Drug Safety 1998 April; 18 (4): 273-279
0114-5916/98/0004-0273/$03.50/0

Retinoic Acid Syndrome
Recognition, Prevention and Management

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Summary

The introduction of treatment with tretinoin (all-*trans* retinoic acid) and its combination with antineoplastic therapy has improved the outcome of acute promyelocytic leukaemia (APL). Retinoic acid syndrome is the major adverse effect of tretinoin and it occurs in about 25% of treated APL patients in the absence of prophylactic measures and is often fatal. Generally, the retinoic acid syndrome is associated with increasing leucocyte counts and is probably caused by the release of several cytokines by maturing blast cells. The retinoic acid syndrome gives a clinical picture of bodyweight gain, respiratory distress, serous effusions and cardiac and renal failure. Adequate prophylaxis, based on the addition to tretinoin of dexamethasone and also, according to most authors, antineoplastic therapy (in case of rapidly increasing leucocyte counts) has decreased the incidence of retinoic acid syndrome to about 15%. Most importantly, these measures have reduced its mortality to about 1% of all treated patients.

Acute promyelocytic leukaemia (APL) is a specific type of acute myeloid leukaemia (AML) which is characterised by: the morphology of blast cells (M3 in the French American British classification of AML);[1,2] the t(15;17)[3] translocation which fuses the PML gene on chromosome 15 to the retinoic acid receptor alpha (RARα) gene on chromosome 17;[4,5] and by a coagulopathy combining disseminated intravascular coagulation (DIC) and fibrinolysis.[6,7] Until recently, intensive antineoplastic therapy, usually combining an anthracycline and cytarabine (cytosine arabinoside), was the only effective treatment for APL.[8-11]

Tretinoin (all-*trans* retinoic acid) can differentiate APL blast cells *in vivo* and *in vitro*.[12-14] Treatment with tretinoin followed by anthracycline and

cytarabine antineoplastic therapy has improved the outcome of APL by slightly improving the complete remission (CR) rate, but most importantly by reducing the incidence of relapse.[15-19] With a follow up greater than 4 years, the experience of our European Group in newly diagnosed APL shows that 60 to 70% of the patients can probably be cured by the combination of tretinoin and antineoplastic therapy, as compared to less than 40% with antineoplastic therapy alone (Fenaux et al., unpublished observation).

Tretinoin is usually well tolerated, but a few major adverse effects are associated with this agent, and retinoic acid syndrome is the most important of them.

1. First Clinical Experiences

In the first published clinical experience of retinoic acid syndrome, Huang and colleagues[12] reported that tretinoin often induced hyperleucocytosis in APL, but without major associated symptoms. Our group had also observed, in relapsing APL, a frequent but symptomless increase in white blood cell (WBC) count.[20]

We subsequently reported the first European experience with tretinoin in newly diagnosed APL.[14,21] 39 patients were included in a pilot phase II study of initial treatment of APL with tretinoin.[21] This study initially included 17 patients who had refused antineoplastic therapy or had a major contraindication to intensive antineoplastic therapy (group 1) and these were followed by 22 patients who had no contraindication to antineoplastic therapy (group 2).

Rapidly occurring hyperleucocytosis developed in 10 of the 17 patients included in group 1. This hyperleucocytosis was associated with a variable combination of pulmonary infiltrates, cardiac failure, neurological symptoms and renal failure, interpreted as resulting from leucostasis and thrombosis. All 10 patients with hyperleucocytosis died, and the cause of death was considered to be thrombosis (extensive stroke or myocardial infarction) in 3 cases, and pulmonary bleeding in 7 cases.

In order to prevent this complication occurring in subsequent patients (i.e. group 2), we empirically decided to add antineoplastic therapy to tretinoin in patients developing rapidly rising leucocyte counts. The purpose of this antineoplastic therapy was also to prevent subsequent relapses, as previously published experience had shown that, in patients who achieved a CR with tretinoin alone, a rapid relapse was observed if tretinoin was continued as single maintenance therapy.[12] Therefore, patients in group 2 received a combination of daunorubicin and cytarabine when hyperleucocytosis developed rapidly. This was necessary after 4 to 12 days of tretinoin in 7 of the 22 patients included in group 2, and all 22 patients achieved CR. In both groups 1 and 2, complications occurred only in patients who had, under tretinoin, leucocyte counts $>6 \times 10^9$/L by day 5 of treatment, or $>10 \times 10^9$/L by day 10 or $>15 \times 10^9$/L by day 15 of treatment.[21]

In contrast, no clinical symptoms were seen in patients who remained leucopenic while receiving tretinoin, or who had moderate and slowly developing hyperleucocytosis below the levels mentioned above. We therefore suggested that these leucocyte levels should be used as guidelines for starting antineoplastic therapy in APL patients receiving tretinoin, in order to avoid complications that were interpreted as resulting from leucostasis.

2. Complete Description

After these preliminary experiences, Frankel et al.[22] gave a precise description of the 'retinoic acid syndrome' in patients treated with tretinoin for APL. In the study by Frankel et al.[22] this syndrome occurred in 9 of 35 (25%) of newly diagnosed APL patients after 2 to 21 days of tretinoin treatment. The symptoms included fever, bodyweight gain, dyspnoea, pleural effusion and pulmonary infiltrates on chest x-ray in all patients, renal failure in 6 patients, hypotension in 4 patients, and pericardial effusion in 1 patient. In all cases, symptoms occurred in patients whose WBC count had increased with tretinoin treatment, although in 3

patients the increases were only moderate (WBC counts of up to 6300, 10 600 and 11 400/mm^3).

Five of the 9 patients required transfer to an intensive care unit and received mechanical ventilation, and 3 of these patients eventually died.[22] Leukapheresis, performed in 2 patients, proved ineffective, whereas high dose dexamethasone (10mg intravenously every 12 hours for at least 3 days) yielded rapid improvement of the symptoms in 3 out of the 4 patients where it was used (the remaining patient died).

Post mortem studies in 2 patients found infiltrates of maturing myeloid cells in most organs, especially the lungs, kidneys and pleura, but no thrombosis was seen.

3. Subsequent Experiences

3.1 Incidence

The incidence of retinoic acid syndrome in published reports is shown in table I.[15,18,23-28] The incidence ranged from 7 to 27%. Reasons for variable incidences among published reports possibly include differences in prophylactic approaches. A higher incidence in recent studies could also be because of better recognition of the syndrome, since Frankel et al.[22] gave a precise description of the syndrome in their 1992 article. On the other hand, because diagnosis of retinoic acid syndrome remains purely clinical, it may be in some cases difficult to distinguish from other complications of APL, particularly sepsis.

Median time to occurrence of retinoic acid syndrome was 10 to 12 days after the start of tretinoin therapy in published studies, but retinoic acid syndrome has been seen as early as day 2 of tretinoin treatment. A few cases where a clinical picture of retinoic acid syndrome was observed before the onset of tretinoin have been reported.[29] We have observed 2 such cases in our experience, both of whom presented with high WBC counts.(Fenaux et al., unpublished observations)

3.2 Clinical Symptoms

The clinical picture of retinoic acid syndrome in our ongoing APL93 trial[23] was very similar to that reported by Frankel et al.,[22] with a great variety in the intensity of symptoms, ranging from moderate pleural effusion discovered on chest x-ray to major respiratory distress requiring mechanical ventilation. Clinical symptoms found so far in the 61 cases of retinoic acid syndrome reported in our APL93 trial are shown in table II.[23]

Clinical signs became apparent within 6 days of the onset tretinoin therapy in 43% of cases, between 7 and 16 days in 38% of the cases, and after day 16 in 19% of the cases. Interestingly, in 16% of the cases, retinoic acid syndrome occurred upon recovery from the phase of aplasia secondary to the addition of antineoplastic therapy (indicated because of high WBC counts at diagnosis or during tretinoin treatment), a circumstance where, to our knowledge, retinoic acid syndrome has not been so far. Conversely, in 2 patients who presented with high WBC counts, clinical signs of retinoic acid syndrome were present before the onset of tretinoin therapy.

3.3 Predictive Factors

High WBC counts at diagnosis or rapidly increasing WBC counts during tretinoin treatment are the main predictive factors of retinoic acid syndrome. Furthermore, in our experience in the APL93 trial,[23] patients presenting with high WBC counts had an earlier onset of retinoic acid syndrome. They also tended to have more severe forms, requiring mechanical ventilation more often. However, retinoic acid syndrome may occur in patients with WBC counts below 10 000/mm^3, as for instance in 4 of the 21 cases of retinoic acid syndrome reported by Vahdat et al.;[24] however, 3 of those patients had experienced an increase in WBC counts to greater than 5000/mm^3, a figure which is high for patients with APL). 32 of the patients reported by Vahdat et al.[24] whose WBC counts increased above 20 000/mm^3 did not develop the retinoic acid syndrome. Vahdat et al.[24]

Table I. Incidence and outcome of retinoic acid syndrome in acute promyelocytic leukaemia (APL) treated with tretinoin (all-*trans* retinoic acid)

Reference	No. of patients	No. of patients with retinoic acid syndrome (%)	Prophylaxis of retinoic acid syndrome	Treatment of retinoic acid syndrome	Outcome of retinoic acid syndrome		Overall incidence of fatal retinoic acid syndrome (%)
					CR (%)	death (%)	
Fenaux et al.[15] (APL91 trial)	54	6 (11%)	Antineoplastic therapy added if: (i) WBC > 5000/mm^3 at diagnosis; (ii) WBC > 6000, 10000, 15000/mm^3 by days 5, 10 and 15 of tretinoin therapy, respectively	Symptomatic	100	0	0
Kanamaru et al.[18]	109	7 (6%)	Antineoplastic therapy added if: (i) WBC >3000/mm^3 at diagnosis (ii) circulating blast cells >1000/mm^3 during treatment	DXM : 3 cases	ND	14	1
Vahdat et al.[24]	78	21 (27%)	No prophylaxis	DXM; leukapheresis	72	28	7
Wiley & Firkin[25]	22	2 (9%)	(i) If WBC <10 000/mm^3 initially, add oral prednisone (ii) if WBC >10 000/mm^3 initially, add antineoplastic therapy	Antineoplastic therapy	50	50	
Avvisati et al.[26]	20	2 (10%)	Antineoplastic therapy in all patients	DXM	50	50	
Tallmann et al.[27]	172	47 (27)%	Hydroxycarbamide (hydroxyurea) if: (i) WBC >10 000/mm^3 at APL diagnosis (ii) WBC >30 000/mm^3 with tretinoin	DXM	ND	7	1
Fenaux et al. (APL93 trial)[23]	403	61 (15%)	Same as for APL 91 trial	DXM	89	8	1
Cortes et al.[28]	17	4 (24%)	Antineoplastic therapy added if blast cell + promyelocyte count >10 000/mm^3 at diagnosis or increases with tretinoin	Antineoplastic therapy Leukapheresis	75	25	

Abbreviations: CR = complete response; DXM = dexamethasone; ND = non data; WBC = white blood cell.

also found that basal expression of CD13 on APL blast cells was strongly associated with both development of the retinoic acid syndrome as well as with an elevated WBC count.

3.4 Outcome

Mortality associated with the retinoic acid syndrome ranged from 7 to 28% in published reports.[15,18,23-28] Thus, except in the New York study,[24] where 6 of the 78 total number of patients included in the study died because of the retinoic acid syndrome, the overall mortality by retinoic acid syndrome was in the range of 1% in large studies (table I).

4. Pathophysiology

The pathophysiology of the retinoic acid syndrome is still poorly understood. The retinoic acid syndrome is not caused by leucostasis and/or thrombosis[22] and, because its clinical signs are

reminiscent of those observed in the endotoxic shock and adult respiratory distress syndromes (ARDS), a possible stimulatory effect of tretinoin on cytokine expression by APL cells has been proposed.[30-32] Indeed, APL cells express and secrete colony stimulating factors and cytokines that are responsible for autocrine growth stimulation of AML cells [interleukin (IL)-1β and IL-6] and leucocyte activation [IL-8, tumour necrosis factor (TNF) α, IL-1β and IL-6]. Our group observed no correlation between haematopoietic growth factor expression and hyperleucocytosis at diagnosis in APL, but *in vitro* incubation with tretinoin significantly increased IL-1β and granulocyte colony-stimulating factor levels in 30% of APL cases. This was correlated to both an increase of the viable cell count and to hyperleucocytosis *in vivo*. Thus, tretinoin induction of IL-1β and granulocyte colony-stimulating factor secretion by APL cells may contribute to the increase of peripheral blast cells *in vivo*. IL-1β, IL-6, TNF-α, and IL-8, implicated in the activation and adherence of leucocytes, have an important role in the development of ARDS, and their secretion by APL cells under differentiation by tretinoin may suggest a pathogenetic role of these cytokines in the retinoic acid syndrome.[30-32]

Another explanation for hyperleucocytosis could be a change in the deformability of APL cells, thus allowing their release from the bone marrow. Using single-cell aspiration tests into a glass restrictive channel, we found that early tretinoin-induced hyperleucocytosis seemed to be associated with a low initial mean marrow cell viscosity value, close to that of mature neutrophils. An asynchronism between rheological and morphological maturation (mature pattern of deformability in cells of immature aspect) could thus explain the occurrence of tretinoin-induced hyperleucocytosis. Modulation of APL cell adhesive properties during the differentiating process induced by tretinoin might also trigger the release of differentiating leukaemic cells from the marrow toward peripheral blood and tissues. Indeed, we observed an increase in CD54/ICAM-1 surface adhesion molecule expression by the leukaemic cells during tretinoin-induced differentiation in some patients, and the rapidity of this CD54/ICAM-1 modulation seemed to be associated with the occurrence of hyperleucocytosis.[33]

5. Prophylaxis and Treatment

Because of the severity of the prognosis of the retinoic acid syndrome, once full blown symptoms have developed, prophylaxis or at least early treatment, at the first signs of the syndrome, are mandatory. Leukapheresis is incapable of sufficiently lowering WBC counts and preventing the retinoic acid syndrome in APL, and other approaches are required.

The most common approach, used by the European and Japanese groups,[15-18] is to add anthracycline-cytarabine antineoplastic therapy to tretinoin in the following circumstances.

- From the onset of tretinoin treatment in patients presenting with high WBC counts (see table I for details; WBC above 3000/mm^3 and 5000/mm^3 at diagnosis are considered as 'high' in the Japanese and European studies, respectively).

Table II. Clinical symptoms in the 61 patients (26 women, 35 men, mean age 45 years) included in APL93 trial who experienced retinoic acid syndrome.[23]

Symptoms	No. of patients	% of patients
Symptoms		
Fever	49	80
Dyspnoea	55	90
Pulmonary infiltrates	51	83
Pleural effusion	27	44
Pericardial effusion	11	18
Bodyweight gain	29	48
Renal failure	25	41
Hypotension	8	13
Mechanical ventilation	14	23
Dialysis	2	3
Time of onset[a]		
Before day 7	26	43
Between days 7 and 16	23	38
After day 16	12	19

a Median (range) = 7 (0 to 35) days.

- During tretinoin treatment if increases in the WBC counts are seen. For instance, the threshold chosen by our European group for starting antineoplastic therapy, based on our first experiences (see section 1) was, a WBC count above 6000/mm^3, 10 000/mm^3, and 15 000/mm^3 by days 5, 10 and 15 of tretinoin treatment, respectively (see table I for criteria used by other groups).

This second approach proved effective on a multicentre basis, as the retinoic acid syndrome was seen in only 61 of the 403 patients treated in Europe,[23] 7 of 109 patients treated by the Japanese group,[18] and, most importantly, only 6 patients out of the total of 512 died as a result of the retinoic acid syndrome. A disadvantage of this approach was that about two thirds of the patients treated with tretinoin also received early antineoplastic therapy. However, we found that in this case, the duration of neutropenia and thrombocytopenia was significantly shorter than when antineoplastic therapy was administered alone, an effect that may be linked to the effect of tretinoin on normal granulocytic proliferation and differentiation. Furthermore, intensive antineoplastic therapy, if not administered early, would have to be administered later on as consolidation treatment.

Other groups, like the Italian GIMEMA group[26] or the MD Anderson group,[28] use a similar but more systematic prophylactic approach to treating the retinoic acid syndrome, where antineoplastic therapy is systematically added to tretinoin after 2 to 4 days of treatment.

Another approach, used by the New York group and Australian groups[19,24,25] is to prevent fatal cases of retinoic acid syndrome by administration of high dose intravenous corticosteroids (intravenous dexamethasone at 10mg twice daily for 3 or more days) as soon as the first symptoms occur. This treatment proved efficient in the New York experience: although 6 of the 78 patients treated by this group died from the retinoic acid syndrome, only 1 death occurred in the last 2.5 years of the study.[24] The Australian group, initially using the same approach, observed fatal toxicity from the retinoic acid syndrome in 1 of 19 newly diagnosed APL patients who received tretinoin.[25] This approach avoids the early use of antineoplastic therapy and its adverse effects. However, it has mainly been used by a few experienced groups and has not been tested on a large multicentre basis.

The US intergroup[27] used a somewhat intermediate approach, where single agent antineoplastic therapy with hydroxycarbamide (hydroxyurea) was administered before tretinoin in patients presenting with a WBC count above 10 000/mm^3 or was added to tretinoin if the patients WBC count rose above 30 000/mm^3. The incidence of retinoic acid syndrome (27%) was perhaps slightly higher than in European and Japanese studies, but the outcome was similar (the overall incidence of death caused by the retinoic acid syndrome was about 1%).

These approaches are obviously not mutually exclusive. There is consensus over the fact that very often patients presenting with high WBC counts (i.e. more than 10 000 to 20 000/mm^3) will develop severe retinoic acid syndrome with tretinoin alone, and require antineoplastic therapy and intravenous dexamethasone from the onset of treatment. Some of these patients, as mentioned earlier, even present with symptoms analogous to those of the retinoic acid syndrome before the onset of treatment.

Finally, once diagnosed, the retinoic acid syndrome must be treated by high dose dexamethasone (if not started earlier), transient discontinuation of tretinoin (unless patients have received less than 5 to 7 days of tretinoin) and symptomatic treatment, including mechanical ventilation and haemodialysis if required.

6. Conclusion

In conclusion, the retinoic acid syndrome is a potentially severe adverse effect of treatment with tretinoin. Its incidence, or at least the incidence of severe forms, can be reduced by close monitoring of leucocyte counts and of clinical signs during treatment. Rapidly increasing leucocyte counts or the appearance of typical symptoms should lead to

the addition of intravenous dexamethasone and according to most authors, of antineoplastic therapy to tretinoin.

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