A BRIEF REVIEW ON SYSTEMIC RETINOIDS

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Key words: Retinoids, Vitamin A, Keratinization disorders, Adverse effects

ABSTRACT: Retinoids are the derivatives of Vitamin A and have similar action to that of Vitamin A. Sources of Vitamin A such as eggs and meat are known to contain a chemical, retin-A which is known to be useful for treating various dermatological disorders. Tretinoin, a first generation retinoid was first used orally for the treatment of acne in 1940s. Topical tretinoin was later developed as a result of potential adverse effects when given orally and it showed promising therapeutic effect for keratinizing disorders such as actinic keratosis and ichthyosis. Other systemic retinoids such as isotretinoin, acitretin and bexarotene were also studied consecutively which gained approval from US-Food and Drug Administration for a number of keratinisation disorders like acne vulgaris, psoriasis and mycosis fungoides respectively. Along with these disorders, systemic retinoid are widely used for various off label dermatological conditions but due to their potentially serious adverse effects, their use has been contraindicated in a number of conditions, especially for pregnant women where it is reported to cause serious embryo-foetal abnormalities. Also, it is not recommended to take concurrently with some medicine as many studies have suggested serious toxicity. Patients who are on retinoid therapy need to be monitored carefully with proper laboratory investigations and patient compliance. Although retinoid are broadly used, concrete information on its proper use along with the mechanism of its potential adverse reaction and drug interactions is not available in the medical literatures. So, it is suggestive that further researches are necessary for proper use of retinoid.

INTRODUCTION: Retinoids are the derivatives of Vitamin A that includes both synthetic and natural compounds that has the similar action as that of Vitamin A. Vitamin A is considered to play a vital role in dermatological conditions as its deficiency is thought to cause numerous keratinisation disorders as well as certain precancerous conditions 1. Vitamin A is acquired through diet such as eggs and milk and is present as retinol (Vitamin A alcohol), retinal (Vitamin A aldehyde) and retinoic acid (Vitamin A acid) 1-4.

Retinal is important for visual function whereas retinol is important for reproduction. Retinoic acid plays a vital role in normal growth and epithelial differentiation. Vitamin A was first used for dermatologic condition in 1940s for the treatment of acne. Tretinoin, when given orally, showed auspicious results for the treatment of keratinisation disorders initially but due to its adverse effect which was studies later, oral tretinoin was not preferred. Nevertheless, therapeutic efficacy was reported for topical tretinoin for disorders of keratinisation such as actinic keratoses and ichthyosis 2.

Similarly, Isotretinoin was studied for the treatment of acne vulgaris which resulted in vivid improvement in patients with acne with high severity for which it was approved by the US Food and Drug Administration in 1982 for
nodulocystic acne. The aromatic retinoids, etretinate and acitretin were developed for the treatment of psoriasis and other dermatological condition. Initially in the late 80s etretinate was used for psoriasis treatment but was replaced by its metabolite, acitretin because the former was reported to be present in the subcutaneous fat for a longer period of time.

**Classification:** Systemic retinoids are classified into three generations which are listed in Table 1. First generation retinoids are formed by changing the polyene side chain and polar end group of Vitamin A. These retinoids are of great value in the field of dermatology and oncology. Second generation retinoids are formed by the replacement of cyclic end group of Vitamin A with various substituted and non-substituted ring systems and has great therapeutic value.

**TABLE 1: CLASSIFICATION OF RETINOIDS**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Tablets or capsule size</th>
<th>Standard dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Generation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>10, 20, 30, 40 mg</td>
<td>0.5-2 mg/kg/day</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>10 mg</td>
<td>45 mg/m²/day</td>
</tr>
<tr>
<td>Second Generation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etretinate</td>
<td>10, 25 mg</td>
<td>0.25-1 mg/kg/day</td>
</tr>
<tr>
<td>Acitretin</td>
<td>10, 25 mg</td>
<td>25-50 mg/day</td>
</tr>
<tr>
<td>Third Generation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bexarotene</td>
<td>75 mg</td>
<td>300 mg/m²/day</td>
</tr>
<tr>
<td>Alitretinoin</td>
<td>10, 30 mg</td>
<td>30 mg/day</td>
</tr>
</tbody>
</table>

The third generation retinoids are formed through cyclization of the polyene side chain. Even though these are more potent than the previous generation, their increased toxicity is responsible for their lower significance.

**Mechanism of Action:** Retinoid, which is a hormone, shows its effect by activating the nuclear receptors and regulating the gene transcription. Retinoids show their physiological effect by interacting with a specific protein called as retinol binding protein (RBP). This potentiates the intracellular transfer from the retinoid receptor into the cytoplasm and further binds to the Cellular receptor binding proteins (CRBP). Retinol is then metabolized into Retinaldehyde (Rh) via enzyme retinol dehydrogenase (RoDH) and is further converted to Retinoic acid (RA) via enzyme Retinaldehyde dehydrogenase (RALDHs).

This RA is bound by the Cellular Retinoic Acid Binding Protein (CRABP) and makes it more polar which enters into the nucleus and binds to Retinoic acid receptors (RARs) and Retinoic X receptors (RXRs). These receptors themselves heterodimerizes and binds to a sequence of DNA known as RARE (Retinoic acid response element). Finally it activates the gene transcription of the target genes. The mechanism of action is shown in Fig. 1.
**Pharmacokinetics:** Improved oral bioavailability is seen with food intake in case of retinoid especially for acitretin and bexarotene. Synthetic retinoid are stored in the liver as that of Vitamin A. Isotretinoin and acitretin are comparatively water soluble whereas etretinate is 50 times more lipophilic than acitretin which makes the use of acitretin more advantageous in treating psoriasis especially in women with child bearing potential. Retinoids are metabolized in liver by the induction of oxidative metabolism.

Isotretinoin is metabolized into 4-oxo-isotretinoin via oxidation whereas acitretin is metabolized into 13trans and 13cis acitretin via isomerization. These are further demethoxylated and are eliminated through bile as glucuronide derivatives or via kidneys as soluble metabolites. Among all three generations, tretinoin has the shortest half-life followed by bexarotene, Isotretinoin and acitretin whereas etretinate has longer half-life. The pharmacokinetics of all three generation of retinoid is given in Table 2.

**TABLE 2: PHARMACOKINETICS OF RETINOID**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Peak levels (hrs)</th>
<th>Bioavailability (%)</th>
<th>Protein Binding (%)</th>
<th>Half Life</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>First generation</td>
<td>Tretinoin</td>
<td>1-2</td>
<td>-</td>
<td>Albumin 99</td>
<td>40-60 mins</td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>Isotretinoin</td>
<td>3</td>
<td>25</td>
<td>Albumin 99</td>
<td>10-20 hrs</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Second generation</td>
<td>Etretinate</td>
<td>4</td>
<td>44</td>
<td>Lipoprotein 99</td>
<td>80-160 days</td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>Acitretin</td>
<td>4</td>
<td>60</td>
<td>Albumin 95</td>
<td>50 hrs</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Third generation</td>
<td>Bexarotene</td>
<td>2</td>
<td>No data</td>
<td>Plasma protein 95</td>
<td>7-9 hrs</td>
<td>Hepatic</td>
</tr>
</tbody>
</table>

**Indication:** FDA has approved three systemic retinoids for the treatment of dermatological conditions.

1. Acitretin for psoriasis.
2. Isotretinoin for Acne Vulgaris
3. Bexarotene for selected cases of mycosis fungoides.

**Psoriasis:** Psoriasis is a common dermatological condition that mainly causes itchy patches of reddish skin and silvery scales. It mainly affects elbows, knees, scalp, back, face, pal and feet. Many treatment therapies help in treating psoriasis out of which retinoids have shown some promising effect.

**As Monotherapy:** Acitretin is the only approved systemic retinoid after the removal of etretinate for the treatment of psoriasis. Many positive results are demonstrated for the treatment of psoriasis when acitretin was used as monotherapy, particularly when higher doses (50mg, 75mg) were used to that of lower doses (10mg, 25mg).

Studies have also shown that acitretin as a monotherapy decreased thickness, plaques and itching. The effectiveness can be seen in 4-6 weeks and can take up to 3-4 months depending on the severity. Research has shown that 25mg of acitretin can be taken daily and can be increased based on effectiveness as well as patient drug tolerance.

**As Combination Therapy:** Significant improvement has been reported when acitretin is used in combination with UVB therapy as compared to UVB therapy alone. It is recommended that a combination of acitretin and UVB therapy should include a dose of 25 mg acitretin 2 weeks prior to the initiation of phototherapy. Acitretin has also been evaluated in combination with PUVA which resulted in improving the efficacy of PUVA.

Acitretin can be used along with methotrexate and cyclosporine in specific situations but very consciously because of the risk of adverse effects of liver in case of Acitretin - Methotrexate combination and increased triglyceride level in case of Acitretin - Cyclosporin combination.

**Acne Vulgaris:** Acne vulgaris is a dermatological condition that appears due to clogging of hair follicles with the oil and dead cells of the skin. Some common characteristic features are blackheads, whiteheads, oily skin and pimples. Isotretinoin is the only FDA approved systemic
retinoid for the treatment of acne. It is recommended that a dose of 0.5-1mg/kg/day until a total cumulative dose of 100-140 mg/kg is reached for the treatment of nodular acne. It is reported that during the first 4-6 weeks of isotretinoin therapy, the complexation of the patient tends to worsen but after 4-5 months of therapy they are likely to see improvement.22

Mycosis Fungoides: Mycosis fungoides is a condition where the lymphocytes become malignant (cancerous) and affects the skin. Some characteristic features include rash, itchy skin, skin lesions and tumours. Treatment includes ultra violet light, corticosteroids, chemotherapy and radiotherapy. Along with these, bexarotene, a systemic retinoid is also approved by the US-FDA. Bexarotene was approved for the treatment of cutaneous manifestation of T-cell lymphoma in the patients who were noncompliant to at least one former systemic therapy. The exact mechanism of Bexarotene in the management of cutaneous T-cell lymphoma is not currently known but it is thought to act by the induction of the apoptosis of malignant cells23-25.

Other off label Dermatological Uses: Various off label dermatological conditions are treated by systemic retinoids but only a few are discussed based on the literature availability. Some of them are:

Ichthyosis: Ichthyosis is a group of genetic disorders which are characterized by cutaneous scaling and excessive dry surface scales. Although there is no cure for ichthyosis, retinoids have shown some beneficial effects. Retinoids have shown positive effects in treating various keratinization disorders but due Hypervitaminosis, a syndrome caused by systemic retinoids, and its use have been limited26-28.

Isotretinoin, acitretin and etretinate have been used for studying numerous keratinization disorders out of which they have shown promising effect in lamellar ichthyosis. Also, moderate response was noted for Bullous congenital ichthyosiform erythroderma and congenital ichthyosiform erythroderma29-30.

Pityriasisrubra Pilaris: It is a group is rare skin disease which is characterized by scaly patches of reddish-orange colour with well-defined borders. Mostly elbows, knees, palms and soles are affected. Topical emollients are used for dryness and cracking and retinoids are reported to be effective in severe conditions. It is recommended that isotretinoin 1-1.5 mg/kg/day or etretinate 1mg/kg/day are to be taken for optimum therapeutic effect31-32.

Lichen Planus: Lichen planus is basically a skin rash triggered by the immune system. The condition usually subsides within several weeks or months but certain medications can be used to relieve the symptoms as it can be uncomfortable. The medication often prescribed is retinoids, corticosteroids, antihistamines and non-steroidal creams along with light therapy.

Average results have been reported for both isotretinoin and etretinate for the treatment of lichen planus when 1mg/kg/day were given. The systemic retinoids were further studied and concluded that retinoids may be useful in hypertrophic and oral erosive lichen planus for which monotherapy or combination with low dose corticosteroids can be convenient33.

Lupus Erythematosus: It is an autoimmune disease which mainly affects the skin, brain, kidney, joints and other organs. Although there is no cure for these conditions, certain medication can be used to lower the symptoms. Mild cases are treated with low dose corticosteroids, hydroxychloroquine, NSAIDs whereas severe cases are treated with higher dose of corticosteroids. Retinoid has been studied recently and positive results have been reported. Patients with generalized discoid lupus and substrate lupus erythematosus responded well when a dose of 1mg/kg/day of both isotretinoin and etretinate were given and the response was seen within 4 weeks in bulk of the patients34.

Darier’s Disease: Darier’s disease is a rare genetic disorder which is characterized by scaly and crusted papules. The area which is mainly affected are scalp, neck, chest, back, skin fold and seborrheic areas of the face such as forehead, ears, eyebrows, scalp margin, beard and nostril area. Retinoids are studied for the treatment of Darier’s disease and has shown some positive results.
Studies have shown a positive response to Darier’s disease lesions when both isotretinoin and acitretin were given. Clinical experts say that the response is dependent over individual patient where one may respond well to one of these agents than two other. So, if one doesn’t show response then the other drug can be given for desired therapeutic effect. Retinoids are highly soluble in lipids and are more likely to get into breast milks. It is estimated that a suckling infant consumes 1.5% of the maternal dose of the drug and is highly restricted in breast feeding women.

**Chemoprevention of Malignancy:** Systemic retinoids have been studied in the prevention of genetic susceptibility to skin malignancy along with nevoid basal cell and xeroderma pigmentosum. It has been reported that even though higher dosage of retinoids are required in reducing the lesion, the effect vanished upon withdrawing the treatment. There have been the reports signifying that retinoids may have some activity that prevent non-melanoma skin cancers with the requirement of long term therapy and risk of potential long term adverse effects.

**Contraindication:** Systemic retinoids are contraindicated in the following:

**Pregnancy:** Pregnant or women who are likely to become pregnant are contraindicated to take systemic retinoids. All systemic retinoids come under Pregnancy category X. Systemic retinoids are reported to have caused retinoid induced malformation such as embryo foetal toxicity (foetal death, child born with less IQ, premature birth, spontaneous abortion), both internal abnormalities (hydrocephalus, microcephaly, cerebral abnormalities) and external abnormalities (skull abnormality, micropinna, small or absent external auditory canals) are reported.

It is extremely important to the women in this category to realize that they must not consider being pregnant while the therapy has started or while continuing the therapy or being pregnant for defined period of time after the discontinuation of the therapy.

**Non-Compliance to Contraception:** Retinoid, when used along with progestin only birth control pill might make the pills less effective and might increase the chance of becoming pregnant.

**Nursing Mothers:** Nursing mothers are contraindicated to take systemic retinoids.

**Hypersensitivity to Parabens:** Retinoids are contraindicated in the patients who are hypersensitive to parabens, which are used as preservatives in the gelatine capsule. It has been reported to cause anaphylactic and other allergic reactions along with cutaneous allergic reaction like allergic vasculitis often with bruises and red patches.

**Hypothyroidism:** Treatment with bexarotene is contraindicated in patient with hyperthyroidism. It is reported that increased peripheral degradation of thyroid hormones is responsible in contributing bexarotene induced hypothyroidism.

**Significant Hepatic Dysfunction:** Retinoids are reported to have caused hepatitis and abnormal liver function test results. If the patient already has liver issues then he should not take systemic retinoids.

**Significant Renal Dysfunction:** Impaired kidney function may lead to inability of the kidney to clear retinoids from the body and might increase the level of retinoids such as isotretinoin and acitretin in the body which will further increase the risk of side effects.

**Adverse Effects:** Higher doses of acitretin are known to cause more uneasiness than etretinate when it comes to alopecia, muco-skeletal distress and peeling of skin. Retinoids are comparatively safe when used in short term and is linked to least and reversible adverse effects provided that the patient is not contraindicated from its use.

Whenever necessary, the patient should be prescribed systemic retinoids based on risk-benefit ratio along with careful monitoring of their side effects. A list of potentially serious adverse effects due to systemic retinoids and their management are listed in Table 3 and a list of relatively common minor adverse effects and their management are listed in Table 4.
### TABLE 3: POTENTIALLY SERIOUS ADVERSE EFFECTS OF SYSTEMIC RETINOIDS

<table>
<thead>
<tr>
<th>System Affected</th>
<th>Side effects</th>
<th>Drugs responsible</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular</td>
<td>Reduced Night vision, Persistent Dry Eyes, S. aureus infections</td>
<td>Isotretinoin</td>
<td>Cessation of therapy</td>
</tr>
<tr>
<td>Bone</td>
<td>Diffuse skeletal hyperostosis, Osteoporosis</td>
<td>Isotretinoin</td>
<td>Monitor patients for skeletal effects for those who are taking high dose retinoids for a long period</td>
</tr>
<tr>
<td>Lipids</td>
<td>Hypercholesterolemia, Hypertriglyceridemia</td>
<td>Eretinate, Bexarotene, Isotretinoin</td>
<td>Weight reduction, Proper diet, Cessation therapy</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Inflammatory Bowel Disease flare (IBD), Pancreatitis</td>
<td>Isotretinoin</td>
<td>Close monitoring of the patients for IBD are recommended when treating with isotretinoin</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Transaminase elevations, Toxic hepatitis (rare)</td>
<td>Acitretin, Isotretinoin</td>
<td>Discontinuation, in case of severe elevation</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypothyroidism, Diabetes Mellitus</td>
<td>Bexarotene</td>
<td>Low dose levothyroxine and monitoring the thyroxine level is recommended when the patient is on bexarotene therapy</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Leukopenia, Agranulocytosis</td>
<td>Bexarotene</td>
<td>Dose reduction or discontinuation of therapy</td>
</tr>
<tr>
<td>Neurologic</td>
<td>PseudotumorCerebri</td>
<td>Combination of other systemic retinoids with tetracyclines</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Muscle</td>
<td>Depression, suicidal ideation, Myopathy</td>
<td>Isotretinoin, Isotretinoin</td>
<td>Close monitoring of psychiatric symptoms, Dose reduction of isotretinoin along with corticosteroid therapy</td>
</tr>
</tbody>
</table>

### TABLE 4: RELATIVELY COMMON MINOR ADVERSE EFFECTS

<table>
<thead>
<tr>
<th>System involved</th>
<th>Side effects</th>
<th>Drugs responsible</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td>Xerosis, Retinoid dermatitis, Photosensitivity, S. aureus infection, Pyogenic granulomas, Stickiness sensation (palm, soles)</td>
<td>Isotretinoin, Acitretin</td>
<td>Drug discontinuation or dose reduction</td>
</tr>
<tr>
<td>Hair and Nails</td>
<td>Telogen effluvium, Abnormal hair structure, Paronychia, Onycholysis, Nail Softening</td>
<td>Acitretin, Eretinate, Isotretinoin, Bexarotene</td>
<td>Discontinuation or dose reduction</td>
</tr>
<tr>
<td>Oral</td>
<td>Chellitis, Sore mouth and tongue, Dry mouth</td>
<td>Isotretinoin, Acitretin</td>
<td>Reducing dose or discontinuation of the drug</td>
</tr>
<tr>
<td>Nasal</td>
<td>Epistaxis, Nasal mucosa dryness, Sore mouth and tongue</td>
<td>Acitretin</td>
<td>Dose reduction or drug continuation</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, Diarrhoea, Abdominal pain</td>
<td>Isotretinoin</td>
<td>Monitor the patient closely while he is on isotretinoin therapy</td>
</tr>
<tr>
<td>Ocular</td>
<td>Dry eyes, Blepharoconjunctivitis, Photophobia</td>
<td>Isotretinoin</td>
<td>Artificial tears, Discontinue using contact lens</td>
</tr>
<tr>
<td>Mucoskeletal</td>
<td>Arthralgias, Myalgias, Fatigue, Tendinitis</td>
<td>Isotretinoin</td>
<td>Monitor creatinine phosphate level</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Headache, Mild depression</td>
<td>Isotretinoin</td>
<td>Cessation of therapy</td>
</tr>
</tbody>
</table>
Drug Interaction: Only limited studies have been conducted for drug interaction with retinoids. Systemic retinoids are found to cause drug interactions of different levels of severity with the following drugs.

Tetracyclines: Systemic retinoids, when co-administered with tetracyclines causes serious adverse reaction. It may increase the risk of pseudotumor cerebri which is also known as benign intracranial hypertension. Similar reactions are reported when retinoids are given together with other class of tetracyclines such as doxycycline, demeclocycline, lymecycline, minocycline and oxytetracycline. The combination is not recommended to be co-administered. The symptoms of pseudotumor cerebri such as visual disturbances, visual loss, headache, nausea, vomiting and papilledema typically tend to resolve after discontinuation of the treatment 52.

Vitamin A: Co-administration of Vitamin A and retinoids may result in hypervitaminosis and other additive toxicities. Serious adverse effects such as vision impairment, pseudotumor cerebri, mucositis, pancreatitis, colitis, hepatitis and hypertriglyceridemia can occur. If signs of hypervitaminosis such as inflammation of gums, pruritis, vertigo, dry scaly skin, alopecia and erythema occurs then the drug should be discontinued 53.

Methotrexate: Co-administration of methotrexate and retinoids tend to induce hepatotoxicity and potentiate the risk of liver injury and can lead to hepatitis, cirrhosis, chronic fibrosis, necrosis and elevation of liver enzymes. Monitoring of hepatic function is very important 54.

Mifepristone: Co-administration of mifepristone and retinoids may increase the plasma concentration of the drugs which are substrate of CYP450 2C8/2C9. These enzymes are inhibited by the action of mifepristone that decreases the clearance. Dose adjustment along with clinical and laboratory monitoring is important 55.

Gemfibrozil: Co-administration of bexarotene and gemfibrozil leads to increased bexarotene level due to the inhibition of enzyme CYP3A4. This increases bexarotene toxicity and leads to serious side effects, so this combination is generally avoided 56.

Phenytoin: Co-administration with the inducers of CYP450 3A4 may decrease the plasma concentration of bexarotene. Other drugs which are known to interact with similar mechanism include rifampicin, phenobarbital and carbamazepine. The interaction is minor but can be given with close monitoring of the drug-plasma level 56.

Cyclosporin: Co-administration with bexarotene may reduce the plasma concentration of the drugs which are primarily metabolized by enzyme CYP450 3A4 as a result of induction activity of bexarotene. Other drugs which act by the same mechanism include atorvastatin, paclitaxel and tamoxifen. The co-administration of bexarotene with these drugs needs extreme cautiousness, especially those with narrow therapeutic index. Appropriate dose adjustment along with clinical and laboratory investigation is advisable 57.

Teriflunomide: With Isotretinoin and Acitretin: Using the teriflunomide with isotretinoin and acitretin is known to induce hepato-toxicity and tends to increase the risk of liver injury associated with leflunomide. Elevated liver enzymes, jaundice, hepatic failure, hepatitis and acute hepatic necrosis have been reported for teriflunomide, which is the principal active metabolite of leflunomide. The combination has to be used with extreme caution. It is very important to measure the liver enzyme and bilirubin levels before starting teriflunomide therapy. The combination should be avoided if the patient has elevated liver enzymes or any pre-existing liver disease. Teriflunomide should be discontinued if the patient develops elevated serum ALP levels and wash out procedures with activated charcoal should be performed 58.

With Bexarotene: Using these drugs in combination may increase the risk of infection. Studies have reported serious infection like sepsis, pneumocystis jiroveci pneumonia, pulmonary and extra-pulmonary tuberculosis and aspergillosis. Similar interaction as that with isotretinoin and acitretin has been reported in recent studies. The combination with bexarotene may induce hepatotoxicity and may increase the risk of liver
injury. Close monitoring is essential as the interaction may appear even when these agents are initiated after discontinuation with teriflunomide because of its prolonged half-life. Treatment should be stopped if there is evidence of serious hepatotoxicity, infection or bone marrow suppression and activated charcoal can be administered for accelerated elimination.  

Ciprofloxacin: The combination may increase the plasma concentration of bexarotene. It is known that bexarotene is inducer of CYP450 3A4 and tends to reduce plasma concentration of CYP450 3A4 inhibitors that are the substrates of the isoenzyme like macrolides, mifepristone, azole antifungals and some calcium channel blockers. Other drugs which act by similar mechanism include fleroxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin. The clinical significance is currently unknown.

Medroxyprogesterone: The combination of medroxyprogesterone along with systemic retinoids is contraindicated because of potential serious foetal malformation during retinoids therapy. The exact mechanism is currently unknown. The use of progestin-only contraceptives is not enough so at least two method of effective contraception is recommended during retinoid therapy.

Monitoring Guidelines:

1. Collect complete medical history and perform complete physical examination.
2. Identifying patients who are at higher risk for adverse effects.
3. Documenting concomitant medications which may interact with systemic retinoids.
4. Laboratory investigations such as Serum or urine pregnancy test, complete blood count, lipid profile test, liver function test, renal function test and urinalysis (in case of renal disease).
5. X-rays of ankles, wrist and spine in case of long term therapy.
6. Ophthalmic examination in case of history of cataract or retinopathy.
7. Monitoring patient’s response to the drug and possible adverse effects.  

CONCLUSION: Retinoid, a Vitamin A derivative has been used for treating various dermatological disorders. Because of their promising therapeutic efficacy, the US-FDA has approved systemic retinoids for treatment of certain dermatological conditions. Although retinoids are widely used, its adverse effects have limited their practice. These drugs, if used irrationally can lead to severe adverse reaction. These are also contraindicated for the use in certain conditions such as pregnancy because of higher risk of embryo-foetal abnormalities and also in combination with certain drugs such as tetracycline, medroxyprogesterone, teriflunomide, mifepristone and other similar drugs because of potential toxicities. It is very important to monitor the patient closely by examining the improvement along with monitoring certain laboratory investigations. There is limited information on the accurate mechanism of adverse effects and drug interaction so conducting further studies is necessary for safe and effective use of retinoids.

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