REVIEW ARTICLE

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Neuromuscular Adverse Effects Associated with Systemic Retinoid Dermatotherapy

Monitoring and Treatment Algorithm for Clinicians

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Contents

Abstract

Although neuromuscular adverse effects represent significant clinical manifestations of hypervitaminosis A syndrome, surprisingly little attention has been paid to the potential neuromuscular toxicity of vitamin A derivatives (retinoids). Since isotretinoin and acitretin are currently the two most commonly used oral retinoids in systemic dermatotherapy, this review focuses exclusively on their neuromuscular adverse effects and proposes a neuromuscular algorithm for appropriate monitoring of patients treated with these two compounds.

The most frequent CNS adverse effect associated with oral isotretinoin is headache, either as an independent adverse effect or as part of benign intracranial hypertension, which is additionally characterized by nausea and visual changes. Isolated cases of stiff-person-like syndrome, epileptic seizures and generalized muscle stiffness syndrome, possibly or probably related to oral treatment with isotretinoin, have also been reported. In addition, oral isotretinoin has reportedly been associated with muscular adverse effects that most frequently manifest as myalgia and stiffness and, in rare cases, as true myopathy or rhabdomyolysis. Creatine phosphokinase, a specific marker

of muscle destruction, has been found to be elevated, occasionally by up to 100 times the normal value (with or without muscular symptoms and signs), in a variable percentage of patients receiving isotretinoin treatment and particularly in those undergoing vigorous physical exercise.

Oral acitretin has been found to cause peripheral nerve dysfunction, particularly of sensory fibres, which in rare cases leads to clinically evident sensory disturbances. Less clear is the causal relationship between acitretin and benign intracranial hypertension or myopathy, whereas an isolated case of cranial nerve IV (oculomotor) palsy and a further case of thrombotic stroke during treatment with oral acitretin have been reported.

Systemic diseases with involvement of nervous and/or muscle tissue and neuromuscular disorders should be regarded as exclusion criteria for initiation of oral retinoid therapy. Additionally, intense physical exercise and concurrent treatment with neurotoxic or myotoxic drugs should be avoided during treatment with oral retinoids. In order to minimize the potential risk of neuromuscular adverse effects, a neuromuscular algorithm is suggested that may be useful for monitoring patients taking oral retinoids.

In the last 3 decades, numerous clinical trials have demonstrated the efficacy of oral retinoids (vitamin A derivatives) in the management of severe and recalcitrant dermatoses, which previously represented frustrating therapeutic problems. Thus, oral isotretinoin (13-*cis*-retinoic acid), a representative of the first retinoid generation, is widely used as a first-line option in the systemic treatment of severe acne and rosacea.[1] Oral alitretinoin (9-*cis*-retinoic acid), another representative of this generation, shows substantial therapeutic efficacy in chronic hand dermatitis refractory to conventional therapy.[2] Oral acitretin, a representative of the second retinoid generation, is the drug of choice for the management of severe psoriasis and other keratinization disorders,[1] whereas bexarotene, the first synthetic retinoid X receptor-selective agonist, is thought to be a safe and effective alternative for treatment of cutaneous T-cell lymphoma.[3] Furthermore, both isotretinoin and acitretin are successfully used in the chemoprevention and therapy of various forms of skin cancer.[3-6]

Retinoids play essential roles in the growth, differentiation, regeneration, maintenance and apoptosis in the human nervous system,[7-10] and are known to exert pleiotropic effects on the development, differentiation and metabolism of skeletal muscle cells.[11-14] Although neuromuscular adverse effects represent significant clinical manifestations of hypervitaminosis A syndrome,[15] surprisingly little attention has been focussed on the potential neuromuscular toxicity of oral retinoids, compared with that paid to the mucocutaneous, hepatic, metabolic, haematological and skeletal adverse reactions of these compounds.[1,16,17] Since numerous patients worldwide are currently being treated with oral retinoids, it is of paramount importance that clinicians are aware of any possible adverse reactions of these compounds. The clinical use of oral alitretinoin and bexarotene in systemic dermatotherapy is currently markedly limited, compared with that of oral isotretinoin and acitretin. Moreover, no neurological or neurophysiological studies have been conducted in patients treated with oral alitretinoin or bexarotene. Thus, in this review we report exclusively on the neuromuscular adverse effects of oral isotretinoin and acitretin, and propose an algorithm for appropriate monitoring of patients treated with these compounds.

This review is based on all relevant medical reports found by a search of MEDLINE over the period 1982–2009 using the following key words as search terms: 'retinoids', '13-*cis*-retinoic acid', 'isotretinoin', 'acitretin', 'vitamin A analogue' in association with 'cutaneous disorders', 'acne', 'psoriasis', 'ichthyosis', 'keratinisation disorders' and 'neurological' or 'muscular' or 'central nervous

system' or 'nerve', 'adverse effects/reactions or side-effects', 'neuropathy' and 'myositis'. All medical reports (including short communications and letters to the editor) referring to a possible association between isotretinoin or acitretin therapy and neuromuscular adverse-effects were included in this review. Studies referring to adverse effects of other retinoids or studies of adverse effects of retinoid treatment for non-dermatological diseases were excluded.

To facilitate reading, the neuromuscular adverse effects of oral isotretinoin and acitretin are divided into three main sections – those referring to the CNS, peripheral nerves and muscles. In each section, the adverse effects are presented separately for each retinoid.

1. CNS

1.1 Isotretinoin and the CNS

Headache is the most common CNS adverse-effect of oral isotretinoin therapy.[18] It usually occurs with the first 1–6 weeks of treatment onset and has the characteristics of tension- or migraine-type headache. When the headache is severe, persistent and accompanied by nausea, vomiting, and blurred and/or double vision, a condition known as benign intracranial hypertension (also known as pseudotumour cerebri) should be suspected. This diagnosis must be confirmed by the presence of papilloedema and an increase in cerebrospinal fluid (CSF) pressure.[19] As at 2003, four publications had reported approximately 20 cases of benign intracranial hypertension in adolescent or adult patients receiving oral isotretinoin alone or in combination with tetracycline.[18,20-22] More recently, a thorough investigation published in 2004 disclosed 179 cases of benign intracranial hypertension reported between 1982 and 2003 in which the condition developed during oral isotretinoin administration;[23] however, 24% of these patients had been taking other drugs concomitantly (such as tetracycline) that have also been associated with benign intracranial hypertension. In most cases symptoms and signs occurred during the first 2 months of treatment and resolved within several weeks to a few months after drug discontinuation.[18,23] Furthermore, in 3% of these patients, benign intracranial hypertension relapsed upon re-initiation of isotretinoin. It has been suggested, therefore, that an aetiological relationship may exist between benign intracranial hypertension and oral isotretinoin administration, and that fundoscopy should be performed in patients complaining of persistent headache during oral isotretinoin treatment in order to exclude papilloedema.[24] The exact role of oral isotretinoin in the pathogenesis of benign intracranial hypertension remains to be elucidated. However, it is possible that this retinoid may induce either an increase in CSF production by the choroid plexus or a decrease in CSF absorption by the arachnoid villi.[25]

There are two anecdotal reports of epileptic seizures occurring in patients receiving oral isotretinoin.[26,27] However, since epilepsy is a common condition in the general population and often cryptogenic in origin, the possibility of a causal association requires further confirmation. A possible association between oral isotretinoin and a single demyelinating lesion in the cerebellum, manifested by tinnitus and a feeling of faintness, has been suggested in a recent report.[28] The significance of this observation is presently unknown since the prevalence of CNS demyelinating diseases in the general population, particularly in the younger population (age 20–40 years), is high, with more than 2 million people being affected worldwide.[29] According to the excellent review of Bigby and Stern,[18] two unusual complications, a disulfiram reaction after alcohol intake and an oculogyric crisis, are thought to have been possibly related to oral isotretinoin therapy.

Oral administration of isotretinoin (1 mg/kg/day) for 10 days to an 18-year-old male patient with severe acne resulted in generalized muscle stiffness and superimposed painful spasms, which responded favourably to diazepam and resolved completely within 2 weeks after isotretinoin withdrawal.[30] The clinical manifestations matched the diagnosis of stiff-person syndrome, which is considered to be due to inactivation of GABAergic inhibitory circuits within the CNS. Interestingly, a similar case of muscle rigidity and diffuse myalgias accompanied by headache and

fever has been recently reported in one patient during oral isotretinoin therapy.[31] It is possible that impairment of the crosstalk between GABAergic receptors and isotretinoin signalling systems, or stimulation of production of antibodies against glutamic acid decarboxylase (an enzyme that catalyzes the decarboxylation of glutamate to GABA) may be involved in the pathogenetic mechanisms underlying the isotretinoin-induced stiff-person syndrome.[32-34]

A small number of laboratory studies have revealed subclinical alterations of brain function in association with oral retinoid treatment, the exact clinical relevance of which remains to be elucidated. In a prospective neurophysiological study, Nikiforidis et al.[35] observed prolongation of latency and reduction in amplitude of auditory-evoked potentials in 3 of 33 patients treated with oral isotretinoin, compared with the pretreatment phase. These investigators suggested that these subclinical alterations may have been due to an isotretinoin-induced synaptic malfunction or to a conduction defect in the auditory nerve fibres caused by this retinoid. Confirming these results, a recent study of the effects of oral isotretinoin on auditory- and visual-evoked potentials showed a significant prolongation of latency of the third and fifth wave of auditory-evoked potentials in the isotretinoin-treated group, and an increase of P100 latency of the visual-evoked potentials in 6 of 32 treated patients.[36]

Along the same lines but in the psychiatric field, a recent brain imaging study suggested that oral isotretinoin may affect brain function, thereby identifying a potential biological mechanism that could lead to depression in a minority of vulnerable acne patients.[37] The investigators conducted [^{18}F]positron emission tomography in 28 adult patients with acne who were treated with oral isotretinoin. After 4 months of continuous treatment, metabolism was found to be decreased in patients' orbitofrontal cortex, a region where low metabolic rate has been observed in depressed individuals.

1.2 Acitretin and the CNS

Although benign intracranial hypertension is a well known adverse effect of etretinate,[38,39] the parent compound of acitretin, until 2004 there was a paucity of data in both the published literature and postmarketing surveillance reports with regard to an association between oral administration of acitretin and the occurrence of benign intracranial hypertension.[40] A retrospective survey disclosed only three reported patients with benign intracranial hypertension probably caused by oral acitretin over a period of 20 years.[24] This scarcity of scientific evidence for a clear-cut relationship between oral acitretin and benign intracranial hypertension may be related to a different pattern of neurotoxicity of this compound compared with etretinate. Alternatively, benign intracranial hypertension may more frequently occur in acitretin-treated patients but is under-diagnosed and under-reported, possibly because of lack of awareness and poor monitoring.

Royer et al.[41] reported on a 52-year-old female psoriatic patient who sustained an ischaemic stroke in the territory of the vertebral-basilar system after 1 month of oral acitretin therapy. These investigators suggested that administration of this drug could possibly be related to the thrombotic process precipitating the stroke since no other obvious cause was detected in this case. Although this hypothesis cannot be definitely ruled out, we believe the skin disorder of the patient in this case should also be considered a possible pathogenetic factor for stroke since the prevalence of stroke and other vascular diseases in patients with psoriasis is significantly higher than that observed in the general population.[42]

2. Peripheral Nervous System

2.1 Polyneuropathies

2.1.1 Isotretinoin and Peripheral Nerves

A limited number of studies have investigated the potential of oral isotretinoin to cause peripheral nerve dysfunction. A case of sensorimotor demyelinating polyneuropathy[43] reportedly developed 3 months after the initiation of oral isotretinoin treatment and subsided following withdrawal of the drug; however, the nature and severity of the reported nerve damage remain unclear. Absence of any clinical symptoms and signs points towards a subclinical neuronal dysfunction,

electrophysiological findings favour a multifocal severe demyelinating process and active nerve regeneration found at nerve biopsy implies a preceding axonal degeneration. Pritchard et al.[44] reported on two patients who developed Guillain-Barré syndrome (GBS) in temporal relationship to oral isotretinoin treatment. In view of the relatively high annual incidence of GBS in the general population (about 2 cases/100 000[45]) and the lack of other reported cases among the numerous patients treated with oral retinoids over the last 3 decades, these investigators expressed doubts about a possible causal relationship between isotretinoin and GBS in their two patients.

In an attempt to unfold the full spectrum of oral isotretinoin adverse effects on peripheral nerves, we conducted a prospective follow-up study of 18 consecutive patients receiving oral isotretinoin but were unable to detect any clinical or electrophysiological evidence of nerve dysfunction after 1 and 3 months of treatment.[46] In contrast, another similarly designed study including the same number of patients reported subclinical electrophysiological findings, indicating a predominantly sensory neuropathy.[47] A direct comparison of the results between the two studies is not possible since the actual numerical values of the neurophysiological parameters evaluated in the latter study were not presented. Nevertheless, the authors of the second study commented on the absence of patient-by-patient changes, although a groupwise analysis showed significant differences in some electrophysiological parameters.[48]

2.1.2 Acitretin and Peripheral Nerves

In an attempt to substantiate the possible effects of acitretin on peripheral nerve function, we conducted a prospective neurological and neurophysiological study of 13 dermatological patients receiving oral acitretin.[49] After 3 months of therapy, nine patients (69%) were found to have alterations in one or more neurophysiological, mainly sensory, parameters, all of which remained subclinical. In 2002, we reported a patient with a normal pretreatment neurological and neurophysiological profile who developed a sensorimotor polyneuropathy after 3 months of oral treatment with acitretin; the disturbance subsided 2 months after cessation of therapy.[50] One year later, we reported two further patients with sensory neuropathies that occurred after 3 and 4 months of oral acitretin therapy, respectively, and which resolved completely 2 and 2.5 years, respectively, after drug discontinuation.[51] In view of these data, it seems reasonable to suggest that oral acitretin is capable of causing damage to peripheral nerves, which in most cases remains subclinical.

2.2 Cranial Mononeuropathies

2.2.1 Isotretinoin and Cranial Mononeuropathies

Among >2000 possible ocular adverse events of oral isotretinoin therapy that were spontaneously reported to the US FDA and WHO by March 1999 there were 35 cases of diplopia, 473 cases of blurred vision, 394 cases of keratitis and 50 cases of cataract.[52] Nevertheless, it remains unknown whether the reported cases of diplopia and strabismus due to dysfunction of oculomotor nerves, usually of the cranial sixth nerve, were manifestations of the benign intracranial hypertension syndrome. To our knowledge, cases of isolated cranial mononeuropathies due to oral isotretinoin treatment have not been reported.

2.2.2 Acitretin and Cranial Mononeuropathies

A patient who developed isolated cranial sixth nerve palsy after 3 months of oral acitretin administration was reported by Arnault et al.[53] However, no definite causal relationship between oral acitretin and this mononeuropathy can be inferred on the basis of this single case, given the high frequency of cranial sixth nerve palsy in the general population (11 cases/100 000, 25% idiopathic[54]) and the negative re-challenge reported in this patient.[53]

3. Muscles

3.1 Isotretinoin and Muscles

The most frequently reported muscle-related adverse effects of oral isotretinoin therapy over the period 1982–2005 were myalgia, muscle

tenderness and stiffness, occurring in 16–51% of patients.[55,56] These manifestations are usually mild and quickly reversible after discontinuation of isotretinoin;[39,57] only in several rare reported cases has myalgia persisted for several months.[18] True myopathy is relatively rarely observed during oral treatment with isotretinoin. Two reports,[58,59] each describing two patients who manifested weakness, muscle pain, stiffness and fatigue several days to a few months after onset of oral isotretinoin therapy, have been published. These manifestations were typical for acute myopathy, the diagnosis of which was confirmed by needle electromyography. Histo-pathological examination of muscle biopsy by light microscopy revealed a slight variation or reduction in the size of muscle fibres. At the ultrastructural level (one case), elongated, elliptical, non-membrane bound bodies unrelated to cytoplasmic organelles were observed. Severe alterations were also found at the neuromuscular junction with atrophy of the nerve terminals and a lack of synaptic vesicles; in addition, the folded sarcolemma contained only primary clefts.[58] Interestingly, full recovery was reported in all four patients within 1–2 months following drug discontinuation.

Serum creatine phosphokinase (CPK) levels are known to increase upon muscle breakdown or impairment of the muscle plasma membrane and are therefore considered to be the most sensitive and specific marker of muscle destruction. Surprisingly, in patients treated with oral isotretinoin, serum CPK levels have been reported to be increased in both the presence or absence of myopathy,[58,60,61] and normal despite clinical symptoms of myopathy.[59] In a retrospective analysis of the medical records of 60 patients treated with oral isotretinoin, elevated CPK was found in 41% of patients.[56] In the largest reported series, consisting of 442 patients, elevated CPK was found in 37.3% of patients, but only 1.58% of patients had CPK levels >5000 U/L (normal level <200 U/L), suggestive of massive muscle damage.[60] The percentage of patients with increased CPK levels appeared to be very low in the most recent study, in which only 5 of 89 enrolled patients (5.6%) had CPK levels 2–5 times the normal limit.[61] No explanation for the discrepancy in the results of these studies has been suggested.

The most severe and potentially dangerous muscle-related adverse effect of oral isotretinoin is acute rhabdomyolysis, which is characterized by generalized muscle pain, fatigue, profound weakness, a 5-fold or greater increase in serum CPK levels and, often, myoglobinuria.[62] If left untreated, acute rhabdomyolysis can lead to acute renal failure related to obstruction of renal tubules by the precipitated myoglobulin. Two cases of rhabdomyolysis with complete recovery following cessation of oral isotretinoin treatment have been recorded.[62,63]

Increased serum CPK levels (without clinical myopathy) in patients treated with oral isotretinoin might be due to cytokine-mediated muscle damage during concurrent intense physical activity or viral infections.[18,56,60,64,65] Additionally, an *in vitro* study in rat liver showed that, in the presence of isotretinoin (or other retinoids), the mitochondrial membrane potential is rapidly decreased, cytochrome c is released into the cytosol of hepatocytes and apoptosis is initiated.[66] Interestingly, depletion of cytochrome c, which is part of the mitochondrial respiratory chain, has been implicated in mitochondrial myopathies characterized by exercise intolerance and recurrent myoglobinuria.[67]

3.2 Acitretin and Muscles

Oral administration of the parent compound of acitretin (etretinate) has rarely been associated with increased serum CPK levels, electromyographic evidence of muscle damage or true clinical myopathy.[38,58] Muscle pain and weakness have been reported in a few patients taking oral acitretin[38] but only one well documented case of severe myopathy has been observed in a 64-year-old male patient 14 days after initiation of oral acitretin.[68] The myopathy in this case was characterized by generalized weakness, mild muscle swelling and markedly raised CPK levels, and resolved within 2 months following discontinuation of retinoid administration.

The available clinical and experimental evidence suggest that oral isotretinoin and acitretin

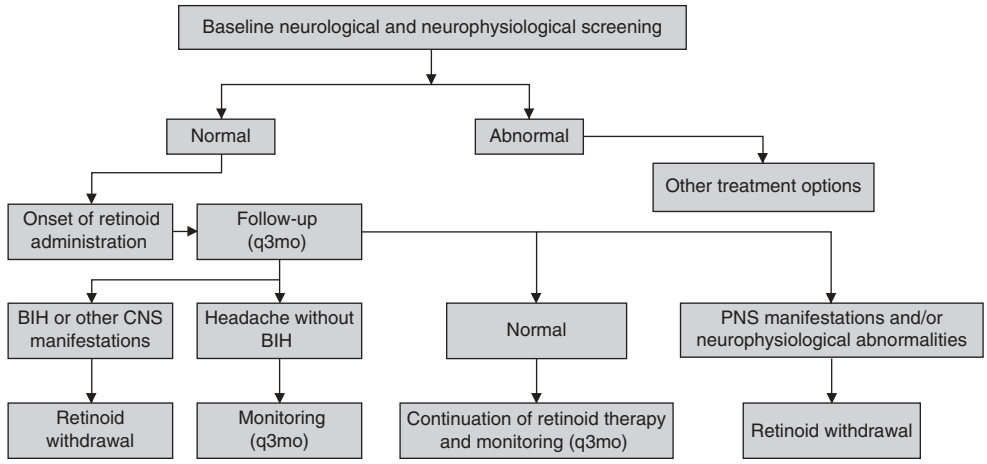

Fig. 1. Algorithm for monitoring patients treated with oral retinoids with regard to CNS and peripheral nervous system (PNS) adverse effects of these drugs. **BIH** = benign intracranial hypertension; **q3mo** = every 3 months.

may be capable of differentially affecting the function of the nervous system and muscles, and of causing corresponding adverse effects of varying frequency and severity which in most cases are completely reversible upon withdrawal of these drugs. Indeed, the CNS and the muscles seem to be primarily affected by oral isotretinoin, whereas oral acitretin may act mainly on peripheral nerves. Further studies are now warranted to define the validity of this hypothesis.

4. Suggested Neuromuscular Algorithm of Retinoid Treatment

In view of the reported central and peripheral nervous system-related adverse effects of oral retinoids, a standard baseline neurological evaluation prior to onset of retinoid therapy and follow-up examinations are advisable (figure 1). If the findings of the baseline neurological and neurophysiological screening are abnormal, other treatment options should be considered for the patient. Otherwise, oral retinoid treatment can be initiated and the patient should then be followed up every 3 months. Treatment should be discontinued in patients presenting at follow-up examinations with benign intracranial hypertension or other CNS manifestations, or with peripheral nerve manifestations and/or neurophysiological abnormalities. Retinoid therapy should be continued in patients with normal results at follow-up examinations and in those who experience headache but who do not meet the criteria for the diagnosis of benign intracranial hypertension.

Retinoids should be prescribed with caution in the presence of medical conditions, such as thyroid dysfunction, Cushing's disease, systemic lupus erythematosus, obesity, prolonged corticosteroid therapy and corticosteroid withdrawal, all of which are known to cause benign intracranial hypertension. For the same reason, concurrent administration of retinoids with tetracycline, lithium or other drugs that have been independently associated with benign intracranial hypertension should be avoided. Additionally, since the adverse effects of oral retinoids in patients with pre-existing peripheral nerve damage (secondary to systemic disorders or other neurotoxic drugs) could be augmented, administration of these agents to such patients is not recommended.

The baseline neurological evaluation should also include assessment of skeletal muscles (figure 2). Other treatment options should be considered for patients with abnormal baseline serum CPK levels and/or abnormal findings on the clinical examination of the muscles. Conversely, oral retinoid therapy can be initiated in patients with normal values for these parameters. Therapy should be continued

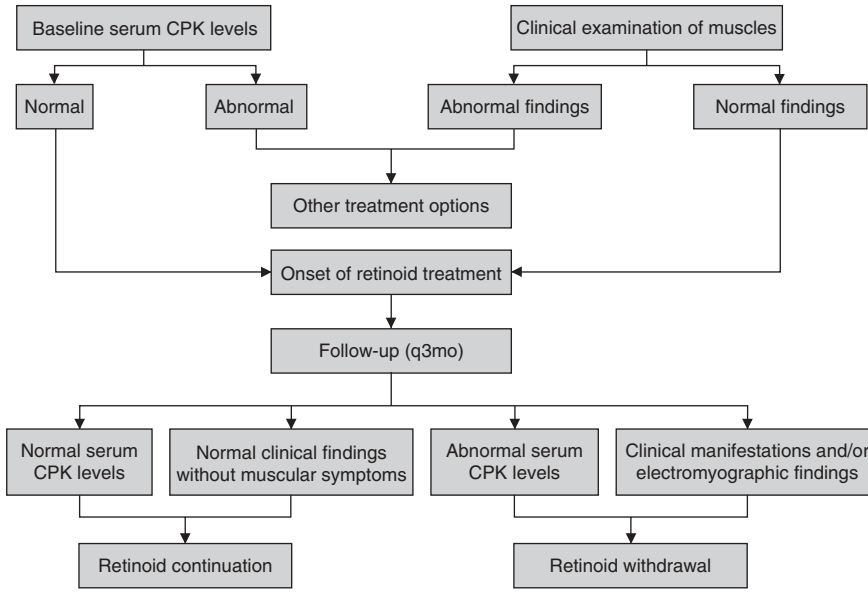

Fig. 2. Algorithm for monitoring patients treated with oral retinoids with regard to the muscle adverse effects of these drugs. **CPK** = creatine phosphokinase; **q3mo** = every 3 months.

in retinoid-treated patients who present for follow-up examination every 3 months and who have normal serum CPK levels and normal clinical findings without muscular symptoms. Treatment should be discontinued in patients who present for follow-up examination with abnormal serum CPK levels, clinical manifestations and/or pathological electromyographic findings. Intense physical exercise during oral retinoid treatment must be avoided to reduce the risk of muscle adverse effects. Moreover, clinicians should be extremely reluctant to prescribe retinoids for patients being concurrently treated with drugs that possess myotoxic potential (HMG-CoA reductase inhibitors ['statins'], corticosteroids, colchicine, penicillamine and alcohol).

5. Conclusions

Oral isotretinoin and acitretin are capable of affecting the nervous system and muscles, causing corresponding adverse effects of varying frequency and severity, which in most cases are completely reversible upon withdrawal of these drugs. It seems that CNS and muscles may be primarily affected by oral isotretinoin, whereas oral acitretin may act mainly on peripheral nerves. In order to minimize the potential risk of neuromuscular adverse effects of oral retinoid treatment, the following should be considered.

- Neuromuscular disorders and systemic diseases with involvement of nervous and/or muscle tissue should be regarded as exclusion criteria for the initiation of oral retinoid therapy.
- The suggested neuromuscular algorithms may be useful for monitoring retinoid-treated patients.
- Intense physical exercise and concurrent treatment with neurotoxic or myotoxic drugs should be avoided during treatment with oral retinoids. However, the type and level of exercise that could be harmful to the muscle tissue of patients taking oral retinoid therapy is currently unknown. Indeed, we have regularly observed in a number of oral retinoid-treated patients that daily mild physical exercise surprisingly led to a remission of retinoid-induced myalgia with CPK levels indicating no abnormality (Chroni E et al., unpublished observations).

Prospective clinical trials involving large numbers of patients should address the following

major issues with regard to the neuromuscular adverse effects of oral retinoids.

- The exact prevalence, reversibility and management of oral retinoid adverse reactions on the central and peripheral nervous system and the muscles.
- The influence of patient-related factors (sex, age, cutaneous disorder, concurrent diseases and medications, diet, polymorphisms and mutations of genes encoding major enzymes in retinoid metabolism, radiation exposure, immune status) and retinoid therapy-related factors (daily and cumulative retinoid dose, duration, continuous or intermittent mode of administration) on expression of oral retinoid neurotoxicity and myotoxicity.

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