The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/24192

Please be advised that this information was generated on 2018-11-24 and may be subject to change.
Acrodermatitis continua of Hallopeau in a patient with myelodysplastic syndrome

P.C.M. van der Kerkhof,* P.M. Steijlen* and R.A.P. Raymakers†
Departments of *Dermatology and †Haematology, University Hospital, Nijmegen, the Netherlands
Accepted for publication 21 April 1995

Summary

Acrodermatitis continua of Hallopeau (ACH) is a rare manifestation of pustular psoriasis which may considerably disable affected patients. In this case report we confirm the efficacy of acitretin in the treatment of ACH and, in addition, describe the course of the myelodysplastic syndrome (MDS) from which the patient was suffering. During acitretin treatment, there was a transformation into acute myeloid leukaemia. We discuss the effect of retinoids on the bone marrow of normal subjects, patients with MDS, and patients with acute myeloid leukaemia.

Our experience in the present case, and the information from the available literature, lead us to advise against the use of the aromatic retinoids, acitretin and etretinate, in patients with MDS. If such treatment is indicated, intensive haematological supervision is mandatory.

Acrodermatitis continua of Hallopeau (ACH) is a rare type of localized pustular psoriasis. The condition is characterized by the occurrence of pustules on the fingers and toes. Systemic antipsoriatic treatments are indicated in ACH. Although no controlled studies are available, ACH is reported to respond well to systemic corticosteroids, methotrexate, acitretin, and cyclosporin.1-9

Recently, we have treated a patient with ACH, who also had a myelodysplastic syndrome (MDS) with a refractory anaemia (RA) and a severe thrombocytopenia. The severity of the ACH necessitated systemic treatment, and the patient was given acitretin with careful monitoring of the blood parameters.

Case report

In 1989, a 53-year-old man presented with an erythematous and pustular eruption of the toes. Haematological investigation showed severe thrombocytopenia (platelet count 5-20 × 109/l), and a bone marrow examination was hypercellular, with myelodysplasia, and a low number of megakaryocytes. The disorder was classified as MDS, RA-type since there were normal blast counts. HLA typing revealed: -A3, -A28, B27, -B35, -CW1, and -CW4. Treatment was started with methylprednisolone, 50 mg/day. Although the skin condition showed some improvement with this treatment, the thrombocytopenia was relatively unaffected. The patient was treated with β-acetyl digoxin, 0-2 mg/day and-propranolol, 40 mg three times a day, because of a supraventricular tachycardia, and he took omeprazole for gastrointestinal discomfort and bleeding.

ACH, with chronic plaque psoriasis, was diagnosed, and the patient was treated with low-dose methotrexate, firstly at a dose of 5 mg/week and, later, 10 mg/week. Methylprednisolone was continued, at a dosage of 25 mg/day and, in addition, the patient used potent topical corticosteroids.

Episodes of epistaxis, purpura, and gastrointestinal bleeding required frequent transfusions of blood and platelets. Cytogenetic investigations showed trisomy 10, which confirmed the diagnosis of MDS. Methotrexate, methylprednisolone and propranolol were stopped. Treatment was started with interleukin (IL)-3, at a dosage of 10 μg/kg per day. According to the EORTC protocol for MDS, IL-3 was stopped, after 3 weeks, because of fever, loss of appetite, and general malaise. During this treatment, the patient’s skin condition got worse and required additional treatment.

Examination showed well-demarcated, erythematosquamous lesions, covered with yellow crusts, on three fingers of the right hand, and on all 10 toes (Fig. 1). A paronychia and distal onycholysis of the first finger of the left hand, was present. On the soles, scalp and neck, there were well-demarcated erythematosquamous plaques, with a psoriasiform appearance. In the intergluteal area, a well-demarcated erythema was seen. On the buttocks and upper legs there was purpura. Cultures for fungi were negative.
In January 1992, acitretin (Neotigason; Hoffman LaRoche) was started, at a dosage of 35 mg/day (the patient weighed 84 kg). Topical treatment with corticosteroids and tar preparations was continued. After 2 weeks of treatment, a substantial improvement was seen (Fig. 2). Subsequently, the dosage of acitretin was increased to 40 mg/day, and there was a mild cheilitis, indicating that the dosage was sufficient. During subsequent months, the skin condition improved further, to the extent that only minimal residual changes persisted. During the 7 months of treatment with acitretin, at a dosage of 35–40 mg/day, no side-effects, apart from mild cheilitis, were recorded. The serum cholesterol, triglycerides, and transaminases remained within the normal range. No joint complaints were recorded.

However, during this period, clinically evident bleeding from the gastrointestinal tract necessitated platelet transfusions. The frequency of these transfusions was comparable to that in the period before treatment with acitretin. The platelet counts remained in the same range as before treatment with acitretin, i.e. 5–40 x 10^9/l. In February 1992, anaemia developed, and a gradual increase in the leucocyte and blast counts was seen. In May 1992, whilst the patient was still on treatment with acitretin, acute myeloid
leukaemia was diagnosed. An MDS high-risk regimen (EORTC), with idarubicin and Ara C, was instituted. After the first course, complete remission was not obtained and a pancytopenia persisted. During the second remission-induction course, the patient died, after 5 weeks, due to cerebral bleeding.

Discussion

Although there are no placebo-controlled studies for acitretin in ACH, the use of acitretin in localized and generalized pustular psoriasis is well established. So far, there are only two case reports on the treatment of ACH.\textsuperscript{2,9} Our report confirms the efficacy of acitretin in this rare condition. The decision to initiate treatment with acitretin was justified by the severe and disabling symptoms, but was complicated by the coexistence of MDS, which necessitated intensive haematological supervision. The published literature is not clear as to whether treatment with systemic retinoids is allowed or contraindicated in patients with MDS. Studies in the 1920s reported a reduction of haematopoietic cells in the bone marrow of vitamin A-depleted animals.\textsuperscript{10,11} In human vitamin A deficiency, moderate anaemia develops despite ample dietary sources of all essential nutrients except the vitamin A.\textsuperscript{12} Etretinate, the ester of acitretin (at $10^{-8}$ to $10^{-7}$ mol/l) has been reported to increase the clone size of colony-forming unit-granulocyte macrophage (CFU-GM) from normal human bone marrow, in contrast to the inhibitory effect of 13-cis-retinoic acid.\textsuperscript{13} The effects of retinoids on the normal bone marrow are not well understood.

Several reports in the literature indicate that retinoids have a beneficial effect on the course of MDS. Clark \textit{et al.} reported a significant increase in the 1-year survival, from 30 to 77%, in the treated group in non-side-roblastic patients, and no significant effect in patients with sideroblastic anaemia.\textsuperscript{14} Koeffler \textit{et al.} did not find a significant response in patients with MDS.\textsuperscript{15} However, the patients in this group had either high-risk disease or sideroblastic anaemia. In these, the result of Clark \textit{et al.} also indicate no significant improvement.\textsuperscript{15} In cultures from patients with MDS, 20 of 34 cases showed greater inhibition of total colony numbers than controls, and some patients proved to have greater sensitivity than normal subjects with respect to the inhibitory effect of retinoic acid.\textsuperscript{15} In short-term liquid cultures of bone marrow from 13 patients with MDS, 13-cis-retinoic acid induced a significant decrease in the number of pro-myelocytes and Leu-M3 positive cells. Hence, retinoids seem to induce a shift from monocytoid to myeloid differentiation. However, etretinate in culture did not show any capacity to induce differentiation.\textsuperscript{16}

Malignant transformation in MDS has been described.\textsuperscript{17-20} MDS is a stem cell disorder which, in 30% of the patients, progresses to acute myeloid leukaemia. Expansion of the abnormal cell population is accompanied by selection of subclones with a growth advantage, resulting in leukaemia. Do retinoids contribute to this leukaemic transformation? Breitman \textit{et al.} found that retinoic acid induces promyelocytic leukaemia cells to differentiate into functionally mature granulocytes.\textsuperscript{21,22} Others have shown that this agent induces erythroid differentiation of Friend erythroleukaemia cells.\textsuperscript{23} In contrast to growth stimulation of normal haematopoietic progenitor cells, retinoid acid inhibited the proliferation of myeloid leukaemic blasts.\textsuperscript{24} Retinoic acid appears to act directly on the myeloid progenitors, probably by increasing the responsiveness of these cells to the action of colony-stimulating factor.\textsuperscript{25} All-trans-retinoic acid was shown to induce differentiation in patients with acute promyelocytic leukaemia.\textsuperscript{26} Flynn \textit{et al.} and Nilsson\textsuperscript{27} both describe patients with promyelocytic leukaemia in whom incubation of immature blood cells with retinoic acid in \textit{vitro} resulted in maturation, and treatment with retinoic acid resulted in maturation of blood cells together with a temporary clinical remission. In 1988, Meng-re \textit{et al.} described 24 patients with promyelocytic leukaemia who were treated with all-trans retinoic acid.\textsuperscript{29} All patients showed complete remission and, in 14 of the 15 patients in whom \textit{in vitro} studies were carried out, morphological maturation of blood cells was shown.\textsuperscript{29} Similar results were reported by Castaigne \textit{et al.} The role of acitretin and its ester, etretinate, in the development of promyelocytic cell lines and leukaemia is less clear. Several authors report etretinate to be unable to induce differentiation in U-937 and HL-60 cell lines.\textsuperscript{31-33} This lack of efficacy, in contrast to the effect of all-trans retinoic acid, was shown in the case of acute promyelocytic leukaemia.\textsuperscript{34} Conversely, some reports suggest that retinoids might have an unfavourable effect on the course of leukaemia. Lawrence \textit{et al.} noted that, in some patients with acute myeloblastic leukaemia, clonal growth of CFU-GM \textit{in vitro} was stimulated sometimes by retinoic acid, and that \textit{in vivo} the effect may vary from patient to patient. Awareness of the deleterious effect of retinoid therapy is important in patients who have the more malignant variants of MDS. Garewal \textit{et al.} noticed acceleration of disease in two out of 15 patients with MDS who were treated with fenretinide [N-(4-hydroxyphenyl) retinoid].\textsuperscript{16}
In our patient, transformation into acute myeloid leukaemia occurred shortly after treatment with acitretin was started. We are unaware of any other cases of MDS showing this type of transformation during acitretin treatment. MDS should not be regarded as an absolute contraindication for treatment with retinoids, but if patients with this disorder are treated, intensive haematological supervision is indicated.

References


