JAK-Inhibitors introduction

The janus kinase (JAK) family, constituting JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), are a class of cytoplasmic tyrosine kinases.[1] JAKs dock to the intracellular part of cytokine receptor chains to generate functional signalling complexes and regulate the inflammatory process through activating the cytoplasmic transcription factors termed as signal transducer and activator of transcription (STAT). When activated, STAT proteins produce dimers, which translocate into the nucleus and either positively or negatively regulate downstream target gene expression of inflammatory mediators, suggesting that inhibiting JAK activity may be more effective than targeting a single cytokine. Beyond interrupting cytokine-driven inflammatory responses in the skin, JAK inhibition has been reported to attenuate chronic itch and improve skin barrier function by regulating the expression of skin barrier protein filaggrin.[2, 3]

Special considerations

JAK-Inhibitors are also effective in certain other inflammatory diseases and are approved for their treatment in some cases. Therefore, patients with AE and with concomitant inflammatory diseases, such as alopecia areata, rheumatoid and juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis or inflammatory bowel diseases are likely to experience additional beneficial effects for these concomitant diseasess, but the effect size may vary according to the JAK-Inhibitor used.

General safety issues

Following a review of the benefit-risk balance of oral JAK-Inhibitors, which confirmed, that tofacitinib (oral JAK-Inhibitor; not approved for AE) increases the risk of major cardiovascular problems, cancer, venous thromboembolism and serious infections compared to TNF-alpha inhibitors[4], the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) proposed measures to minimize the risk of serious side effects associated with JAK-Inhibitors in 2022.[5, 6] It was recommended that oral JAK-Inhibitors should only be used in patients aged ≥65 years or with a history of atherosclerotic cardiovascular disease, other risk factors for cardiovascular disease (e.g. long-term smoking) or with increased risk of cancer if no suitable treatment alternatives are available, and with caution in patients at risk of pulmonary embolism or deep vein thrombosis.[5, 6] If treatment with JAK-Inhibitors is initiated in these patients, this should be done with the lower dose in each case. The PRAC concluded that these safety findings apply to all approved uses of JAK inhibitors in dermatological, rheumatological or gastroenterological chronic inflammatory diseases.[5, 6]

Screening and monitoring

The label's requirements for monitoring are mentioned per JAK-Inhibitor. In practice, the guideline group considers the same baseline screening and treatment monitoring investigations applicable to all JAK-Inhibitors. For baseline screening this is a full blood count, renal, liver and lipid profile and hepatitis, HIV and TBT. For monitoring purposes during treatment we propose a full blood count, renal, liver and lipid profile at four weeks into treatment and then three-monthly while on therapy. The guideline group does not advocate for mandatory monitoring of creatinine phosphokinase levels in asymptomatic patients.

Pregnancy

All JAK-Inhibitors are considered strictly contraindicated during pregnancy. Safe contraception should be ensured for women of childbearing age.

References

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