How does smoking alter the immune system with an effect that persists long after quitting? Why do many autoimmune diseases affect more women than men? Does the response to psoriatic arthritis advanced treatments differ between women and men? What are the 2023 EULAR recommendations for fatigue management? All this and more in our first edition of **Immune-Mediated Inflammatory Disease Insights**

We are excited to launch our newsletter, Immune-Mediated Inflammatory Disease Insights, dedicated to providing valuable information and updates on immune-mediated inflammatory diseases (IMID) and relevant treatments. The field of IMID therapy is rapidly evolving, and with new clinical trials, real-world evidence, and treatment guidelines emerging regularly, it can be challenging to stay up to date. Our newsletter aims to help you stay current by providing accurate, and timely information about the latest developments and advances in IMID treatments as well as basic science research. In the May edition, we have compiled a list of recent publications that we believe will be of great interest to you.

1 Smoking alters the immune system with persistent effects

Using data from the Milieu Intérieur project, a research initiative designed to study the variability in the immune system, Saint-André *et al*. examined 136 variables that might contribute to differences in cytokine secretion, including socio-demographics, diet, and lifestyle. Immune response phenotype was determined according to the secretion of cytokine proteins as a response to immune stimulation. The concentrations of 13 disease- and medically-relevant cytokines (CXCL5, CSF2, IFNγ, IL-1β, TNF, IL-2, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-17 and IL-23) were measured after 22 h of whole-blood stimulation with 11 immune agonists for the 1,000 Milieu Intérieur donors, as well as in a non-stimulated control (null condition). "The authors observed that smoking status, CMV (cytomegalovirus) latent infection, and BMI, in addition to age, sex, genetic variation, DNA methylation levels, and immune cell subsets, are the variables most associated with variation in cytokine secretion upon immune challenge. Current smokers showed an increased inflammatory response following bacterial stimulation, which quickly lost upon smoking cessation. Conversely, the smoking effects on T cell responses persist years after individuals quit smoking."

Read more

2 In female mammals, X-chromosome inactivation is linked with autoimmune disorders

Xist is a long non-coding RNA (lnc-RNA) present only in females which silences one of the X-chromosomes in all female cells. A new study in *Cell* used mouse models to show that the Xist RNA protein complex (Xist RNP), in which Xist associates with multiple binding proteins, may underlie female-biased autoimmunity. Inducing transgenic Xist RNP formation in male animals allowed the study of female-specific lncRNA in a male background using a chemically induced SLE (Systemic Lupus Erythematosus) model. "Both increased disease severity and elevated autoreactive lymphocyte pathway signatures were observed in the mouse models of pristane-induced SLE. Concurrently, an antigen array was designed to test autoimmune patient seroactivity to XIST-associating proteins and detected significant reactivity toward multiple components of the XIST RNP. Altogether, the new data point to a substantial role for the Xist RNP as a driver for autoimmunity that may underly the sex-biased female preponderance for developing autoimmune diseases."

Read more

3 PsA RWE in Australia: Tofacitinib exhibits longer persistence than TNFi in a matched population

Recently published in *Clinical Rheumatology,* this retrospective study utilized the Optimising Patient outcomes in Australian rheumatoLogy (OPAL) dataset to assess clinical effectiveness, treatment persistence, and treatment patterns in PsA patients treated with tofacitinib or bDMARDs (n = 406 tofacitinib, n = 416 IL-17i and n = 664 TNFi). 19.2% of tofacitinib patients were first line, compared with 41.8% of IL-17Ai and 62.8% of TNFi patients. In the overall population, the median persistence was 16.5 months (95% CI 13.8 to 19.5 months), 17.7 months (95% CI 15.8 to 19.6 months), and 17.2 months (95% CI 14.9 to 20.5 months) in the tofacitinib, IL-17Ai and TNFi groups, respectively. Persistence was similar in the tofacitinib/IL-17Ai propensity score-matched population; however, in the tofacitinib/TNFi matched population, persistence was longer in the tofacitinib group (18.7 months, 95% CI 15.6 to 21.4 months) compared with the TNFi group (12.2 months, 95% CI 10.9 to 14.9 months). Around half of patients discontinued treatment across groups, mainly due to lack of efficacy. Adverse reaction accounted for discontinuation in 15%, 7%, and 6% of patients treated with tofacitinib, IL-17i, and TNFi, respectively. Remission or LDA as measured by DAS28(3)- CRP reached approximately 80% in all patient groups by 3 months and was generally maintained through 12 months.

Read more

4 CorEvitas Registry: Tofacitinib effectiveness demonstrated, regardless of regimen, line of therapy, time of initiation, and dose

A recently published real-world analysis in *The Journal of Rheumatology* assessed baseline demographics/characteristics and treatment patterns/effectiveness in patients with rheumatoid arthritis (RA) initiating tofacitinib in the United States (US) CorEvitas RA Registry. This publication is an updated analysis of previously communicated studies using a larger cohort followed over a longer period. In total, 2,874 patients with RA initiated tofacitinib on or after November 06, 2012. Of these, 1,298 and 1,712 patients had a qualifying 12-month and 6-month follow-up visit, respectively, and were included in the analysis. "This analysis showed that tofacitinib was used as early (13.6% 2nd line) and more commonly as later (66.5% 4th line) lines of therapy in real-world settings of patients

with RA. Tofacitinib effectiveness was demonstrated at 12 and 6 months for all treatment regimens, lines of therapy (including 4th line), time periods of initiation, and doses."

Read more

5 Sex-related differences in patient characteristics, and efficacy and safety of advanced therapies in randomised clinical trials in psoriatic arthritis

In *The Lancet Rheumatology*, Lihi Eder and colleagues report a systematic review and meta-analysis of 54 studies on the sex-related differences in patient characteristics and efficacy and safety of targeted therapies in randomized clinical trials in psoriatic arthritis. Female patients were older (means and CI's), with higher BMI (means and Cis), and burden of musculoskeletal signs and symptoms (assessment – means and CIs) at study entry, while males had more severe psoriasis (assessment - means and CI's)) and higher concentrations of inflammatory markers (CRP – means and CIs). The data showed a tendency to higher treatment response to biological treatment, as measured by ACR20, in male patients versus female patients with interleukin (IL)-17 inhibitors (odds ratio 1·70 [95% CI 1·38–2·11]), IL-23 inhibitors (1·46 [1·20–1·78]), IL-12 and IL-23 inhibitor (2·67 [1·39–5·09]), and tumor necrosis factor inhibitors (1·55 [1·11–2·18]), but not with JAK and TYK2 inhibitors (1·10 [0·87–1·38]).

Read more

6 2023 EULAR recommendations for the management of fatigue in people with inflammatory rheumatic and musculoskeletal diseases

A multidisciplinary task force comprising 26 members from 14 European countries was convened and formulated new recommendations for fatigue management in inflammatory rheumatic and musculoskeletal diseases. The work was presented at the 2023 EULAR congress and published in *the Annals of Rheumatic Diseases*. Four overarching principles (OAPs) and four recommendations were developed. OAPs include health professionals' awareness that fatigue encompasses multiple biological, psychological, and social factors that should inform clinical care. Fatigue should be monitored and assessed, and people with I-RMDs should be offered management options. Recommendations include offering tailored physical activity and/or tailored psychoeducational interventions and/or, if clinically indicated, immunomodulatory treatment initiation or change. Patient-centered fatigue management should consider the individual's needs and preferences, clinical disease

activity, comorbidities, and other psychosocial and contextual factors through shared decision-making.

Read more

We invite you to read the content and share your thoughts. We look forward to keeping you informed and inspired in the field of IMID and the relevant treatments.
For more medical information on IMID and related therapeutics, please visit the website of the Inflammation and Immunology department of Pfizer Israel, Pfizer Science.

The Inflammation and Immunology Team, Pfizer Israel
Helena.magrisso@pfizer.com