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Use of N-Acetylcysteine at high doses as an oral treatment for patients hospitalized with COVID-19

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Abstract

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Infection by SARS-CoV-2 causing coronavirus disease 2019 (COVID-19) can be associated with serious and life-threatening conditions, including acute respiratory distress syndrome (ARDS). Severity and mortality have been related to a cytokine storm, an imbalance of oxidative stress, and a pro-thrombotic state.

We conducted an observational retrospective cohort study from a community-based large population of hospitalized COVID-19 PCR + patients admitted from March 01, 2020, to January 24, 2021, with integrated primary to tertiary care information in Castilla la Mancha, Spain. We explored the potential benefits of the antioxidant, anti-inflammatory and anti-thrombotic drug N-acetylcysteine (NAC) administered orally in high doses (600 mg every 8 h), added to standard of care in COVID-19 patients by using the free text information contained in their electronic health records (EHRs).

Out of 19,208 patients with a diagnosis of COVID-19 hospitalized, we studied 2071 (10.8%) users of oral NAC at high doses. COVID-19 patients treated with NAC were older, predominantly male, and with more comorbidities such as hypertension, dyslipidemia, diabetes, and COPD when compared with those not on NAC (all $p < 0.05$). Despite greater baseline risk, use of NAC in COVID-19 patients was associated with significantly lower mortality (OR 0.56; 95%CI 0.47–0.67), a finding that remained significant in a multivariate analysis adjusting by baseline characteristics and concomitant use of corticosteroids. There were no significant differences with the use of NAC on the mean duration of hospitalization, admission to the intensive care unit or use of invasive mechanical ventilation. The observed association signaling to better relevant outcomes in COVID-19 patients treated with NAC at high doses should be further explored in other settings and populations and in randomized controlled trials.

Keywords: COVID-19, N-acetylcysteine, mortality, use of health services, treatment

Introduction

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Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a recently identified strain of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). [1] It is transmitted mainly by close contact inhalation and aerosols, and the disease usually manifests with fever, respiratory symptoms (cough, dyspnea, etc.), myalgia, and up to 150 symptoms. [2] Complications lead to serious and life-threatening conditions, including acute respiratory distress syndrome (ARDS). Patients with severe complications (respiratory and non-respiratory) require hospitalization, close monitoring and, in some cases, must be transferred to the intensive care unit (ICU).[3,4] A number of risk factors associated with severe COVID-19 have been identified, namely: male gender, increasing age (> 56 years), smoking, overweight/obesity and those people with previous health conditions (for example, cardiovascular disease, respiratory or diabetes), who are particularly susceptible and are therefore more likely to experience severe or critical COVID-19.[5,6]

Severe complications, both pulmonary and extrapulmonary, have been attributed to a so-called "cytokine storm" with a systemic inflammatory response uncontrolled by the immune system. [7] During acute SARS-CoV-2 infection, there is a release of cytokines and chemokines by immune cells. Moreover, in some COVID-19 patients, an elevation of IL-8, a strong neutrophil chemoattractant factor, has been described.[8,9] Once activated by infection, neutrophils are rapidly recruited to sites of inflammation, where they produce and secrete cytokines, enzymes, including elastase (NE), reactive oxygen species (ROS), and release DNA to form extracellular neutrophil traps.[10,11] In the most severe forms of COVID-19, in addition to the cytokine storm, an imbalance of oxidative stress has been shown to occur. [12] N - Acetyl - L - cysteine (NAC) is a precursor to reduced glutathione (GSH). [12] It has been suggested that its early use at high doses may become an effective strategy in the treatment of COVID-19 patients.[12,13]

Given that the replacement of some antioxidants can restore the immune cell response, potentially reducing the incidence or severity of viral pneumonia, it can be hypothesized that NAC, in addition to preventing damage caused by certain respiratory viruses, can improve cellular immunity when it is compromised and can modulate the immune response responsible for the most serious complications of COVID-19. Furthermore, the pro-thrombotic status induced by SARS-CoV-2, a potentially life-threatening mechanism in some COVID-19 patients, can be counterbalanced by the anti-thrombotic effects of NAC. [14]

Artificial Intelligence tools, combined with the availability of large amounts of data, have allowed us to improve our understanding of COVID-19. [15] In this paper, the real-world evidence that Electronic Health Records (EHRs) can offer is exploited to understand the potential benefits of NAC in the treatment of COVID-19.

Methods

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This paper describes an observational, retrospective study that is performed based on the data contained in the EHRs of patients diagnosed with COVID-19. The clinical data, in text form, corresponds to all patients registered in the regional health system of a region in Spain, Castilla La-Mancha. The data that were collected include all available departments at the hospital and primary care, also including the emergency room. The study period was March 1st, 2020 – January 24, 2021. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies. [16] The study has been approved by the ethics and research committee of the University Hospital of Guadalajara (Spain).

All patients in our study had a clinical diagnosis of COVID-19 confirmed by RT-PCR. NAC was prescribed according to some local protocols that included this drug, as standard treatment, at doses of 600 mg every 8 h, together with other treatments, irrespective of the initial severity or clinical characteristics of COVID-19 patients. These COVID-19 patients were compared with a reference group of COVID-19 patients within the same population domain who were not prescribed NAC. As this is a non-interventional study, the decision to prescribe any product was taken prior to, and independently from the decision to the study.

The information contained in the EHRs was processed using Natural Language Processing (NLP), which is able to extract the information and shape it in a structured manner. Because this is a Big Data study, the study population will include all patients with confirmed COVID-19 in the participating sites.

The processing of EHRs was performed using SAVANA Manager®, a powerful NLP engine that works over several languages and is able to extract the content in clinical records independently of the EHR system they operate. SAVANA Manager recognizes the medical terms and fits them into a hierarchy of concepts based on SNOMED. SAVANA Manager reads the notes in the electronic health records as well as the laboratory values, which are translated into numerical variables. This results in transforming the data in the records into information that can be treated by Big Data techniques.

The study database is created by applying a four-step methodology which is described in this section a) Acquisition: it is hospitals which, with the help of the IT department in Savana, are responsible for this step, which is undertaken in accordance with the General Data Protection Regulation (GDPR). This includes anonymization before transfer to Savana. Then, the data are integrated b) into the database. The next step c) is the application of EHRead®, the NLP technology system created by Savana. This results in a synthetic patient database where individual patients cannot be tracked. The next step is d) Validation, which is undertaken by a team of doctors and researchers. In the validation step, the results of the NLP processing are evaluated to make sure that they represent faithfully the contents of the EHR.

The integrated data are presented in a structured form based on terminology that is based on SNOMED CT, [17] although it includes several other sources. The terminology includes not only medical concepts such as symptoms, diagnoses, body structures and substances but also synonyms and definitions. A lengthier account of EHRead® can be found in.[4,18]

The statistical analyses were carried out using SPSS (v 25.0) and OpenEpi (v 3.01). Categorical variables are reported as absolute frequencies and percentages, while continuous variables are presented using mean and standard deviation. For the assessment of the statistical significance of quantitative variables, we used T-tests or ANOVA for independent samples. To measure the relative distribution of patients assigned to different categories of qualitative variables, we used Chi^2 tests. The number and percentages of COVID-19 treated with each drug, such as corticosteroids, NAC and others, were either observed or calculated directly from observed magnitudes. A logistic regression on summary data was applied in order to estimate the effect of NAC while adjusting for other covariates, including corticosteroid prescription. In all cases, a P-value lower than 0.05 was considered for statistical significance.

All legal and regulatory requirements and the research practices described in the ICH Guide to Good Clinical Practice, the Declaration of Helsinki in its latest edition, good pharmacoepidemiology practices, GDPR, the code of Good Data protection practices for Big Data studies and local regulations were respected. Informed consent was not necessary, because this is an observational study based on anonymous patients.

Results

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During the study period between March 1, 2020, to January 24, 2021, 19,208 patients with a clinical diagnosis of COVID-19 confirmed with a + PCR test were hospitalized in Castilla la Mancha (Spain). Of the 2071 (10.8%) were treated with NAC at dose of 600 mg every 8 h. The patient participation flowchart of these COVID-19 patients is in Figure 1.

Figure 1.

Flowchart depicting the total number of patients with available electronic health records (EHRs), the number of patients with COVID-19, the number of patients treated with NAC, and of those who died during the study period (march 1, 2020 to January 24, 2021). All percentage values are computed in relation to the level immediately above.

The demographic and clinical characteristics of these COVID-19 hospitalized patients eventually treated or not with oral NAC at a high dose are shown in Table 1. Overall, mean ± SD age was 66.6 ± 20.9, and 53.6% were men. The most common diagnosis in hospitalized patients treated with NAC was pneumonia (100% of patients), with great variability of radiological expression.

Table 1.

Demographic and clinical characteristics of hospitalized COVID-19 patients, by NAC use.

	Total COVID19	**without NAC**	**with NAC**	***P* value OR (CI95%)**
N	19.208	**17.137**	**2071**	
Age. Years (SD)	66.6 (20.9)	**65.9** **(21.4)**	**70.1** **(15.6)**	$P < 0.001$
Sex. Male (%)	53.6	**52.6**	**60.1**	$P < 0.001$
COPD %	1483	**1247** **7.3**	**236** **11.4**	1.64 (1.41–1.90)
Atrial Fibrillation %	2802	**2483** **14.5**	**319** **15.4**	1.08 (0.95–1.22)
Diabetes mellitus %	5109	**4519** **26.4**	**590** **28.5**	1.11 (1.01–1.23)
Arterial Hypertension %	10.606	**9379** **54.7**	**1227** **59.2**	1.20 (1.10–1.23)
Dyslipidemia %	6512	**5745** **33.5**	**767** **37**	1.16 (1.06–1.28)

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Compared with NAC-free patients, those treated with high-dose NAC were on average 4.2 years older, and more frequently male (both $p < 0.001$) and with more prevalence of comorbidities, namely hypertension, dyslipidemia, diabetes and COPD (all $p < 0.05$), but not atrial fibrillation (Table 1). Further, the proportion of patients treated with corticosteroids, hydroxychloroquine, azithromycin, and enoxaparin was significantly higher in patients treated with NAC (all $p < 0.05$) (Table 2).

Table 2.

Concomitant treatments associated with the use of NAC in hospitalized COVID-19 patients.

	Total COVID19	**COVID19 without NAC**	**COVID19 with NAC**	**OR (CI95%)**
N	19.208	**17.137**	**2071**	
Corticosteroids %	7479	**6038** **(35.2)**	**1441** **(69.58)**	4.20 (3.81–4.64)
Hydroxychloroquine %	3324	**2783** **16.2**	**541** **26.1**	1.82 (1.64–2.03)
Azithromycin %	4021	**3325** **19.4**	**696** **33.6**	2.10 (1.91–2.32)
Enoxaparin %	6649	**5443** **31.8**	**1206** **58.2**	2.99 (2.73–3.29)
Acenocoumarin %	1917	**1703** **9.9**	**214** **10.3**	1.04 (0.89–1.21)

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Despite older age and greater comorbidity, COVID-19 patients treated with oral NAC at a high dose were associated with lower mortality (OR 0.56; 95%CI 0.47–0.67). Better survival was also observed with corticosteroids (OR 0.59; 95%CI 0.53–0.65) and enoxaparin (OR 0.47; 95%CI 0.43–0.53). By contrast, the use of acenocoumarin was associated with higher mortality (OR 1.60; 95%CI 1.40–1.83). In fact, those treated with acenocoumarin had a higher prevalence of hemorrhagic complications (27.8% versus 13.5%; $p < 0.001$), of which 38% were digestive. (Table 3)

Table 3.

Association of drugs with mortality in hospitalized COVID-19 patients.

	Total COVID19	COVID19 No dead	COVID19 Dead	OR (CI95%)
N	19.208	**17.162**	**2046**	
NAC	2071	**1935**	**136**	0.56 (0.47–0.67)
%		**11.3**	**(6.6)**	
Corticosteroids	7479	**6898**	**581**	0.59 (0.53–0.65)
%		**40.2**	**28.4**	
Enoxaparin	6649	**6213**	**436**	0.47 (0.43–0.53)
%		**36.2**	**21.3**	
Acenocoumarin	1917	**1624**	**293**	1.60 (1.40–1.83)
%		**9.5**	**14.3**	

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Further, a multivariate analysis was conducted to confirm the crude association observed with NAC. A logistic regression on summary data was applied in order to estimate the effect of NAC while adjusting for baseline covariates and corticosteroid administration. The beneficial association of NAC on mortality remained with corticosteroids (OR 0.72; IC95% 0.60–0.87) and without corticosteroids (OR 0.53; IC95% 0.48–0.59).

Finally, the use of health services was explored. There were no significant differences with the use of NAC on the mean duration of hospitalization, Intensive Care Unit Admission, or use of invasive mechanical ventilation.

Discussion

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Our study found that NAC administered orally at a high dose was associated with better survival when added to standard treatment in patients with COVID 19 hospitalized with pneumonia. Despite admitted COVID-19 patients treated with NAC being older, more frequently male and had more comorbidities, the signal of an association with reduced mortality was strong for NAC and sustained in multivariate analysis. We did not observe positive associations of NAC on the mean duration of hospitalization, being in the Intensive Care Unit or requiring non-invasive ventilatory support. However, these findings must be assessed in the context of a collapse in health services that occurred early in the pandemic, conditioned not exclusively by medical factors.

NAC has been used since the 1960s as a mucolytic drug in chronic respiratory diseases, especially COPD. [19] There are other indications such as an antidote for paracetamol overdose at doses up to 150 mg/kg, with a good safety profile. [20]

At present, its use is common as a mucolytic at a dose of 600 mg/day. However, in higher doses (≥1200 mg), NAC also acts as an antioxidant through complex mechanisms that can improve situations of oxidative stress. For this reason, it has been proposed its potential for early administration in the community for patients at greater risk of severe COVID-19. [12]

In COVID-19, as a consequence of oxidative stress, there is a significant increase in glutathione reductase in blood, mainly in the most severe patients. [21] In these cases, reduced glutathione is a very important defense pathway since ROS and Thiol antioxidants, including reduced glutathione, also intervene in the regulation of the immune response at various levels.[11,12] This mechanism is particularly relevant in elderly patients where there is a sustained inflammation, which produces oxidative stress and cytokine production.[22,23] In immune cells of the elderly or immunosuppressed, ROS are increased due to the decrease in glutathione, which causes dysregulation of the immune response, in particular, that mediated by T cells. This may explain the depression of the immune response mediated by cells and increased mortality in older people with infectious diseases, such as pneumonia.[24,25]

The role of neutrophils is also relevant; a high neutrophil/lymphocyte ratio has been proposed to be a predictor of more severe COVID-19.[26,27] The interrelationship of oxidative stress and inflammation in COVID-19 occurs and several mediators contribute. Among others, IL-1beta, IL6, TNF-alpha, and a kappa B (κB-α)/nuclear factor kappa B (NF-κB)-independent pathway, that mediates the redox-dependent regulation of inflammatory cytokines. Additionally, previous studies have shown that NAC has antiviral activity against influenza A (H3N2 and H5N1). These positive effects of NAC in lower respiratory tract viral infections have been associated with inhibition of IL-8, IL-6, and TNF-α expression and discharge in alveolar type II cells infected with influenza virus A and B or respiratory syncytial virus.[10,12]

At the onset of the COVID-19 pandemic, it was already known that ROS play a central role in inflammatory responses and viral replication and that antioxidants that exert antiviral and anti-inflammatory effects may also be effective for the treatment of cytokine storm, a characteristic later found in a subgroup of patients with severe COVID-19. Further to pulmonary impairment, COVID-19 can cause multiple extrapulmonary complications, especially cardiological and thrombotic. NE activity may, in part, explain the significant increase in D-dimer and thrombotic or hemorrhagic phenomena seen in patients with COVID-19.[8,12]

By integrating all this evidence with NAC, there was a rationale for the use of this well-known drug, especially if we take into consideration the absence of effective treatments at the beginning of the pandemic and the safety profile of NAC. For this reason, NAC was introduced from the beginning in the protocol of some hospitals of Castilla-La Mancha for all patients hospitalized for COVID-19, regardless of their initial severity, while in other hospitals this treatment was not incorporated at any moment. This decision was made in accordance with local protocols for COVID19 treatment. Some local protocols, but not others included NAC as usual treatment in patients hospitalized for COVID-19, regardless of the severity of the disease or any other specific characteristic of the patient.

During our study period, little information was available for prescribers, mainly coming from sporadic case reports. More recently, in a larger cohort study, Ibrahim et al. [28] demonstrated that intravenous NAC significantly improved disease conditions in 10 severe ventilator-dependent COVID-19 patients, aged 38 to 71 years, including one with glucose-6 phosphate dehydrogenase (G6PD) deficiency. Their IV administration of NAC significantly reduced inflammation. Eight patients were eventually discharged, and two remaining patients showed improvement.

Of interest, several clinical trials using NAC in COVID-19 have been registered, although many of them have not recruited patients yet, and only one has ended. [29]

Emerging and rapidly evolving diseases such as COVID-19 are best understood using readily available, population-based registries with updated follow-up information, before evidence is compiled via randomized trials. In this context, the combination of Real-World Data (RWD) with Big Data analytics/Artificial Intelligence (AI) holds the potential to increase our understanding of COVID-19 in a timely fashion and help identify new therapeutic intervention strategies. A chief data source with the above characteristics is the clinical information contained in patients' EHRs. Thus, in our study we reuse the clinical information contained in the EHRs of a large COVID-19 population to evaluate the prognosis and clinical outcome of patients treated with NAC. The inclusion or not inclusion of NAC for all patients in the protocols reduces the bias of selection by the characteristics of the patients and can be evaluated as an effect added to standard treatment at this moment.

In our study, the use of NAC, corticosteroids and enoxaparin were associated with lower mortality. Dexamethasone and metilprednisolone were used almost from the very beginning in patients with pneumonia due to COVID-19, but its effect on mortality was confirmed later in randomized controlled clinical trials [30] Our results confirm in real-life a favorable effect of NAC regardless the concomitant use of corticosteroids. The use of enoxaparin, mainly for preventive purposes, is also being investigated in clinical trials, especially considering its potential side effects, although our results also suggest a clear beneficial effect. [31]

On the contrary, the negative association observed with the anticoagulant treatment with acenocoumarin justifies a careful use in these patients and specific studies with this medication. In our study we did not explore other drugs initially used in COVID-19, since some were quickly eliminated from clinical guidelines due to lack of efficacy (lopinavir and ritonavir, etc.) and in other cases, their use has not been regular throughout our study period (Remdesivir, etc.).

Our research has several limitations: our study is observational, and therefore, it is merely hypothesis-generating waiting for new evidence. Very recently, in an Intermediate Respiratory Care Unit with 274 patients suffering from severe respiratory failure due to viral pneumonia caused by SARS-CoV-2, Heili-Frades, et al. reported consistent results. [32] However, in both cases, recommendations cannot be drawn, for which a controlled clinical trial would be required. Our large study base of 19.208 COVID-19 patients with available EHRs is verifiable and includes their full clinical management without selection bias since we collected information from the entire population. Another limitation is missing information. Natural language processing of free text from EHRs is an advanced and established tool, comprehensive and quick, but it depends on the original quality of the clinical reports, which often do not collect full patient information. Because this is not a study based on a strict registry of variables collected in a protocolized research form, some values may not be adequately documented. Specifically, in this study we have only included the information about which we have the assurance that it is of high quality and of great clinical relevance, but information on height/weight, smoking and other variables would have been welcome.

Finally, as of November 2021, several variants of the original SARS-CoV-2 have been identified and circulate globally at different speeds by country/area. The now labeled Delta variant (formerly as B.1.617.2 in Pango Lineage), initially identified in India in October 2020, is the predominant variant of concern, [33] and it is fair to believe that NAC might have the same type of effect in COVID-19 patients affected by Delta than with any other variants.

We conclude that oral treatment with NAC at a high dose in COVID-19 admitted patients was associated with significantly lower mortality despite these patients being older, more frequently male and comorbidities. Due to its favorable safety profile, our data support further exploring the use of NAC in hospitalized patients with COVID-19 for severe pneumonia, in other settings and eventually with a higher level of evidence with randomized controlled clinical trials.

Author biographies

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José Luis Izquierdo is the chief of Pneumology at the Servicio de Neumología of Hospital Universitario de Guadalajara and a Full Professor of Medicine at Universidad de Alcalá (Madrid), both in Spain. Previously he had a clinical and fellowship at de McGill University (Montreal, Canada). He has 260+ publications mainly in COPD H index (google scholar) 39.

Joan B Soriano works at the Servicio de Neumología of Hospital Universitario de la Princesa and is an Associate Professor of Medicine at Universidad Autónoma de Madrid, both in Madrid, Spain. He has 390+ publications in PubMed in the fields of clinical epidemiology and treatment of respiratory and tobacco-related disease, and a SCOPUS Hirsh index of 81 with 39,000+ individual citations. In May 2011 he received the Josep Trueta Award for scientific and medical achievements, and in 2014 he was appointed Fellow of Chest and Foundational Fellow of the ERS. Just like many others, since February 2020 Joan has recently suffered a covidization of his research (PMID: 32719486). He just served in 2021 as a Senior Consultant of the COVID-19 Clinical Management Team, at the headquarters of the World Health Organization, based in Geneva, Switzerland.

Yolanda González is a full-time employee of Savana®. Founded in 2014, it is an international medical company that has developed a scientific methodology that applies artificial intelligence (AI) to unlock all the clinical value embedded within Electronic Medical Records (EMR) free-text.

Sara Lumbreras holds a PhD and an MSc Eng. in Industrial Engineering and Systems Modelling. She is a professor at the Institute for Research in Technology and teaches at the Industrial Management Department at the ICAI School of Engineering and the Financial department at the ICADE School of Business and Law. She is currently Deputy Director of Research Results at the Institute of Research in Technology. Her research focuses on the development and application of decision support techniques for complex problems, including the health sector, the energy sector and finance. She works with classical optimization techniques (such as Benders' decomposition), metaheuristics and artificial intelligence. She has authored over 50 academic publications and led or participated in more than 20 projects in collaboration with private companies and also institutions like the European Commission. In addition, she develops a line of research in philosophy of technology and the implications of artificial intelligence in anthropology. She was chosen as a Global Shaper of the World Economic Forum and a Marshall Memorial Fellow.

Julio Ancochea is the head of the Pneumology Department of Hospital Universitario de la Princesa (HUP) since 2000, and he is tenured Professor of Medicine at Universidad Autónoma de Madrid, both in Madrid, Spain. Between 1994 and 1998 he was the Medical Director of HUP. He is the author of several publications, which include 10 books, 62 book chapters and nearly 300 articles published in international and national journals, director of 36 PhD courses and 14 PhD theses. He was a professor and guest lecturer at more than 500 courses and conferences and principal investigator in more than 35 clinical trials. He has received several awards, such as the Doctor of the Year (2007), Spanish Patient Forum Award (2009), Social Commitment Award from the Spanish Society of General and Family Medicine (2010), ASOMEGA/Madrigallego Gold Award for Merit in Medicine (2010), Pneumologist of the Year (NeumoMadrid, 2010), award for innovation and progress in the field of Pneumology (NeumoMadrid, 2013), award for Galician Health Personality (2014), award for the Spanish Doctor with the best reputation in the speciality of Pneumology (MRS, 2014) and award for Social and Health Personality of the Year (NeumoMadrid, 2016).

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Footnotes

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