

On the association of Hydroxychloroquine and Azithromycin in treating Covid-19 in Italy

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A survey of news and literature about the association of two drugs, hydroxychloroquine and azithromycin, in treating Covid-19 is proposed. In particular, the survey of news has been focussed on Italy, with the aim of understanding how large is the use of this association of drugs in the country. The recommendations of AIFA are also reported.

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In [1], we listed the trials and some drugs used in Italy against infection due to virus Sars-Cov-2. Here we add some notes about a drug mentioned by the web site of the Italian Government, the Azithromycin. It is mentioned in the web page where we find trials Solidarity and Hidro-stop [2,3]. As we can find in news and literature, Azithromycin, associated with Hydroxychloroquine, is and has been used in Italy to treat Covid-19. It seems that this treatment followed the announcement, made by a research group, spokesperson Didier Raoult, on 16 March 2020, that a trial involving patients from the south east of France supported the claim that Hydroxychloroquine and Azithromycin were effective against Covid-19¹.

In this discussion, we will propose a survey of news, in particular concerning what was written in Italy, with the aim of understanding how large is the use of this association of drugs in the country. The recommendations of AIFA² are also reported.

Information from Italian Government

At the link of the Italian Government (dated 11 April 2020; archived <http://archive.is/25XbJ>) www.salute.gov.it/portale/malattieInfettive/dettaglioNotizieMalattieInfettive.jsp?lingua=italiano&id=4433 it is told that "Solidarity" is an international trial³. "Si tratta di uno studio randomizzato, in cui si valutano differenti strategie terapeutiche tra cui antivirali (remdesivir e lopinavir/ritonavir da solo o in combinazione con interferone beta), cloroquina e idrossicloroquina". Solidarity is a randomized study, in which different therapeutic strategies are evaluated including antivirals (remdesivir and lopinavir/ritonavir alone or combined with interferon beta), chloroquine and hydroxychloroquine.

After Solidarity, in the web page, we find the trial "Hidro-stop - somministrazione precoce di Idrossicloroquina" - Lo studio "Hidro-stop - somministrazione precoce di idrossicloroquina" autorizzato da AIFA per la sperimentazione clinica dell'Idrossicloroquina è volto a valutare l'efficacia di questo medicinale, rispetto allo standard di cura, per il trattamento domiciliare di pazienti che presentano un quadro clinico lieve di COVID-19 e che si trovano in isolamento

- 1 <https://www.connexionfrance.com/French-news/French-researcher-in-Marseille-posts-successful-Covid-19-coronavirus-drug-trial-results> - Archived <http://archive.is/111sq> - In particular, for the use of the association of Hydroxychloroquine and Azithromycin, see the video, dated March 16, 2020, at <https://www.mediterranee-infection.com/coronavirus-diagnostiquons-et-traitons-premiers-resultats-pour-la-chloroquine/>
- 2 AIFA - Agenzia italiana del farmaco. https://it.wikipedia.org/wiki/Agenzia_italiana_del_farmaco
- 3 <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments>

domiciliare". The study "Hidro-stop", which concerns an early use of hydroxychloroquine, authorized by Aifa for the clinical trial of Hydroxychloroquine, is aimed at evaluating the efficacy of this drug, compared to standard, for the treatment at home of patients with a clinical mild COVID-19, in isolation at home.

After information about Solidarity and Hidro-stop, we find a section mentioning Azithromycin. "L'Azitromicina è un antibiotico della famiglia dei macrolidi⁴, autorizzato per il trattamento di infezioni delle alte e basse vie respiratorie, Esistono prove – riporta Aifa nella scheda - che i macrolidi esercitano effetti benefici nei pazienti con malattie polmonari infiammatorie, oltre alla loro capacità di inibire la replicazione dei batteri patogeni. Riguardo il trattamento di Covid-19 con Azitromicina l'Aifa rileva, però, che la mancanza di un solido rationale e l'assenza di prove di efficacia non consente di raccomandare l'utilizzo dell'Azitromicina, da sola o associata ad altri farmaci con particolare riferimento all'Idrossiclorochina, al di fuori di eventuali sovrapposizioni batteriche". Azithromycin is an antibiotic of the macrolide family, authorized for the treatment of upper and lower respiratory tract infections, There is evidence - AIFA reports in the fact sheet - that macrolides have beneficial effects in patients with inflammatory lung diseases, in addition to their ability to inhibit the replication of pathogenic bacteria. Regarding the treatment of Covid-19 with Azithromycin, Aifa notes, however, that the lack of a solid logic foundation (rationale) and the absence of any evidence about its effectiveness does not allow the recommendation of the use of Azithromycin, alone or associated with other drugs, with specific reference to Hydroxychloroquine, except in the case of bacterial overlaps.

The web page does not tell that Azithromycin is associated to Solidarity or Hidro-stop trials⁵.

AIFA document (April 8, 2020)

In [3] (archived <http://archive.is/zgdgv>), we can find an AIFA document (date: April 8, 2020) about Azithromycin and its use in Covid-19. This is the document mentioned by the Italian Government and reported in the previous section. The AIFA document contains an information concerning the association of two drugs, hydroxychloroquine and azithromycin, in treating Covid-19, as proposed by a study made in France⁶, led by Didier Raoult. It is told that "l'unica evidenza attualmente disponibile riguarda i risultati preliminari di un recentissimo studio, condotto in Francia su pazienti ricoverati affetti da COVID-19 asintomatici, sintomatici con disturbi a carico delle alte vie respiratorie o sintomatici con disturbi alle basse vie respiratorie con caratteristiche non meglio precisate. ... La forza e l'attendibilità del dato tuttavia vengono messe in discussione da importanti criticità metodologiche: studio non randomizzato, bassa numerosità campionaria complessiva ... Infine, un recentissimo report relativo ad un piccolo studio francese, ha mostrato che su 11 pazienti con COVID-19 ricoverati consecutivamente e trattati con idrossiclorochina più azitromicina secondo lo stesso schema posologico usato da Gautret et al., uno è deceduto, 2 sono stati trasferiti in

4 "Macrolide: One in a class of antibiotics that includes Biaxin (Clarithromycin), Zithromax (Azithromycin), Dificid (Fidoximycin), and Erythromycin. The macrolides inhibit the growth of bacteria and are often prescribed to treat rather common bacterial infections. ... They act by inhibiting protein synthesis, specifically by blocking the 50S ribosomal subunit. They are broad spectrum antibiotics". <https://www.rxlist.com/script/main/art.asp?articlekey=11422>

5 For the last AIFA News about Clinical Trials in Italy for Covid-19. see <http://doi.org/10.5281/zenodo.3830907>

6 According to Wikipedia (<http://archive.is/ZXZTt>), "On 17 March 2020, [Didier] Raoult announced in an online video that a trial involving 24 patients from the south east of France supported the claim that Hydroxychloroquine and Azithromycin were effective in treating for COVID-19. On 20 March he published a preliminary report of his study on-line in the International Journal of Antimicrobial Agents. The French Health Minister, Olivier Véran, was reported as announcing that "new tests will now go ahead in order to evaluate the results by Professor Raoult, in an attempt to independently replicate the trials and ensure the findings are scientifically robust enough, before any possible decision might be made to roll any treatment out to the wider public". ... Raoult, who was one of 11 prominent scientists named on 11 March to a committee to advise on scientific matters pertaining to the epidemic in France, left the committee He defended chloroquine as a drug that has suddenly been declared dangerous after having been safely used for 80 years". About the news, see also Footnote 1.

terapia intensiva, in uno il trattamento è stato interrotto per l'allungamento dell'intervallo QT. Dei 10 pazienti sopravvissuti, 8 erano ancora positivi per SARS-CoV2 5-6 giorni dopo l'inizio del trattamento. A fronte delle suddette incertezze in termini di beneficio, si ritiene utile sottolineare il rischio potenziale del prolungamento dell'intervallo QT indotto dall'associazione dei due farmaci (in particolare in presenza di fattori di rischio noti)."

The AIFA document, dated 8 April 2020, tells that the only evidence currently available [at the time the document was published, about the use of the association of two drugs, hydroxychloroquine and azithromycin, in treating Covid-19] concerns the preliminary results of a very recent study, made in France on hospitalized patients with asymptomatic COVID-19, symptomatic with upper respiratory tract disorders or symptomatic with lower respiratory tract disorders However, the relevance and reliability of the data are questioned because of important methodological criticality: non-randomized study, low overall sample size ... Finally, a very recent report concerning a small French trial showed that, out of 11 patients with COVID-19 consecutively hospitalized and treated with hydroxychloroquine plus azithromycin, according to the same dosage schedule used by Gautret et al.⁷, one died, two were transferred to intensive care, in one case the treatment was interrupted due to the lengthening of QT interval. Of the 10 surviving patients, 8 were still positive for SARS-CoV2 5-6 days after starting treatment. Due to the aforementioned uncertainties in terms of benefit, it is considered useful to underline the potential risk of the QT interval prolongation induced by the association of the two drugs (in particular in presence of known risk factors)⁸.

Where is the association of azithromycin and hydroxychloroquine used?

In any case, according to news, in Italy the association of azithromycin and hydroxychloroquine has been used at least in Piedmont, Lombardy, Tuscany and Sicily.

Piedmont - In news - 14 May 2020 - https://www.corriere.it/salute/malattie_infettive/cards/covid-19-punto-farmaci-studi-corso-dati-scientifici/metodo-trasparenza_principale.shtml (article by Laura Cuppini, archived in <http://archive.is/qL5Pt>). "Un trial coordinato dall'Università del Piemonte Orientale valuta l'associazione di idrossiclorochina più azitromicina versus idrossiclorochina in pazienti con polmonite di recente insorgenza, di gravità lieve/moderata e che non necessitano di ventilazione meccanica". We have also the news in <https://www.aifa.gov.it/-/covid-19-aifa-autorizza-tre-nuovi-studi-clini-1> - article dated 7 May 2020. (Archived <http://archive.is/kmfMg>)

The trial is made in Novara. "L'azienda ospedaliera universitaria di Novara capofila di una sperimentazione nazionale per la cura del Covid". «L'obiettivo generale di questo studio ... è valutare se la terapia di associazione tra idrossiclorochina e azitromicina è in grado di determinare rispetto alla terapia con sola idrossiclorochina una guarigione clinica più frequente e rapida tale da permetterne più precocemente la dimissione da ricovero ospedaliero. Si tratta di un obiettivo di interesse primario per il paziente, ma anche per la sanità pubblica che ha l'urgente necessità di ridurre il numero dei pazienti ricoverati in ospedale riducendo la durata dei ricoveri per polmonite da Covid 19». (article dated May 7, 2020, archived <http://archive.is/FjveX>) <https://www.lastampa.it/novara/2020/05/07/news/l-azienda-ospedaliera-universitaria-di-novara-capofila-di-una-sperimentazione-nazionale-per-la-cura-del-covid-1.38815624>

7 This is the study mentioned in Footnotes 1 and 5. It is published as "Gautret, P., Lagier, J.C., Parola, P., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Vieira, V.E., Dupont, H.T. and Honoré, S., 2020. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International journal of antimicrobial agents*, p.105949".

8 "QT prolongation is a measure of delayed ventricular repolarisation, which means the heart muscle takes longer than normal to recharge between beats. It is an electrical disturbance which can be seen on an electrocardiogram (ECG). Excessive QT prolongation can trigger tachycardias such as Torsades de Pointes (TdP). QT prolongation is an established side effect of anti-arrhythmic medicines, but can also be caused by a wide range of non-cardiac medicines, including antibiotics, antihistamines, opioid analgesics and complementary medicines". https://en.wikipedia.org/wiki/Drug-induced_QT_prolongation

Lombardy - In news - April 2, 2020 - We find that Hydroxychloroquine and Azithromycin are used with Celecoxib, a COX-2 selective nonsteroidal anti-inflammatory drug. «Terapie a casa, un mix di farmaci Potassio e magnesio per il cuore» Per fare chiarezza su come affrontare l'infezione, Regione Lombardia ha istituito una Rete per la valutazione farmacologica e terapeutica dei pazienti con Covid-19 - (Laura Cuppini, archived <http://archive.is/805aA>) - https://www.corriere.it/salute/malattie_infettive/20_aprile_02/terapie-casa-mix-farmaci-potassiomagnesio-il-cuore-82314fac-744a-11ea-b181-d5820c4838fa.shtml

In this article, it is remarked that "Tutti i pazienti dovrebbero assumere supplementi di potassio e magnesio per scongiurare il rischio di aritmie cardiache, possibile effetto collaterale della combinata idrossiclorochina-azitromicina". All patients should take potassium and magnesium supplements to avoid the risk of cardiac arrhythmias, a possible side effect of the combined hydroxychloroquine-azithromycin.

"Il celecoxib (durante la fase sperimentale noto anche con la sigla SC-58635) è un farmaco anti-infiammatorio non steroideo (FANS) appartenente alla famiglia degli inibitori selettivi della COX-2. ... Il farmaco è dotato di proprietà antinfiammatoria e analgesica. Il farmaco è una molecola della ricerca Searle e in Italia è venduto dalla società farmaceutica Pfizer Italia con il nome commerciale di Celebrex, nella forma farmaceutica di capsule rigide contenenti 100 mg o 200 mg di principio attivo". <https://it.wikipedia.org/wiki/Celecoxib>

In news - https://www.corriere.it/salute/cardiologia/20_aprile_24/idrossiclorochina-combinata-antibiotici-pericolosa-il-cuore-c337f070-858c-11ea-b71d-7609e1287c32.shtml (Laura Cuppini, archived <http://archive.is/gKU7q>) - April 24, 2020 - «Idrossiclorochina combinata con antibiotici pericolosa per il cuore» - "A ribadire i possibili effetti collaterali di una terapia in sperimentazione contro Covid-19 è l'Agenzia europea dei medicinali (Ema)". To reaffirm possible side effects of an experimental therapy against Covid-19 is the European Agency Ema.

For what concerns potassium, let us stress that in [4], we have reported about the observation of Hypokalemia due to Covid-19. Therefore the control of potassium is fundamental.

Tuscany - In news - "Antibiotico, eparina e antimalarico: la terapia che i medici utilizzeranno per la cura domiciliare" (Ilaria Bonuccelli, dated April 1, 2020, archived <http://archive.is/Rf4vH>) - <https://iltirreno.gelocal.it/regione/toscana/2020/04/01/news/antibiotico-eparina-e-antimalarico-la-terapia-che-i-medici-utilizzeranno-per-la-cura-domiciliare-1.38664049> "Un farmaco anti-malarico. Rinforzato da un antibiotico. E anche dall'eparina. I pazienti con infezione lieve da coronavirus (fino alla polmonite "leggera") in Toscana d'ora in avanti si curano a casa. Con terapie decise dai medici di medicina generale. Estese, se necessario, anche agli altri membri di famiglia". Di quali farmaci stiamo parlando? «Intanto dell'idrossiclorochina: si tratta di un farmaco anti-malarico; deve essere assunto (se non ci sono controindicazioni) insieme ad azitromicina, un antibiotico in compresse. L'antibiotico potenzierebbe l'effetto anti-virale del farmaco antimalarico. Insieme, inoltre, viene indicata la somministrazione dell'enoxaparina, eparina a basso peso molecolare, per l'effetto anti-trombotico. Infatti ci siamo resi conto che nelle infezioni da coronavirus ci sono anche complicanze trombotiche. Quindi è consigliato l'uso di questa sostanza, nella speranza che abbia anche una qualche efficacia anti-virale».

Therefore, in Tuscany, it is used for therapy at home, the association of Hydroxychloroquine and Azithromycin, with Enoxaparin sodium.

Sicily - <https://newsicilia.it/cronaca/acireale-dimessa-unaltra-paziente-guarita-dal-covid-nessun-paziente-in-terapia-intensiva/556949> - May 12, 2020. Archived <http://archive.is/jxvFB> . "Infatti, un'altra paziente nel catanese, esattamente ad Acireale, è guarita dal Covid-19 e sarà dimessa oggi dall'UOC di Anestesia e Rianimazione dell'ospedale acese. La donna, di 71 anni, residente nel Catanese è stata trattata con terapia standard che combina l'utilizzo di azitromicina, idrossiclorochina, antivirale e eparina." Here it is told that hydroxychloroquine and azithromycin are combined with an antiviral drug and enoxiparin.

Then we have seen that hydroxychloroquine, combined with azithromycin and other drugs, is used in Italy. A reasonable question exists and it is the following: how many persons are using a combination drug⁹, based on hydroxychloroquine, in Italy?

How many people in Italy?

However, another question can be posed too, and it is the following. How large is the use of drugs, made by Italian citizens, with the aim of protecting themselves from virus? And also, what is the drug mainly used? These are proper questions, in particular after reading news in the press, like the following.

In "**La Stampa**", newspaper of Turin, it was published, on April 16, 2020, the following article. <https://www.lastampa.it/salute/2020/04/16/news/cloroquina-e-l-idrossicloroquina-a-ruba-nelle-farmacie-le-molecole-nemiche-del-coronavirus-1.38724080> Archived <http://archive.is/VwwWy>

"CORONAVIRUS, LA GUIDA PER LA SALUTE - Cloroquina e idrossicloroquina, a ruba nelle farmacie le molecole nemiche del coronavirus. Ora scarseggiano per i malati reumatici cronici. Gli antimalarici utilizzati anche a scopo profilattico per le categorie più a rischio nell'emergenza da Covid-19. Hanno prezzi accessibili, ecco perché diminuiscono le quantità a disposizione. Molti, tra medici e infermieri, li stanno assumendo anche a scopo profilattico. Le prime evidenze riguardanti il potenziale che la cloroquina e l'idrossicloroquina (due tra i più noti antimalarici) avrebbero nel trattamento del Covid-19 hanno aperto un doppio fronte di discussione all'interno della comunità scientifica. ... Il ruolo della cloroquina al tempo del Coronavirus - L'Organizzazione Mondiale della Sanità lo ritiene uno dei farmaci potenzialmente in grado di curare Covid-19. Questo perché, partendo da quanto osservato ai tempi della Sars, la cloroquina ha dimostrato di poter bloccare anche la replicazione del materiale genetico del Sars-CoV-2. Considerando questa premessa, i ricercatori di diversi Paesi hanno avviato studi clinici mirati a valutare l'effetto sui pazienti affetti dalla polmonite interstiziale provocata dal Coronavirus. Le evidenze preliminari suonano come una conferma, alla luce del miglioramento della sintomatologia degli affetti da Covid-19. «C'è un razionale scientifico dietro la possibile efficacia della cloroquina da parte di questi pazienti», è la sintesi fatta da quattro ricercatori dell'Università di Palermo in un lavoro pubblicato sul «Journal of Critical Care»."

In the health guide of La Stampa, it is this told that Chloroquine and Hydroxychloroquine, the molecules which are enemies of coronavirus, went off the shelves of pharmacies. Now they are scarce for patients having chronic rheumatic diseases. Antimalarials are also used for prophylactic purposes by people exposed to risks in the emergency from Covid-19. They have affordable prices, and this is the reason of the fact that their availability is decreasing. Many doctors and nurses are also taking them for prophylactic purposes. The first evidence concerning the potentiality that the chloroquine and hydroxychloroquine (two of the best known antimalarials) would have in the treatment of Covid-19 opened a debate within the scientific community The role of chloroquine at time of coronavirus - The World Health Organization considers it as one of the drugs potentially capable of curing Covid-19. This is because, starting from what had been observed at the time of Sars, chloroquine has shown that it can also block the replication of the genetic material of Sars-CoV-2. After this premise, researchers from different countries have launched clinical studies aimed at evaluating its effect on patients suffering due to interstitial pneumonia caused by Coronavirus. The preliminary evidence sounds like a confirmation, in the light of the improvement of the symptoms of people affected by Covid-19. "There is a scientific rationale behind the possible efficacy of chloroquine in these patients", is the summary made by four researchers from the University of Palermo in a work published in the "Journal of Critical Care". "

This is what is told in La Stampa (let us stress that chloroquine is a drug different from hydroxychloroquine). The link given by La Stampa ("Journal of Critical Care") is the following:

⁹ A combination drug is also known as "combo".

<https://www.sciencedirect.com/science/article/pii/S0883944120303907> - Let us stress also that La Stampa is referring, by means of the given link, to a review of clinical reports from China.

The reference is [5]. The title is "A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19". Of the chloroquine, in the highlights it is told "Specific pre-clinical evidence and expert opinions suggest potential use against SARS-CoV-2". "A search in trial registries shows that 23 clinical trials are ongoing in China". The method of the Ref.5 is the following "PubMed, EMBASE, and three trial Registries were searched for studies on the use of chloroquine in patients with COVID-19". Results of [5] are: "We included six articles (one narrative letter, one in-vitro study, one editorial, expert consensus paper, two national guideline documents) and 23 ongoing clinical trials in China. Chloroquine seems to be effective in limiting the replication of SARS-CoV-2 (virus causing COVID-19) in vitro".

In La Stampa it is told «C'è un razionale scientifico dietro la possibile efficacia della cloroquina da parte di questi pazienti», "There is a scientific rationale behind the possible *efficacy*¹⁰ of chloroquine in these patients". The sentence is referring to coronavirus patients. In the article [5] it is told: "There is rationale, pre-clinical evidence of *effectiveness* and evidence of safety from long-time clinical use for other indications to justify clinical research on chloroquine in patients with COVID-19. However, clinical use should either adhere to the Monitored Emergency Use of Unregistered Interventions (MEURI) framework or be ethically approved as a trial as stated by the World Health Organization. Safety data and data from high-quality clinical trials are urgently needed". And also: "There is sufficient pre-clinical rationale and evidence regarding the effectiveness of chloroquine for treatment of COVID-19 as well as evidence of safety from long-time use in clinical practice for other indications [6] to justify clinical research on the topic."

Let us continue about news concerning risks of using the association of hydroxychloroquine and azithromycin.

Risks during treatment

In news - May 5, 2020 - COVID-19: evidenze e linee di indirizzo del trattamento con idrossiclorochina e azitromicina, article written by Paolo Spriano for Uniflash - <https://www.univadis.it/viewarticle/covid-19-evidenze-e-linee-di-indirizzo-del-trattamento-con-idrossiclorochina-e-azitromicina-719671> - Archived <http://archive.is/ltumI> .

"Il trattamento di combinazione di idrossiclorochina e azitromicina (HCQ / AZ) può avere un effetto favorevole sugli esiti clinici ... Le linee di indirizzo di AIFA sui farmaci utilizzabili in COVID-19 da un lato affermano che "l'uso terapeutico dell'idrossiclorochina può essere considerato sia nei pazienti COVID-19 di minore gravità gestiti a domicilio sia nei pazienti ospedalizzati" e dall'altro richiamano l'attenzione dei clinici sui rischi di reazioni avverse del trattamento di combinazione idrossiclorochina e azitromicina perché, in studi su altre popolazioni, entrambi i farmaci hanno dimostrato indipendentemente di aumentare il rischio di prolungamento dell'intervallo QT, torsione di punta e morte cardiaca improvvisa". The combined treatment with hydroxychloroquine and azithromycin (HCQ /AZ) can have a favourable effect on clinical outcomes ... AIFA guidelines on drugs which can be used in COVID-19, on the one hand, state that "the therapeutic use of hydroxychloroquine can be considered both in COVID-19 patients of lesser severity managed at home and in hospitalized patients", on the other hand, these guidelines draw the attention of clinicians on the risks of adverse reactions of the combined treatment with

10 <http://www.treccani.it/vocabolario/efficacia/> *efficàcia* s. f. - Capacità di produrre pienamente l'effetto voluto, e l'ottenimento stesso dell'effetto. Therefore, I opted for translating "efficacia" into "efficacy", that is the ability to produce a desired or intended result. However, as told in <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3726789/> "Archie Cochrane, British famous clinical epidemiologist, defined two concepts related to assessing healthcare interventions. Efficacy is the extent to which an intervention does more good than harm under ideal circumstances. Effectiveness assesses whether an intervention does more good than harm when provided under usual circumstances of healthcare practice".

hydroxychloroquine and azithromycin because, in studies on other populations, both drugs have independently shown to increase the risk of QT prolongation, torsade de pointes and sudden cardiac death.

The news is referring to an article in Nature (link is not working). We could suppose it was the article in Ref.7. In [7], it is told that "although there are no approved drugs to prevent or treat SARS-CoV-2 infection, a recent report suggested that the combination of hydroxychloroquine and azithromycin (HY/AZ) may have a favorable effect on the clinical outcomes and viral loads of infected patients; this resulted in massive adoption of the regimen by clinicians worldwide. However, both medications have been independently shown to increase the risk in other populations for QT-interval prolongation, drug-induced torsades de pointes (a form of polymorphic ventricular tachycardia) and drug-induced sudden cardiac death". That is, risks exist.

It does not work

Is the treatment a proper treatment against Covid-19? In news - from La Repubblica.

April 23, 2020 - Archived <http://archive.is/3UurE> https://www.repubblica.it/salute/medicina-e-ricerca/2020/04/23/news/coronavirus_1_idrossiclorochina_non_funziona_aumentano_i_rischi_cardiaci-254794509/ - Coronavirus: il farmaco antimalarico non funziona. Aumentano i rischi cardiaci - A sostenerlo l'analisi della rivista scientifica Prescrivere sui più recenti studi sull'idrossiclorochina, by Antonio Calitri. "La cura miracolosa contro l'infezione da Covid19 a base di idrossiclorochina non funziona. Ancor meno se rinforzata con l'antibiotico azitromicina, come suggerito dal primo sostenitore di questi farmaci in Europa, il dottor Didier Raoult, direttore dell'istituto universitario delle malattie infettive di Marsiglia. Ad arrivare a questa conclusione, in attesa dei risultati dello studio europeo Discovery su 3.200 pazienti, è stata la rivista scientifica Prescrivere, che ha analizzato i principali studi effettuati finora sull'utilizzo del farmaco antimalarico". Coronavirus: the antimalarial drug does not work. Cardiac risks are increasing - This is supported by the analysis of the scientific journal Prescrivere on the most recent studies on hydroxychloroquine. Article by Antonio Calitri. "The miracle cure against Covid19 infection, based on hydroxychloroquine, does not work. Even less, if reinforced by the antibiotic azithromycin, as suggested by the first advocate of these drugs in Europe, Dr. Didier Raoult, Director of the University Institute of Infective Diseases of Marseille. To draw this conclusion, while waiting for the results of the European study Discovery on 3,200 patients, it was the scientific journal Prescrivere, which analysed the main studies carried out so far on the use of the antimalarial drug.

Be careful

In news - April 6, 2020 - "Idrossiclorochina con azitromicina per trattare COVID-19, scienziati consigliano cautela" al link <https://notiziescientifiche.it/idrossiclorochina-con-azitromicina-per-trattare-covid-19-scienziati-consigliano-cautela/> Archived <http://archive.is/zckMs> .

It is told that "Un team di cardiologi, in uno studio pubblicato su Cardiology Magazine, ... consiglia cautela per quanto riguarda l'eventuale trattamento contro la patologia respiratoria COVID-19 a base di idrossiclorochina combinato con l'antibiotico azitromicina. È quanto si legge in un comunicato apparso sul sito dell'Oregon Health & Science University (OHSU). In collaborazione con altri ricercatori dell'Università dell'Indiana, i ricercatori dell'OHSU hanno pubblicato una nuova guida nella quale raccomandano ai medici che trattano che i pazienti affetti da COVID-19 con questa combinazione di farmaco antimalarico e di antibiotico di considerare di monitorare attentamente gli stessi pazienti per quanto riguarda l'aritmia ventricolare". That is, "As some consider treating coronavirus patients with a combination of the malaria drug hydroxychloroquine and the antibiotic azithromycin, cardiologists are advising caution because both medications can increase the risk for dangerous abnormal heart rhythms" [8,9].

Nuova scheda informativa AIFA

In this section Italian is mainly used, because specifically devoted to Italy.

<http://www.fpress.it/attualita/azitromicina-nei-pazienti-covid-19-nuova-scheda-informativa-dellaifa/> - archived <http://archive.is/Rg8S5> - According to this article dated April 11, 2020, AIFA tells that "La prescrizione dell'azitromicina, da sola o associata ad altri farmaci e in particolare all'idrossiclorochina, nel trattamento di pazienti con covid-19 può essere presa in considerazione «soltanto nell'ambito di studi clinici. Gli impieghi non previsti dalle indicazioni autorizzate e non raccomandati restano una responsabilità del prescrittore e non sono a carico del Ssn». E' quanto scrive l'Aifa nella scheda informativa – la quarta della collana – che aggiorna i risultati conseguiti nella pratica clinica dall'uso "off label" di azitromicina, uno dei farmaci utilizzati con maggiore frequenza nelle terapie sui malati di covid (le pubblicazioni precedenti erano dedicate a darunavir/cobicistat, idrossiclorochina e lopinavir/ritonavir). ... Come riferisce la scheda tecnica del farmaco, dunque, nel valutare i rischi-benefici di azitromicina si dovrà tenere in considerazione il rischio del prolungamento dell'intervallo qt in pazienti in trattamento con altri principi attivi che prolungano l'intervallo, quali antiaritmici della classe IA (chinidina e procainamide) e della classe III (amiodarone e sotalolo), cisapride e terfenadina, farmaci antipsicotici come pimozide, antidepressivi come citalopram, fluorochinoloni come moxifloxacina, levofloxacina e cloroquina e idrossiclorochina; con alterazioni degli elettroliti, specialmente nei casi di ipopotassiemia e ipomagnesiemia; con bradicardia clinicamente rilevante, aritmia cardiaca o grave insufficienza cardiaca".

"Con il termine intervallo QT si intende il tratto di ECG che si estende dall'inizio del complesso QRS fino al termine dell'onda T. L'intervallo QT esprime il tempo necessario al miocardio ventricolare per depolarizzarsi e ripolarizzarsi". https://it.wikipedia.org/wiki/Intervallo_QT

And then, let us arrive to the following news. **Aifa: uso off label farmaci per anti-Covid, cambiano condizioni di prescrizione e dispensazione.** This is told by REDAZIONE BIOETICA NEWS TORINO, May 6, 2020. (Archived <http://archive.is/0fi2A>). <http://www.bioeticanews.it/aifa-autorizza-uso-off-label-farmaci-per-anti-covid-e-cambia-condizioni-di-prescrizione-e-dispensazione/> "Per l'uso terapeutico dell'idrossiclorochina può essere considerato sia nei pazienti Covid-19 di minore gravità gestiti a domicilio sia nei pazienti ospedalizzati. Allo stato attuale delle conoscenze è *sconsigliato l'uso di idrossiclorochina in associazione con lopinavir/ritonavir o con azitromicina al di fuori di studi clinici.* Entrato nella pratica clinica sulla base di evidenze incomplete è auspicabile per l'uso terapeutico dell'idrossiclorochina la partecipazione a studi randomizzati che ne valutino l'efficacia. E l'uso profilattico deve essere considerato esclusivamente nell'ambito di studi clinici in quanto basato esclusivamente su osservazioni in vitro. ... La FDA, agenzia americana, avverte di essere a conoscenza di segnalazioni di gravi problemi del ritmo cardiaco in pazienti ospedalizzati e non con Covid-19 trattati con HCQ o CQ, spesso in associazione con azitromicina e altri medicinali che prolungano il QT, specialmente in pazienti con insufficienza renale. Tali segnalazioni di reazioni avverse includono tachicardia o fibrillazione ventricolare o torsades de pointes e comprendono alcuni casi fatali. L'OMS comunica che l'utilizzo di alte dosi di HCQ o CQ può essere associato a eventi avversi seriamente negativi per la salute. Gli antibiotici non devono essere usati come mezzo di prevenzione o trattamento di Covid-19."

Here some links: <https://www.aifa.gov.it/aggiornamento-sui-farmaci-utilizzabili-per-il-trattamento-della-malattia-covid19> And also the document "Azitromicina nella terapia dei pazienti adulti con COVID-19. Update del 5 maggio 2020. (prima pubblicazione: 9 aprile 2020) ".

https://www.aifa.gov.it/documents/20142/1123276/azitromicina_05.05.2020.pdf/272d910e-1f59-d69c-28f0-805f096ae4d3

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Sei studi retrospettivi (per la maggior parte non pubblicati ufficialmente) sull'utilizzo in emergenza dell'HCQ, da sola o in associazione con azitromicina, mostrano alcuni segnali di sicurezza di cui è importante tenere conto.

In the screenshot, it is shown the beginning of a very long section which is reporting about six studies, five of them concerning Covid-19.

Now, let us consider some scholar articles.

Scholar articles

In [10], it is the publication concerning the French study led by Didier Raoult, IHU-Méditerranée Infection, Marseille. In [10], the authors tells that "Chloroquine and hydroxychloroquine have been found to be efficient on SARS-CoV-2, and reported to be efficient in Chinese COV-19 patients". The researchers "evaluate the role of hydroxychloroquine on respiratory viral loads". Results given are the following: "Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms. Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination".

Elsevier published a Joint ISAC and Elsevier statement on Gautret et al. paper [PMID 32205204] <https://www.isac.world/news-and-publications/isac-elsevier-statement>

In [11], about [10], it is told "The trial of Gautret and colleagues, with consideration of the effect sizes, and p-values from multiple models, does not provide sufficient evidence to support wide-scale rollout of HCQ monotherapy for the treatment of COVID-19; larger randomized studies should be considered".

In [12] it is told in the title that " No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection". In [13], risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin is discussed.

PRO and CONTRO time-series

And here a very interesting time series of PRO and CONTRO opinions about the association Hydroxychloroquine and Azithromycin in treating Covid-19.

PRO - March 19, 2020 - in news <https://www.nursetimes.org/coronavirus-farmaco-contro-la-malaria-efficace-nel-75-dei-casi/82974> REDAZIONE NURSE TIMES 19/03/2020 - Archived <http://archive.is/rk3Fy> . "Dopo essere stato più volte indicato come trattamento efficace per combattere le infezioni da Covid-19, utilizzato sia in Cina (con 20 studi su 100 persone in corso) che in Corea, arriva l'annuncio del primo studio europeo sull'efficacia dell'idrossiclorochina. Il farmaco utilizzato da anni contro la malaria sembra accendere una speranza per la cura immediata dei pazienti affetti da coronavirus, anche nei casi più gravi. Secondo il professor Didier Raoult, direttore dell'Istituto ospedaliero universitario Méditerranée Infection di Marsiglia, che ieri ha presentato i risultati del primi studio, ... , il 75% dei pazienti trattati con il Plaquenil, uno dei farmaci a base di idrossiclorochina, "dopo sei giorni di trattamento aveva una carica virale negativa", ovvero non aveva più il virus attivo all'interno del proprio corpo. Non solo. L'idrossiclorochina, abbinata all'antibiotico azitromicina, utilizzato normalmente contro la

polmonite batterica, ha portato alla guarigione dei pazienti in una settimana".

CONTRO - April 24, 2020 - in news <https://www.nursetimes.org/coronavirus-la-cura-col-farmaco-antimalarico-non-funziona/86200> REDAZIONE NURSE TIMES 24/04/2020 Archived <http://archive.is/NYSQs> . "A questa conclusione è arrivato uno studio francese sulla terapia a base di idrossiclorochina. La cura miracolosa contro l'infezione da Covid-19 a base di idrossiclorochina non funziona. Ancor meno se rinforzata con l'antibiotico azitromicina, come suggerito dal primo sostenitore di questi farmaci in Europa, il dottor Didier Raoult, direttore dell'Istituto universitario delle malattie infettive di Marsiglia. Ad arrivare a questa conclusione, ... , la rivista scientifica Prescrire, che ha analizzato i principali studi effettuati finora sull'utilizzo del farmaco antimalarico attualmente disponibili. Secondo la rivista, mentre non ci sono risultati favorevoli sugli effetti antivirali dell'idrossiclorochina rispetto a pazienti che non l'hanno utilizzata, sono invece evidenti gli effetti indesiderati, soprattutto a danno del sistema cardiovascolare di quelli che invece l'hanno utilizzata, ancora di più se in combinazione con l'antibiotico azitromicina".

Here the link to **Prescrire**, <https://english.prescrire.org/en/81/168/58640/0/NewsDetails.aspx> Archived <http://archive.is/AFtPB> - "New data on the cardiac adverse effects of the combination of hydroxychloroquine (Plaquenil) with azithromycin (Zithromax or other brands) - NEWS UPDATE As of mid-April 2020, more and more clinical data are confirming that the combination of hydroxychloroquine (Plaquenil) with azithromycin (Zithromax or other brands) carries a risk of serious cardiac adverse effects: prolongation of the QT interval with a high risk of cardiac arrhythmia and torsade de pointes, and cardiovascular mortality, which is increased by the addition of azithromycin. Several cases of cardiac arrest have been reported. The combination of hydroxychloroquine, an anti-malarial drug with immunosuppressant activity, and azithromycin, a macrolide antibiotic, is a treatment under evaluation for patients with covid-19. As of 15 April 2020, there is no evidence that the combination has clinical efficacy in this situation."

This last sentence has the LINK to the following news (archived <http://archive.is/LP1SS>): <https://english.prescrire.org/en/81/168/58639/0/NewsDetails.aspx>

Covid-19 and hydroxychloroquine (Plaquenil): new data show no evidence of efficacy NEWS UPDATE The results of a new randomised comparative but non-blinded trial of high-dose hydroxychloroquine (Plaquenil) versus standard care in 150 patients hospitalised for covid-19 have been published. The only notable difference between the groups was the high incidence of adverse effects in the group treated with hydroxychloroquine. The results of other studies (non-randomised and providing only low-quality evidence) show no evidence that hydroxychloroquine has efficacy against covid-19.

And also <https://www.cnn.com/2020/05/11/coronavirus-trump-touted-drug-doesnt-help-patients-but-raises-heart-attack-risk-study-says.html> Archived <http://archive.is/LuuHR> "Hydroxychloroquine taken in conjunction with azithromycin was associated with "significantly elevated levels of cardiac arrest" even after adjusting for factors such as sex, age, underlying health conditions and more severe illness, according to a new study in the JAMA Network published Monday." But now, another combination is proposed - hydroxychloroquine, zinc sulphate and azithromycin, (archived <http://archive.vn/gaSTX>) , <https://www.nyl.com/nyc/all-boroughs/news/2020/05/12/nyu-study-looks-at-hydroxychloroquine-zinc-azithromycin-combo-on-decreasing-covid-19-deaths> is announcing another combination - hydroxychloroquine, zinc sulphate and azithromycin.

In conclusion, the main question is the following. How many persons are using these drugs - hydroxychloroquine (or chloroquine) and azithromycin - in Italy? This is an open question, which has a great importance, to understand whether this association has any effectiveness in Covid-19 or not. The same question can be proposed for the use of hydroxychloroquine or chloroquine.

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