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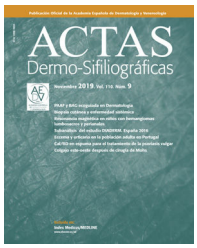

PRACTICAL DERMATOLOGY

[Translated article] Practical Guide to New Treatments for SARS-CoV-2 Infection in Dermatology Patients Being Treated With Common Immunomodulators

M. Viedma-Martínez*, G. Gallo-Pineda, D. Jiménez-Gallo

Servicio de Dermatología, Hospital Puerta del Mar, Cádiz, Spain

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Abstract Immunosuppressants and immunomodulators are widely used in dermatology. Some of these drugs, however, can increase the risk of severe COVID-19. New antivirals against SARS-CoV-2 have been shown to reduce progression to COVID-19 pneumonia in susceptible patients, but their availability is limited. On May 23, 2022, the Spanish Agency for Medicines and Medical Devices (AEMPS) updated its priority eligibility criteria for SARS-CoV-2 antiviral therapy. In this practical guide, we review the indications for these new drugs and provide guidance on which patients with mild to moderate COVID might benefit from their use in dermatology.

PALABRAS CLAVE
COVID;
Inmunosupresores;
Paxlovid

Guía práctica de las nuevas alternativas terapéuticas frente a SARS-CoV-2 en pacientes con inmunomoduladores de uso frecuente en Dermatología

Resumen En Dermatología es frecuente el uso de inmunosupresores e inmunomoduladores, algunos de los cuales pueden predisponer al desarrollo de enfermedad grave por SARS-CoV-2. Las nuevas terapias antivirales frente al SARS-CoV-2 han demostrado reducir la progresión a neumonía por COVID-19 grave en pacientes susceptibles. El pasado 23 de mayo, la Agencia Española de Medicamentos y Productos Sanitarios publicó la última actualización sobre los criterios para la priorización en el acceso precoz a estos fármacos debido a su limitada disponibilidad.

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* Corresponding author.
E-mail address: myriamdermatologiacadiz@gmail.com (M. Viedma-Martínez).

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En esta guía práctica revisamos los pacientes dermatológicos que en caso de contraer COVID-19 leve-moderada pueden beneficiarse de los nuevos antivirales, así como su indicación.

Several antivirals are available for the treatment of SARS-CoV-2 infection, but their availability is limited. On May 23, 2022, the Spanish Agency for Medicines and Medical Devices (AEMPS) updated its priority eligibility criteria for SARS-CoV-2 antiviral therapy.[1] In this practical guide, we review the indications for these drugs and provide guidance on which dermatology patients with mild to moderate COVID-19 could benefit from their use.

Immunosuppressants and immunomodulators are widely used in dermatology, but a number of these drugs may increase the risk of severe COVID-19.[2,3] New antivirals have been shown to reduce progression to severe COVID in patients on immunomodulators classified as high risk.[4] The following immunomodulators, all frequently used in dermatology, have been classified as high risk by the AEMPS (Table 1): high-dose or long-term corticosteroids; immunosuppressive drugs administered in the previous 3 months; and certain immunomodulatory biologics administered in the previous 3 months (or previous 6 months in the case of anti-CD20 therapy). Patients on immune checkpoint inhibitors and other cancer treatments that do not increase infection risk, such as targeted therapy drugs for melanoma and hedgehog pathway inhibitors, are not eligible for new antivirals according to the AEMPS priority criteria (Table 1). Finally, there are many immunomodulatory drugs commonly used in dermatology on which the AEMPS has not taken a position (Table 2). Evidence of their safety in COVID is scarce, although reports to date do not seem to indicate an increased risk of progression to severe disease. Some authors have even proposed that some of these drugs may help curb the cytokine storm induced by the virus.[5,6]

New treatment options for SARS-CoV-2 infection can be divided into 2 classes (Table 3): antivirals and monoclonal antibodies. Antivirals include nirmatrelvir/ritonavir (Paxlovid), remdesivir (Veklury), and molnupiravir (Lagevrio), which block enzymes that are crucial to viral replication.[7–9] Monoclonal antibodies include casirivimab/imdevimab (Ronapreve) and sotrovimab (Xevudy), which bind to different epitopes on the spike protein of SARS-CoV-2, preventing the virus from entering human cells.[4,10] These drugs are indicated for all patients with mild to moderate COVID-19 who do not require hospital admission and who are being treated with any of the high-risk immunomodulators mentioned, regardless of vaccination status.

Table 1 Immunomodulators Commonly Used in Dermatology Classified by Risk According to the Spanish Agency for Medicines and Medical Devices (AEMPS).

High risk	Treatment with oral corticosteroids (prednisolone) in any of the following regimens in previous 30 days: • $\geq$ 10 mg/d for > 4 consecutive weeks • $\geq$ 10 mg/d for > 10 consecutive weeks • $\geq$ 10 mg/d for > 7 consecutive days Treatment with nonbiologic immunomodulators in previous 3 months: • Oral or subcutaneous methotrexate > 20 mg/wk or > 15 mg/m^2/wk • 6-Mercaptopurine > 1.5 mg/kg/d • Azathioprine > 3 mg/kg/d • Cyclosporine • Mycophenolate • Tacrolimus • Sirolimus • Everolimus Treatment with any of the following immunomodulatory biologics in previous 3 months (or 6 months in the case of anti-CD20 therapies): • Anti-CD20 monoclonal antibodies: rituximab • Anti-CCR4 monoclonal antibodies: mogamulizumab • T-cell inhibition fusion proteins: abatacept • Interleukin 1 inhibitors: anakinra, canakinumab, and rilonacept • Anti-CD52 monoclonal antibodies: alemtuzumab • Protein kinase inhibitors: imatinib • Janus kinase inhibitors: tofacitinib, baricitinib, upadacitinib
Low risk	• Immune checkpoint inhibitors: pembrolizumab, nivolumab, avelumab, cemiplimab • Targeted therapy drugs: dabrafenib-trametinib, vemurafenib-cobimetinib, encorafenib-binimetinib • Hedgehog pathway inhibitors: vismodegib, sonidegib

Table 2 Immunomodulatory Drugs Used in Dermatology That Have Not Been Classified by the Spanish Agency for Medicines and Medical Devices (AEMPS).

Immunomodulatory drugs	Target
Adalimumab, etanercept, infliximab, certolizumab	TNF-α
Dupilumab	Interleukin 4/13
Tocilizumab	Interleukin 6
Ustekinumab	Interleukin 12/23
Ixekizumab, secukinumab, brodalumab	Interleukin 17
Guselkumab, tildrakizumab, risankizumab	Interleukin 23
Omalizumab	Immunoglobulin E
Apremilast	Phosphodiesterase 4

Table 3 New Treatment Options for SARS-CoV-2 Infection.

Drug	Type	Time of administration	Administration route	Dosage
Nirmatrelvir/ritonavir Paxlovid	Antiviral	First 5 days	Oral	300 mg nirmatrelvir + 100 mg ritonavir every 12 h, 5 d
Remdesivir Veklury	Antiviral	First 7 days	Intravenous	Day 1: 200 mg Days 2 and 3: 100 mg
Molnupiravir (Lagevrio)	Antiviral	First 5 days	Oral	800 mg every 12 h, 5 d
Casirivimab/imdevimab Ronapreve	Monoclonal antibodies	First 7 days	Intravenous or subcutaneous	600 mg casirivimab + 600 mg imdevimab, single dose
Sotrovimab Xevudy	Monoclonal antibodies	First 5 days	Intravenous	500 mg, single dose

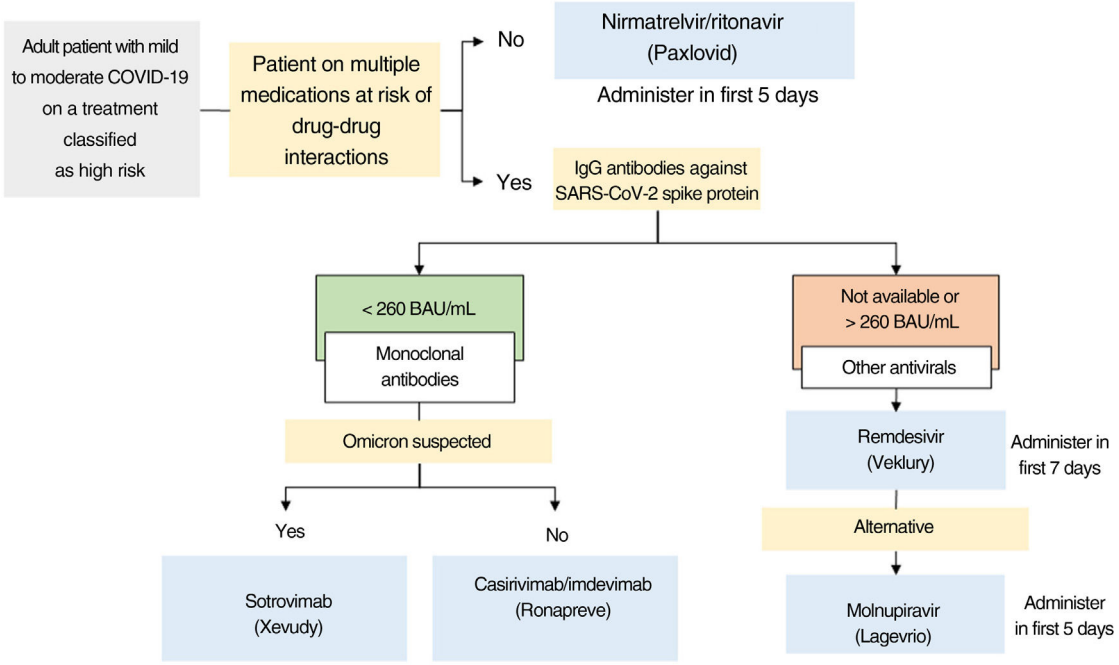

Figure 1 Treatment algorithm for new antivirals against SARS-CoV-2 in adults (adapted from Spanish Agency for Medicines and Medical Devices [AEMPS] guidance). BAU indicates binding antibody units; Ig, immunoglobulin.

For adults (Fig. 1), the AEMPS recommends nirmatrelvir/ritonavir for 5 days as the treatment of choice because it is effective, easy to prescribe, and readily accessible. Drug-drug interactions are the main contraindication, as ritonavir is a strong inhibitor of cytochrome CYP3A.[7] Choice of drug for patients in whom nirmatrelvir/ritonavir is contraindicated (Table 4) depends on immunoglobulin G titers against the SARS-CoV-2 spike protein. Monoclonal

Table 4 Drug Interactions with Paxlovid (Based on Summary of Product Characteristics).

Main active ingredients that are contraindicated with paxlovid			
Fusidic acid	Diazepam	St. John's wort	Propoxyphene
Alfuzosin	Dihydroergotamine	Lomitapide	Quetiapine
Amiodarone	Dronedarone	Lovastatin	Quinidine
Astemizole	Encainide	Lurasidone	Ranolazine
Avanafil	Ergonovine	Methylergonovine	Rifampicin
Bepridil	Ergotamine	Midazolam oral	Sildenafil
Carbamazepine	Estazolam	Neratinib	Simvastatin
Cisapride	Phenytoin	Pethidine	Terfenadine
Clorazepate	Phenobarbital	Pimozide	Triazolam
Clozapine	Flecainide	Piroxicam	Vardenafil
Colchicine	Flurazepam	Propafenone	Venetoclax
Main active ingredients that require close monitoring			
Abemaciclib	Delamanid	Itraconazole	Risperidone
Afatinib	Dexamethasone	Ketoconazole	Rivaroxaban
Alprazolam	Desipramine	Lamotrigine	Rosuvastatin
Amitriptyline	Digoxin	Levothyroxine	Salmeterol
Amlodipine	Diltiazem	Loratadine	Sertraline
Amphetamine	Divalproex	Maraviroc	Sulfamethoxazole/
Apalutamide	Efavirenz	Methadone	Trimethoprim
Atorvastatin	Encorafenib	Parenteral midazolam	Tacrolimus
Atovaquone	Erythromycin	Morphine	Tadalafil
Bedaquiline	Ethinylestradiol	Nifedipine	Theophylline
Bosentan	Everolimus	Nilotinib	Thioridazine
Budesonide	Fentanyl	Norbuprenorphine	Triamcinolone
Buprenorphine	Fexofenadine	Nortriptyline	Vinblastine
Bupropion	Fluoxetine	Paroxetine	Vincristine
Buspirone	Fostamatinib	Prednisolone	Vorapaxar
Ceritinib	Glecaprevir/pibrentasvir	Propionate fluticasone	Voriconazole
Ciclosporin	Haloperidol	Raltegravir	Warfarin
Clarithromycin	Ibrutinib	Rifabutin	Zidovudine
Dasatinib	Imipramine	Riociguat	Zolpidem

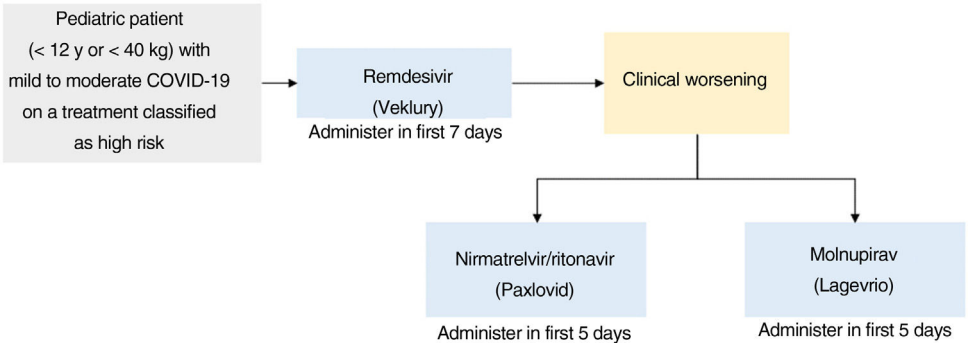

Figure 2 Treatment algorithm for new antivirals against SARS-CoV-2 in pediatric patients (adapted from Spanish Agency for Medicines and Medical Devices [AEMPS] guidance).

antibodies are the first-line option for patients with a titer of less than 260 binding antibody units per milliliter, while antivirals are indicated for patients with higher titers or for whom serology is not available. Choice of monoclonal antibody depends on the SARS-CoV-2 variant suspected. When omicron is suspected, the treatment of choice is sotrovimab, the only monoclonal antibody to have shown in vitro neutralizing activity against this variant.[11] In other cases, casirivimab/imdevimab is used. The antiviral of choice is remdesivir. When this is not available, molnupiravir, an unauthorized drug with a use recommendation from the Committee for Medicinal Products for Human Use, can be used. Monoclonal antibodies and antivirals should both be started within 5 to 7 days of symptom onset.

Remdesivir is also the treatment of choice for pediatric patients under the age of 12 years or weighing less than 40 kg (Fig. 2). Classes of drugs other than monoclonal

antibodies should be considered in patients whose condition is worsening despite remdesivir.

In conclusion, immunomodulators are a mainstay treatment for many patients in dermatology, where inflammatory and autoimmune disorders are common. Dermatologists must be familiar with the treatments available for SARS-CoV-2 infection, as some of their patients might be in a high-risk situation. We hope that this guide will help.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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