

## Case Report

# Refsum's Disease—Use of the Intestinal Lipase Inhibitor, Orlistat, as a Novel Therapeutic Approach to a Complex Disorder

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Refsum's Disease is an inherited metabolic disorder in which a metabolite of branched chain fatty acids accumulates due to lack of appropriate oxidative enzymes. Patients have elevated plasma phytanic acid levels and high concentrations of phytanic acid in a variety of tissues leading to progressive tissue damage. Besides retinal degeneration or retinal dystrophy associated with adult onset retinitis pigmentosa, additional symptoms include chronic polyneuropathy, cerebellar ataxia, sensorineural hearing loss, anosmia, ichthyosis, as well as skeletal, cardiac, hepatic, and renal abnormalities. Current management includes avoidance of dietary sources of branched chain fatty acids and regular plasmapheresis to prevent accumulation of these compounds to ameliorate progressive neurological deficits. Two brothers with Refsum's disease who experienced progressive symptoms despite optimal diet and plasmapheresis were commenced on a novel therapy. We report the effect of the intestinal lipase inhibitor, Orlistat, which led to significant reduction ( $P$ -value < 0.001 on 2-sample unpaired  $t$ -test) of mean preplasmapheresis phytanic acid levels with retardation of the progression of most of their dermatological and neurological symptoms.

## 1. Introduction

Refsum's Disease, also known as hereditary ataxia polyneuritisformis (HAP), was described by Norwegian neurologist Sigvald Refsum in 1946. It is a rare complex disorder that affects many organs. It has an autosomal recessive pattern of inheritance due to mutations on chromosome 10p13. Carriers are unaffected, however they may asymptotically exhibit slightly elevated phytanic acid levels, whereas Refsum's disease patients have markedly elevated levels (normal <0.70 mg/dL) [1].

Phytanic acid is a branched-chain fatty acid (BCFA), formed by bacterial degradation of chlorophyll in the intestinal tract of ruminants, invertebrates and, pelagic fish [2]. Individuals with Refsum's disease are unable to metabolize phytanic acid by the  $\beta$ -oxidation pathway due to

deficiency of the peroxisome enzyme phytanoyl-CoA hydroxylase (PAHX) [2–5] (Figure 1). It is essential for the 3-methyl group in the  $\beta$ -position of this BCFA to be removed by an  $\alpha$ -oxidation step, activated by PAHX (within the endoplasmic reticulum) in order to proceed with the  $\beta$ -oxidation pathway. Peroxisomal  $\beta$ -oxidation is the most efficient mechanism for the metabolism of phytanic acid. As a result, high levels of phytanic acid accumulate in blood and other tissues, especially adipose tissue, neural tissue, and astrocytes, where they cause oxidative stress in mitochondria and oxidative damage during chronic exposure [3, 6, 7]. In a subset of patients, a mutation of a second gene encoding for PEX7- peroxin 7 receptor protein, involved in peroxisomal import of proteins, has been identified as a cause for the phenotype of Refsum's disease [2, 5].

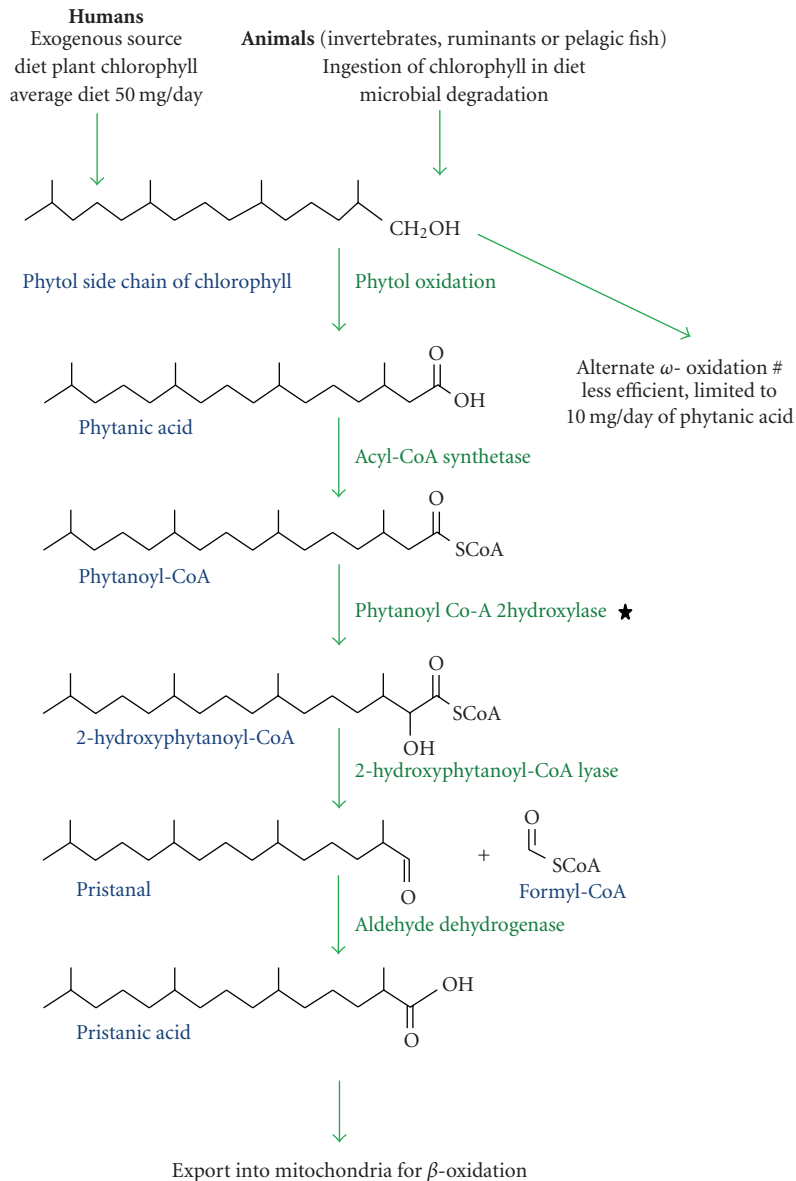


FIGURE 1: Metabolic pathway of phytanic acid. Phytanic acid is derived from microbial degradation of the phytol side chain of chlorophylls ingested by ruminants, invertebrates, or pelagic fish. In humans the source is phytol from diet chlorophyll, or from meat, pelagic fish, or dairy. When digested it is incorporated into chylomicrons/VLDL and then transported to liver and tissues for further metabolism. Most fatty acids are metabolised by  $\beta$ -oxidation pathways in peroxisomes and mitochondria. ★ denotes the enzyme deficient in patients with Refsum disease. # denotes the alternate less efficient  $\omega$ -oxidation pathway.

Early diagnosis of HAP or Refsum's disease is important because treatment is available to minimize progression. Classical Refsum's disease is usually diagnosed during childhood or early adulthood when visual problems due to retinitis pigmentosa become apparent [1, 8]. Accumulation of phytanic acid beneath the retina results in progressive visual impairment. The presenting symptom is usually night blindness followed by gradual loss of peripheral vision. Cataracts, which are common in patients with retinitis pigmentosa, may develop. Refsum's disease leads to other sensory complications, including impaired sense of smell,

usually occurring in early childhood but some times undiagnosed until other symptoms become apparent. Gradual or sudden hearing loss can occur in adulthood, usually after the 3rd decade. Cardiac abnormalities include cardiomyopathy or even fatal arrhythmias. Other neurological manifestations include peripheral neuropathy, paraesthesia, and cerebella ataxia. Ichthyosis, malaise, anorexia, and skeletal bone abnormalities such as bony prominences around elbows, knees and ankles and short digits of tubular bones of hands or feet (especially the metatarsal of the fourth toe) are also common. Renal and hepatic manifestations include tubular



FIGURE 2: Shortening of AF's fourth toe, characteristic of Refsum's Disease.

dysfunction, aminoaciduria, and fatty degeneration [1, 5, 8–11].

Humans have a secondary, less efficient pathway for phytanic acid metabolism via  $\omega$ -oxidation, which is not affected in these patients [2, 5] (Figure 1). However the capacity of  $\omega$ -oxidation is limited and it is only sufficient to process the reduced supply of phytanic acid associated with dietary restriction. It is reported in animal studies that fibrates may induce this  $\omega$ -oxidation pathway of phytanic acid metabolism [2].

**1.1. Current Management.** Patients with Refsum's disease require multidisciplinary monitoring to detect cardiac, ophthalmic, and neurological manifestations. Humans do not synthesize phytanic acid, obtaining it almost exclusively from their diet. Phytanic acid is found in meat, pelagic fish, and dairy products [2]. Humans also convert phytol, a side chain of chlorophyll found in green leafy vegetables, to phytanic acid. It is impossible to achieve a diet that is completely free of phytanic acid. Management of Refsum's disease requires a diet restriction of intake of phytanic acid to <10–20 mg/day (i.e., about 10% of that in a normal western diet) [1]. These low phytanic acid (<10 mg/dL) diets are very stringent [1].

Lowering of plasma phytanic acid levels by the long-term adherence to diets low in phytanic acid and phytol may be enhanced by serial plasma exchange to prevent development or progression of neuropathy, ataxia, cardiac arrhythmias, and ichthyosis [1, 10]. It is less certain whether progression of retinitis pigmentosa, anosmia or deafness can be prevented. It is important that patients maintain body weight, since rapid weight loss releases phytanic acid stored in body tissues and increases symptoms. Similarly fevers, pregnancy, and catecholamine released during plasmapheresis have been associated with acute or subacute presentations that mimic Guillain-Barre Syndrome or chronic inflammatory demyelinating polyneuropathy.

**1.2. Rationale for Treatment with Orlistat.** Orlistat (Xenical) is an inhibitor of intestinal lipase that blocks the digestion of triglycerides. We hypothesised that it would therefore

reduce absorption of dietary branched chain fatty acids, in particular phytanic acid. Orlistat is usually prescribed for weight loss and has a favourable safety profile which has contributed to the decision to make it available across the counter. Side effects associated with Orlistat therapy include diarrhoea, faecal incontinence following excessive fat ingestion, and a slight decrease in absorption of fat soluble vitamins. It must be noted that Orlistat-induced weight loss might release adipose stores of phytanic acid, thereby increasing plasma levels. We guarded against this possibility by advising our patients to increase their calorie intake so as to maintain weight.

## 2. Methods and Patients

The family comprised five children, four brothers and one sister, born of consanguineous parents. There is no clear history of a similar disorder in other generations of the family. Brothers AF (50 years) and VF (48 years) were diagnosed following the detection of the disorder in their older brother ALF (56 years) who was living overseas. The diagnosis of Refsum's disease was made when ALF presented to an ophthalmologist with progressive visual symptoms due to retinitis pigmentosa. The family was screened, and the younger brothers AF and VF were found to have elevated plasma phytanic acid levels (AF 18.5–36 mg/dL and VF 33–41 mg/dL). In retrospect, brothers AF and VF reported long standing symptoms of poor sense of smell, tinnitus, loss of peripheral vision, and clumsiness. Examination revealed anosmia, retinitis pigmentosa, constricted visual fields, nystagmus, impaired coordination, and ataxia on heel-toe walking. AF also had an episode of nonsustained cardiac arrhythmia, long-standing irritable bowel syndrome, and a characteristic deformity in his fourth toes (Figure 2) which was reported to be a feature in brother ALF as well. The additional features in younger brother VF included hearing impairment, ichthyosis, long slender toes, and multiple bony prominences which are associated with Refsum's disease.

Following confirmation of the diagnosis by serum phytanic acid measurements, both brothers commenced a low phytanic diet and plasmapheresis. The plasma phytanic acid levels at base-line and with dietary treatment plus plasmapheresis are shown in Figure 3(a). Despite this intensive treatment, the two brothers continued to have progressive symptoms and incomplete control of plasma phytanic acid levels (greater than 10 times the upper limit of normal). Substantially lower treatment goals were recommended to minimize complications or progression of disease.

At this stage they were referred to the lipid and metabolic disorder clinic at Royal Prince Alfred Hospital in Sydney for further optimisation of treatment.

**2.1. Method.** AF and VF commenced treatment with Orlistat at the standard dose of 120 mg three times a day before meals. However their compliance was incomplete and they managed only two doses per day over the first few months. They continued a suitable low-phytanic acid diet with adequate calorie intake to avoid weight loss and regular

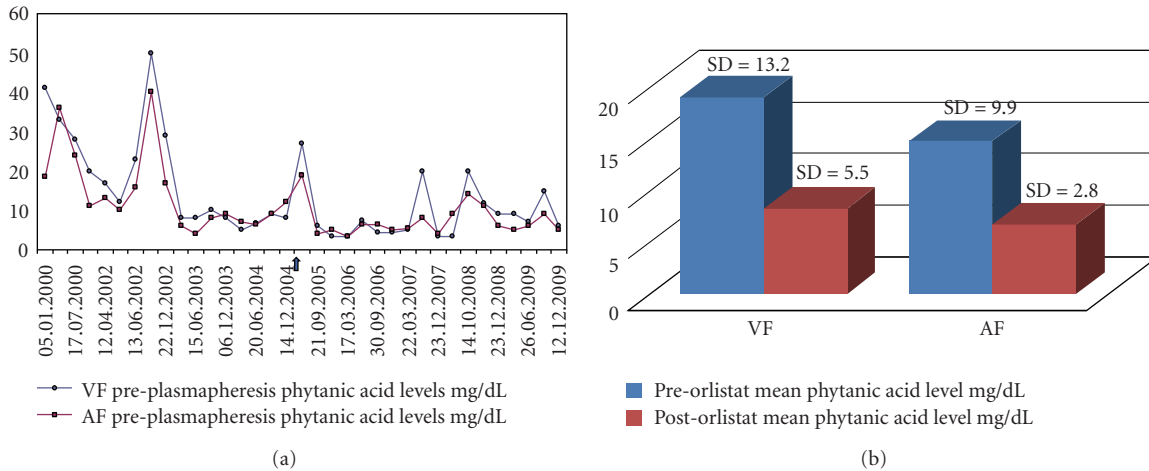


FIGURE 3: (a) Pre-plasmapheresis plasma phytanate (phytanic acid) levels. AF's and VF's preplasmapheresis phytanic acid levels before and after addition of Orlistat (Xenical) therapy to diet and regular plasmapheresis (shown by arrow in June 2005) showing good control of phytanic acid levels except during periods of non compliance with Orlistat therapy (in 2008) and weight loss (in 2007 and 2009). (b) AF's and VF's mean plasma phytanic acid levels (mg/dL) before and after addition of Orlistat therapy to regular plasmapheresis and stable low phytanic acid diet. AF's and VF's mean phytanic acid level before addition of Orlistat was 14.8 mg/dL (SD 9.9) and 19.0 mg/dL (SD 13.2), respectively. AF's and VF's mean phytanic acid level after addition of Orlistat therapy was 6.7 mg/dL (SD 2.8) and 8.2 mg/dL (SD 5.5), respectively, with a  $P$ -value  $< 0.05$  on two-sample  $t$ -Test.

(every 3 weeks) plasma exchanges. The mean pre plasmapheresis phytanic acid levels were calculated for the periods before (April 2000–June 2005) and during (June 2005–January 2010) Orlistat therapy, (Figure 3(b)). Nutritional biochemical markers including fat soluble vitamin levels were monitored at baseline and at regular intervals but supplements were not required. Phytanic acid was measured by gas chromatography using a 25 m  $\times$  0.32 mm i.d. SGE BP-20 capillary column; nonadecanoic acid (19:0) methyl ester was used as internal standard and calibrated against phytanic acid methyl ester (Ultra Scientific, USA).

### 3. Results

In AF, mean plasma phytanic acid level (Figure 3(b)) on diet and plasmapheresis every 3 weeks was 14.8 mg/dL (SD 10 mg/dL), falling to 6.7 mg/dL (SD 2.8 mg/dL) after the addition of unblinded orlistat therapy ( $P < 0.05$  on two-sample  $t$ -Test). He reported clinical improvement in symptoms of polyneuropathy, ataxia, ichthyosis, irritable bowel syndrome, and cardiac arrhythmia. In VF, mean plasma phytanic acid level (Figure 3(b)) on diet and plasmapheresis was 19.0 mg/dL (SD 13.0 mg/dL), falling to 8.2 mg/dL (SD 5.5 mg/dL) during unblinded orlistat therapy ( $P < 0.05$ , two-sample  $t$ -Test). This was associated with improvement in symptoms of ataxia, hearing loss, and pruritus. However VF continued to suffer progressive impairment of vision, which has improved following bilateral cataract surgery. During this period AF and VF maintained stable weight most of the time with brief periods of weight loss associated with a slight increase in measured phytanic acid levels resolving with weight stabilisation, (Figure 3(a)).

### 4. Discussion

Early diagnosis of HAP or Refsum's disease is important because early treatment will minimize accumulation of phytanic acid and progression of functional impairment [1, 2]. Specific treatment for Refsum's disease is limited. We considered the use of Orlistat (Xenical), an intestinal lipase inhibitor, hypothesising that it has the potential to reduce the bioavailability of dietary phytanic acid. This occurs because the inhibition of intestinal lipase by Orlistat results in intestinal fat accumulation. Lipid soluble materials such as phytanic acid are likely to partition into the triglyceride phase and remain there until excreted. Indeed, significant reductions in mean pre-plasmapheresis plasma phytanic acid levels were demonstrated, (Figure 3(b)) in these two patients, without significant adverse effects or sustained weight loss. Liberalisation of the restrictive diet or reduction in the frequency of plasmapheresis may be feasible in the setting of continued Orlistat therapy. Orlistat reduces dietary triglyceride absorption by approximately 30%. In future, it may be possible to intensify reduction in intestinal lipolysis by the additional inhibition of lingual lipase. This offers the prospect of greater reductions in phytanic acid absorption, but this must be balanced against the possibility that associated weight loss might release tissue stores. It has provided the most effective means of reducing phytanic acid levels and disease progression.

Orlistat might be useful in the treatment of other metabolic disorders in which lipid soluble materials from the intestine contribute to pathology. More specific treatment for sitosterolaemia is available via the NPC1-L1 inhibitor, ezetimibe. We have used Orlistat to treat chylomicronaemia associated with massive hypertriglyceridaemia, which poses

a risk of acute pancreatitis. These patients remained free of pancreatitis during Orlistat therapy, but triglyceride levels and the clinical course of this condition are notoriously variable. A large-scale randomised clinical trial of the use of Orlistat would be required to assess its potential for the prevention of pancreatitis in chylomicronaemia. This report of the therapeutic effect of Orlistat in Refsum's disease requires confirmation in other patients. The use of Orlistat to reduce plasma phytanic acid levels may permit a reduction in the intensity of diet therapy and plasmapheresis, which would result in significant benefit to the patient and reduction in the cost burden to health systems. It may also favourably modify the progression of the clinical manifestations of Refsum's disease.

### Conflict of Interest

The authors report no conflict of interest.

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