in Table S1. Among TetraC in daily practice, Doxycycline (DOX) and Minocycline (MIN) are the most prescribed ones due to their safety profile, availability and efficacy, adequate to treat in an outpatient setting.[10] Their profiles together with their antiviral property make TetraC an encouraging candidate to treat dermatological outpatients with mild forms of COVID-19 (Table S2). Furthermore, during the Italian lockdown (March-May 2020) no pharmacological treatment, unless symptomatic ones, were approved for mild COVID-19 and patients had to stay in their home and use telemedicine. Thus, we performed an observational study on dermatological outpatients with mild COVID-19 and concurrent dermatoses with TetraC indication.

2 | MATERIALS AND METHODS

2.1 | Rationale

TetraC displayed in humans and animals interesting antiviral properties not previously tested on Coronaviruses. Furthermore, no therapeutic protocols were present for mild COVID-19 outpatients, so dermatological patients treated with TetraC at home and positive for SARS CoV-2 represent a unique real-life opportunity to evaluate in vivo TetraC antiviral properties.

2.2 | Ethical evaluation

The present study fulfilled the ethical principles regarding human experiments contained in the Declaration of Helsinki and their subsequent, included the last one in October 2013. The study received a full approval by ethical committees of all the involved institutions and every patient signed an informed consent form.

2.3 | Study design

We performed a multicenter, prospective observational study.

Among all dermatological patients evaluated consecutively with teledermatology in three primary referral center in Italy (AOU Maggiore della Carità in Novara, IRCCS Istituto Ortopedico Galeazzi in Milan and San Gallicano Dermatological Institute in Rome) during COVID-19 outbreak (March 9th to May 3rd), we selected the ones affected by a dermatoses treated at home with TetraC and a concurrent certain/suspected COVID-19 diagnosis.

All patients were evaluated according to the clinical, epidemiological, laboratory, and radiological criteria of the case definition for COVID-19 established by European Centre for Disease Prevention and Control (available at https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition). After receiving confirmed or suspected diagnosis of SARS-CoV-2 infection, all patients were quarantined at home and followed-up through telemedicine. The visual analog scale (VAS) has been used to assess cough severity; it consists of a linear scoring method, where 0 represents no symptom, and 10 indicates

TABLE 1 Main list of the tetracycline in dermatology

TetraC generic name (Abbreviation) Chemical name PubChem CID	Discovery/first report in the literature (year) Status	Source Molecular formula	Route of administration	
			Oral	Parenteral
Tetracycline (TETRAC) Tetracycline 54 675 776	1953 Marketed	Semi-synthetic $C_{22}H_{24}N_2O_8$	✓	
Lymecycline (LYM) 2-*N*-Lysinomethyltetracycline 54 707 177	1961 Marketed	Semi-synthetic $C_{29}H_{38}N_4O_{10}$	✓	
Doxycyxline (DOX) 6-Deoxy-5-hydroxytetracycline 54 671 203	1967 Marketed	Semi-synthetic $C_{22}H_{24}N_2O_8$	✓	✓
Minocycline (MIN) 7-Dimethylamino-6-demethyl-6-deoxytetracycline 54 675 783	1972 Marketed	Semi-synthetic $C_{23}H_{27}N_3O_7$	✓	✓
Sarecycline (SAREC) (4S,4aS,5aR,12aR)-4-(dimethylamino)-1,10,11,12a-tetrahydroxy-7-[[methoxy(methyl)amino]methyl]-3,12-dioxo-4a,5,5a,6-tetrahydro-4H-tetracene-2-carboxamide 54 681 908	2007 FDA approved in moderate-to-severe acne (October 2018)	Semi-synthetic $C_{24}H_{29}N_3O_8$	✓	

Note: Main contraindications: (a) pregnancy (risk of maternal hepatotoxicity, permanent teeth discoloration in the fetus and/or impairment of fetal long bone growth; (b) children under 8 years of age (mainly for the risk of teeth discoloration and inhibition of bone growth); (c) renal failure (consider dose reduction and/or increase the interval between doses). Although the calcium of the breastmilk is able to chelate the TetraC and, thus, to reduce the side effects in infants, they still should not be used breastfeeding. Major adverse events: (a) GI distress (including abdominal discomfort, epigastric pain, nausea, vomiting, and anorexia); (b) photosensitivity; (c) hepatotoxicity; (d) worsening of preexisting renal failure; (e) intracranical hypertension and/or *pseudotumor cerebri*.

the most severe symptom. Patients were also asked to register daily temperatures and other signs and symptoms.

2.3.1 | Inclusion and exclusion criteria

In this subset, we selected the patients who matched all the following inclusion criteria: (a) age >18 years; (b) systemic treatment with TetraC for a dermatological disease; (c) signs and symptoms related to COVID-19 infection. Only not hospitalized patients were considered. Patients under the age of 18 were excluded, as it is known that SARS-CoV-2 infection generally has an indolent course in adolescents. Furthermore, we excluded subjects affected by dermatological and venereological infectious diseases characterized by systemic signs and symptoms matching those of COVID-19, such as patients simultaneously treated with drugs with known or potential antiviral effects (ie, hydroxychloroquine, azithromycin, lopinavir/ritonavir, etc).

3 | RESULTS

3.1 | Dermatological characteristics of the enrolled patients

The clinical characteristics of the COVID-19 dermatological patients described in this report are detailed in Table 2. Globally, we enrolled 38 adult outpatients, affected contextually by a skin disease, and symptomatic SARS-CoV-2 infection. Patients were 20 females and 18 males, with a mean age of 42.6 years, range 21-67. They were mainly affected by inflammatory facial dermatoses: 15 had pustular acne and 11 had pustular rosacea; also, 7 suffered from hidradenitis suppurativa (HS), while the remaining 5 showed a skin infection (2 cases of erisipela, 1 impetigo, 1 panniculitis, and 1 folliculitis).

All subjects, due to the skin condition, received the specialist indications to start TetraC oral therapy. Specifically, we recommended DOX in 25 cases (200 mg/day for 15 patients, 100 mg daily for the remaining 10 patients), and MIN in 13 cases (50 mg/day for 8 patients, 100 mg/day in 3 patients, and 200 mg/day in 2 patients).

TABLE 2 Clinical characteristics of COVID-19 confirmed and suspected dermatological patients in treatment with TetraC

	COVID-19	
	Confirmed cases	**Suspected cases**
Skin disease F/M (%)		
Pustular acne	5/3 (47%)	4/3 (33,3%)
Pustular rosacea	3/2 (29.4%)	4/2 (28.6%)
HS	1/0 (5.9%)	2/4 (28.6%)
Skin infection	1/2 (17.7%)	0/2 (9.5%)
Total (F/M)	17 (10/7)	21 (10/11)
Mean age (year) (range)	42.88 (27-66)	42 (21-67)
Signs and symptoms		
Fever	17 (100%)	14 (66.6%)
Cough	17 (100%)	15 (71.4%)
Dyspnea	11 (67.7%)	2 (9.5%)
Bilateral interstitial pneumonia	10 (58.8%)	0
Fatigue	9 (52.9%)	5 (23.8%)
Anosmia	8 (47%)	4 (19%)
Ageusia	7 (41.2%)	2 (9.5%)
Bilateral conjunctivitis	4 (23.5%)	5 (23.8%)
Rhinorrhea	1 (5.9%)	0
Myalgia	0	3 (14.2%)
Pharyngodynia	0	1 (4.7%)
Chilblain	0	1 (4.7%)
Tetratracyclines therapy		
Doxycycline (%)	13 (76.5%)	12 (57.2%)
100 mg/day	10	0
100 mg bid	3	12
Therapy days, median (range)	15 (10-30)	22.5 (14-30)
Minocycline (%)	4 (23.5%)	9 (42.8%)
50 mg/day	2	6
100 mg/day	1	2
100 mg bid	1	1
Therapy days, median (range)	30 (10-30)	30 (15-30)

3.2 | COVID-19-related clinical data

All patients described, developed signs and symptoms referable to COVID-19 disease within 7 days of the specialist dermatological consultation and were quarantined at home. All cases presented mild COVID-19 symptoms, which not required hospitalization. In detail, cough and fever were the most frequent findings, reported by 32 and 31 patients respectively. Cough VAS score never reached the maximum value for any subject analyzed; fever never exceeded 40°C (37.8°C and 39.7°C). Bilateral interstitial pneumonia was radiological observed in 10/17 COVID-19 confirmed cases; dyspnea, fatigue, and myalgia were reported respectively in 34.2%, 36.8%, and 7.9% of all patients. Anosmia and ageusia were referred by 12/38 (31.6%) and 9/38 (23.7%) subjects, respectively; bilateral conjunctivitis was present in 9/38 subjects, while rhinorrhea, paryngodynia, and chilblain were reported by 2.6% of cases, respectively.

3.3 | Tetracylines treatment in COVID-19 dermatological patients

No patients reported vomiting or diarrhea. No side effects related to TetraC therapy were registered, except for mild occasional nausea in cases treated with the highest doses of DOX.

During the TetraC treatment, symptoms related to COVID-19 infection completely resolved in all patients within 10 days, range 3-10 days. Remarkably, the body temperature returns to normal within 4 days in all cases, with a median of 2.5 days. Cough and dyspnea also improved rapidly in all patients, with a significant reduction within 3 days from the beginning of TetraC therapy. Of note, the higher dosages (200 mg/day both for DOX and MIN) showed faster response times than lower dosages, in terms of fever, fatigue, and respiratory symptoms.

The infection-related ageusia and anosmia disappeared in all patients within 7 days of TetraC treatment.

4 | DISCUSSION

Our real-life data support that TetraC may exert a therapeutic effect on COVID-19 infection by mitigating mild symptoms. Due to the COVID-19-related dermatology overwhelming, several patients with inflammatory and infectious dermatoses were evaluated and treated by distance especially if they display COVID-19 compatible mild symptoms.[11-15] In this scenario, TetraC represent an ideal treatment for inflammatory dermatoses for their immunomodulatory properties, bacterial infections for their antibacterial effect and mild forms of COVID-19 for their antiviral effect. In literature a growing body of data prove TetraC direct and indirect antiviral effects and postulate their use in coronavirus-induced human diseases (Table S2).

Among all tetracyclines family, DOX and MIN have the stronger antiviral evidence demonstrating their inhibition on viral replication exerted on several human and animal RNA viruses.[1,16-27] In 2001, Aurisicchio et al demonstrated in C57/B6 mice infected with a lethal dose of coronavirus that DOX induces antiviral genes expression via IFN(alpha), findings replicated also in Porcine Reproductive and Respiratory Syndrome virus (PRRSV), two Coronaviruses belonging to the gender of *Nidovirales*.[27,28]

Recently, Wu et al in a computational study focusing on new therapeutic targets for SARS-CoV-2 found that DOX and other TetraC (lymecycline, demeclocycline, and oxytetracycline) display high binding affinity to the 3-chymotrypsin-like protease (3CLpro), an enzyme that plays a pivotal role in SARS-CoV-2 replication.[1] Two further computational, drug-repurposing studies also suggested that TetraC (DOX, MIN, TetraC, Demeclocycline, and Eravacycline) may play a key role in antagonizing SARS-CoV-2 main proteases.[20,28] Moreover, He et al demonstrated in vitro that COL-3, a chemically modified tetracycline, directly modify the expression of several pro-inflammatory cytokines and chemokines (ie, Tumor Necrosis Factor-alpha [TNF-α] in HCC515 line of human lung cells treated with ACE2 inhibitor, theoretical application in COVID-19-related lung injury disease.[21]

Our results, together with the existing literature, may also enforce the idea that TetraC exert indirect antiviral effect mediated by immunomodulatory, antiinflammatory, antiapoptotic/antioxidant properties. TetraC immunemodulation inhibits neutrophil chemotaxis, alter endothelial permeability by Matrix Metalloproteinases (MPPs) MMP-2 and MMP-9, decrease proinflammatory cytokines (ie, TNFα, IL1β) production, and release by both neutrophils M1 macrophages, both infiltrating COVID-19 patients' alveoli. Specifically, DOX reduces proinflammatory cytokines (ie, IL-6, IL-1, IL-8, and TNF-α), results with a great clinical relevance especially in viral infections with a prominent inflammatory reaction, as dengue.[29-31] Fredeking et al evaluated 231 patients with dengue hemorrhagic fever treated with DOX (twice daily for 7 days) and observed a significant lower mortality concurrent with lower serum levels of TNF and IL-6 compared with age-matched and sex-matched controls.[32]

These findings are promising also for severe COVID-19 patients in which IL-6 is the main driver of the "cytokinic storm" and consequent mortality, as testified by the encouraging results obtained using tocilizumab, an IL-6 receptor inhibitor, on lung lesions.[33] Furthermore, TetraC also inhibits high-mobility group box 1 protein (HMGB1), a cytokine that polarizes macrophages in the proinflammatory line (M1) during lung inflammation.[34] HMGB1 binds TLR2 and TLR4 increasing TNFα, IL1β, and IL-6 transcription.[34,35] Together with chronic obstructive pulmonary disease (COPD), also obese patients display higher IL-6 serum level and increased mortality, so TetraC may be considered also in mild COVID-19 patients with comorbidities increasing IL-6 production.

Then, TetraC antiinflammatory effect via phospholipase A2 inhibition and Ca^{2+} dependent and independent antioxidant/antiapoptotic effect further suggest including tetracycline in the COVID-19 *armamentarium*.[35-37].

Our study described in detail the effect of TetraC monotherapy in 38 mild COVID-19 outpatients in therapy for preexisting inflammatory dermatological skin disorders and suggest a potential beneficial effect. Currently, only Bonzano et al reported a sudden improvement of COVID-19 symptoms, including anosmia, in 6 patients treated with DOX 200 mg/day at least for 8 days.[22] In our larger cohort, both DOX and MIN rapidly improved symptoms in all patients in a dose dependent manner within 10 days, whereas the average duration of symptoms reported in the literature in COVID-19 patients quarantined at home is approximately 20 days.[38] Remarkably, no drug-induced adverse events were recorded in COVID-19 patients undergoing TetraC. In fact, TetraC are easy to handle drugs, which can be used on also large cohorts of home patients without special precautions, except for pregnant and breastfeeding women and in children less than 8 years. Further studies are mandatory to evaluate TetraC as potential drug in mild COVID-19 outpatients.

To the best of our knowledge, this report presents the first real-life experience regarding the potential use of DOX and MIN as monotherapy in nonhospitalized mild COVID-19 patients. Our preliminary observation suggests that TetraC, specifically DOX and MIN, may mitigate COVID-19 related mild symptoms (ie, cough).

Due to their low toxicity, high safety profile, and costs, TetraC should be considered in the *armamentarium* during COVID-19 outbreak for outpatients with mild forms. Further studies, as well as a rapid screening algorithm to evaluate by distance possible COVID-19 patients, are warranted to improve teledermatology and telemedicine during pandemics.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Laura Cristina Gironi and Giovanni Damiani: Conceptualization; Laura Cristina Gironi, Giovanni Damiani, and Alessia Pacifico: Methodology and Validation; Giovanni Damiani and Ottavio Cremona: Software; Giovanni Damiani: Formal analysis; Laura Cristina Gironi, Giovanni Damiani, Elisa Zavattaro, Alessia Pacifico, Pierachille Santus, and Paolo Daniele Maria Pigatto: Investigation; Pierachille Santus, Paolo Daniele Maria Pigatto, and Paola Savoia: Resources; Giovanni Damiani and Alessia Pacifico: Data Curation; Laura Cristina Gironi, Giovanni Damiani and Pierachille Santus: Writing - Original Draft; Paolo Daniele Maria Pigatto and Ottavio Cremona, and Paola Savoia: Writing - Review & Editing: Visualization Supervision; Laura Cristina Gironi, Giovanni Damiani, Elisa Zavattaro, and Alessia Pacifico: Project administration.

DATA AVAILABILITY STATEMENT

These data are available on the tables.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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