

*Dr Gelfand served as a consultant for Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, Janssen Biologics, Novartis Corp, UCB (Data Safety and Monitoring Board), Sanofi, and Pfizer Inc, receiving honoraria; receives research grants (to the Trustees of the University of Pennsylvania) from AbbVie, Janssen, Novartis Corp, Celgene, Ortho Dermatologics, and Pfizer Inc; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly, Ortho Dermatologic, and Novartis. Drs Noe, Sbin, and Webner have no conflicts of interest to declare.*

*IRB approval status: Not applicable.*

*Reprints not available from the authors.*

*Correspondence to: Megan Noe, MD, MPH, MSCE, Department of Dermatology, Brigham and Women's Hospital, 221 Longwood Ave, Boston, MA 02115*

*E-mail: [mnoe2@bwh.harvard.edu](mailto:mnoe2@bwh.harvard.edu)*

#### REFERENCES

1. Dowell D, Haegerich TM, Chou R. CDC Guideline for prescribing opioids for chronic pain - United States, 2016. *MMWR Recomm Rep*. 2016;65(1):1-49.
2. Lee YC, Kremer J, Guan H, Greenberg J, Solomon DH. Chronic opioid use in rheumatoid arthritis: prevalence and predictors. *Arthritis Rheumatol*. 2019;71(5):670-677.
3. Reddy S, Orenstein LAV, Strunk A, Garg A. Incidence of long-term opioid use among opioid-naïve patients with hidradenitis suppurativa in the United States. *JAMA Dermatol*. 2019;155(11):1284-1290.
4. Chen SK, Feldman CH, Brill G, Lee YC, Desai RJ, Kim SC. Use of prescription opioids among patients with rheumatic diseases compared to patients with hypertension in the USA: a retrospective cohort study. *BMJ Open*. 2019;9(6):e027495.

<https://doi.org/10.1016/j.jaad.2020.03.080>

### **The adverse effect profile of acitretin in a pediatric dermatology population—Longitudinal cohort study and recommendations for monitoring**



*To the Editor:* The clinical benefit of acitretin has been amply shown in the treatment of disorders of keratinization in childhood, particularly in psoriasis and ichthyosis. The adverse effects (AEs) of acitretin are well studied in adults, and

monitoring guidelines were issued by the British Association of Dermatologists.<sup>1</sup> However, AEs in childhood are less well studied, particularly in non-psoriasis cohorts.

A retrospective case note review was undertaken of all 174 patients prescribed acitretin between 1993 and 2015. Patient variables collected were diagnosis; demographics; age at starting acitretin; length of time monitored while receiving acitretin (as measured by age at stopping treatment or age of transfer to adult services if still receiving the medication); starting, maximal, and final doses; and AEs. Children were usually seen by a dermatologist on a three-monthly basis and none were lost to follow-up in the study period. Clinical AEs were defined as any reported clinical symptom that had arisen since starting and could be attributed to acitretin. Laboratory AEs were defined as hepatic transaminase levels twice the upper limit of the normal range for age, and/or alkaline phosphatase levels at least 1.2-fold the upper limit of normal range for age, and/or triglyceride levels greater than 2.3 mmol/L. Primary outcome measures (clinical and laboratory AEs) were modeled with respect to 5 patient variables (sex, diagnosis, age at starting, dose/kg at starting, and length of time receiving acitretin) by multiple logistic regression (SPSS, version 22; SPSS Inc, Chicago, IL). A Bonferroni correction for multiple testing was applied, reducing the level of significance to  $P < .005$ . Response to treatment was not a primary outcome but has been recorded here for comparability with other studies.

Cohort data are shown in [Table I](#). There were no fatal or irreversible AEs documented due to acitretin. Clinical AEs were reported in 24%, leading to permanent cessation of treatment in 10% of the total cohort, although this overlapped with lack of adequate response to the medication—in other words, the balance of beneficial and adverse clinical AEs was important and not easily measurable. Laboratory AEs occurred in 22%, leading to permanent cessation in 4% of the total cohort. Importantly, laboratory AEs were very rare after 2 years of uneventful treatment (Supplemental Figure 1; available via Mendeley at <https://data.mendeley.com/datasets/x7cp29vtgk/draft?a=11828aec-97a2-46f7-8dd2-49a213c6ddc0>). Reduced bone density was seen in 3 patients with ichthyosis, a known risk factor for vitamin D deficiency, but was not routinely screened for. There were no significant associations between clinical or laboratory AEs and the 5 patient variables. Half of those children who had acitretin stopped for any AE subsequently had the drug restarted.

**Table I.** Cohort demographics and incidence of clinical and laboratory adverse effects potentially due to acitretin therapy

Demographics of the total cohort (N = 174)	Count*
Male/female, n	90/84
Age at starting acitretin, y, mean $\pm$ SEM (range)	8.1 $\pm$ 0.4 (0.0-18.78)
Mean duration of treatment, y, mean $\pm$ SEM (range)	3.5 $\pm$ 0.3 (0.02-17.58)
Mean starting dose, mg/kg, mean $\pm$ SEM (range)	0.42 $\pm$ 0.01 (0.15-0.68)
Mean maximum dose, mg/kg, mean $\pm$ SEM (range)	0.45 $\pm$ 0.02 (0.14-1.24)
Clinical diagnostic groupings, n/total (%)	
Congenital ichthyosis	94/172 (54.7)
Psoriasis	50/172 (29.1)
Other	14/172 (8.1)
Palmoplantar keratoderma	5/172 (2.9)
Eczema	4/172 (2.3)
Immunodeficiency	4/172 (2.3)
Pityriasis rubra pilaris	1/172 (0.6)
Missing data on diagnosis	2/172 (1.2)
Clinical AEs, all reversible, n/total (%)	
Increased skin irritation, fragility, or rash	18/174 (10.3)
Dry lips	16/174 (9.2)
Nausea	3/174 (1.7)
Tiredness/malaise	2/174 (1.1)
Mood swings	1/174 (0.6)
Hair thinning	1/174 (0.6)
Abdominal pain	1/174 (0.6)
Clinical AEs of any type, n/total (%)	42/174 (24.1)
Missing data on clinical AEs	0/174
Laboratory AEs, all reversible, n/total (%)	
Abnormal alkaline phosphatase level alone	10/170 (5.9)
Abnormal alanine transaminase level alone	4/170 (2.4)
Abnormal alanine transaminase and alkaline phosphatase level	1/170 (0.6)
Abnormal triglyceride levels alone	17/170 (10)
Abnormal liver function test results (alanine transaminase or alkaline phosphatase) and triglyceride levels	4/170 (2.4)
Laboratory AE but missing detail on type	2/170 (1.2)
Laboratory AEs of any type	38/170 (22.4)
Missing data on laboratory AEs	4/174
Reasons for stopping acitretin during study period, temporarily or permanently, n/total (%)	
Limited or no clinical improvement	33/172 (19.2)
Clinical AEs (other than worsening of skin disease)	21/172 (12.2)
Sustained clinical improvement	17/172 (9.9)
Worsening of skin disease	10/172 (5.8)
Laboratory AEs	7/172 (4.1)
Other causes	3/172 (1.7)
Total stopped acitretin due to any cause, n/total (%)	91/172 (52.9)
Missing data on stopping	2/174

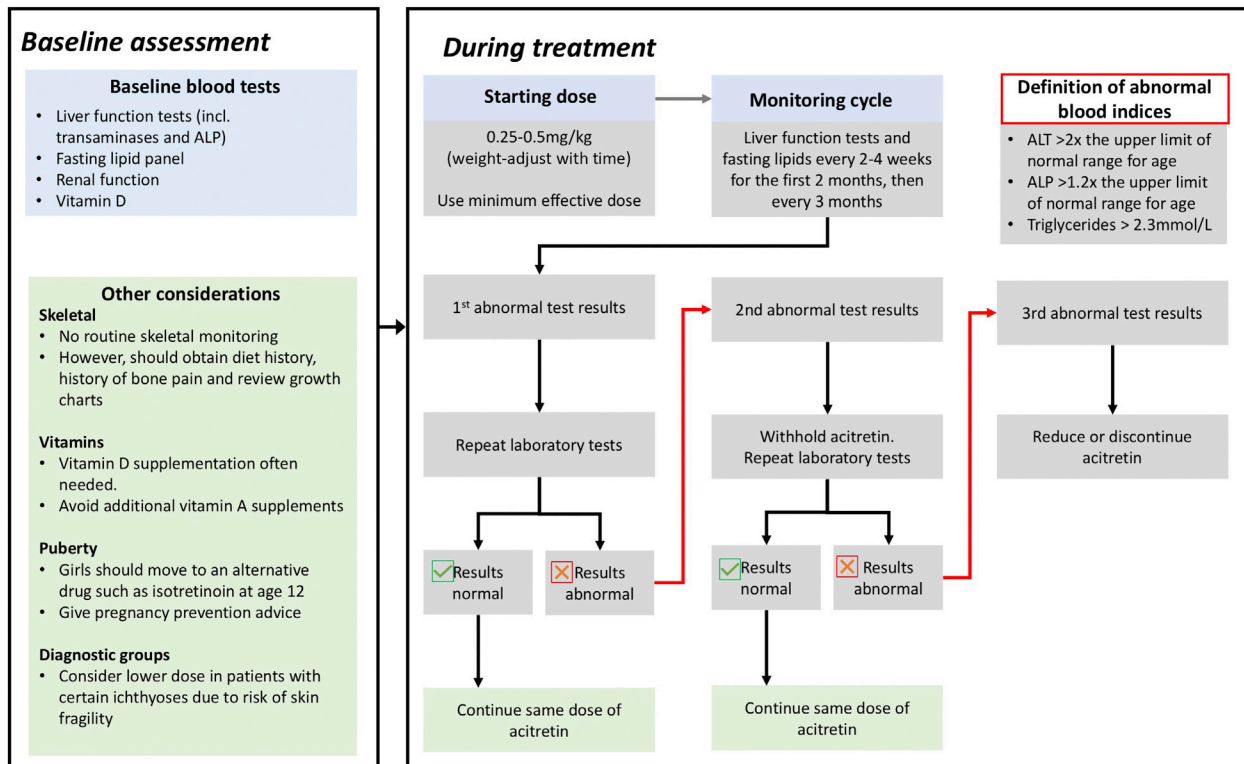
AE, Adverse event; SEM, standard error of the mean.

\*Where the total cohort number does not equal 174, this is due to missing data.

In this cohort, acitretin was therefore a safe drug at the dose used and for the duration of follow-up, subject to clinical and laboratory monitoring. Incidence of AEs was unaffected by sex, diagnosis, age at starting, dose, or duration of therapy; however, laboratory AEs after 2 years of uneventful treatment were uncommon. The overall pattern of AEs is comparable to that in previous studies of

acitretin in children,<sup>2-5</sup> as is the number of children stopping acitretin due to clinical AEs.<sup>4</sup> As reported previously, minor changes in blood indices have been associated with acitretin use and do not tend to lead to changes in therapy.<sup>5</sup>

In conclusion, our current practice is based on the published adult guidelines<sup>1</sup> and these findings, and is summarized in Fig 1.



**Fig 1.** Suggested guidelines for monitoring the use of acitretin in children in association with the published guidelines in adults. ALP, Alkaline phosphatase; ALT, alanine transaminase.

Anna Cave, MD,<sup>a</sup> Isabella Plumpton, MD,<sup>a</sup> Jemima E. Mellerio, MD,<sup>b</sup> Anna E. Martinez, MD,<sup>a</sup> and Veronica A. Kinsler, MD, PhD<sup>a,c</sup>

From the Great Ormond St Hospital for Children and UCL GOS Institute of Child Health, London, United Kingdom<sup>a</sup>; Guys and St Thomas' Hospital, London, United Kingdom<sup>b</sup>; and Mosaicism and Precision Medicine Laboratory, The Francis Crick Institute, London, United Kingdom.<sup>c</sup>

**Funding sources:** This work was supported by the UK National Institute of Health Research through the Biomedical Research Centre at Great Ormond St Hospital for Children and the University College London Great Ormond Street Institute of Child Health. Prof Kinsler was funded by the Wellcome Trust (award number WT104076MA).

**Conflicts of interest:** None disclosed.

**IRB approval status:** Not required as this was a retrospective case note review.

**Reprints not available from the authors.**

**Correspondence to:** Professor Veronica Kinsler, MD, PhD, Professor of Paediatric Dermatology and Dermatogenetics, Great Ormond Street Hospital for Children NHS Foundation Trust, London WC1N 3JH

E-mail: [v.kinsler@ucl.ac.uk](mailto:v.kinsler@ucl.ac.uk)

#### REFERENCES

1. Ormerod AD, Campalani E, Goodfield MJ, BAD Clinical Standards Unit. British Association of Dermatologists guidelines on the efficacy and use of acitretin in dermatology. *Br J Dermatol.* 2010;162:952-963.
2. Dunn LK, Gaar LR, Yentzer BA, O'Neill JL, Feldman SR. Acitretin in dermatology: a review. *J Drugs Dermatol.* 2011;10:772-782.
3. Charbit L, Mahe E, Phan A, et al. Systemic treatments in childhood psoriasis: a French multicentre study on 154 children. *Br J Dermatol.* 2016;174:1118-1121.
4. Bronckers IM, Paller AS, van Geel MJ, van de Kerkhof PC, Seyger MM. Psoriasis in children and adolescents: diagnosis, management and comorbidities. *Paediatr Drugs.* 2015;17:373-384.
5. Lacour M, Mehta-Nikhar B, Atherton DJ, Harper JL. An appraisal of acitretin therapy in children with inherited disorders of keratinization. *Br J Dermatol.* 1996;134:1023-1029.

<https://doi.org/10.1016/j.jaad.2020.03.082>

#### Reflectance confocal microscopy as a diagnostic tool for mastocytoma in children



**To the Editor:** Mastocytoma is a variant of cutaneous mastocytosis, and its diagnosis is confirmed by histopathology. Because this condition primarily affects children, dermoscopy and reflectance confocal microscopy (RCM) are potentially useful