WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 16, 568-581. Review Article ISSN 2277– 7105

REVIEW ON: AFAMELANOTIDE IMPLANT AS EFFECTIVE DRUG TO TREAT VITILIGO AND ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

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Article Received on
12 July 2018,
Revised on 02 August 2018,
Accepted on 23 August 2018
DOI: 10.20959/wjpr201816-13266

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ABSTRACT

Vitiligo is an acquired cutaneous disorder of pigmentation. About 0.5 to 2% of worldwide people are affected by vitiligo. During vitiligo depigmentation occurs, which subsequently form white patches on skin. There are two types of vitiligo viz. Segmental vitiligo and Non-segmental vitiligo. It occurs due to various factors. The leading causes of vitiligo are autoimmune default, oxidative stress, defective melanocyte and nerve damage. It is seen that the presence of autoantibodies against melanocyte antigens in vitiligo patient, indicates autoimmune involvement in cause of vitiligo. The melanin pigments are produced in the skin via melanin synthesis pathway. Various treatments are used to treat vitiligo i.e. topical corticosteroid, systemic corticosteroid, phototherapy, surgical modalities and depigmentation. Recent novel and potentially effective treatment of vitiligo i.e. Afamelanotide implants brand named as SCENESSE® (afamelanotide 16mg). It is implanted in subcutaneous layer of skin. Afamelanotide is a synthetic analogue of naturally occurring alpha-melanocyte stimulating hormone, which has a potent and long lasting properties. It is also used to treat Erythropoietic Protoporphyria (EPP) i.e. rare photodermatosis.

KEYWORD: vitiligo, erythropoietic protoporphyria, autoimmune, melanin.

INTRODUCTION

Acquired cutaneous disorder of pigmentation is known as vitiligo. Globally worldwide about 0.5 to 2% of people are affected by vitiligo. Hypothesis for the pathogenesis of vitiligo as

following: Biochemical / cytotoxic, neutral and autoimmune. Recent data is a strong evidence supporting an autoimmune pathogenesis of vitiligo. There is major effect on quality of life of patient, which is suffering from vitiligo. During early stage when disease is active, any treatment can be considered by patient. Researcher research directed toward find out treatment to stop progress of vitiligo and regrow pigment i.e. repigmentation. Vitiligo can be treated by various treatment viz. topical corticosteroids, phototherapy including UV-A and UV-B light therapy, surgery, combination therapies, depigmentation of normally pigmented skin.[1] Afamelanotide is a synthetic analogue of naturally occurring alpha-melanocyte stimulating hormone which has a potent and long lasting properties. Afamelanotide gives a novel and potentially effective treatment for vitiligo. The use of combined therapy of NB-UVB and afamelanotide emerge to promote melanoblast differentiation, proliferation and eumelanogenesis. Effective rapid repigmentation is shown in combination therapy of afamelanotide with NB-UVB Phototherapy.[2] It is used in implant (afamelanotide implant 16 mg) as a dosage form, which is administered under the skin i.e. subcutaneous layer of skin. It is named by brand name SCENESSE® (afamelanotide 16mg).[3] It increased skin pigmentation owing to increased expression of eumelanin for longer period of time. It is also beneficial in treatment of erythropoietic protoporphyria.[4] EPP is a rare photodermatosis. It is occur due to an innate defect of heme biosynthesis characterised by excessive production and subsequent accumulation of metal- free protoporphyrin (PP) in erythrocytes, plasma, skin and liver.[5,8]

Vitiligo: Vitiligo is acquired cutaneous disorder in which depigmentation of the part of skin occurs. In this disorder melanocyte lost their functioning which is responsible to vitiligo. But real pathogenesis of vitiligo is not yet estimated. However, the pathogenesis condition of vitiligo include autoimmune, genetic, neutral, viral infection and oxidative stress, these are leading cause of vitiligo.[1,9] The impact of vitiligo is spread between 0.5 to 2% in all over the world.[10]

Types of vitiligo

1) Segmental vitiligo: Segmental vitiligo is an acquired chronic pigmentation disorder. It is characterised by white patches on skin, which are in unilateral distribution.

2) Non-segmental vitiligo: In this disorder white patches often seen symmetrical that usually increase with increase in time. In this epidermal and in same causes hair follicles melanocyte start massive loss in their functioning.[11]

Symptoms

Depigmentation or loss of melanocyte is leading symptom of vitiligo, which is characterised by white patches on skin of vitiligo patient. In starting phase of the disease patch appears to be small, it enlarges over the time. The skin lesions are dominantly seen on the face, hand and wrists.[12]

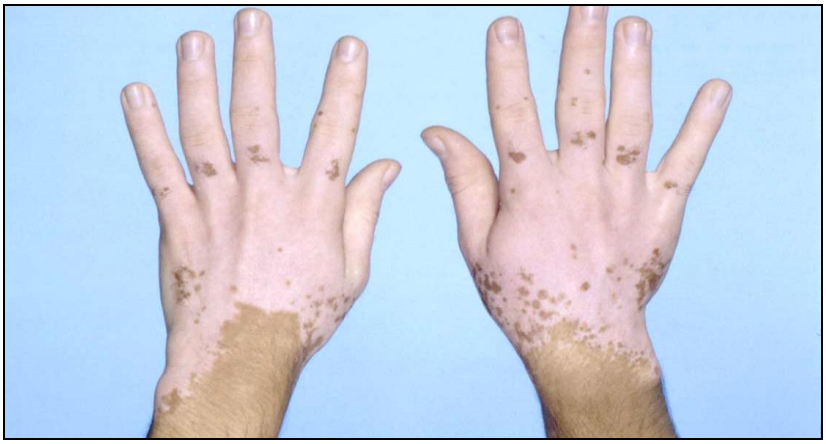


Fig.1: Symptoms of vitiligo.

Leading cause of vitiligo

1) Autoimmune default: The faulty autoimmune produce specific antibodies and especially CD8+T cells which promote destruction of the melanocytes. These immune cells are elevated in the vitiligo patients.[13] It is found that presence of autoantibodies against melanocytes antigens cause destruction of melanocytes. Increase in serum level of immunoglobulin G (IgG) anti melanocytes/vitiligo antibodies (V-IgG) which induce melanocyte damage.[14]

2) Defective melanocytes: Some melanocytes are associated with intrinsic defects i.e. they possess shorter life span. This defect has effect on the growth.[46]

3) Oxidative stress: Melanocytes can damage by harmful reactive oxygen species i.e. hydrogen peroxide and peroxynitrite due to oxidative stress. Some of the antioxidants (including enzymatic and non-enzymatic antioxidant systems) which counterattack on reactive oxygen species. However, when the level of these antioxidant gets decreased under the skin, as a result melanocytes get damaged by the reactive oxidizing species. The defective antioxidant system in vitiligo patients can restore by using the oral and topical antioxidants in association with conventional vitiligo treatment.[47]

4) Nerve damage: According cohort study, the level of nerve growth factor (NGF) is significantly increased in vitiligo. NGF expression in hair follicles is regulated by stress up.

Similarly stress up decreases the high affinity of TrkA receptor, increases production of p75NTR NGF-receptor, and increases in dorsal root ganglia the substance P neurons.[46]

Melanin Synthesis Pathway

There are main three types of melanin i.e. eumelanin, pheomelanin & neuromelanin which is mixture of both eumelanin and pheomelanin. Eumelanin and pheomelanin are present in the skin, hair, & eyes. Melanin pigments are also present in the iris and the inner ear. Not only eumelanin but also pheomelanin are produced by same pathway. In this pathway first phenylalanine is converted into tyrosine in the presence of enzyme i.e. phenylalanine hydroxylase. Then tyrosine is converted into dopa and subsequently into the dopaquinone. Dopaquinone then coupled with cysteine and form two intermediates before formation of pheomelanin. Alternatively, dopaquinone can be converted to leucodopachrome, dopachrome and then indole and quinone intermediates which subsequently produce eumelanin.[48,49]

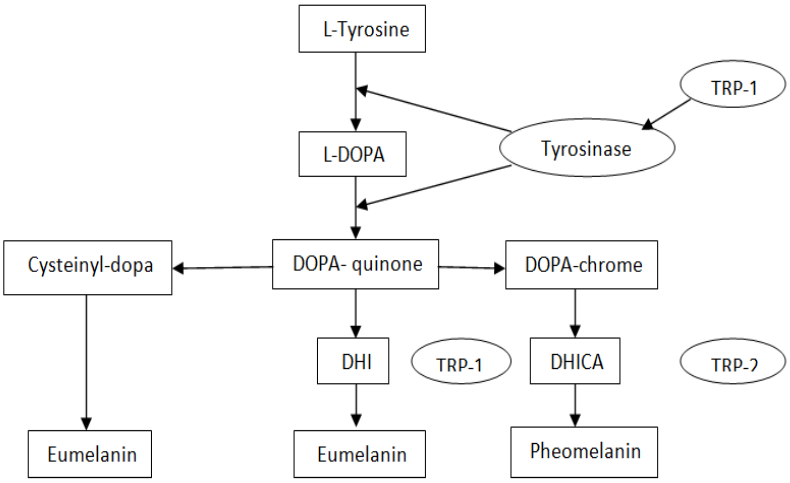


Fig. 2: Melanin synthesis pathway[49]

Effect of Autoantibodies

Tyrosine hydroxylase antibody (TH-Ab): In vitiligo it is generally accepted as autoantigen by using phagedisplay technology. Tyrosine Hydroxylase is important for synthesis of melanin by providing a substrate L-dopa for tyrosinase which then converts L-tyrosine to dopaquinone, which is a precursor of melanin. However, TH-Ab increases in the patient of vitiligo, which subsequently attack on Tyrosine Hydroxylase in non-segmental vitiligo. TH-Ab are not found in the segmental vitiligo.[14]

Treatment used in vitiligo: To stop the progress of disease and restores the loss of melanocytes in the lesions, these are main aims to treat vitiligo effectively. Some treatment can be done by achieving both the aims.[15]

Treatment of vitiligo

1) Topical corticosteroid: It is used as the first line therapy treatment for vitiligo. It might be effective to treat vitiligo.

Boons of topical corticosteroid[16,17,18]

1) To provide ease of application over anatomical site.
2) It has high rate of compliance.
3) It has low cost of treatment.

e.g. Most effective topical corticostroid is the CLOBETASOL, because it is very often to produce pigment.

2) Systemic corticosteroid: Use of systemic corticosteroid helps to stabilize disease by rapid progress.[19] Complement-mediated cytotoxicity can be reduce by using systemic corticosteroid. Autoantibodies to melanocytes and antigens titer to the surface antigens of melanocytes in serum of users.[20,21] Common side effects of systemic corticosteroid are weight gain, menstrual irregularity and hypertrichosis.[22]

Topical corticosteroid and Systemic corticosteroid are used the effective combination treatment on vitiligo. e.g. Combination of methylprednisolone oral minipulse therapy and topical fluticasone. Vitiligo patient can be achieve good to excellent repigmentation at the end of therapy.[23]

Systemic corticosteroid is able to stop the progress of vitiligo and reproduce pigment, but it is observed with inconsiderable side effects.[24]

3) Phototherapy: Phototherapy is backbone treatment of vitiligo for several years. Phototherapy include ultraviolet (UV) based therapy i.e. UV-A and UV-B, Photochemotherapy (psoralen+UV-A/(PUVA)) and targeted Phototherapy (excimer laser and excimer lamp).[25] Phototherapy is effective to some lesional locations, while face and neck lesions are effectively treated by phototherapy. It seen that acral lesions are resistant to phototherapy.[26] Use of photosensitizers in photochemotherapy increase sensitivity of the

skin (psoralen). It also increases sensitivity of melanocytes (Khellin) by activating melanocytes, melanosomes and inducing Interleukin-1-synthesis. PUVA-treated vitiligo patient may be get suffer from skin cancer.

There are two form of UV-B

1) Narrow band (NB-UVB) (311nm-313nm)

2) Broad band (BB-UVB) (290nm-320nm)

It can prevent cytokines, secretion and stimulation of inactive melanocytes of the outer root sheath of hair follicles which is achieved by migration of vitiligo lesions.

Boons of NB-UVB

1) It is suitable in pregnancy and for the children.

2) It does not cause phototoxicity, xerosis or hyperkeratosis as usually seen with PUVA.[27]

3) After taking 6 months of NB-UVB therapy, approximately 42.9% of repigmentation was seen in vitiligo patient.[28]

4) Surgical modalities: It is only treatment which is appropriate for stable vitiligo.[29] It is appropriate for face and back of hands which is cosmetically sensitive site. This treatment is not recommended for the children. Rapid and desirable amounts of repigmentation is achieved by surgical treatment. If patient is suffering from ko" bner phenomenon, post inflammatory hyperpigmentation, keloids or hypertropic scars in past, then it is not suitable candidate for surgical interventions.

There are different procedure used for surgical modalities viz. tattooing, organ-cultured fetal skin allografting, epidermal culture grafting, melanocyte culture grafting, autologous noncultured melanocyte-keratinocyte cell transplantation, epidermal blister grafting, thin thiersch split skin grafting and miniature punch grafting. From the above procedure method, the highest means success rate are achieved by using split skin grafting and epidermal blister grafting.[30]

5) De-pigmentation: De-pigmentation is the removal of all the skin melanin pigment to render the skin an even colour. It is done by using topical drugs like monobenzone, mequinol or hydroquione. The removal of all skin pigment is vigorous and permanent after application of monobenzone. Sun-safety must be adhered in patient entire life to avoid severe sunburn.

Patient must have to avoid severe sunburn and melanomas i.e. most serious type of skin cancer after de-pigmentation therapy. It does take a year to complete treatment.

Table: Treatment for vitiligo.

Sr. No.	Therapy	Primary outcomes	Adverse effect	Drugs	Reference No.
1)	Depigmentation	Render the skin an even colour.	Severe sunburn & melanomas.	monobenzone,mequinol.	1
2)	Topical corticosteroid	It provide's ease of application, high rate of compliance, low cost of treatment. It produce pigment.	Not reported	Clobetasol	16, 17, 18
3)	Systemic corticosteroid	Reduces complement-mediated cytotoxicity.	Weight gain, menstrual irregularity and hypertrichosis	Methylprednisolone oral minipulse	19, 20, 22
4)	Combination of topical and systemic corticosteroid.	Gives good to excellent repigmentation.	Inconsiderable side effects.	Methylprednisolone oral minipulse + topical fluticasone	23
5)	Phototherapy: UV-A & UV-B, PUVA, excimer laser & excimer lamp.	Face & neck lesions are effectively treated. NB-UVB: It is suitable in pregnancy & for the children. Phototoxicity is avoided. 42.9% of repigmentation is done.	Resistant to acral lesions. Xerosis or hyperkeratosis & skin cancer are seen in PUVA.		25,26, 27, 28
6)	Surgical modalities.	Rapid & desirable amounts of repigmentation is achieved.	Not for children. Contraindicated for patient suffering from ko"bner phenomenon, post inflammatory hyperpigmentationand hypertropic scars in past.		15, 21

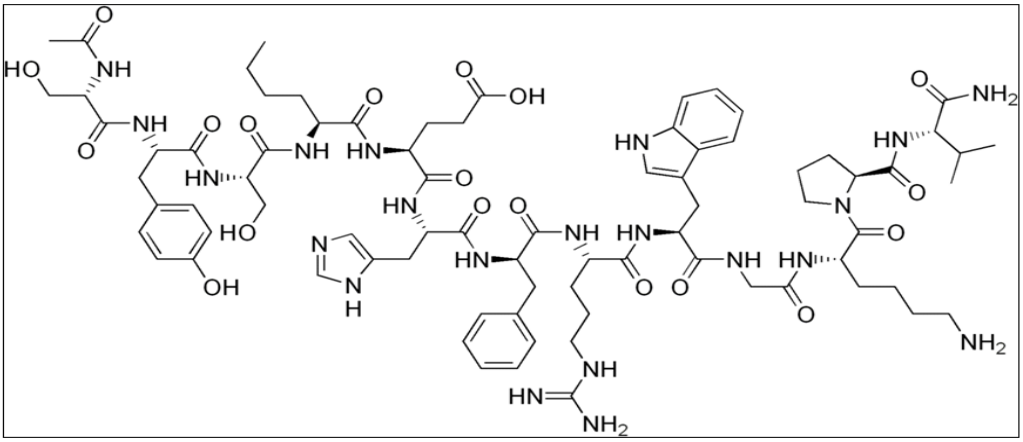
Active drug substance (Afamelanotide)

Structural analogue of alpha-MSH or melanotropin is an afamelanotide.

Chemical Name

N-acetyl-L-serinyl-L-tyrosyl-L-seryl-L-norleucyl-L-glutamylL-histidinyl-D-phenylalanyl-L-arginyl-L-tryptophanyl-glycyl-L-lysyl-L-prolyl-L-valinamide

Structure of afamelanotide



It is also called by [N-le4, D-Phe7]-α-melanocyte stimulating hormone (NDP-MSH).

The chemical structure of afamelanotide is adequately demonstrated by amino acid analysis by GC (gas chromatography) and MS (mass spectrometry), sequencing by MS/MS (Tandem mass spectrometry). It has enantiomeric purity by chiral GC-MS and nuclear magnetic resonance (NMR) spectroscopy: which are viz. 1D 1H NMR, two-dimensional Correlation Spectroscopy proton Nuclear Magnetic Resonance (2D-COSY 1H NMR), 2D Heteronuclear Single Quantum Correlation (HSQC) 1H-13C NMR and 2D Heteronuclear Multiple Bond Correlation (HMBC) 1H-13C NMR. The apperance of afamelanotide is a white to off-white hygroscopic amorphous power.

Solubility of Afamelanotide

1) It is freely soluble in methanol, 1% acetic acid and water.

2) It is slightly soluble in ethanol and practically insoluble in acetonitrite and 1-octanol. The content of afamelanotide drug is peptide, which contain 11-L amino acids, one D-phenylalanine and one glycine. The theoretical stereochemistry of drug is confirmed by chiral gas chromatography-mass spectrometry.[45]

Mechanism of Action of Afamelanotide

Afamelanotide (SCENESSE®, Clinuvel Pharmaceuticals, Melbourne, Australia) (N-leu4, D-phe7, alpha-MSH) is an analogue of human alpha-MSH, the naturally occurring hormone that

stimulates the synthesis of melanin.[31,32] It was first described in 1980, afamelanotide is synthetic tridecapeptide that differ from human alpha-MSH, at the fourth and seventh amino acid, where norleucine is replace by methionine and D-phenylalanine is replace by L-phenylalanine.[33,34]

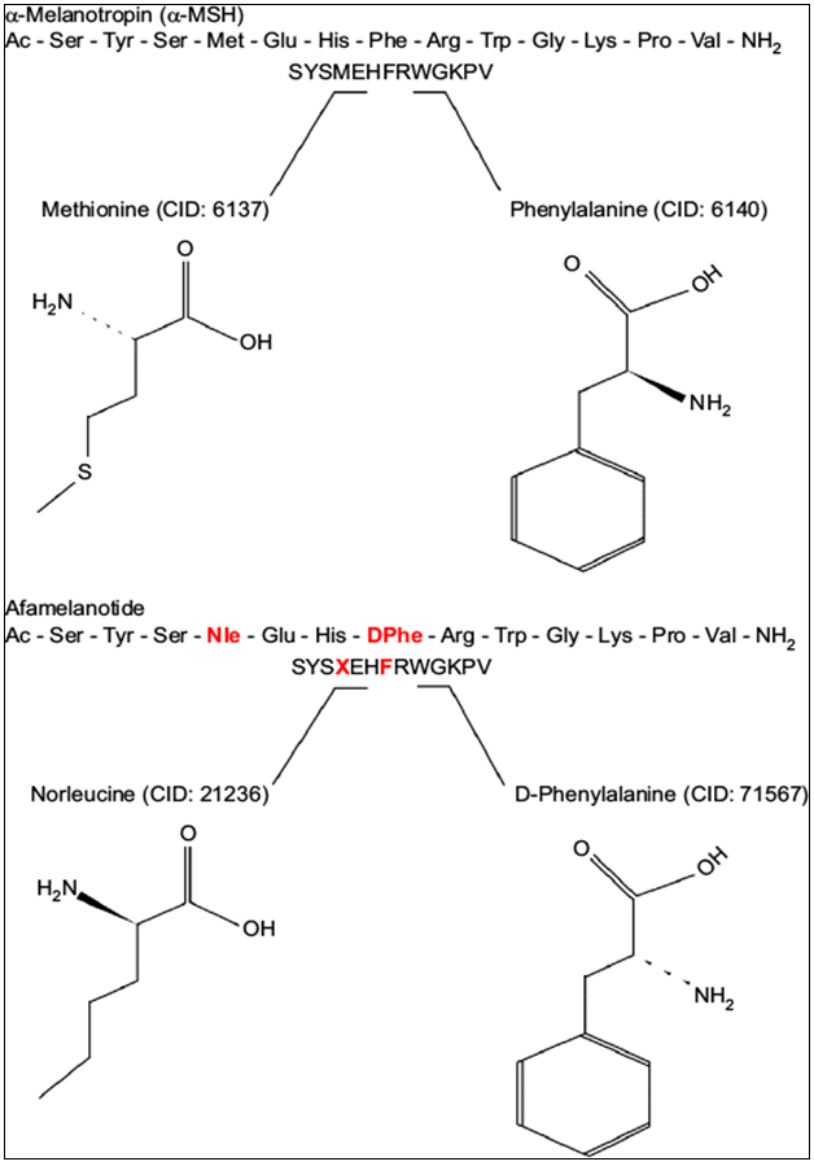


Fig.3: Difference between afamelanotide and alpha-MSH.[50]

These changes give unique biological properties such as contradict to enzymatic degradation, prolonged plasma half-life and increased duration of action. All of these properties proof that afamelanotide arise as a potent melanocortin ligand.[33,35] The G-protein coupled melanocortin 1 receptor (MC1R) is present in dermal cells, including melanocytes. Afamelanotide mirrors the activity of alpha-MSH by binding to the G protein coupled melanocortin 1 receptor (MC1R) to activate melanogenesis.[34] Melanin synthesis transitions

from the less protective yellow-red pheomelanin to more protective brown-black eumelanin is occur when the MC1R is stimulated by alpha-MSH.[31,36,37] Eumelanin gives photoprotection by absorbing and scattering visible UV light, scavenging free radicals and reactive oxygen species, and functioning as a neutral density filter capable of equal reduction of transmission of all wavelegth of light.[31,32,37,39] Afamelanotide stimulates synthesis of eumelanin which is independent of exposure to UV radiations, as opposed to endogenous alpha-MSH. Eumelanin is produced in response to UV damaged skin cell to prevent further damage.[38,39]

In the early 1990's it was first demonstrated to induce skin pigmentation and tanning. Afamelanotide increase eumelanin density in normal subject as well as patient with EPP.[41] In normal volunteers, Afamelanotide administered subcutaneously at a dose of 0.16 mg/kg/d. It induced tanning with an increase in eumelanin: In the sun exposure pheomelanin ratio accompanied by significant increase in eumelanin at different anatomical sites. Additionally, after use of afamelanotide, apoptotic sunburn cell injury was reduced by more than 50%.[40] Afamelanotide is administered into subcutaneous layer of skin. This route of administration is mostly effective for many protein and peptide based drugs, as penetration of tridecapeptide in the epidermis does not occurred. After oral administration degradation of drug occurred in gastrointestinal tract.[42,43] After once afamelanotide implanted, active drug substance is released within 2 days and in between 5 days 90% of active substance is released. Biological half-life of afamelanotide is between 30-50 minutes. The drug shows its effect for upto 60 days, although with reduction in efficacy frequently noted by approximately 40-45 days and implant is completely reabsorb within this time.[34] There is limited data available regarding the use of afamelanotide in patient with renal or hepatic impairment, special populations (paediatric, adolescent, elderly) or in pregnancy or lactation.

CONCLUSION

Acquired cutaneous disorder of pigmentation i.e. vitiligo was studied. Their types, symptoms, pathogenesis and recurrent treatment was studied. Also melanin synthesis pathway and effect of autoantibodies was studied. Afamelanotide is a synthetic analogue of naturally occurring alpha-melanocyte stimulating hormone, which has a potent long lasting properties. It's chemical structure and action of mechanism was studied. Afamelanotide implant brand named as SCENESSE® (afamelanotide 16mg) did give a novel and potentially effective treatment to vitiligo and EPP.

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