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## JAK-inhibitors in the management of atopic dermatitis

Atopic dermatitis (AD) is a chronic, or relapsing remitting, pruritic inflammatory skin disorder that affects up to 20% of children and around 2-8% of adults. The pathogenesis of AD is complex and involves multiple components including genetic, immunologic, and environmental factors, leading to skin barrier defect and immune dysregulation, with strong activation of T-helper type 2 (Th2) immune response. The development of biologic therapies targeting Th2 pathway, such as IL-4/IL-13 inhibitors, is a major breakthrough in the management for moderate-to-severe AD. The landmark phase 3 randomised controlled trials, SOLO 1 and SOLO 2 studies, showed that dupilumab, a monoclonal antibody against IL-4 and IL-13, significantly improved all aspects of AD, which include Investigator's Global Assessment (IGA) score, Eczema Area and Severity Index (EASI), pruritus, symptoms of anxiety and depression, and quality of life, as compared to placebo. Nonetheless, the EASI-75 response of dupilumab monotherapy at week 16 was around 50% only, which means around half of patients with moderate-to-severe AD failed to achieve significant improvement. With a better understanding of the pathogenesis of AD, we now know that it is actually a heterogenous disease. Apart from strong Th2 immune response, there is additional activation of Th22, Th17/Th23 and Th1 immunity.

The JAK-STAT pathway is a classical intracellular signal transduction pathway which is involved in the pathogenesis of numerus immune-mediated inflammatory diseases, such as rheumatoid arthritis, axial spondyloarthritis, inflammatory bowel diseases, psoriasis, and atopic dermatitis. In particular, JAK-1 protein is involved in the downstream signaling of various cytokines of Th2 pathway and beyond, which include IL-4, IL-5, IL-13, IL-22, IL-31, and thymic stromal lymphopoietin (TSLP). These cytokines all contribute to the inflammation and itch in AD.

JAK inhibitors have been shown to be effective therapeutic agents for AD. Currently, there are three oral JAK-inhibitors that are approved for the treatment of moderate-to-severe AD in Hong Kong, and they are Baricitinib (JAK-1/2 inhibitor), Upadacitinib (JAK-1 inhibitor), and Abrocitinib (JAK-1 inhibitor). In this article, the evidence of these three agents will be reviewed.

### Baricitinib

The efficacy of baricitinib monotherapy in adults, who had moderate-to-severe AD unresponsive to topical therapies, was studied in two parallel, multicenter, double-blind, phase 3 randomised placebo-controlled trials: BREEZE-AD1 and BREEZE-AD2. Subjects were required to have an EASI score ≥16, vIGA-AD (Validated Investigator Global Assessment scale for Atopic Dermatitis) ≥3, and ≥10% body surface area (BSA)

involved. vIGA-AD is a validated 5-point scale that assesses physicians' impression of overall disease severity of AD, with 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe disease. At week 16, 16.8% and 13.8% of patients receiving baricitinib 4 mg in BREEZE-AD1 and BREEZE-AD2 respectively achieved the primary endpoint of vIGA-AD score of 0 or 1 with a ≥ 2-point reduction from baseline, compared to 4.8% and 4.5% for placebo (P≤0.001). EASI-75 response of baricitinib 4mg at week 16 were 24.8% and 21.1% respectively for BREEZE-AD1 and BREEZE-AD2, compared to 8.8% and 6.1% for placebo (P≤0.001). There was also significant improvement with baricitinib 4 mg in other key secondary endpoints, including EASI-50, EASI-90, SCORAD-75, and various patient-reported outcomes scales for itch, skin pain, sleep and quality of life. Baricitinib was overall safe. The most frequently reported adverse events (AEs) were nasopharyngitis, upper respiratory tract infection, creatine phosphokinase (CPK) elevation and headache. Herpes simplex was more common in baricitinib group and occurred in 3.3% to 7.2% of patients, while herpes zoster was observed in 0.8% and 0.2% of patients on baricitinib and placebo respectively. Most AEs were mild or moderate in severity, and only 1.2% of patients receiving baricitinib 4 mg discontinued the study due to AEs. No deaths, malignancies, gastrointestinal perforations, major adverse cardiovascular events (MACEs), venous thromboembolic events (VTEs), and opportunistic infections were reported in baricitinib group for both trials.

The long-term efficacy of baricitinib was examined in an extension trial – BREEZE-AD3.8 In this study, responders and partial responders in BREEZE-AD1 and BREEZE-AD2, defined as patients achieving vIGA-AD score of 0 or 1 (responders), or 2 (partial responders), continued with baricitinib for a further of 52 weeks, resulting in a total of 68 weeks of baricitinib therapy. Majority of patients were able to maintain a good response with continuous treatment. Among responders and partial responders on baricitinib 4 mg, a vIGA-AD score of 0 or 1 was achieved in 45.7% at baseline and 47.1% at the end of study. Corresponding percentages for patients receiving baricitinib 2 mg were 46.3% and 59.3%.

Pooled safety analysis of 8 prospective trials with over 2500 adult AD patients on baricitinib showed a low overall rate (<2.5%) of serious adverse events (SAEs). The most common serious infections were eczema herpeticum, cellulitis and pneumonia, with annual incidence rates (IRs) of 0.5, 0.3 and 0.1 per 100 patients respectively. The overall annual IRs of MACEs and VTEs were both 0.09 per 100 patients, which are comparable to the background rates of these events. Malignancies other than non-melanoma skin cancers occurred in 5 cases, resulting in an annual IR of 0.22 per 100 patients. The annual IR of study drug discontinuation due to AE were low at 4.6%.

## Upadacitinib

The efficacy of upadacitinib monotherapy in adolescents and adults, who had moderate-to-severe AD unresponsive to topical therapies, was studied in two replicate, multicentre, double-blind, phase 3 randomised placebo-controlled trials: Measure Up1 and Measure Up2. Eligible patients were adolescents and adults with moderate-to-severe AD, defined as EASI score ≥16, vIGA-AD ≥3, BSA ≥10%, and Worst Pruritus Numerical Rating Scale (WP-NRS) score ≥4. At week 16, 62% and 52% of patients receiving upadacitinib 30 mg in Measure Up1 and Measure Up2 respectively achieved a vIGA-AD response (defined as a vIGA-AD score of 0 or 1 with a ≥ 2-point improvement from baseline), compared to 8% and 5% for placebo (P≤ 0.0001). EASI-75 response of upadacitinib 30 mg at week 16 were 80% and 73% respectively for Measure Up1 and Measure Up2, compared to 16% and 13% for placebo (P≤0.0001). Upadacitinib was also shown to be superior to placebo in all ranked secondary

endpoints, including EASI-90, EASI-100, 4-point reduction in WP-NRS, and other outcomes measurement on impact of AD on sleep, emotional state, daily activities, and quality of life. Moreover, clinical response was rapid, and significant improvement in vIGA-AD, EASI and WP-NRS was observed as early as 1-2 weeks. The most frequently reported AEs were acne, upper respiratory tract infection, nasopharyngitis, headache and elevation in CPK. Herpes zoster was more common in upadacitinib group (1.8%) than placebo (<1%). Rates of SAEs were comparable between upadacitinib group (2-3%) and placebo (3%). Malignancies other than non-melanoma skin cancers occurred in 3 cases (0.6%) in patients receiving upadacitinib 30 mg. No deaths, adjudicated MACEs and VTEs were reported.

The long-term efficacy and safety of upadacitinib were examined in an extension trial. In this trial, all patients from Measure Up1 and Measure Up2 were enrolled into a blinded extension. Patients who had been on placebo were re-randomised to receive upadacitinib 15 mg or 30 mg, while those on upadacitinib continued dosages as originally assigned. At week 52, both doses of upadacitinib maintained efficacy responses achieved at week 16: EASI-75 were 82% and 79% for 15 mg, and 85% and 84% for 30 mg upadacitinib in Measure Up1 and Measure Up2 respectively; while vIGA-AD response were maintained at 59% and 53% for 15 mg, and 63% and 65% for 30 mg upadacitinib. No new safety signals were detected.

Upadacitinib also demonstrated superior efficacy to dupilumab. In a head-to-head, phase 3b, multi-centre, randomised, double-blinded, double-dummy, active-controlled trial, adults with moderate-to-severe AD were randomised to receive upadacitinib 30 mg daily or subcutaneous dupilumab 300 mg every other week. At week 16, the primary endpoint, EASI-75, was achieved in 71% of patients on upadacitinib vs 61% of those on dupilumab (P=0.006); while EASI-90 and EASI-100 were achieved in 61% and 28% for upadacitinib, and 39% and 8% for dupilumab respectively (P<0.001). Despite the superiority in efficacy, rates of serious infection, eczema herpeticum, herpes zoster, and laboratory-related AEs were higher in patients receiving upadacitinib.

## Abrocitinib

The efficacy of abrocitinib monotherapy in adolescents and adults with moderate-to-severe AD was studied in two parallel, multicenter, double-blind, phase 3 randomised placebo-controlled trials: JADE MONO-1 and JADE MONO-2. Patients aged 12 years or above with moderate-to-severe AD, defined as EASI score ≥16, vIGA-AD ≥3, BSA ≥10%, and Peak Pruritus Numerical Rating Scale (PP-NRS) score ≥4, were included. At week 12, vIGA-AD response was achieved in 44% and 38% of patients receiving abrocitinib 200 mg daily in JADE MONO-1 and JADE MONO-2 respectively, compared to 8% and 9% for placebo (P<0.001); EASI-75 was achieved in 63% and 61% for abrocitinib vs 12% and 10% for placebo (P<0.001). Similarly, higher proportions of patients on abrocitinib achieved EASI-50 and EASI-90. There was also significant improvement in PP-NRS and other patient-reported outcome measures including Dermatology Life Quality Index (DLQI), Patient-Oriented Eczema Measure (POEM), and Hospital Anxiety and Depression Scale (HADS). The most commonly reported AEs were nausea and vomiting, nasopharyngitis, headache, upper respiratory tract infection, and acne. Herpes zoster occurred in 1-1.3% of patients receiving upadacitinib 200 mg. The rates of serious infections were low and comparable between groups. No malignancies, MACEs, VTEs and treatment-related deaths were observed.

Head-to-head comparison between abrocitinib and dupilumab showed superior efficacy for abrocitinib. In JADE COMPARE, a phase 3, multicentre, randomised, double-blind, double-

dummy, placebo-controlled trial in adult patients with moderate-to-severe AD, the vIGA-AD response at week 12 for abrocitinib 200 mg, dupilumab 300 mg every other week, and placebo were 48%, 37%, and 14% respectively; corresponding EASI-75 were 70%, 58% and 27%. Nausea, acne, and herpes zoster were more common in patients on abrocitinib, but rates of severe AEs were similar across trial groups.

Long-term efficacy and safety of abrocitinib were evaluated in an extension trial: JADE EXTEND. All patients from JADE MONO-1, JADE MONO-2 and JADE COMPARE were enrolled into JADE-EXTEND. Patients who had been on abrocitinib continued the same dose as originally assigned, while those on placebo or dupilumab were re-randomised to abrocitinib 100 mg or 200 mg. At week 48, 52% and 39% of patients on abrocitinib 200 mg and 100 mg achieved vIGA-AD 0/1, while EASI-75 response was achieved in 82% and 67%. Moreover, among prior dupilumab non-responders, 47% and 80% of patients on abrocitinib 200 mg were able to achieve vIGA-AD 0/1 and EASI-75 respectively. Safety profile was consistent with previous reports.

The efficacies of biologics and JAK inhibitors in moderate-to-severe AD were compared in a recent systematic review and meta-analysis. Nineteen randomised controlled trials over 6000 patients were included. In monotherapy, upadacitinib 30 mg had the numerically highest efficacy regarding EASI-50, EASI-75 and EASI-90. When combined with topical corticosteroids, abrocitinib 200 mg had the highest score regarding EASI-75 and EASI-90. The authors therefore suggested that upadacitinib and abrocitinib seem to have the greatest potential in treating patients with AD. Nonetheless, given the black-box warning of JAK inhibitors on serious infections, malignancies, MACEs and VTEs, and the lack of real long-term safety data on these novel agents, pros and cons of the use of JAK inhibitors need to be carefully balanced and thoroughly discussed with patients with moderate-to-severe AD.

***Learning points:***

JAK inhibitors are effective treatment for moderate-to-severe atopic dermatitis. Rates of serious adverse events remain low but long-term safety data are required.