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Navigating Travel with Novel Oral JAK and BTK Inhibitors: Beyond Biologics

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Abstract

The field of immune based therapeutics for treatment of common chronic illnesses has exploded leading to significant improvement in the disease processes but a downstream impact on infections. Janus kinase (JAK) inhibitors and Bruton Tyrosine kinase (BTK) inhibitors are becoming more widely used in treatment of chronic inflammatory diseases and chronic leukemias because of simplicity of oral administration. As such, many patients will have improvement in their underlying illnesses and will have greater flexibility to travel. Thus, it is important for travel medicine practitioners to be aware of these agents, their adverse effects and impact on drug interactions and immunizations.

Keywords: Newer biological therapies, Trip planning, Vaccinations.

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Introduction

The advent of affordable air travel, the internet, and modern medications has made it easier than ever to travel the world, even for those with chronic conditions. The incidence of world travel from the United States has increased by about 30% since 2010. In 2019, about 40% of the U.S. population traveled internationally, and 89.1 million international arrivals were made to the United States [1]. The COVID-19 pandemic had a profound global impact on travel, and while travel has shown some signs of improvement, there is still a considerable decrease in travel of approximately 20% compared to the pre-pandemic time [2]. Between 43% to 79% of travelers visiting low- and middle-income countries experience a travel-associated health problem. While most of these illnesses are mild, there are cases where travelers become ill to the extent that they seek medical care from healthcare providers [3].

The utilization of biological therapies in treating cancer, autoimmune diseases, multiple sclerosis, psoriasis, rheumatoid arthritis, and inflammatory bowel disease continues to increase. Therapeutic regimens for these have evolved from requiring intravenous or subcutaneous injection of biologics to orally bioavailable small molecule kinase inhibitors such as Janus kinase inhibitors (JAKi) and Bruton Tyrosine kinase inhibitors (BTKi). In the United States, the number of patients taking JAKi and BTKi has significantly increased over the last few years [4]. In the past, people with chronic inflammatory diseases and B cell hematologic malignancies often had to choose between taking their medications and traveling, as most of the injectable biologics required refrigeration or were not available in other countries. The introduction of oral JAKi and BTKi has not only led to an improvement in their underlying illness but has also provided the benefit of enjoying travel.

JAKi blocks JAK proteins, hindering cytokine and growth factor signaling pathways, inhibiting STAT protein activation, and suppressing the immune response, aiding in the treatment of inflammatory arthritis and autoinflammatory diseases [5].

BTKi block Bruton's tyrosine kinase, inhibiting B-cell signaling, and effectively treat B-cell malignancies like CLL, Mantle cell lymphoma and Waldenström's macroglobulinemia., while also showing promise in rheumatoid arthritis and lupus treatment [6].

In this article, we aim to review the novel oral JAK and BTK inhibitors and guidance of travel precautions for patients using them.

Approach

Travel is an engaging process, often requiring different modes of transportation, varied housing arrangements, exposure to new environments and foods. These each carry potential risk. For travelers on JAKi, it's important to recognize the increased risk of thromboembolic events and prepare them to prevent deep vein thromboses. It's important for these travelers to plan for the possibility of health-related issues by either establishing a plan for local care, evacuation, or remote telemedicine if available. Since some of these medicines may not be available outside the US, it's important to have an adequate supply and to be aware of limitations to obtaining these medications abroad in the event of an extended trip or accident.

Travelers most often have concerns regarding the infectious diseases they may encounter while traveling. These most often include viral respiratory illnesses such as influenza and SARS-CoV2 but also pneumonia. Since most of these travelers would be eligible for early antiviral therapy for COVID-19, it's important to counsel them on their risks and how to mitigate them. Preventive vaccination against influenza, RSV and Streptococcus pneumonia may be helpful if they had not been administered prior to starting immune suppression. Screening for latent TB in those who travel to locations with high rates of TB should be considered post-travel. Additional protection might include the use of N-95 respirators when in limited spaces with poor air circulation and carrying self-testing kits for SARS-CoV2. With the recent FDA approval of Paxlovid (Nirmatrelvir, ritonavir), travelers may wish to carry a standby course of therapy if they test positive. It's important to counsel them on the use and interactions of this therapy before traveling.

Travelers may become exposed to a diverse group of endemic infectious diseases that vary in prevalence in different regions around the world. Their risk for infectious complications is influenced by their exposures, immunologic susceptibility, age, underlying diseases and their treatment, and immunosuppressive drugs.

Diarrhea is one of the most common illnesses experienced by travelers. Those taking JAKi and BTKi are at high risk for bacterial infections due to E coli, Campylobacter, Shigella and Salmonella associated with travelers' diarrhea. Thus, a clear discussion on risks of food and water-borne diseases is critical for these travelers. What may be a simple annoyance for some, may become a life-threatening infection for these immune suppressed travelers. As diarrhea is one of the common adverse reactions from these medications, this could delay the diagnosis and treatment of infectious travelers' diarrhea. These travelers should carry loperamide for mild diarrhea and use azithromycin in the event of moderately severe diarrhea.

Most travel clinic practitioners have limited knowledge of biologic drugs and should consult with the prescribers or infectious diseases specialists to assist with providing appropriate advice. In 2011, Ruxolitinib (Jakafi) became the first JAKi approved by the FDA, and Ibrutinib (Imbruvica), the first BTKi, in 2013. Since then, numerous JAKi and BTKi have received approval for diverse indications. As the utilization of these medications continues to grow, and a greater number of individuals on these embark on international travel, it becomes imperative for travel practitioners to have a better understanding of the medications, potential complications, risks of infections associated with their use[7, 8] (Table 1), drug-drug interactions, and the implications of vaccinations for these patients. Choosing the appropriate prophylactic treatment can be challenging for the travel physician in these patients.

Table 1: List of JAKi and BTKi, indications and adverse effects [6,7]

Drug class	Name	Indications	Risks (Infectious and Noninfectious)
JAKi	Ruxolitinib (Jakafi)	Myelofibrosis, Polycythemia vera, Rheumatoid arthritis	Tuberculosis Invasive Fungal infections, Pneumocystis Viral-Herpes Zoster, Herpes Simplex, Influenza, Hepatitis B, Hepatitis C UTI Pneumonia Nasopharyngitis Urinary tract infections Musculoskeletal/ Connective tissue disorders GI perforation (Tofacitinib) Rheumatoid arthritis (Tofacitinib/baricitinib) Embolism and Thrombosis CAD CVA Malignancy/ Neoplasms especially skin Pancytopenia Myelofibrosis and Polycythemia vera (Ruxolitinib)
JAKi	Tofacitinib (Xeljanz)	Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, atopic dermatitis, ankylosing Spondylitis, COVID-19	
JAKi	Baricitinib (Olumiant)	Rheumatoid arthritis, Alopecia areata, COVID-19	
JAKi	Upadacitinib (Rinvoq)	Inflammatory arthritis, Inflammatory bowel disease, Atopic dermatitis	
JAKi	Fedratinib (Inrebic)	Myelofibrosis	
JAKi	Abrocitinib (Cibinqo)	Atopic dermatitis	
JAKi	Pacritinib (Vonjo)	Myelofibrosis	

Drug class	Name	Indications	Risks (Infectious and Noninfectious)
BTKi	Ibrutinib (Imbruvica)	CLL, GVHD, Waldenstrom macroglobulinemia	Pneumonia Fungal-Aspergillus, Pneumocystis Bacterial- Staphylococcus aureus, Mycobacterium tuberculosis, Listeria Viral-Herpes, PML, Cytomegalovirus disease, opportunistic infections, reactivation of HBV, reactivation of latent Epstein-Barr Secondary malignancy Heart failure Atrial and Ventricular arrhythmias Hypertension Pancytopenia Lymphocytosis Major hemorrhage Liver damage
BTKi	Acalabrutinib (Calquence)	CLL, Mantle Cell Lymphoma, Waldenstrom macroglobulinemia	
BTKi	Zanubrutinib (Brukinsa)	CLL, Mantle Cell Lymphoma, Waldenstrom macroglobulinemia, Marginal Lymphoma	
BTKi	Pirtobrutinib (Jaypirca)	Mantle Cell Lymphoma (Relapse or refractory)	

There is an increased risk of viral infections such as varicella zoster, influenza, and reactivation of Hepatitis B and a lesser, but increased risk of bacterial infections such as pneumococcal and meningococcal disease[9]. Thus, the administration of Pneumococcal, meningococcal, inactivated Varicella-Zoster (RZV-Shingrix), and Hepatitis B vaccine are all recommended before starting JAKi and in travelers who did not receive them previously.

BTKi suppress the activity of macrophages involved in fungal defense [10]. Ibrutinib has been associated with infection in 56% of patients [11]. The most common invasive fungal infection associated with Ibrutinib use was Aspergillosis [12]; cryptococcosis [13], *Pneumocystis jirovecii* pneumonia[14], coccidioidomycosis[15], histoplasmosis[11], tuberculosis, cytomegalovirus and PML[16] have also been reported. Thus, preparing the traveler going to endemic areas for certain fungi (Histoplasma, Coccidiodes, Blastomyces, Paracoccidiodes, Talaromyces) may involve additional counseling. High-risk travel patients on these drugs are recommended to receive prophylaxis with Trimethoprim/Sulfamethoxazole and potentially anti-fungal regimens before travel. Since these medications are also often associated with adverse events and photosensitivity, the travel practitioner must be aware of these issues. Most of these travelers will have received testing for latent TB prior to initiation of therapy. However, it is prudent to screen for tuberculosis periodically and post-travel to endemic areas. The travel practitioner should inquire into the specific activities planned (i.e., caving, excavation, construction, forestry), as specific activities which may increase the risk of fungal and bacterial infections should be avoided. Seasonal influenza vaccination is advised with emphasis prior to travel. JAKi do not seem to inhibit the response to influenza vaccines whereas impaired responses to influenza vaccination have been noted in patients treated with Ibrutinib[17].

Immunization for SARS-CoV2 should be updated in these travelers. Hepatitis A vaccine and Tetanus booster are strongly suggested per routine travel advice.

Live bacterial (Typhoid oral) or viral vaccines (Yellow Fever, MMR, Varicella) are often avoided in immunocompromised patients. When Yellow Fever vaccine is clearly indicated, it is best to counsel the traveler on the vaccine and exposure risks. If Yellow Fever vaccine is given, it should be done 4 weeks prior to starting JAKi / BTKi and it is contraindicated in patients currently receiving them [18], so travel to a Yellow Fever endemic area should be avoided.

Due to their inhibition of immune regulatory pathways, JAKi/ BTKi drugs may increase the risk of malaria. Drug interactions between JAKi/BTKi and anti-malaria medications require careful management. Chloroquine and hydroxychloroquine, may potentially interact with JAK inhibitors, leading to unpredictable outcomes. However, Atovaquone/ proguanil (Malarone), Mefloquine, and Tafenoquine do not have significant interactions with JAKi/BTKi. Since both drugs are metabolized by the same hepatic enzymes, patients should be cautioned regarding risks of hepatitis.

Conclusions:

The knowledge required to provide effective pre-and post-travel counseling extends beyond simply the administration of vaccines and prophylactic medications. As more immune suppressed people travel, its critical to understand the mechanisms of action of these newer agents and their impact on the potential health of travelers. This article provides a review of two of the newer classes of immune modulators and the concerns for travel health practitioners.

Highlights

What Is Already Known?

The incidence of travel in patients on chronic immunosuppressants is increasing. Additionally, more people are using biologic drugs to manage their chronic conditions.

What Does This Study Add?

As immune-suppressed individuals travel more, understanding new immune modulators is crucial. This article reviews two recent classes of these agents. It discusses key issues for those managing travel health and advise on travel precautions in them.

Authors' Contributions

Both authors have contributed equally in drafting and editing the paper

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None to declare.

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