

How to overcome cardiovascular challenges in COVID-19 patients: a guide for common practice

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Summary. The COVID-19 epidemic initially started in Wuhan, China in December 2019 due to SARS-CoV-2. SARS-CoV-2 is genetically similar to the bat beta-coronavirus genus, but the novel specie of this genus can infect humans. The most common clinical features of COVID-19 are fever, cough, myalgia, fatigue, expectoration, and dyspnea. The primary reported mortality rate was about 2-3% in China; however, it reached up to 10% among patients with underlying cardiovascular diseases. The primary epidemiological investigations showed a high prevalence of underlying cardiovascular diseases in more than 40% of infected patients. A high prevalence of hypertension, ischemic heart disease, and diabetes were reported among deceased patients in Italy. Previous experiments in different pandemic situations showed that the cardiovascular system has been affected in many ways. Previous studies on SARS-CoV and MERS-CoV reported that cardiovascular co-morbidities had a direct correlation with the risk of infection, the severity of disease, and the mortality rate. Therefore, brief and available protocols for controlling the negative effects of this novel respiratory infection on the cardiovascular system, especially in a high-risk populations with underlying cardiovascular conditions, is one of the most serious concerns among healthcare providers. Herein, we aimed to review the available data on the cardiac manifestation of COVID-19. Besides, we described useful maps for the better treatment of COVID-19 infection in patients with underlying cardiovascular conditions, as a high-risk group of patients. (www.actabiomedica.it)

Key words: COVID-19, SARS-CoV-2, Cardiovascular disease, Heart; Severe Acute Respiratory Syndrome

Introduction

The COVID-19 epidemic initially started in Wuhan, China in December 2019 (1). Although the first origin of this outbreak was in china, it rapidly spread all over the world in less than 30 days (2). The virus was then named SARS-CoV-2 in February by the WHO and the disease caused by the virus was named COVID-19(3). Exponentially new cases of COVID-19 continued to rise and this disease spread all around the world and create a new pandemic(3). As of May, 24th, 2020, about 5,205,000 people struggled with this new type of coronavirus family all around the world,

and also around 338,000 deaths have been recorded according to the 125th situation report published by the world health organization (WHO)(4).

SARS-CoV-2 is genetically similar to the bat beta-coronavirus genus, but the novel specie of this genus can infect humans. Contrary to SARS-CoV and MERS-CoV, COVID-19 is highly contagious among humans (5, 6). The most common clinical features of COVID-19 are fever, cough, myalgia, fatigue, expectoration, and dyspnea (7, 8). The overall fatality rate, according to Chinese evidence, is about 2% and it reached up to 8% in the elderly (2). Also, it shows a predilection for the male population, especially elderly

males with underlying disorders, including cardiovascular diseases (CVDs) (9).

Although the primary reported mortality rate was about 2-3% in China, it reached up to 10% among patients with underlying cardiovascular diseases (10). The primary epidemiological investigations in Italy showed a high prevalence of underlying cardiovascular diseases in more than 40% of the infected patients (10). A high prevalence of hypertension (HTN), ischemic heart disease, and diabetes were reported among deceased patients in Italy (10). In addition, they showed a higher prevalence of underlying cardiovascular diseases among ICU admitted patients due to coronavirus infection (10).

Previous experiments in different pandemic situations showed that the cardiovascular system has been affected in many ways. Previous studies on SARS-CoV and MERS-CoV reported that cardiovascular co-morbidities had a direct correlation with the risk of infection, the severity of disease, and the mortality rate (11). Therefore, brief and available protocols for controlling the negative effects of this novel respiratory infection on the cardiovascular system, especially in a high-risk populations with underlying cardiovascular conditions, is one of the most serious concerns among healthcare providers. Herein, we aimed to review the available data on the cardiac manifestation of COVID-19. Besides, we described useful maps for the better treatment of COVID-19 infection in patients with underlying cardiovascular conditions, as a high-risk group of patients.

Cardiovascular complications of COVID-19 infection

Myocardial infarction (MI) is one of the most serious cardiac complications of viral respiratory infections. It was first detected in influenza pandemic in 1990 (10). However, in seasonal outbreaks of the influenza the sporadic cases are detected, yet (10). In this situation, viral infections provide a suitable condition for the peeling of the coronary plaques via inducing inflammatory cytokine. So, these plaques are exposed to thrombotic materials in vessels (2). This complication is also probable in patients with acute respiratory syndrome due to COVID-19 (2)

Acute heart injury is also among the major complications after the severe type of COVID-19 infection (11). The SARS-CoV-2 virus not only injures the lung but also attacks other tissues, including heart (2). Non-ischemic myocardial injury, which is detected by high levels of cardiac troponin, is the result of acute heart injury in these patients (12). Recent studies in COVID-19 patients reported high levels of hs-cTn in more than 46% of deceased patients, while high levels of hs-cTn were detected only in 1% of the survivors. Furthermore, it seems not only the level of troponin at the onset of the infection in the non-survivor group was higher, but also the troponin augmentation was faster and more notable in this group (12). Myocarditis is also a common form of myocardial injury among these patients. In a recent retrospective study, myocarditis was considered as a reason for death in 33% of deceased patients due to COVID-19 (13). Chest pain and dyspnea were common among the subjects of COVID-19 myocarditis. In their chest X-rays, enlargement of the heart could be detected. Their CT-scan showed heart enlargement and pleural effusion which shared common features with COVID-19 pneumonia. In some cases, ST-segment elevation and increased level of cardiac troponin were also present that could be the features of myocardial infarction without coronary vessel obstruction (14). The echocardiography in the subjects of COVID-19 myocarditis showed a significant reduction of left ventricular systolic function (14). In these patients, diuretic agents, including Furosemide and Torsemide could decrease the preload, and Norepinephrine could improve the blood pressure. Prednisolone (200 mg/day, 4 days) also reduced inflammatory responses. Finally, milrinone improved myocardial contractility (14).

Vascular complications were also observed. In one study, small and mid-sized pulmonary artery thrombosis was observed in post-mortem biopsies of COVID-19 cases (15).

Cardiac arrhythmia was another less common cardiac complication of COVID-19. This complication usually presented with tachycardia and heart palpitation and was mostly detected in ICU admitted patients with severe pneumonia (13).

Anti-viral treatments for COVID-19 and possible cardiovascular side-effects

Currently, the US Food And Drug Administration (FDA) does not strongly approve any specific medication for COVID-19 treatment(16, 17). However, to date, mechanical ventilator support and supplemental oxygen have been strongly recommended in critical cases (16). Also, several investigations have attempted to find and suggest solutions with many pharmaceutical agents (16). Primarily data reported antiviral effects of hydroxychloroquine and chloroquine invitro against COVID-19 (18). Therefore, chloroquine and Hydroxychloroquine are among the first drugs used as treatment options of COVID-19 infection in clinics (16, 18). These agents are antimalarial drugs that have been used in autoimmune diseases such as lupus erythematosus and rheumatoid arthritis (19). Although the side effects of hydroxychloroquine are lower than those of other quinine analogs, there is a narrow margin between therapeutic and toxic doses in quinine analogs (20, 21). Thus, NIH guideline is against the use of those drugs outside of clinical trial and hospital setting due to the toxicity of high dose levels (16). The toxic dose of hydroxychloroquine leads to serious cardiovascular issues (such as polymorphic ventricular tachycardia due to long QT-interval and cardiomyopathy) and underlying CVD could accelerate the toxicity of hydroxychloroquine (22). However, the therapeutic and effective dosage of this medication currently is not clear(18). As for chloroquine, 500 mg oral usage, every 12 h was reported in most of the literature. Additionally, for hydroxychloroquine, 400 mg twice a day was used on the first day and continued 200 mg twice a day for about 5 days (23, 24). However, a recent multinational observational COVID-19 study by Mehra et al. showed that quinine analogs not only are not associated with survival of hospitalized patients but also the risk of de novo ventricular arrhythmia was increased in those patients (25). Therefore, it seems that quinine analogs not only have no benefits but also have even many risks (25).

Lopinavir, an aspartate protease inhibitor used in the Human Immunodeficiency Virus (HIV) type 1, is another antiviral drug used as a potential option for the treatment of COVID-19 (26). Combination ther-

apy of Lopinavir and Ritonavir (Kaletra) also showed a positive effect in mitigating respiratory manifestation of SARS-COV and MERS-COV (27). Therefore, the primary published studies suggested that this combination therapy could also be effective in COVID-19 pneumonia (1). Kaletra helps to increase the half-life of Lopinavir against the P450 enzyme (26). Nevertheless, Kaletra has several side effects that could lead to the interruption of treatment (16). QT prolongation is the serious cardiac side effect of this drug. This side effect is often detected in the long-duration of treatment with this agent (26). In this regard, a published trial showed that lopinavir-ritonavir combination treatment does not have a significant effect on the treatment of severe COVID-19 patients and cannot reduce mortality rates(28). Therefore, more cautions must be paid to using this medication(28).

Ribavirin is a nucleoside analog with a wide spectrum of antiviral effects (29). The addition of Ribavirin to Kaletra was previously suggested as a measure to decrease the risk of acute respiratory distress syndrome (ARDS) and mortality in COVID-19 subjects(16, 30). However, nowadays is not recommended as a treatment regimen for COVID-19 patients(16, 28). The important general point in the case of ribavirin usage is that it should be administrated in combination with Interferon- α (30). Although Interferon- α has been used in the treatment of COVID-19 myocarditis (31), some cardiac events including sick sinus syndrome were reported for the combination of ribavirin and Interferon- α (32).

Favipiravir has also been reported to exert a promising effect on SARS-CoV-2 (33). Primary studies reported a better antiviral effect of thoracic CT imaging in the improvement of COVID-19 patients compared to Kaletra (18, 33). Nevertheless, there are many limitations to the effect of favipiravir in COVID-19 patients(18). Moreover, this drug showed many adverse cardiovascular side effects in previous studies (18). Favipiravir can interact with anticoagulants, statins, and antiarrhythmic drugs. It may also cause severe hemolytic anemia (34).

Remdesivir is another antiviral agent with a broad-spectrum effect (35). Among the candidate therapeutic pharmaceutical regimens, this drug is effective in COVID-19 treatment in vivo and in vitro

(36). Hence, improvement of COVID-19 patients with Remdesivir is supported by several studies and clinical trials data support the effectiveness of this medication (35). Therefore, based on these findings, the US FDA published an authorization that allows the emergency use of Remdesivir as an investigational therapy choice (35). However, many other clinical trials should be designed for justifying the use of these drugs (35). In the case of Remdesivir usage, Hypotension, and arrhythmia must be considered as the possible cardiovascular side effect of this drug (34).

Cardiac consultation for COVID-19 patients with underlying HTN

Analysis of deceased cases of COVID-19 showed that HTN is a major co-morbidity in these patients (7). Furthermore, a study in Hubei, China showed that 30% of the patients with COVID-19 had HTN as a co-morbid condition (7). The epidemiological evidence in China estimated the mortality rate of 6% among patients with HTN (37).

The role of Angiotensin-Converting Enzyme 2 (ACE2) as a receptor for SARS-COV-2 in the lung cells leads to the hypothesis that over-expression of ACE2 receptors in patients with underlying HTN may exacerbate the outcome in this high-risk group (38). However, more basic and clinical investigations are needed to detect the role of HTN in the prognosis of COVID-19 infection (13). Although there is no evidence to confirm the correlation of ACE2 receptor expression and the mortality rate or severity of the infection in the patients with COVID-19 (39), some investigations showed the correlation of the usage of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II receptor blockers (ARBs) with the more severe outcome and death (40). Some previous limited studies on the role of ARBs in SARS-CoV-2 reported that these agents possessed a positive protective role against SARS-CoV-2 infection with lung involvement (11, 41). Whereas, some other studies believed that ACEI and ARBs could upregulate ACE2 receptors and make the patients more prone to SARS-CoV-2 infection (42). We could not ignore this fact that these drugs are prescribed in patients with car-

diovascular co-morbidities and old ages, a more prone population to COVID-19 infection (43). Overall, the recommendations about the administration of these drugs are conflicting. It seems that the discontinuation of these drugs may exacerbate the underlying condition such as HTN and heart failure, two of the important co-morbidities in COVID-19 subjects (41). However, there are some reports which showed better outcome with the discontinuation of these agents (42). More studies are needed to fully clarify the role of these drugs in infected patients with SARS-CoV-2 (18).

The other important point in hypertensive patients is the interaction between the antiviral agents and anti-hypertensive drugs, including ACEIs and ARBs. Kaletra has been shown to increase the serum concentration of Valsartan and decrease the serum concentration of Losartan (44). Most diuretics can safely be continued, except Indapamide which needs dose-adjustment in the co-administration with Kaletra. Eplerenone and Spironolactone are two major members of anti-mineralocorticoid agents. Eplerenone is contraindicated in COVID-19 patients treated with Kaletra; however, it seems that spironolactone is safe (44). The dosage of Amlodipine, as another common antihypertensive drug, should be reduced in the co-administration with Kaletra (44).

It is recommended that the infected patients with emergent HTN be admitted in the intensive care unit (ICU). Due to several stressors, such as pain and anxiety, the available anti-anxiety drug (such as Oxazepam and Lorazepam) and analgesic agents (such as Paracetamol) should be administered. Sodium-nitroprusside can be a safe choice in emergent HTN in ICU; however, the dosage of Labetalol and Nicardipine needs to be adjusted in the co-administration with Kaletra (44).

Cardiac consultation for COVID-19 patients with underlying heart failure

According to epidemiological studies, heart failure (HF) accompanies with poor prognosis in COVID-19 cases (12). Previously, HF was reported as an indicator of poor prognosis in viral respiratory infection, including influenza (45). On the other hand, it has been

shown that most of the mortalities due to influenza occurred in patients with cardiovascular disease, especially HF (10). HF and Cardiomyopathy is not just a co-morbidity in these patients. Studies showed that HF has been detected in 23% of infected patients with COVID-19. Moreover, it seems that COVID-19 accounts for the exacerbation of HF, and in rare cases, triggers the new onset of HF (13).

Beta-blockers are common agents prescribed in HF patients (12). Hydroxychloroquine, by inhibiting the CYP2D6, leads to an increase in the serum concentration of beta-blockers. Therefore, frequent monitoring of heart rate and blood pressure are recommended. Also, Kaletra increases the serum level of Beta-blockers and Calcium channel blockers. Thus, dose-adjustment and accurate monitoring of heart rate and blood pressure in these patients are recommended, except for Bisoprolol which does not need ECG monitoring. Digoxin is another agent, frequently used in HF patients. Kaletra could also increase the serum level of Digoxin. So, monitoring the digoxin level and adjusting its dosage is of importance (44).

Ivabradine, another drug used in HF patients, should be eliminated from the drug list of COVID-19 patients treated with Kaletra. Also, in case of appropriate indication for the use of Sacubitril-Valsartan, its dosage should be reduced in co-administration with Kaletra (46-48).

The flu vaccination is also recommended in patients with Heart Failure (HF). It appears that this prevention against influenza infection helps the patients to decrease their anxiety because of the similar manifestations of influenza with COVID-19 (10).

Cardiac consultation for COVID-19 patients with underlying coronary artery disease (CAD) / Ischemic heart events

Acute myocardial infarction is a life-threatening cardiovascular event with a high mortality and morbidity rate (49). Primary percutaneous coronary intervention is considered as an effective and recommended therapy in these patients (49).

Because of COVID-19 pandemic and growing numbers of infected patients and an ever-increasing

necessity for ICU and ward beds, the major portion of elective procedures are delayed (50). About catheterization, it is important to recognize the urgent cases from elective ones (50). Especially in patients who need to be hospitalized for more than two days, the exposure to infected patients will increase. In addition, the concomitant co-morbidities deteriorate the outcome in these patients (13). It is necessary to differentiate the stable cases with ischemic heart disease from unstable ones which may need urgent PCI. Postponing of elective PCIs, especially in the stable group, helps to decrease the infection, complication, and mortality rate in this high-risk group (13).

The paramount point is that high cardiac demand state due to tachycardia, fever, hypoxia, pain, and anxiety may lead to coronary plaque instability and rupture, coronary artery spasm, and acute coronary state (51). So, reducing the high demand state, correction of hypoxia, suppression of fever, and administration of anxiolytics and analgesics are recommended in this state. Beta-blockers, in the absence of contraindications, play an important role in this setting (51).

A conservative approach with full medical treatment should be the mainstay of cardiac consultation for non-ST-elevation MI (NSTEMI) (52). An early invasive strategy should be reserved for those NSTEMI in COVID-19 patients with recurrent and ongoing chest pain refractory to full medical treatment, concomitant with life-threatening arrhythmias or cardiac arrest, accompanied by acute heart failure or cardiogenic shock, mechanical complications of MI and recurrent dynamic ST-T changes, particularly intermittent ST-elevation (52). Due to less strict door-to-balloon time, SARS-CoV-2 infection should be excluded first. In postponed cases, accurate and remote follow-up is also vital (53).

STEMI is another challenging state that may occur during the admission time of COVID-19 patients. This state may be so stressful for cardiologists to make the best decision. Summarizing the limited current data for COVID-19 patients showed that primary PCI (If is available in the center) could be the best option for the patients who are not in critical state and do not have hemodynamic instability, life-threatening recurrent arrhythmias or recurrent ongoing chest pain. Thrombolytic therapy would be recommended for the other STEMI COVID-19 patients in the absence of

contraindications. For those COVID-19 patients with the diagnosis of STEMI who are in a critical illness (respiratory) setting, optimal medical therapy may be a reasonable recommendation (53).

Another issue in Acute Coronary Syndrome (ACS) patients is the need for intubation before catheterization in suspected cases of COVID-19 infection. In these cases, usually there is not enough time for a PCR-test. So, some solutions have been recommended to protect the health care personnel against suspected cases. BIPAP replacement, and contriving HEPA filter between the bag of intubation and the tube are recommended (49).

Acute coronary syndrome is not just numbered as an underlying issue in this pandemic. It appears that it is also a complication of severe forms of COVID-19 infection. In a recent interesting study by Tam *et al.*, the quality of care in hospitalized patients with STEMI was analyzed. They evaluated 7 patients who seek medical care with chest pain complain and STEMI diagnosis in the COVID-19 pandemic in terms of first symptom-onset-to-first-medical-contact time and door-to-device time. They compared the results with previous similar data from last year. They found significant delays in both parameters. It seems that a major portion of this delay was due to the provision of protection against SARS-COV-2 (49).

The drug interactions between anti-viral agents and anti-ischemic cardiovascular drugs are also considerable. The recommended anticoagulant treatment regimen in ACS is named Dual Antiplatelet Therapy (DAPT), including antiplatelet therapy with aspirin and P2Y12 receptor inhibitors (clopidogrel, prasugrel, or ticagrelor) (54).

Aspirin, as an antiplatelet agent, is considered to be safe in COVID-19 patients. In combination therapy of Kaletra and Clopidogrel, the dosage of Clopidogrel is needed to be increased (Twice daily could be a reasonable choice). On the other hand, Kaletra increases the serum concentration of Ticagrelor, so the discontinuation of Ticagrelor is recommended (44). Moreover, these antiviral agents have no drug interactions with intravenous P2Y12 inhibitor like Cangrelor. Concerning this point that Prasugrel activity is not reduced in the co-administration with antiviral agents, it is recommended as a choice among oral P2Y12 inhibi-

tor (in the absence of TIA/CVA history) beside aspirin in ACS patients (46–48).

Statins are also usual agents used in patients with cardiovascular disease, especially those with a positive history of coronary artery disease (CAD), MI, PCI, and coronary artery bypass graft (CABG). Kaletra increases the serum level of statin that may lead to rhabdomyolysis or myopathy. So, it is preferred to decrease the dosage of statins or to avoid their prescription (13). Kaletra increases the serum level of Simvastatin and Lovastatin and could cause myopathy and hepatotoxicity. Therefore, these drugs are contraindicated in combination therapy with Kaletra. Rosuvastatin and atorvastatin should not exceed 10 mg/day and 20 mg/day, respectively. Furthermore, Ezetimibe and Evolocumab could be safely administered for COVID-19 patients treated with antiviral agents such as Kaletra (55).

Besides, Kaletra increases the serum concentration of Nitrates. In urgent situations, the accurate vital signs monitoring is necessary in ACS subjects who received Kaletra in combination with Nitrates (46–48). Ranolazine should be eliminated from the drug list of COVID-19 patients with stable angina treated with Kaletra. Moreover, cardiologists should be careful with the co-administration of Ranolazine and Hydroxychloroquine to avoid QT-interval prolongation and possible Torsades de pointes (56).

Cardiac consultation for COVID-19 patients with underlying valvular heart disease (VHD) / Prosthetic valves

Unfortunately, there is no published evidence about the outcome of SARS-Co-2 in patients with underlying valvular heart diseases. So, we investigated the available data on other viral infections with respiratory systems involvement. A case report by Qian *et al.* reported that influenza infection with respiratory syndromes may increase the risk of myocarditis and atrioventricular blocks in patients with valvular heart disease (57).

Endocarditis is also one of the serious complications of VHD (58). This complication can be missed during pandemic situations. The most common complaint of endocarditis is long-term fever. Fever could

be detected in more than 90% of patients (59). Blood culture could help to distinguish endocarditis from COVID-19 infection in case of long-term fever. Experiences of previous pandemics showed that other differential diagnoses for mutual symptoms is prone to be missed. So, it appears necessary for cardiologists to pay attention to endocarditis as an unusual differential diagnosis for COVID-19 infection in case of long-term fever in patients with underlying VHD.

Warfarin is one of the most common drugs prescribed in patients with VHD or prosthetic valves. Ribavirin and Warfarin have interaction with each other. Ribavirin may reduce the efficacy of warfarin (60). Therefore, increasing the dosage of Warfarin during treatment with Ribavirin is essential. Previous studies recommended at least a 50% increase in Warfarin dosage (61). Also, Ritonavir (100mg/day) could increase the activity of P450, leading to a decrease in the serum concentration of Warfarin (62). So, the dosage of warfarin should be adjusted in the co-administration with Ritonavir. In these cases, the more frequent monitoring of INR is recommended (62). It appears that Heparin and Enoxaparin are two reasonable alternatives for warfarin among COVID-19 subjects treated with Kaletra or Ribavirin (60).

In recent years, the number of patients who underwent transcatheter aortic valve replacement (TAVR) has been increasing due to acceptable results of this approach in aortic stenosis subjects (44, 54). Aspirin is a safe choice for these patients treated with Kaletra. According to the potential interaction of warfarin and clopidogrel with Kaletra, these drugs are not recommended in the COVID-19 patients with a history of TAVR more than 3 months ago (44, 54).

As the last point, COVID-19 patients with a history of valvular heart disease, particularly mitral stenosis, are susceptible to high demand state. So, the correction of fever and hypoxia is of great value to prevent further complications.

Cardiac consultation for COVID-19 patients with underlying cardiac arrhythmia

Cardiac arrhythmia is another co-morbidity that can increase the risk of mortality and severe manifes-

tations in COVID-19 patients (7). Therefore, controlling the underlying disease is crucial to avoid further complications.

Kaletra can raise the serum concentration of most anti-arrhythmic agents. This combination therapy can lead to QT prolongation in almost all of the anti-arrhythmic agents, except Lidocaine. Adjusting the dosage of these agents and frequent ECG monitoring is the alternative for discontinuation. Discontinuation of Flecainide and Amiodarone is also recommended (63). Mexiletine and Propafenone are relatively safe in combination with Kaletra. However, frequent monitoring and dose adjustment are required. Hydroxychloroquine increases the risk of Torsades de point and QT prolongation in combination therapy with anti-arrhythmic agents (except Lidocaine). Therefore, basic ECG evaluation and frequent monitoring of ECG are recommended. Furthermore, the correction of possible hypokalemia and hypomagnesemia is highly recommended (63).

Atrial Fibrillation (AF) is also another serious issue in patients with underlying cardiovascular disease, especially in viral infection. Viral infections make patients more prone to AF and other cardiac arrhythmias. Anti-coagulant agents play an important role in the treatment of AF (64). Kaletra, as an anti-viral agent, induces CYP3A4/5. The induction of CYP3A4/5 may increase the serum level of Rivaroxaban and Apixaban (65). Due to the increased risk of bleeding, the discontinuation of these agents is recommended in this condition (65). Dabigatran, a direct oral anticoagulant (DOAC), is a reasonable and safe agent for the combination therapy with Kaletra (65). In the patients who are under warfarin therapy, dose adjustment should be considered as mentioned earlier.

Conclusion

COVID-19 shares many mutual symptoms with cardiovascular diseases. Underlying cardiovascular disease may change the protocols of COVID-19 management. Also, cardiovascular drugs have serious interactions with antiviral agents. Thus, physicians should be familiar with these interactions and other alternative drugs.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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