# ABOUT THE AUTHOR

## Parameswaran Nair, MD, PhD, FRCP, FRCPC

Dr. Nair graduated in 1989 from the University of Kerala Medical College in Trivandrum in India. He trained in Internal Medicine and in Respiratory Medicine at the University of Kerala, Royal Sussex County and Royal Sunderland Hospitals in the UK, and at McMaster University in Canada, where he did his doctoral thesis on leukotriene biology in asthma. He is currently the Frederick E. Hargreave Teva Innovation Chair in Airway Diseases & Professor of Medicine in the Division of Respirology at McMaster University, an Adjunct Professor of Medicine at McGill University, and a Staff Respirologist at the Firestone Institute for Respiratory Health at St. Joseph's Healthcare Hamilton. At the Firestone Institute, through inter-disciplinary clinics, he looks after patients with severe asthma and other complex airway and eosinophilic disorders, and provides access to them for biologics, molecular microbiology, novel pulmonary imaging, and bronchial thermoplasty, and opportunities to participate in research programs. His laboratory, funded by federal and provincial agencies, the Canada Research Chair program, AllerGen National Centre of Excellence, and industry partners, characterizes the types of bronchitis in airway diseases using biomarkers in sputum, identifies mechanisms of persistent bronchitis and airway hyperresponsiveness, and explores targeted therapies using small molecules and biologics. The patient-centred translational research program has been recognized by the Fellowships of the Canadian Academy of Health Sciences, the European Respiratory Society and the American College of Chest Physicians, the ATS Ann Woolcock Award, and the Asthma Society of Canada Bastable-Potts award, and has contributed to over 300 peer-reviewed publications (H-index 67, >21,000 citations) in major respiratory, allergy, and general medical journals. These observations, including 6 publications in the New England Journal of Medicine, paved the way for the development and approval of biologics that are currently available to treat patients with severe asthma.

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# SEVERE ASTHMA PHENOTYPES: CHALLENGES AND OPTIONS FOR CONTROL

## Introduction

The practice of medicine has evolved from "arm-chair medicine" through "evidence-based medicine" to "precision medicine". Medical literature has seen a proliferation of the use of the phrases "precision medicine" and "personalized medicine," with little distinction made between the two. While both strategies promote individualizing patient care, precision medicine is guided by information based on the genes, proteins, metabolites, and other biomarkers in the human body. In addition to these biological markers, personalized medicine would consider various social, economic, behavioural, and environmental factors that might be specific to a particular individual in planning a treatment strategy unique to that individual. The term P4 Medicine (Predictive, Preventive, Personalized and Participatory) has also been proposed to reflect the increased understanding and implications of the pathobiology of disease on management strategies.[1] The use of biologics and cell-based therapies, particularly in cancer therapeutics, has demonstrated the power of these strategies.[2] This brief review will focus on how this strategy is currently being applied in the management of severe asthma.

## Definition of Phenotypes and Endotypes

A precise understanding of the pathobiology of disease and definitions is paramount to the practice of personalized medicine. The concept of "nominalism" as opposed to "essentialism" of asthma definitions is helpful to understand the mechanisms of disease and to identify the "treatable traits" that contribute to asthma symptoms and severity in individual patients.[3] This involves identifying obvious clinical and physiological features (generally referred to as phenotypes),[4] and specific biological characteristics that provide unique mechanistic insights (generally referred to as endotypes).[5] These characteristics are generally identified based on unbiased hierarchical cluster analysis from data collected from large numbers of well-characterized patients in various cohort studies and cross-sectional studies.

Therefore, phenotypes include features such as: "early-onset or late-onset asthma"; "atopic or non-atopic asthma"; "obese or non-obese asthma"; "aspirin-sensitive or non-aspirin-sensitive asthma"; "smoker or non-smoker"; "nasal polyposis-associated asthma or non-nasal polyposis-associated asthma"; and "asthma with fixed airflow obstruction or asthma with significant bronchodilator reversibility". Triggers of bronchoconstriction, including occupational vs non-occupational; virus vs non-virus; exercise; cold air; and thunderstorm-related have also been employed to define phenotypes.[6] While these clinical features are very helpful in predicting the clinical course of disease and, to some extent, responses to treatment, they do not provide precise information about the pathobiology of these features. A good example of this is so-called "exacerbation-prone asthma". The reason for exacerbation might well be inappropriate therapy afforded to the patient rather than a patient characteristic.

Conversely endotyping endeavours to provide significant biological insights into specific disease or symptom manifestations. This requires the development and validation of simple clinically relevant and useful biomarkers that might reflect the underlying biology. The most widely employed marker is the eosinophil number in circulation or in the airway secretions (sputum). The term "eosinophilic" asthma is increasingly being used to classify patients with asthma whose symptoms and severity are believed to be mediated by the eosinophil, although this may not always be the case as a raised eosinophil number alone may not indicate that the key effector cell in the pathobiology of disease in that patient is the eosinophil. Thus, the presence or absence of eosinophils or their numbers is not an endotype. The mechanisms or cytokine pathways that lead to eosinophil recruitment are what truly constitute an endotype. The use of omics platforms has enabled the identification of genes (transcriptome); proteins (proteome); metabolites (metabolome); lipids (lipidome); and environmental factors interacting with biological factors (exposome), among other factors, to further endotype asthma.[7]

## Identification of Phenotypes and Endotypes in Clinical Practice

A summary of the measurements or observations that are currently being used in our clinic at the Firestone Institute for Respiratory Health is shown in **Table 1**. Some of the examples of phenotyping guiding therapy include: "allergic asthma" responding well to allergen immunotherapy or to omalizumab; late-onset eosinophilic asthma responding well to anti-IL5

biologics; "aspirin-exacerbated asthma" responding to aspirin avoidance or aspirin desensitization; "obesity-related asthma" being associated with airway hyperresponsiveness and bronchomalacia; and "neutrophilic or non-eosinophilic asthma" characterized by susceptibility to recurrent airway infections.

Currently, there are only three biomarkers widely available for clinical use with which to gain insights into endotypes (although these markers are not precise indicators of the biology of the disease). These are total (or specific) IgE, eosinophil numbers in blood or in sputum, and the fraction of exhaled nitric oxide (FeNO). The relative merits and disadvantages of these three biomarkers have been extensively reviewed.[8-10] While raised total IgE indicates allergy, it has very limited value in predicting response to a particular biologic. A combination of clinical features such as measuring airway hyperresponsiveness, FeNO, and blood (and preferably sputum) eosinophils can reasonably guide our choice of biologics for severe asthma. There are currently seven biologics approved for use in Canada.

**Application of biomarkers and phenotyping/ endotyping to manage severe asthma**

**A. Current clinical practice**

Current clinical practice, which employs the above biomarkers, are endorsed by most National[11] and International[12] asthma guidelines including the Canadian Severe Asthma guidelines.[13] The general principles are as follows:

a) Confirm diagnosis of asthma with objective demonstration of variable airflow obstruction (peak flow, bronchodilator response or bronchoconstrictor response)

b) Commence treatment with inhaled corticosteroids and bronchodilators (long-acting anti-cholinergics and long-acting beta-agonists), after checking inhaler technique and advising on allergen-avoidance measures, and regularly encouraging adherence to prescribed therapy. Allergen immunotherapy by adequately trained physicians is also effective in patients whose asthma is driven by one or two proven allergen sensitizations.[14]

c) Most clinical trials have suggested that additional biomarkers are unlikely to make a significant difference to asthma outcomes compared to good clinical assessment and a spirometry.[15,16]

d) Increase the dose of inhaled corticosteroids and consider oral corticosteroid in patients with persistent raised blood eosinophil count (typically >300/μL). A persistently raised FeNO (typically >35 ppb), particularly when it is suppressed following a witnessed administration of corticosteroid, would indicate poor adherence.[17]

e) With ongoing symptoms indicating poor control, additional endotyping/phenotyping is recommended. Early-onset asthma, young age and history of clinical allergies, along with raised blood eosinophil or total or specific IgE, would indicate omalizumab as the next step in the therapeutic algorithm. Conversely, late-onset asthma (whether associated with IgE or not); raised blood eosinophils, particularly associated with older age; nasal polyposis; and prednisone dependence (or frequent, 3-4 or more/year) might suggest an anti-IL5 biologic as the first choice.[18] Currently available biomarkers do not help to differentiate between the three anti-IL5 biologics. A persistently raised FeNO (often >35-50 ppb) despite normalizing or modest blood eosinophil count in patients with ongoing nasal polyposis or atopic dermatitis would suggest dupilumab as the next choice of biologic. Currently, there are no unique biomarkers that would help predict response to tezepelumab. It is claimed that biologics might be effective in all asthmatics including those with normal or low blood eosinophils or low FeNO. While this might be true for patients on high doses of inhaled corticosteroids, the efficacy of tezepelumab in the truly prednisone-dependent patients is still unproven.[19]

**B. What can additionally be achieved in a research-supported environment?**

The key to managing severe asthma and practicing precision medicine is to see patients at the time they are experiencing exacerbations,[20] (rather than adhering to the standard action plan of doubling inhaled steroids, or using prednisone or antibiotics); to assess if the symptoms (and reduction in airflow, FEV1) are due to luminal obstruction by eosinophils, neutrophils, other cell types, mucus, smooth muscle constriction, or airway wall thickness (or a combination of the above); and to target the dominant process that is contributing to the pathobiology (**Figure 1a**).[21]

A baseline blood eosinophil count, while a predictor of response to ALL biologics, does not help to discriminate between the biologics, and particularly is not helpful in monitoring the response to biologics or in assessing exacerbations while on biologics.[22] Additional biomarkers that are (and can be) measured include: airway mucus (assessed by a CT mucus score);[23] sputum eosinophils and sputum neutrophils, sputum autoantibodies; sputum cytokines; and immunophenotyping. This includes assessment of primary and secondary immunodeficiencies (including whole exome sequencing), NK cell and macrophage functions, and the consequence of luminal obstruction by functional $Xe^{129}$ ventilation MRI. The application of these technologies to initiate and switch between biologics is summarized in (**Figure 1b**).

This strategy[24] provides direction for deciding between the three anti-IL5 biologics considering the intensity of sputum eosinophilia, the presence of endogenous IgG autoantibodies in sputum, NK cell dysfunction, and anti-drug antibodies. For example, intense eosinophilia in sputum (often >20%) requiring >15 mg daily prednisone and in the presence of endogenous autoantibodies, would be associated with suboptimal response to the approved 100 mg subcutaneous dose of mepolizumab in almost 50% of prednisone-dependent patients.[25] Patients with NK cell dysfunction or anti-drug antibodies might demonstrate sub-optimal response to benralizumab.[26] Patients with severe airway hyper-responsiveness without demonstrable airway inflammation are likely to best respond to bronchial thermoplasty.[27] Persistent airway neutrophilia, unless otherwise proven, indicates an airway infection and should prompt investigations for susceptibility to such infections.[28]

## C. Future Diagnostic and Treatment Modalities

Airway measurements are critical in the management of severe asthma. Point of care assessments of airway eosinophilic[29] and neutrophilic activities[30] are likely to be available for clinical use. Comprehensive assessments, using large scale omics platforms, computational analytics andtopological data analyses would precisely characterize the specific inflammatory pathways (Th2 high or Th2 low) and the airway microbiome; and develop "handprints" for individual patients (as envisaged by the U-BIOPRED program),[31,32] in order to truly individualize therapies for patients with severe asthma (**Figure 2**).

## Summary

In recent years tremendous advances in biotechnology have resulted in the development of effective medications, biologicals and technologies for bio-imaging and bio-intervention to treat patients with asthma. Currently, they are being more widely studied in adult asthmatics than in children with severe asthma. However, the same principles apply to the pediatric population.[33] What is required is to truly practice endotyping and precision medicine rather than giving perfunctory attention to this strategy. It is not possible to practice true precision medicine and to achieve optimal asthma control in every patient by solely monitoring a blood eosinophil count that is simply an overall marker of the burden of a Th2 disease. True personalized medicine requires: careful clinical examination; identifying phenotypes based on clinical characteristics; endotyping based on airway inflammatory responses and the pathways that modulate them; biomarkers and bio-imaging that reflect these processes; and selecting the appropriate therapy for the individual with consideration of their behavioural, social, economic, and environmental factors.

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| Phenotype | Investigations |
|---|---|
| **CLINICAL** | **BLOOD** |
| Atopy | CBC |
| Rhinosinusitis | Vasculitis workup |
| Obesity | Autoantibodies (blood/sputum) |
| Late-onset | B12, tryptase |
| ASA sensitivity | AAT |
| Infective bronchitis | Routine chemistry |
| **PHYSIOLOGICAL** | **IMAGING/PULMONARY** |
| Reversibility | CT/fMRI thorax |
| COPD | CT sinus |
| AHR | Echocardiogram |
| Tachyphylaxis | Full PFT |
| **INFLAMMATORY** | **HAEMATOLOGY (when indicated)** |
| Sputum eosinophilia | Bone marrow |
| Sputum neutrophilia | Cytogenetics |
| Blood eosinophilia | T-cell and receptors |
| Vasculitis | Cytokines |
| HES | |
| **CURRENT TREATMENT** | **OTHER (as indicated)** |
| Prednisone | GI (endoscopy) |
| High dose ICS | Stool |
| LABA | Skin prick test |
| LTRA | Bone density/Optometry |
| LAMA | EMG/NCV |
| Biologics | Sputum microbiome |
| Cytotoxics | FeNO |
| Antibiotics | |
| Nasal CS | **CONSULTS** |
| Sinus surgery | GI |
| Immunotherapy | Psychiatry |
| | ENT |
| **ASTHMA EDUCATION** | Allergy |
| Inhaler technique | Rheumatology |
| Compliance | Endocrinology |
| | Sleep medicine |

***Table 1*** *A checklist of biomarkers and endotyping to assess patients with severe asthma in an outpatient severe asthma clinic; courtesy of Parameswaran Nair, MD, PhD, FRCP, FRCPC*

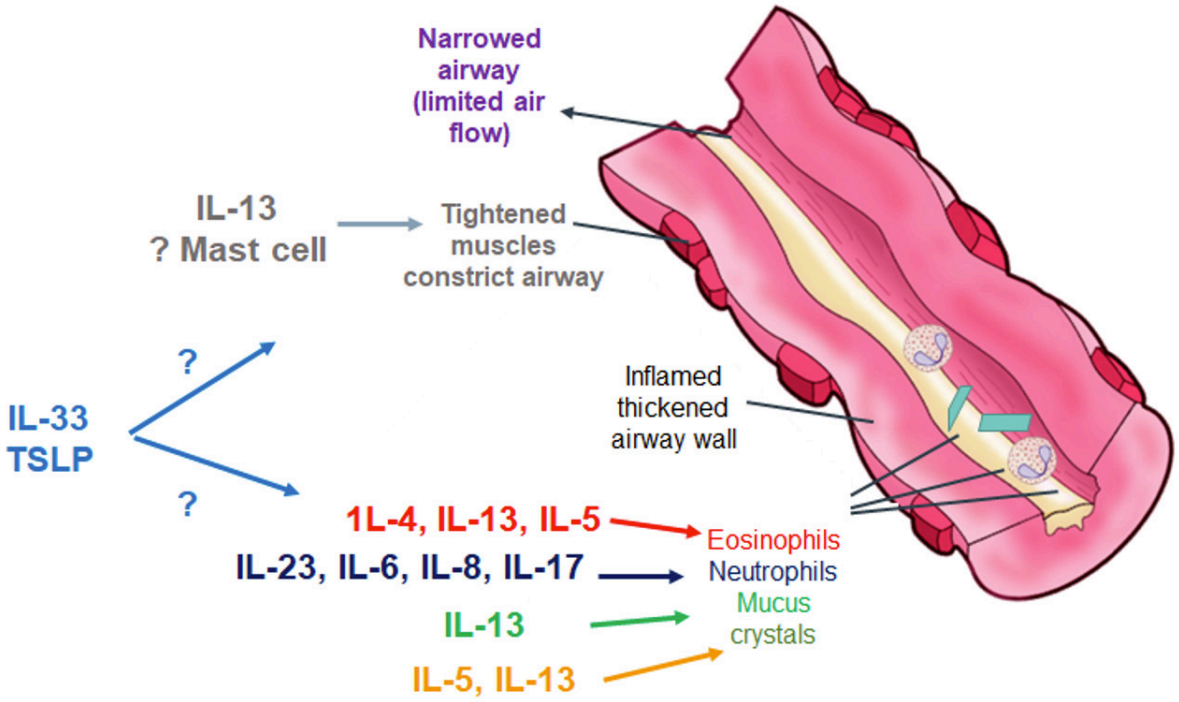


***Figure 1a*** *Contributors to severity and symptoms in asthma; reproduced with permission from Nair et al, 2021.*

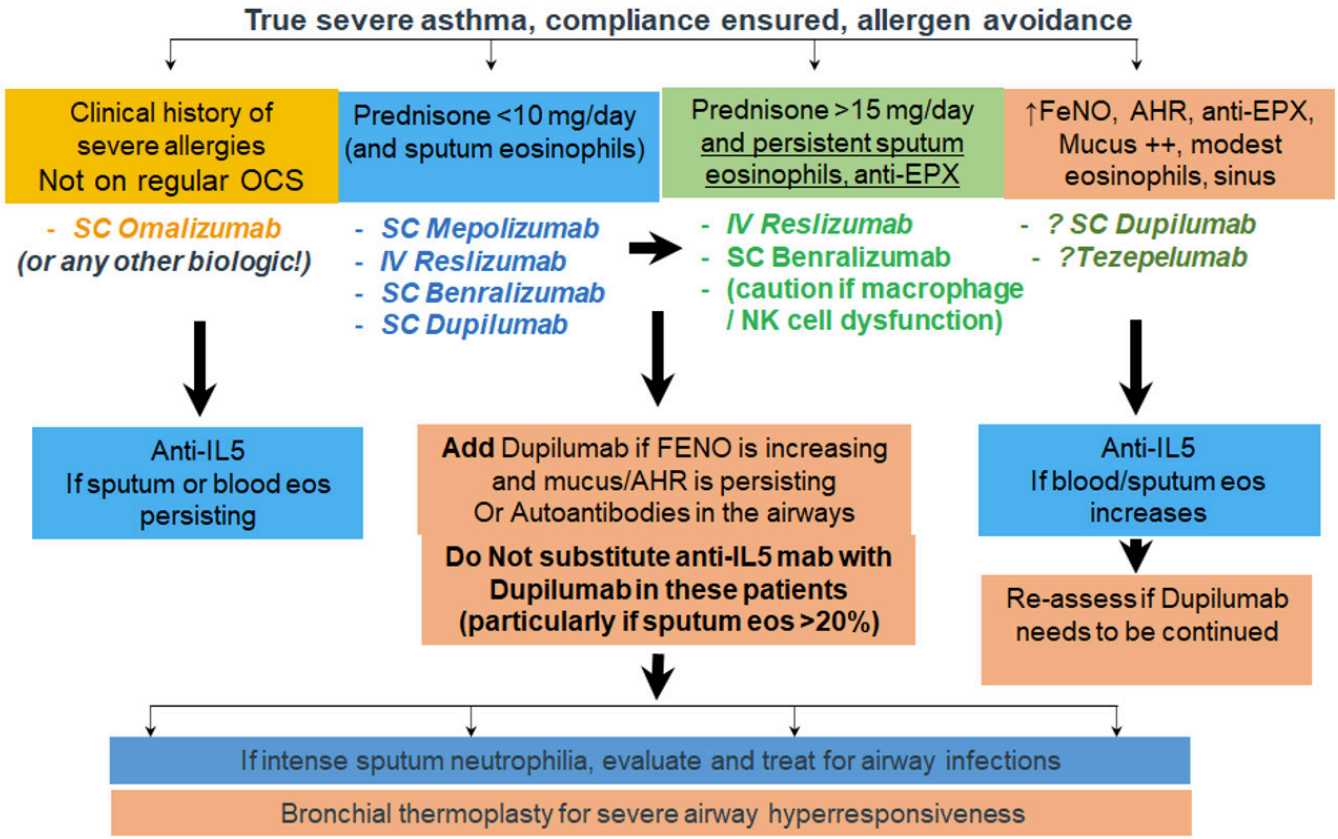


***Figure 1b*** *A strategy to initiate and switch biologics; reproduced with permission from Venegas Garrido C, et al, 2022*

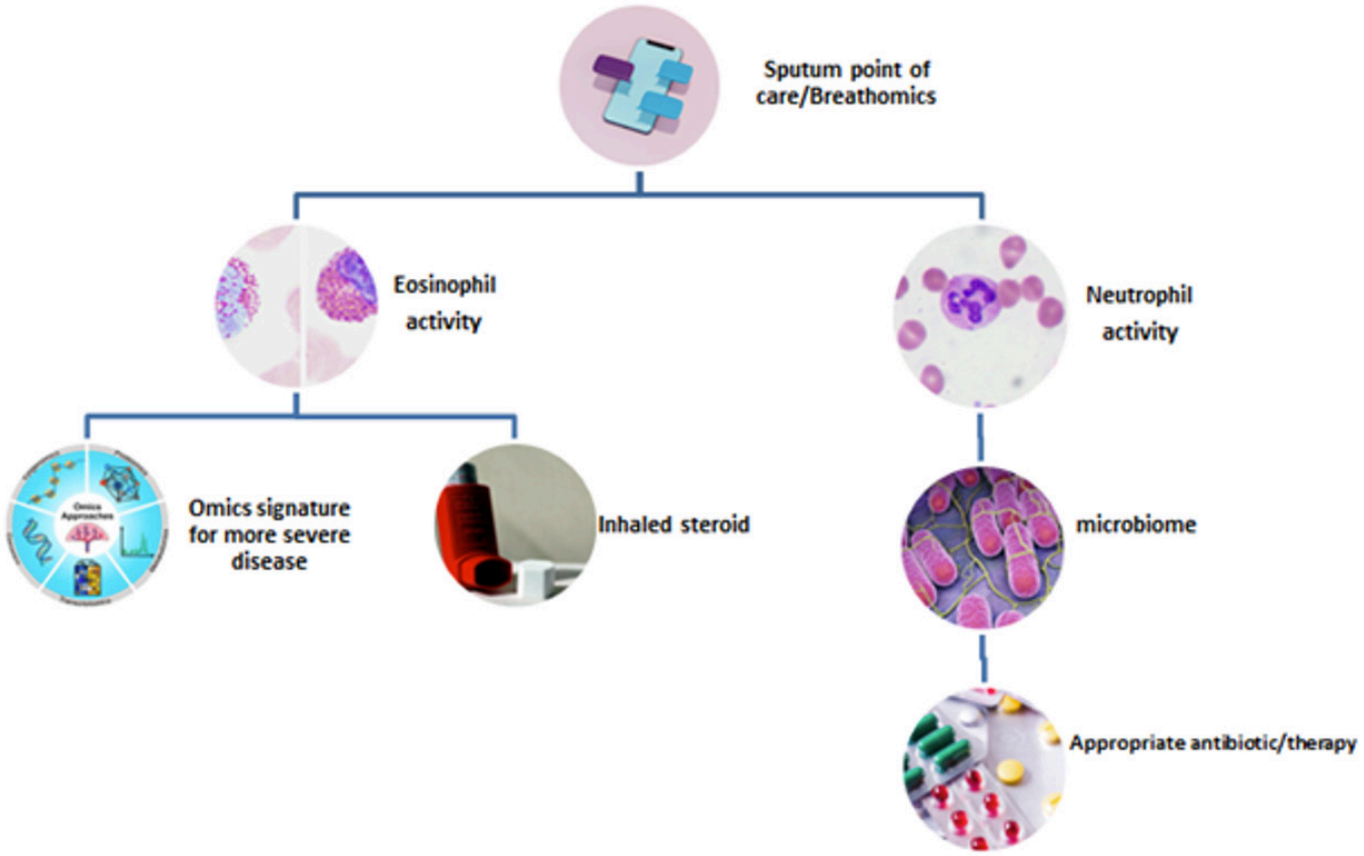


***Figure 2.*** *The concept for the future. Point of care tests would detect eosinophilic or neutrophilic activity in sputum that would then lead to the application of "omics" platforms to precisely identify the Th2 pathways or the microbial dysbiosis that leads to the cellular patterns, to guide therapy; courtesy of Parameswaran Nair, MD, PhD, FRCP, FRCPC*

**Clinical use not mentioned elsewhere in the piece**

RINVOQ should not be used in combination with other Janus kinase (JAK) inhibitors, immunomodulating biologics (e.g., biologic DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

Pediatrics: The safety and efficacy of RINVOQ in adolescents weighing <40 kg and in children aged 0 to less than 12 years with atopic dermatitis have not yet been established. No data are available; therefore, RINVOQ should not be used in this pediatric patient population.

Geriatrics (≥65 years of age): Caution should be used when treating geriatric patients with RINVOQ.

**Most serious warnings and precautions**

**Serious infections:** Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt RINVOQ until the infection is controlled. Reported infections include active tuberculosis (TB), which may present with pulmonary or extrapulmonary disease; invasive fungal infections, including cryptococcosis and pneumocystosis; and bacterial, viral (including herpes zoster), and other infections due to opportunistic pathogens. Test patients for latent TB before RINVOQ use and during therapy. Consider treatment for latent infection prior to RINVOQ use. Do not initiate treatment in patients with active infections including chronic or localized infections. Carefully consider the risks and benefits of treatment prior to initiating therapy in patients with chronic or recurrent infections. Closely monitor patients for signs and symptoms of infection during and after treatment, including the possible development of TB in patients who tested negative for latent infection prior to initiating therapy.

**Malignancies:** Lymphoma and other malignancies have been observed in patients treated with RINVOQ. An increase in malignancies, including lung cancer, were observed in RA patients ≥50 years with at least one additional cardiovascular (CV) risk factor who were taking a different JAK inhibitor, compared with tumour necrosis factor (TNF) inhibitors. Caution should be applied when using RINVOQ in geriatric patients, patients who are current or past smokers, and patients with other malignancy risk factors.

**Thrombosis:** Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with JAK inhibitors, including RINVOQ, for inflammatory conditions. Many of these adverse events were serious and some resulted in death. RA patients ≥50 years with ≥1 additional CV risk factor had a higher rate of all-cause mortality and thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis in a clinical trial with a different JAK inhibitor compared to TNF inhibitors. Consider the risks and benefits prior to treating patients who may be at increased risk for thrombosis. Discontinue RINVOQ and promptly evaluate patients with symptoms of thrombosis.

**Major adverse cardiovascular events:** Major adverse CV events, including non-fatal myocardial infarction, were observed more frequently in RA patients ≥50 years with ≥1 additional CV risk factor in a clinical trial with a different JAK inhibitor compared to TNF inhibitors. Caution should be applied when using RINVOQ in geriatric patients, patients who are current or past smokers, and patients with other CV risk factors.

**Other relevant warnings and precautions**

- Increases in lipid parameters, including total, low-density lipoprotein, and high-density lipoprotein cholesterol
- Gastrointestinal perforations
- Hematologic events
- Liver enzyme elevation
- Patients with severe hepatic impairment
- Concomitant use with other potent immunosuppressants, biologic DMARDs, or other JAK inhibitors
- Immunizations
- Viral reactivation, including herpes (e.g., herpes zoster) and hepatitis B
- Malignancies, including dose-related NMSC
- Increases in creatine phosphokinase
- Monitoring and laboratory tests
- Pregnant women
- Reproductive health
- Breast-feeding
- Geriatrics (≥65 years of age)
- Pediatrics (<12 years of age)
- Asian patients

**For more information**

Please consult the Product Monograph at rinvoq.ca/pm for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling us at 1-888-704-8271.

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