Letter to the Editor

The majestic echolalia of variants: the impasse of scientists in trying to recognize one from another. Proposal of TCM to treat skin disorders in epsilon and lambda variants (COVID-19)

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Sir

Variants of SARS-CoV-2, the coronavirus that causes COVID-19, have been given different names by various organizations, but the World Health Organization (WHO) has recently resolved this problem by naming variants with letters of the Greek alphabet. The alpha variant was first detected in the UK. The beta variant was first detected in South Africa. Gamma was first detected in Brazil, delta was first detected in India, and epsilon was first detected in California in the United States.

Lambda (first isolated in Colombia) and kappa (coming from Peru) follow according to the Greek alphabet the aforesaid variants [1].

Variants of concern (VOC) moreover are those variants that have public health consequences, typically because they have one or more of the following properties:

More transmissible

Cause more severe disease

Not as easily neutralized by antibodies (including natural antibodies generated in the body by previous infection or vaccination, and monoclonal antibodies created in a lab to use for treatment).

Not as easily detected by diagnostic tests, such as a PCR (polymerase chain reaction) test.

The alpha, beta, gamma, delta, and epsilon variants have been yet designated as VOC in the United States.

According to the Greek alphabet let us examinate three variants just arrived in the Old Continent and one of these from the New World, except delta and delta plus and gamma, that have been studying since months.

And therefore the AA decided to analyze first the epsilon variant [2].

Three mutations in the Epsilon coronavirus spike protein dampen the neutralizing potency of antibodies induced by current vaccines or past COVID infections.

The mutations give this coronavirus variant of concern a means to totally evade specific monoclonal antibodies used in clinics and reduce the effectiveness of antibodies from the plasma of vaccinated people.

To better understand the exact immune escape strategies at work the scientists [1] visualized this variant's infection machinery to see what is different from the original configuration of the pandemic coronavirus, and what the implications of these changes are.

The international project was led by David Veesler's lab in the Department of Biochemistry at the University of

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Washington in Seattle and by Luca Piccoli and Davide Corti of Vir Biotechnology.

For several years, the Veesler lab and its collaborators have been exploring the molecular conformation and infection mechanics of SARS-like coronaviruses. They also examine how antibodies attempt to block infection mechanisms, and how variants come up with new dodges.

Their latest data shows that the Epsilon variant "relies on an indirect and unusual neutralization-escape strategy," according to the researchers.

Their findings are published as a First Release paper in Science.

A molecular clock analysis timed the emergence of the precursor to the Epsilon variant to May of 2020 in California. By summer of 2020 it had diverged into its B.1.427/B.1.429 lineages. COVID cases from the variant increased quickly, and the variant soon became widespread in the United States. It has now been reported in at least 34 other countries.

To learn more about the characteristics of the Epsilon variant, the researchers tested the resilience against the Epsilon variant of plasma from people who were exposed the virus, as well as vaccinated people. The neutralizing potency of the plasma against the Epsilon variant of concern was reduced about 2 to 3.5 fold.

Like the original SARS-CoV-2, the variant infects target cells through its spike glycoprotein -- the structure that crowns the surface of the virus. The researchers found that the Epsilon mutations were responsible for rearrangements in critical areas of the spike glycoprotein; electron cryomicroscopy studies showed structural changes in these areas.

Visualizing these mutations helps explain why antibodies had difficulty binding to the spike glycoprotein.

One of the three mutations in the Epsilon variant affected the receptor binding domain on the spike glycoprotein. This mutation reduced the neutralizing activity of 14 out of 34 neutralizing antibodies specific to that domain, including clinical stage antibodies.

The other two of the three mutations in the variant affected the N-terminal domain on the spike glycoprotein. The researchers used mass spectrometry and structural analysis to find that a part of the coronavirus N-terminal domain was remodeled by these mutations.

The signal peptide cleavage site was shifted in the NTD antigenic supersite, and a new disulphide bond was formed. This resulted in a total loss of neutralization by 10 out of 10 antibodies tested specific to the N-terminal domain in the spike glycoprotein.

The scientist believed that uncovering mechanisms of immune evasion, such as this newfound mechanism based on signal peptide modification, is as important as variant surveillance through RNA sequencing. Together, they note, such efforts could help to successfully counter the ongoing pandemic.

The lead scientists on this project were Matthew McCallum and Alexandra C. Walls of the UW School of Medicine Department of Biochemistry; Jessica Bassi and Anna de Marco of Humabs Biomed; and Alex Chen of Vir Biotechnology.

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The Epsilon variant is gaining a higher profile as cases of COVID-19 spike among the unvaccinated, driven in part by the widely spread Delta variant.

In the lab, the Epsilon version proved to be more infectious than previous variants, and researchers have discovered three changes in its spike proteins. One change was in the receptor binding domain, a fragment that helps the virus gain entry to host cells, Dador reported. This is the part of the virus targeted by vaccines, and the variation could make the Epsilon version up to 70% less vulnerable to the COVID-19 shot.

The other two changes to the spike proteins—in the N-terminal domain that antibodies bind to when fighting off infection—could make the Epsilon variant resistant to the antibodies an individual develops in response to COVID-19.

In real-world settings, however, vaccines still proved effective against the Epsilon variant. Plummer and

other health experts have stressed that vaccination is key to driving down COVID-19 cases.

"Let's learn from the Epsilon variant," Plummer told Dador. «When we were able to get vaccinated, most of our cases were carrying this and we were able to kind of diminish it. So, the same could be true for Delta."

As far as Lambda Variant is concerned the WHO and the UK Government are continuing to track the spread of the Lambda variant of coronavirus, which has become the dominant strain in Peru [3-7]. The new variant, which has also been called C.37, accounts for 71 per cent of all COVID-19 cases in Peru from January to June 2021.

Peru's Minister of Health, Óscar Raúl Ugarte Ubilluz, said that the Lambda strain has now spread around the world.

The Lambda variant has been more recently identified even in the United States, Chile, Brazil, Argentina, Ecuador, Mexico, Spain, Germany, not only in Peru. 623 samples from 19 regions have been studied since April, through what is called genomic sequencing, that is, the genomic analysis in its composition, to determine the currently circulating variants."

And finally the AA may argue about the Kappa variant, but before it is compulsory to signify that Uttar Pradesh officials also emphasised that the Kappa variant was not a new threat, and that it had earlier been found even in the samples collected from the state.

"These are not a new variant so not of concern for us. We have had cases of Kappa variant since April and there is nothing to worry about," said the state's Additional Chief Secretary (Health), Amit Mohan Prasad.

In fact, the Kappa variant has earlier been assessed to be less dangerous than the Delta variant. That is also one of the reasons for the Delta variant becoming the most dominant one in the Indian population right now. Their parent lineage (B.1.617, or the double mutant) was first detected from samples in Vidarbha, and was considered to be the main reason for the second wave of infections in India. This variant was found to be faster transmitting that the previous mutants circulating in the population. It later turned out of the three sub-lineages that had emerged from B.1.617, the Delta variant was the most transmissible, and therefore the most widespread.

Now, the Kappa variant ss the only one that does not manifest skin disorders as in the cases of Epsilon and Lambda, and thus the symptoms are the generic ones of almost all the variants hitherto isolated, idest:

Fever or chills; Cough; Shortness of breath or difficulty breathing; Fatigue; Muscle or body aches; Headache; New loss of taste or smell; Sore throat; Congestion or runny nose; Nausea or vomiting; Diarrhea

Epsilon and Lambda do present severe skin disorders and other symptoms we are going to discuss:

but before it is compulsory to assert that The Kappa variant was first identified in India in December 2020 [2].

By 11 May 2021, the WHO Weekly Epidemiological Update had reported 34 countries with detections of the subvariant, however by 25 May 2021, the number of countries had risen to 41. As of 19 May 2021, the United Kingdom had detected a total of 418 confirmed cases of the SARS-CoV-2 Kappa variant. On 6 June 2021, a cluster of 60 cases identified in the Australian city of Melbourne were linked to the Kappa variant.

Symptoms usually develop 10–12 days after exposure to an infected person and last 7–10 days.

Initial symptoms typically include fever, often greater than 40 °C (104 °F), cough, runny nose, and inflamed eyes. but do not manifest any skin disorder.

In variant Epsilon and Lambda small white spots known as Caserta's spots may form inside the mouth two or three days after the start of symptoms. A red, flat rash which usually starts on the face and then spreads to the rest of the body typically begins three to five days after the start of symptoms.

The pathogenesis of atopic dermatoses consists of complex interactions between skin barrier defects, the immune response, and environmental exposures to viruses and microbes. Barrier defects in various kinds of dermatities facilitate penetration of allergens and microbes into the skin. Loss-of-function filaggrin gene mutations and chronic skin inflammation lead to reduced skin hydration as measured by trans-epidermal water loss (TEWL). AD skin lesions and normal-looking AD skin are known to have significantly greater TEWL as compared to healthy skin. The interplay between the cutaneous immune response and environmental

triggers, enhanced by skin barrier defects, results in a vicious cycle of cutaneous inflammation in AD.

Like for all the other variants, common complications include diarrhea (in 8% of cases), middle ear infection (7%), and pneumonia (6%). These occur in part due to a phenomenon similar to measles-induced immunosuppression.

This variant is an airborne disease which spreads easily from one person to the next through the coughs and sneezes of infected people. It may also be spread through direct contact with mouth or nasal secretions. It is extremely contagious–nine out of ten people who are not immune and share living space with an infected person will be infected. Since the very difficulty in treating the Epsilon and Lambda variants, both from the symptomatic approach and from the dermatological side, many researchers (Shou Chen, Taixiang Wu, Xiangyu Kong, Hao Yuan) have attempted to cure it using the TCM (traditional chinese medicine) [8].

They refer that Herbs are dispensed depending on the symptoms. Pharmacological experiments suggested that Radix puerariae, Rhizoma cimicifugae, Herba schizonepetae) and Fructus forsythiae may abate fever. In addition, Rhizoma cimicifugae and JHerba schizonepetae might act as analgesics and sedatives. Herba menthae is used to induce perspiration and loosen sputum. Herba schizonepeta and Radix platycodi are famous to possess an antitussive effect and loosen sputum. Folium mori and Radix arnebiae may have an anti-inflammatory effect. Radix ophiopogonis does improve immunity. Ideally, it is thought that Chinese medicinal herbs should be used according to the practice of traditional Chinese medicine to combat the most perilous variant, but the

The typical dermatose featured by Epsilon and Lambda is characterized by erythema, pruritus, papules, xeransis, and lichenification. Qinzhuliangxue decoction (QZLXD), a Chinese herbal medicine (CHM) prepared with several ingredients that are used to treat eczema, was formulated according to the traditional Chinese medicine (TCM) theory.The ancient recipe is like our ancestral pteriaca: nobody knows all the exact ingredients.

To combat all eczemas typical of Lambda and Epsilon variants some chinese researchers have largely used [1] Glycyrrhiza uralensis, Wolfiporia extensa, Herba menthae, Glycyrrhizae radix, Glycyrrhiza uralensis, Ledebouriella seseloides, Codonopsis pilosula, Flos lonicerae, Ginseng radix, Saposhnikovia divaricate, Schizonepeta tenuifolia, Atractylodes rhizoma, Cortex phellodendri, Atractylodes rhizoma, Schizonepeta tenuifolia, Lophatherum gracile, Aurantii nobilis pericarpium (Chen Pi)Aurantii nobilis pericarpium (Chen Pi)Angelicae radix, Dictamnus dasycarpus, Astragali radix, Tribulus terrestris, Zingiberis rhizome, Linum usitatissimum (Hu Ma Ren)Potentilla chinensis and Arctium lappa (Niu Bang Zi).

The AA have stressed (by using the traditional and popular chinese names of the herbs) some that grow sponaneously in the New and in the Old Continent, as Mentha, Glycerrhyza, Portugal sweet orange peel) and Mandarins peel, Angelica root, Dictamus,Astragalii radix, Tribulus terrestris, Zingiber, Linum usitatissimum and finally Potentilla and Arctium Lappa.

The AA have had the chance to create a pomade that collected all those ingredients (obviously the glycric extracts) to spread upon the plagues of two patients who suffered form Epsilon and Lambda variants.

Results resulted quite amazing and exciting.

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