unpredictable responses to available treatments and no single universally effective agent.[2,3] There is also increasing evidence for JAK inhibitors, which inhibit the signalling of many of these cytokines through the JAK family of receptors, for other inflammatory dermatoses including psoriasis and atopic dermatitis.[4]

In the first trial reported by Alavi *et al.*, 10 patients received 15 mg of INCB054707 daily. In the second, 35 patients aged 18–65 years were randomized to placebo, or 30, 60 or 90 mg of INCB054707 daily (n = 9, 9, 9 and 8, respectively). Three patients in Study 2 had previously received adalimumab. The most common treatment-related adverse effects were fatigue (3%) and headache (15%). Four patients receiving 90 mg developed asymptomatic thrombocytopenia (platelets $<150 \times 10^9$ cells L^{-1}), with recovery in all after a 2-week suspension of therapy. HS clinical response at week 8 was achieved in three patients (43%) in Study 1 and 17 patients (65% overall; 56% with 30 mg, 56% with 60 mg, 88% with 90 mg) in Study 2 receiving INCB054707 vs. four patients (57%) receiving placebo. Analysis of biomarkers at 4 and 8 weeks demonstrated a larger reduction in soluble interleukin-2 receptor α compared with tumour necrosis factor-α.

Compared with biologics for HS, JAK inhibitors are oral agents with shorter half-lives, and may be preferred in patients who dislike injections and do not mind daily medications, or if quick drug clearance with discontinuation is desired. Furthermore, patients with HS have a higher risk of atopic dermatitis and inflammatory arthritis, for which JAK inhibitors are indicated.[5,6]

Common adverse effects with JAK inhibitors for other dermatoses include upper respiratory tract infections and nasopharyngitis, in as many as 10% of patients.[4] Herpes zoster may be more common with JAK inhibitors than with biologics, with rates of 3·8–6·7 per 100 patient-years with upadacitinib, another JAK1 inhibitor, compared with 0·1 with biweekly adalimumab in patients with psoriatic arthritis.[7]

Possibly more concerning are cytopenias, reported with JAK inhibitors affecting JAK2, related to its transmission of erythropoietin, thrombopoietin and haematopoietic cell development cytokines.[8] More data could clarify whether the risk of thrombocytopenia with INCB054707 is restricted to higher doses. A notable concern is the risk of thromboembolic events, prompting a recent black box warning, based on postmarket review of tofacitinib in patients with rheumatoid arthritis, with an odds ratio for pulmonary embolism of 2·46 (95% confidence interval 1·55–3·91).[4]

Despite the positive responses noted in the INCB054707 trials, the results should be interpreted with caution. The significantly high response rate in the placebo group (57%) underscores the need for trials with longer follow-up in larger sample sizes. It may also be helpful to further define responses in populations with different phenotypic subtypes or comorbidities. Several other JAK inhibitors are under investigation for HS, including upadacitinib (also specific for JAK1), brepocitinib (a tyrosine kinase 2/JAK1 inhibitor), ropsacitinib (a tyrosine kinase 2 inhibitor) and two inhibitors of Irak4 (interleukin-1 receptor-associated kinase 4).[2]

Cathryn Sibbald [1,2] and Raed Alhusayen[1,3]

[1]*Division of Dermatology, Department of Medicine, University of Toronto, Toronto, ON, Canada;* [2]*Division of Dermatology, Department of Paediatrics, SickKids Hospital, Toronto, ON, Canada; and* [3]*Division of Dermatology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*
Email: cathryn.sibbald@mail.utoronto.ca

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An accurate diagnosis of dermal CD8$^+$ lymphoproliferative disorders requires clinicopathological and immunophenotypic correlation

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Cutaneous lymphomas are diagnostically challenging from a clinical and pathological perspective. Most cases are CD4$^+$, and the CD8$^+$ lymphoproliferative disorders (LPDs) in the skin are largely accounted for by mycosis fungoides (typically

paediatric and hypopigmented lesions), lymphomatoid papulosis (types D and E) and cutaneous anaplastic large cell lymphoma.[1,2] In 2007, Petrella *et al.*[3] reported the occurrence of a group of LPDs in acral locations (nose, ears and toes/fingers) with a $CD8^+$ phenotype and a benign clinical behaviour. The term 'indolent $CD8^+$ lymphoid proliferation of the ear' was proposed, and was later confusingly changed to 'cutaneous acral $CD8^+$ T-cell lymphoma' ($CD8^+$ ATCL), in the updated World Health Organization–European Organisation for Research and Treatment of Cancer (EORTC) classification of haematopoietic neoplasms (2018).[2] This entity was originally mistakenly perceived by many to be the $CD8^+$ variant of the so-called small-to-medium $CD4^+$ T-cell lymphoma, an entity now believed to be a form of pseudolymphoma.

$CD8^+$ dermal LPDs (excluding mycosis fungoides and $CD30^+$ lymphoid proliferations) are exceedingly rare and diagnostically challenging. The prognosis ranges from an almost entirely indolent process ($CD8^+$ ATCL) to neoplasms with the potential for high rates of local recurrence and aggressive clinical behaviour [$CD8^+$ peripheral T-cell lymphoma (PTCL) not otherwise specified, CD8 PTCL].[4,5] More recently, an unusual subtype of $CD8^+$ LPD has been described

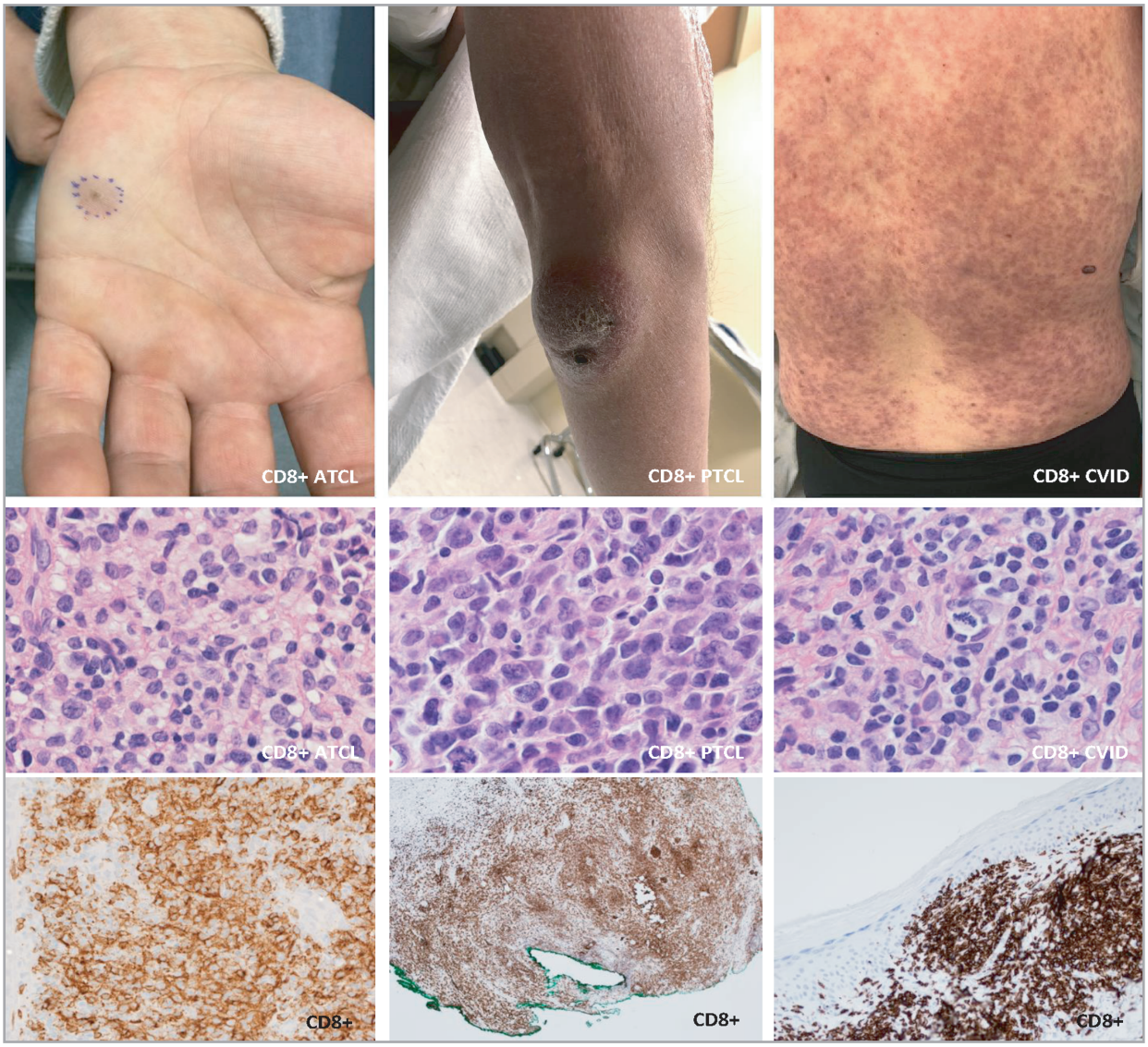

Fig 1 Left panels: an example of $CD8^+$ acral T-cell lymphoproliferative disorder (ATCL) on the hand. A discrete small papule is present. The infiltrate is composed of small-to-intermediate-sized cells (original magnification × 400) strongly positive for CD8 (original magnification × 200). Middle panels: an example of $CD8^+$ peripheral T-cell lymphoma (PTCL). A large tumour is present in the leg. The malignant infiltrate is composed of medium-to-large cells with marked cellular pleomorphism (original magnification × 400) and strong expression of CD8 (original magnification × 40). Right panels: an example of a $CD8^+$ lymphoproliferative disorder in the setting of combined variable immunodeficiency (CVID). There are numerous patches and plaques with a red-brown appearance. The infiltrate has a vague granulomatous pattern (original magnification × 400) and expression of CD8 (original magnification × 100).

in patients with congenital or acquired immunodeficiencies, which show striking expression of CD8, in association with a dermal infiltrate and a granulomatous pattern. The behaviour of such lesions appears to be somewhat dependent on the status of immunosuppression.[6]

Because there is morphological overlap between these three conditions, an accurate clinicopathological correlation that includes immunophenotypic studies is key to differentiate between them. To this end, Kempf *et al.*[4] present the largest series of these three conditions ever reported to date (n = 47), with special focus on $CD8^+$ ATCL. This comprehensive study collected cases from numerous European centres, and the clinical, pathological and immunophenotypic features, and the treatments used, were subsequently reviewed at an EORTC Cutaneous Lymphoma Group workshop. Notably, cases of $CD8^+$ ATCL were solitary acral small nodules of small-to-medium-sized $CD8^+$ lymphocytes, lacking significant cytologic atypia. Immunophenotypically, a dot-like pattern of immunoreactivity with CD68,[7] expression of TIA-1, and absence of granzyme B were characteristic. Like primary cutaneous small-to-medium $CD4^+$ LPD, the Ki67 activity was always below 30%. In contrast, cases of $CD8^+$ PTCL had a higher rate of multifocality (~27%), a higher degree of cellular pleomorphism and higher expression of multiple cytotoxic markers (granzyme B, perforin). They also lacked the CD68 dot-like pattern and had much higher Ki67 proliferation (55% of cases with >50%). Local recurrences were seen in 45% of cases and one patient died from the disease. The patients with immunodeficiency-associated LPD were much younger and had multiple lesions clinically.

From a clinical perspective, a diagnosis of PTCL of the skin has strong clinical connotations, and usually patients receive systemic treatment with chemo- and/or radiotherapy.[8] Separating reproducible diagnostic categories is key to individualizing therapeutic regimens and discovering their molecular profile. This study shows that appropriate distinction of $CD8^+$ dermal LPDs into specific diagnostic categories is possible and reproducible (Figure 1).

Alejandro A. Gru

Department of Pathology & Dermatology, Cutaneous Lymphoma Program, University of Virginia, Charlottesville, VA, USA
Email: aag4b@hscmail.mcc.virginia.edu

Conflicts of interest: Innate Pharma (coinvestigator), Stemline Therapeutics (coinvestigator), Kyowa Kirin (consultant).

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Is heat shock protein 90 inhibition a relevant treatment strategy for psoriasis?

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Over recent decades, several targeted therapies – biologics and small molecules – have been successfully developed and approved for the treatment of moderate-to-severe psoriasis vulgaris. This intense development has been driven by compelling evidence for the major pathogenic contributions of key inflammatory effector cytokines such as tumour necrosis factor (TNF)-α and the interleukin (IL)-23–IL-17 family axis.[1] Among the key regulators of TNF-α- and IL-17-driven inflammatory pathways lies heat shock protein (HSP)90, a protein playing major functions in physiology and in carcinogenesis.[2]

In this issue of the *BJD*, Bregnhøj *et al.* report results from a proof-of-concept, phase Ib study investigating the safety and efficacy of the novel HSP90 inhibitor RGRN-305 in 11 patients with plaque psoriasis over 12 weeks.[3] Although RGRN-305 was primarily developed for cancer, serendipitous observation of psoriasis remission in one patient, and alleviation of psoriasis-like inflammation in a xenografted mouse model provided a rationale for this study. Administered orally at two dosages (250 and 500 mg daily), the drug was associated with ≥50% improvement of Psoriasis Area and Severity Index (range 71–94%) at 12 weeks vs. baseline in six of 11 patients, without a clear dose effect.