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REVIEW ARTICLE

Retinoic acid syndrome: a review

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SUMMARY

The retinoic acid syndrome (RAS) is an unpredictable but frequent complication which may develop after administration of all-*trans* retinoic acid (ATRA) most commonly in patients with acute promyelocytic leukaemia (APL). In this review, we describe the incidence, predictive factors, clinical course, outcome and treatment of RAS in patients with APL treated with ATRA. The incidence of RAS in patients receiving ATRA is about 14–16%, with an associated mortality of about 2%. Initial high white blood cell (WBC) count, rapidly increasing WBC count and/or the presence of the CD 13 expression on leukaemic cells may help in identifying patients likely to develop RAS. Concurrent chemotherapy will probably decrease the risk of developing RAS but often exacerbates bleeding, leading to leucocytosis, thrombocytopenia, disseminated intravascular coagulation and fibrinolysis. Prophylactic steroids are not recommended but prompt administration of steroids at the first sign of unexplained dyspnea, fever, weight gain or pulmonary infiltrate, is critical. Liposomal ATRA is being investigated to induce haematological cure in APL without chemotherapy and to reduce the incidence of RAS but further validation of its usefulness is necessary.

Keywords: **acute promyelocytic leukaemia, acute respiratory distress syndrome, adverse effect, adverse event, all-*trans* retinoic acid, retinoic acid syndrome**

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INTRODUCTION

Acute promyelocytic leukaemia (APL) is a specific type of acute myeloblastic leukaemia affecting both children and adults. It was first recognized as a clinical entity in the 1950s. APL is characterized by the morphology of blast cells, t(15, 17) translocation and coagulopathy. Historically, therapy for APL included anthracycline-based chemotherapy (daunorubicin and idarubicin) combined with cytarabine resulting in complete remission in the majority of patients. In the mid 1980s, the vitamin A derivative all-*trans* retinoic acid (ATRA) was introduced for the treatment of APL. The first patients treated with ATRA for APL were in Shanghai, China in 1986 (1). Subsequent clinical trials established the efficacy of ATRA and current treatment for APL now consists of ATRA 45 mg/m^2/day orally for 45–90 days plus anthracycline chemotherapy for induction. APL is now considered to be the most curable subtype of all the acute myeloid leukaemias (1–4).

Although ATRA is generally well tolerated, development of retinoic acid syndrome (RAS) in some patients is recognized as a distinct complication and a potential life-threatening adverse reaction. The incidence of RAS has been reported to range from 2 to 27% in clinical trials and case reports. The onset of the syndrome ranges from 2 to 21 days (median period of 10 days) after initiating ATRA therapy. RAS is characterized by unexplained fever, weight gain, elevated white blood cells (WBCs), respiratory distress, interstitial pulmonary infiltrates, pleural and pericardial effusion, dyspnea, episodic hypotension and acute renal failure. The most common manifestations include respiratory distress and fever in >80% of patients. Mortality from RAS has been reported to be about 2% of patients treated with ATRA (1–4).

The aetiology of RAS is not well understood. Retinoids are essential in the regulation of a broad

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range of biological processes and/or functions including vision, embryonic morphogenesis, and cellular differentiation and proliferation. ATRA-treated APL cells release inflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-8 and tumor necrosis factor alpha (TNF-α) interacting with the haemostatic system. These inflammatory cytokines may play a role in the development of RAS. In the nucleus, ATRA binds to one of the several retinoic acid receptors (RAR-α, β and δ). Translocation of t(15;17) in APL disrupts the gene encoding RAR-α which is located on chromosome 17, causing its fusion to the PML gene on chromosome 15 resulting in the PML/RAR-α fusion protein, which is involved in leukaemogenesis and myeloid differentiation induced by ATRA (1, 4). ATRA is highly protein bound and normally circulates in plasma at an approximate concentration of 1·5-3·0 ng/ml; it crosses the cell membrane by passive diffusion across a concentration gradient (1).

Establishing an accurate diagnosis of RAS is difficult because of the similar toxicities and complications associated with APL therapy. Risk factors for developing the syndrome are not well understood but may include high WBC count, rapidly increasing WBC count and the expression of cell surface antigens. Subjects affected by APL are often leucopenic and may present with a life-threatening bleeding risk, which can worsen with cytotoxic chemotherapy. Therefore, the diagnosis is made based on clinical features and/or findings in the absence of other causes. At least three of the following signs and/or symptoms should be present to diagnose RAS: fever, weight gain, pulmonary infiltrates, pleural or pericardial effusions, respiratory distress, hypotension and renal failure. Any of these symptoms could also be mistaken for an infection in a patient with APL so, the diagnosis is often delayed while antibiotic therapy is initially given (3). However, RAS can be potentially life threatening; therefore, early recognition is the key for management.

At present, the following are the recommendations for the management of RAS: administration of corticosteroids (a commonly used regimen is dexamethasone 10 mg intravenously twice daily for at least 3 days), cessation of ATRA depending on the severity of RAS or addition of another antineoplastic agent (cytarabine) to ATRA in patients with high WBC count. The major disadvantage of the last approach is the development of bone marrow suppression. The overall outcome from these recommended approaches is similar (1–4). Once RAS is resolved, ATRA can be reintroduced.

CONTROLLED TRIALS AND CASE REPORTS

De Botton and colleagues (5) published the largest case series of ATRA-induced RAS. These authors describe 413 patients with newly diagnosed APL, 64 (15%) of which developed RAS. Median time for the development of RAS after starting ATRA was 7 days (range 1–35 days). Respiratory distress (89%) and fever (81%) were the most common signs of RAS followed by pulmonary infiltrates (81%) and weight gain (50%). Nine patients (14%) died from RAS whereas 86% of the patients with RAS achieved complete remission compared with 94% who did not develop RAS. The authors investigated 10 possible predictive factors for RAS in this series with no factor achieving statistical significance.

Tallman and co-workers (6) published a case series of 44 patients with RAS. These authors found a 26% incidence (44/167) of RAS with a median onset of 11 days (range 2–47 days). Two patients died as a result of developing RAS. The most common symptoms associated with RAS included respiratory distress (84%), fever (81%), pulmonary oedema (54%) and pulmonary infiltrates (52%). A detailed review of potential risk factors for the development of RAS found no statistically significant association.

From these data, it seems clear that there is not one factor or cluster of factors that predict RAS. Some studies noted that the initial WBC count (>5000/μL on day 1) and/or a rapid rise in the WBC count (>10 000/μL on day 15) may be indicative of increased risk. The concurrent administration of chemotherapy with ATRA may also decrease the risk. De Botton *et al.* (7) retrospectively evaluated the results of the APL 93 trial and found a 9·2% (17/184) incidence of RAS in patients taking ATRA and receiving concurrent chemotherapy. Patients who were given ATRA without chemotherapy until remission was achieved had an 18% (22/122) incidence of RAS. Concurrent chemotherapy appears to decrease the incidence of RAS but is not without complications. Chemotherapy obviously adds the additional risk of bone marrow suppression and associated complications.

Wiley *et al.* (8) suggested that concurrent steroid administration with ATRA can decrease the incidence of RAS. These investigators treated 19 patients with ATRA as single-agent therapy. Twelve of these patients, whose WBC count rose above 10 000/μL, also received 75 mg/day of prednisolone as prophylaxis against RAS. Pulmonary toxicity developed in two patients who were subsequently treated with chemotherapy. As two of the 12 patients (17%) developed RAS, these data are not strong evidence for routine prophylactic steroids to prevent RAS and most authors would not recommend their use (2, 3).

Vahdat *et al.* (9) retrospectively reviewed all patients receiving ATRA for APL over a 4-year period. A total of 75 courses of ATRA therapy were evaluated for risk factors for the development of RAS. The strongest predictive factor was the presence of the CD 13 expression on the leukaemic cells. This not only had statistical predictive value ($P < 0{\cdot}05$) for RAS but also for the elevation of WBCs. Retinoids are known to increase the expression of certain surface adhesion molecules while steroid administration can suppress this. CD-13 (also called aminopeptidase N) is a type II glycoprotein expressed on a variety of cell types, such as renal tubules, intestinal epithelium and synaptic membrane cells (9). Several investigators (10, 11) reported that CD-13 expression in patients with APL confers a poor prognosis. Although this is an intriguing observation, no additional studies have been done to confirm this finding and further evidence will be necessary before this can be widely applied to patient care.

Liposomal ATRA has recently been investigated as an alternative to oral ATRA in the treatment of APL. Liposomal ATRA has several advantages over oral ATRA. First, liposomal encapsulated ATRA is metabolized to a lesser extent than oral ATRA resulting in sustained blood levels for a longer period of time. Second, liposomal ATRA, in contrast to oral ATRA, can induce polymerase chain reaction (PCR)-negative chronic remissions without chemotherapy. Finally, it has been suggested that liposomal ATRA may decrease the incidence of RAS as compared with oral ATRA (12–14).

Several investigators (15–18) evaluated liposomal ATRA in newly diagnosed patients with APL. These studies have been non-randomized trials using historical controls (oral ATRA + idarubicin) and small numbers of patients. Of the four studies evaluating liposomal ATRA, a total of 120 patients were treated achieving chronic remission in 92 patients (77%). More important, molecular remission (PCR negative) was achieved in a high number of patients. This is generally not considered possible without the addition of chemotherapy. These preliminary results stimulated further study of liposomal ATRA in APL patients. Unfortunately, of the four studies reporting efficacy of liposomal ATRA, only two (15, 16) reported the incidence of RAS. Sixteen of 52 (3%) patients in these studies developed RAS. Liposomal ATRA is currently undergoing phase I/II trials in the United States under the brand name Atragen (Aronex Pharmaceuticals, Woodlands, TX, USA). It is being investigated for a variety of haematological malignancies and solid tumours in addition to APL. Liposomal ATRA can induce molecular remission in some patients without the use of chemotherapy. Patients benefiting most from liposomal ATRA were those with WBC counts <10 000/μL and elderly patients with co-morbidities. Balancing these advantages are the need for intravenous administration of liposomal ATRA and the lack of long-term adverse effect and outcome data.

Table 1 is a compilation of available published cases of RAS (19–30). Although various doses, ranging from 10 to 100 mg/m^2 have been used; most clinical experience has been with a dose of 45 mg/m^2/day (administered once daily or divided equally in two doses) (1). Median time to development of RAS was 5 days (range 1–20 days). A wide variety of symptoms were associated with RAS although fever and respiratory symptoms were the most common. Three deaths occurred in this series of 14 cases. Table 2 is a listing of available clinical trials of ATRA for APL (8, 9, 31–42). We compiled the incidence of RAS along with the mortality associated with RAS. Mortality incidence (2%) is consistent with reported data. The overall incidence of RAS is slightly lower than the most widely reported numbers in the literature. Note that the lower incidences of RAS tend to occur in the more recent reports. This may reflect the increasing recognition of the syndrome and prompt institution of steroid therapy.

Table 1. Case reports of all-trans retinoic acid (ATRA)-induced retinoic acid syndrome (RAS)

Author	Age (years), sex	Duration of ATRA before RAS (days)	Chemotherapy	Manifestations of RAS	Treatment	Outcome
Kawasaki *et al.* (19)	16, F	5	Daunorubicin Cytarabine	Seizure, respiratory distress	Dexamethasone and Sivelestat given ATRA stopped	Patient received 5 cycles of chemo + ATRA achieving CR
	10, M	1	Daunorubicin Cytarabine	Vomiting, cerebral bleeding, respiratory distress	Dexamethasone Mannitol, Sivelestat ATRA stopped	Patient died on day 13
Leelasiri *et al.* (20)	29, M	13	Idarubicin	Fever, respiratory distress, haematuria, hypotension, DIC	Dexamethasone ATRA stopped	RAS resolved, remission achieved 1 course of consolidation therapy given
Battistella *et al.* (21)	42, F	1	Daunorubicin Cytarabine	Confusion, SOB	Dexamethasone ATRA stopped	Unknown
Garcia-Suarez *et al.* (22)	56, F	5	Idarubicin	Fever, dyspnea, hematuria, respiratory distress	Dexamethasone ATRA stopped Immunoglobulin for HPS	Patient developed HPS; resolved after 2nd course of consolidation therapy (idarubicin + ATRA)
Datta & Gerardi (23)	25, M	5	Cytarabine	Fever, chills, cough, bloody sputum, dyspnea	Methylprednisolone ATRA stopped	Symptoms resolved ATRA restarted and symptoms returned within 3 days
Goldschmidt *et al.* (24)	20, M	2	Cytarabine Daunorubicin	Dyspnea, hypoxia, respiratory distress, pulmonary infiltrates	Dexamethasone ATRA stopped (day 13)	Received further cycles of CT including ATRA
Astudillo *et al.* (25)	46, M	3	Daunorubicin Cytarabine	Fever, rash	Dexamethasone 40 mg/day ATRA stopped	Repeated courses of ATRA were given without occurrence of RAS
Spedini (26)	40, M	20	Idarubicin	Fever, respiratory distress, hypotension, weight gain, hyperleucocytosis	Dexamethasone ATRA stopped	RAS resolved, remission achieved (day 27)

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Table 1. Continued.

Author	Age (years), sex	Duration of ATRA before RAS (days)	Chemotherapy	Manifestations of RAS	Treatment	Outcome
Cupitt (27)	62, F	2	Conventional CT	Fever, spontaneous bleeding from gums, dyspnea	Dexamethasone ATRA stopped	Remained in remission
Raanani *et al.* (28)	36, M	7	Daunorubicin Cytarabine	Dyspnea, fever, haemoptysis	Dexamethasone ATRA stopped	Received 2 further courses of CT patient in CR
	59, M	6	'CT given'	Fever, dyspnea, hypotension, respiratory distress	Dexamethasone ATRA stopped	Patient died on day 29
Nagafuji *et al.* (29)	46, M	20	Cytarabine Aclarubicin	Fever, respiratory distress, oedema, weight gain, hypotension, pleural and pericardial effusion	Methylprednisolone Cytarabine and Idarubicin ATRA stopped	Patient relapsed and died on day 161
Nicolls *et al.* (30)	18, F	15	Hydroxyurea	Haemoptysis, respiratory distress	Dexamethasone ATRA was continued throughout course of therapy (45 days)	Patient received consolidation therapy and achieved CR

CT, chemotherapy; CR, complete remission; DIC, disseminated intravascular coagulation; SOB, shortness of breath; HPS, haemophagocytic syndrome.

Table 2. Incidence of retinoic acid syndrome (RAS) in clinical trials

Author	Total no. of patients	No. of RAS patients (%)	No. of deaths from RAS (%)
Ortega *et al.* (31)	66	3 (4·5%)	2 (3%)
Testi *et al.* (32)	107	2 (2%)	0 (0%)
Lengfelder *et al.* (33)	51	8 (15%)	0 (0%)
Burnett *et al.* (34)	239	(?)	5 (2%)
Sanz *et al.* (35)	123	7 (6%)	1 (0·8%)
Fenaux *et al.* (36)	413	64 (15%)	5 (1%)
Tallman *et al.* (37)	172	45 (26%)	2 (1%)
Avvisati *et al.* (38)	20	2 (10%)	0 (0%)
Kanamaru *et al.* (39)	109	7 (6%)	1 (1%)
Wiley & Firkin (8)	22	2 (9%)	0 (0%)
Cortes *et al.* (40)	17	4 (24%)	1 (6%)
Frankel *et al.* (41)	56	13 (23%)	5 (9%)
Vahdat *et al.* (9)	78	21 (27%)	5 (6%)
Fenaux *et al.* (42)	54	6 (11%)	0 (0%)
Overall incidence	1527	184 (12%)	27 (2%)

CONCLUSION

Retinoic acid syndrome is an unpredictable but frequent complication of ATRA and clinicians treating patients with APL should be aware of this disorder. The best approach for management of RAS is early recognition and prompt administration of steroids at the first sign of unexplained dyspnea, fever, weight gain or pulmonary infiltrate. Identifying and monitoring patients likely to develop RAS (i.e. patients with high WBC counts, rapidly increasing WBC counts and/or the presence of the CD 13 expression on leukaemic cells) may further decrease mortality from this syndrome. Concurrent chemotherapy will probably decrease the risk of developing RAS but carries its own hazards. Concurrent steroids are not recommended. Liposomal ATRA is being investigated to induce haematological cure in APL without chemotherapy and to reduce the incidence of RAS.

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