Effectiveness and safety of topical tacrolimus monotherapy for repigmentation in vitiligo: a comprehensive literature review*

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Abstract: Thus far, several small studies and case reports on the use of topical immunomodulators in vitiligo have been published. We undertook a comprehensive literature review, searching for studies evaluating clinical response to tacrolimus topical therapy for vitiligo. A search was performed on PubMed/Medline using the term "vitiligo", combined with "topical" and "ointment". Our inclusion criteria were: use of tacrolimus ointment as monotherapy to treat vitiligo. We found 29 studies from 2002 to 2014. Overall, 709 patients were treated in 29 studies. Pooling the lesions, 50% repigmentation of vitiligo patches was never achieved before 2 months of treatment, with a peak after 6 months of therapy. The best results were obtained on lesions of the cephalic region, especially the face, with tacrolimus 0.1% ointment two times daily. The percentage of non-responsive patients ranged from 0% to 14%. Treatment was generally well-tolerated; only localized adverse effects were reported. Our objective was to verify the effectiveness and safety of tacrolimus ointment monotherapy. It has good efficacy and tolerability. At present, only small trials and case series are available in the literature. Further, standardized investigations on a larger number of patients are needed.
Keywords: Ointments; Tacrolimus; Vitiligo

INTRODUCTION

Vitiligo is characterized by the progressive disappearance of melanocytes, resulting in depigmentation of the skin and/or hair. The etiology of vitiligo is unknown.[1] Genetic studies support a non-Mendelian inheritance, suggesting that vitiligo is a multifactorial, polygenic disorder. The autoimmune theory remains the most widely accepted. Vitiligo has frequently been reported in association with autoimmune disorders such as thyroid disease, diabetes mellitus and alopecia areata.

Several studies have suggested that the presence of increased antimelanocyte antibodies and the imbalance of T-cell (CD4+/CD8+ and Tregs) subsets, along with their functional defects, may result in melanocyte destruction in vitiligo patients.[2]

The disease affects both genders equally. It can appear at any age and the average age of onset is somewhat variable in different geographic regions. The mean onset age is reportedly 22 in the U.S. and India, 24 in Brazil and 25 in the UK.[3]

Vitiligo treatment remains a challenge. Therapeutic options for vitiligo include: topical and systemic corticosteroids, topical calcineurin inhibitors, calcipotriol, phototherapy, excimer laser, and surgical methods such as skin/single-hair grafting, autologous cultured melanocyte or epidermal suspension transplantations.

Topical corticosteroids are most commonly used drug to treat vitiligo but there are concerns over side effects due to long-term use. Steroid application causes skin atrophy, telangiectasia, hypertrichosis and acne.

Tacrolimus and pimecrolimus are used as topical immunomodulators. They inhibit calcineurin action, thus preventing T-cell activation and the production of various inflammatory cytokines.

Both have been used to treat other inflammatory and immunologic skin disorders, including vitiligo, with encouraging results. [4,5]

Tacrolimus is a macrolide antibiotic produced

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by Streptomyces tsukubaensis with strong T-specific, immunosuppressant activity. The biological activity of tacrolimus takes effect after binding to the cytosolic 12-kd macrophilin FK506 binding protein (FK-BP). The tacrolimus/FK-BP complex inhibits calcineurin-mediated phosphorylation of the transcription factor, the nuclear factor of activated T-cells (NFAT). Hence, the expression of several inflammatory T-cell cytokines is inhibited.

Indeed, topical tacrolimus downregulates proinflammatory cytokines, namely IL-2, IL-3, IL-4, IL-5, IFN-c, TNF-a and granulocyte-stimulating factors. Lan et al.[6] reported that the proliferation of melanocytes was significantly enhanced by tacrolimus-treated keratinocyte supernatant. Further, they noted that the concentration of stem-cell factor and matrix metallopeptidase-9 activity in tacrolimus-treated keratinocyte supernatant increased significantly. They suggested that their results provided in vitro evidence demonstrating the positive effect of tacrolimus on melanocyte growth and migration.

Thus far, several small studies and case reports on the use of topical immunomodulators in vitiligo have been published.

METHODS

To verify the effectiveness of tacrolimus alone, we selected studies that discussed tacrolimus ointment as monotherapy for vitiligo treatment.

A literature search on Medline/PubMed was performed for articles evaluating clinical response using tacrolimus as topical therapy for vitiligo. The keywords were: "vitiligo" combined with "topical" and "ointment".

Inclusion criteria were: 1) case study, review of literature, case report, clinical trial, open-label prospective study 2) tacrolimus used as monotherapy. The exclusion criterion was tacrolimus as a combination therapy.

The entire PubMed database was explored, without time restrictions. Each article was tabulated as follows: authors, year of study, type of study, number of patients, age (in years) and sex of patients, localization of disease, treatment protocol, adverse effects, outcome.

Studies discussing children and adults were included, along with studies describing topical treatment with both tacrolimus ointment 0.03% and tacrolimus ointment 0.1% . English and non-English-language papers were included.

The publications were screened manually and reviewed to identify reports on tacrolimus monotherapy. Three investigators independently reviewed and extracted data from the papers according to the predetermined criteria.

RESULTS

We identified 117 full-text articles; 88 did not meet the inclusion criteria, leaving 29 studies available from 2002 to 2014. Nineteen were open-label trials, 3 were retrospective cohorts, 6 were case reports and 1 was a case series (Chart 1).

Overall, the treatments of 709 patients were described in 29 studies. The main treatment choice was tacrolimus ointment 0.1%, applied twice daily (19/29 studies, 65%) and once daily in 7 studies. Six studies examined treatment with tacrolimus 0.03% once daily.[7-12]

Treatment length was variable, with a mean duration of 5.2 months (ranging from 2 to 18 months). All patients were advised to use sunscreen regularly and avoid intentional sun exposure during the day.

Response rates also varied. Pooling the lesions, 50% repigmentation of vitiligo patches was never achieved before 2 months of vitiligo treatment, with a peak after 6 months of therapy. [13] In all responder-patients undergoing treatment regimens, at least 50% repigmentation was achieved after 6 months of therapy. The best results were obtained on lesions in the cephalic regions, especially the face, applying tacrolimus ointment twice daily. [14-16]

The percentage of non-responsive patients ranged from 0% to 14%. Only Kathuria et al. reported unsatisfactory results and limitations to the drug, with 50% repigmentation after 6 months of therapy in 5.3% of patients. [17]

Treatment was generally well-tolerated; no adverse systemic effects were reported. The most frequent adverse effects were burning sensation and pruritus, local erythema or irritation, acne or folliculitis-like manifestations, dysesthesia, stinging, pickling, formication and soreness. [7,14,15,18-27]

DISCUSSION

Our review aimed to critically assess the studies evaluating monotherapy with tacrolimus ointment to treat vitiligo.

Selection bias and a lack of common outcome measures were among the issues that prevented a proper meta-analysis. Although this review is not a meta-analysis, we critically assessed the literature and tried to identify high-quality studies.

The main limits of this analysis are the low number of patients included in most studies and the high heterogeneity of the study populations. Nevertheless, the studies analyzed as a whole seem to show that tacrolimus ointment provides effective treatment. Substantial repigmentation of lesions (>50%) requires time and consistent application of the product, at least 2-3 months depending on the patient's age and race.[28,29,30]

Treatment with topical tacrolimus is generally

CHART 1: Overview of clinical studies on vitiligo treatment with tacrolimus ointment monotherapy

Author(s), year Type of study	No. of patients, sex, Age(-years)	Localization	Treatment type Treatment time	Adverse effects	Outcome
Smith D.A.et al.[28], 2002 Case report	1 (M) 45 years old	Face and scalp	Topical tacrolimus ointment twice daily 18 months		After 2 months of treatment, areas of repigmentation were noted in the patches of vitiligo on his face and scalp. Progressive improvement was noted at each subsequent follow-up visit, with over 90% repigmentation of these areas after 18 months of therapy.
Grimes P.E et al.[7], 2002 Non-controlled, non-blinded series	6 (2 F, 4 M) Mean age 16 (range 7-38)	All patients had generalized vitiligo affecting less than 20% of the cutaneous surface.	4 patients (<16years old) were treated with 0.03% tacrolimus ointment and 2 patients (>16 y.o.) were treated with 0.1% tacrolimus ointment. The medication was applied to all the lesions twice daily. 1-5 months	In general, side effects were mild in all patients. Burning and stinging sensations occurred at the treated sites, which resolved after 1 to 2 weeks. One of our patients developed localized tinea corporis in an area adjacent to vitiligo patches treated with tacrolimus ointment.	Repigmentation of vitiligo lesions was graded as none, minimal (1%-25%), mild (25%-50%), moderate (50%-75%), and excellent (75%-100%). 4 patients treated with tacrolimus 0.03% ointment: 3 moderate and 1 mild. 2 patients treated with tacrolimus 0.1%: excellent and moderate.
Lepe V.et al.[18], 2003 Double-blind randomized trial	20 (16F,4M) Mean age 9.5 (range 4-17)	Hands, Face, Legs, Elbows, Abdomen, Thorax, Axillae	0.1% tacrolimus ointment,twice a day 2 months	Burning sensation (2 patients)	Repigmentation was 41.3% 5 patients: 75% repigmentation 2 patients: no change of pigmentation.
Travis L.B.et al.[29], 2003 Case series	1(F, 23 years old) 1(M, 24 years old) 1(M, 10 years old)	Affecting 75% of her face, including complete depigmentation of the eyelids, chin, cheeks, and perioral skin. depigmentation of 60% of his body surface area, including the eyelids, chin, axillae, elbows, hips, knees, and back. Depigmentation of the forehead, forearms, chest, back, and calves.	0.1% tacrolimus ointment twice daily 0.1% tacrolimus ointment twice daily 0.1% tacrolimus ointment twice daily		Complete repigmentation in 4 months. Completely repigmented after 2 months Complete repigmentation after 2 months.
Tanghetti E.A.et al.[30], 2003 prospective patient series	15 (5M,10F) Mean age 32 years (4-61)	Face, neck, forehead,left knee,ankle,hands,elbows,chest	Tacrolimus ointment 0.1% 9 months		13 patients (87%) experienced at least partial improvement with tacrolimus ointment 0.1%: 3 had greater than 75% repigmentation, 1 had 50% to 75% repigmentation, and 9 had greater than 0% to 25% repigmentation. Two of the patients had no response to treatment.

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Chart 1: Overview of clinical studies on vitiligo treatment with tacrolimus ointment monotherapy

CONTINUATION

Author(s), year Type of study	No. of patients, sex, Age(-years)	Localization	Treatment type Treatment time	Adverse effects	Outcome
Kanwar A.J.et al.[8], 2004 Open-label prospective	22 children (9 boys and 13 girls) Mean age 7.2		topical 0.03% tacrolimus ointment applied twice daily 12 weeks (3 months)	Side effects were minimal, including pruritus and burning, noted in only three patients.	Response was noted as marked to complete (> 75% repigmentation), moderate (50–75% repigmentation) and mild (< 50% repigmentation). Nineteen (86.4%) children showed some repigmentation at the end of 3 months and another three had no response. Of these 19 children, repigmentation was marked to complete in 11 (57.9%), moderate in five (26.3%) and mild in three (15.7%) children.
Grimes P.E.et al.[19],2004 Open-label prospective	19 (8M,11F) Mean age 39 At least 15 years old	Anatomic sites included face, neck, trunk, upper extremities, and lower extremities.	All patients applied tacrolimus 0.1% ointment twice daily for 24 weeks.	Signs and symptoms of irritation were minimal.	At 24 weeks, 17 of 19 patients (89%) achieved varying levels of repigmentation.
Silverberg N.B.et al.[9], 2004 Review of cases	57 (32F,25M) Mean age 9.2 (range 4-16)		Patients were treated with tacrolimus 0.03% or 0.1% ointment for at least 3 months. 26 children were treated with the 0.03% ointment and 31 with the 0.1% ointment.	Burning	Overall, 84% of the children responded at least partially to therapy. Of the 48 children placed on twice daily application regimens, 41 responded (85%). In contrast, only 55% of the 9 patients who used the medication once daily responded.
Prats Caelles I.et al.[31], 2005 Case report	1 (F) 8 years old	Symmetrically involving the extensor surfaces of her arms, thighs, and knees.	Tacrolimus 0.1% ointment Two months	Two months after starting therapy and without previous injuries, the patient noticed hair growth over her right knee (focal hypertrichosis).	Slow but evident focal repigmentation in all locations . Areas of vitiligo showed frank repigmentation with no other secondary findings.
Almeida P.et al.[24], 2005 Open-label prospective	12 (9M , 3F) Mean age 22 (range 4-66)	Face, hands, arms, legs, foot, trunk, genitals.	Topical tacrolimus 0.1 % twice a day	Pruritus in the eyelid area in two patients during the first week of treatment (2 patients).	50 % of the patients treated showed repigmentation with good (50 %-75 %) or excellent (> 75 %) improvement after 6 months.
Bakos L.et al.[14], 2007 Case report	1 (F) 18 years old	Left side of her chin and neck and on both sides of the dorsum.	Topical 0.1% tacrolimus once daily 3 months	At the end of 3 months, the cervical and chin spots showed an extensive eruption of inflammatory and noninflammatory lesions of acne, with papules, pustules, and closed comedones.	Repigmentation of nearly 90% of the chin and cervical lesions and 50% of the dorsal spots.

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Chart 1: Overview of clinical studies on vitiligo treatment with tacrolimus ointment monotherapy

CONTINUATION

Author(s), year Type of study	No. of patients, sex, Age(-years)	Localization	Treatment type Treatment time	Adverse effects	Outcome
Hartmann A. et al.[20], 2008 Prospective placebo-controlled right-left comparison study	30 (23F,7M) Mean age 43.7 (Range 19–65)	Depigmented lesions of the face and neck (21 out of 31 patients) as well as of the right upper and lower extremity (31 patients). In 20 patients with widespread depigmentation on the right arm and leg, tacrolimus ointment was combined with overnight occlusive dressings in previously defined areas.	Tacrolimus 0.1% ointment twice daily 12 months (3 months)	Side-effects were documented in 80% of the patients. Transient facial flushing (n = 16), enhanced heat intolerance (n = 9), especially when drinking alcohol, burning (n = 4), mild pruritus (n = 2), and mild perioral folliculitis (n = 2).	After 6 months, 23 of 30 patients (77%) showed distinct Repigmentation. The best results were achieved when a hydrocolloid foil was used as occlusive dressing (mean repigmentation 50%). After 12 months, 17 out of 21 patients (81%) with vitiligo lesions on the face showed repigmentation. Overall repigmentation was 60.5 % in the responding patients.
Lotti et al.[13], 2008 Open-label study	22 (range 18–72)		Tacrolimus 0.1% twice daily 6 months		Percentage of repigmentation: Excellent (> 75%) 61% Marked (50–75%) 16.1% Moderate (25–50%) 18.4% Minimal (< 25%) 4.5%
De. D. et al.[10], 2008 Case report	1 (M) 10 years old	Infraorbital area, arms, thighs, and around the knees and ankles	Tacrolimus ointment 0.03% 2 months	Brownish hyperpigmentation in the previous patch of vitiligo in infraorbital area (hyperpigmentation).	After 2 months of therapy, all the lesions repigmented completely with excellent color matching except those in the infraorbital area.
Choi C.W.[32], 2008 Retrospective review	51	Face, hand, foot	Tacrolimus ointment 0.1% 6 months		>60% responders
Xu A.E.[21], 2009 Prospective study	30 (9M, 21F) Mean age 22.3 (range 7–40)	In all, 40 target lesions were treated. Among them, 10 lesions were on the cheek, 7 lesions were on the forehead, 2 lesions were on the eyebrow, 5 lesions were on the eyelid, 3 lesions were on the prenarse, 3 lesions were perioral, 5 lesions were on the neck, 4 lesions were on the trunk, and 1 lesion was on the back of the hand.	0.1% tacrolimus ointment twice a day 4 months	Burning (4 patients)	Twenty-five (83.3%) patients showed some repigmentation at the end of 4 months and the other five patents had no response.
Z.A. Taher Z.A. et al.[33], 2009 Open-label prospective	20 (10 M, 10 F) Mean age 40.45 All above the age of 18 years	Right thigh,Left thigh, Left arm, Right cheek,Right axilla, Left neck, Right thigh, Right abdomen, right postauricular,Left axilla,Left flank, Left forearm, Left chest, Right hip, Posterior neck.	Tacrolimus (0.1%) ointment, twice daily 3 months		Qualitatively, all patients completing the study demonstrated improvements in lesion size following treatment, with follicular repigmentation in all cases.

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Chart 1: Overview of clinical studies on vitiligo treatment with tacrolimus ointment monotherapy — CONTINUATION

Author(s), year Type of study	No. of patients, sex, Age(-years)	Localization	Treatment type Treatment time	Adverse effects	Outcome
Radakovic S.et al.[34], 2009 Controlled prospective, randomized, observer-blinded trial	15 (10 F, 5 M) Mean age 32 (range 10-61)		Once or twice-daily application of 0.1% tacrolimus 6 months		Twice-daily treatment for 6 months induced some repigmentation in 10 out of 15 (67%) lesions. Once-daily application of tacrolimus resulted in some repigmentation in 7 out of 15 (46%) lesions.
Stinco G. et al.[15], 2009 Open randomized	12 (2 M, 10 F) Mean age 43.2 (range 30-61)	Face Neck Upper limbs Hands/Wrists Trunk Lower limbs Feet/Ankles	Tacrolimus 0.1% ointment twice daily 24 weeks (6 months)	Nine patients, 7 female and 2 male, described a heat sensation on the face during the first days of application; in one case the application of the ointment was reduced to once a day for two weeks, leading to disappearance of the symptoms. One female patient related soreness; 1 female patient reported pruritus on the eyelids associated with formication of the lips, and 1 female patient presented erythema of the bulbar conjunctiva. Five patients described the appearance of redflushing on their face after consuming a small amount of alcohol (a glass of beer or wine). All side effects resolved within 2-3 weeks.	treatment outcome was calculated for each anatomical site according to a scale ranging from 0 to 4 and classified as “absent” , “ poor” (1-25%), “moderate” (26-50%), “good” (51-75%), and “excellent” (> 75%). All treated patients with vitiligo lesions localized on the face, neck and upper limbs obtained a variable repigmentation, from poor to excellent; for the other anatomical sites (hands/wrists, trunk and upper and feet/ankles) cases of lack of repigmentation were recorded. The only patient with lesions on the feet/ankles showed no signs of repigmentation. The best results of repigmentation were obtained for the face , followed by the neck, upper limbs and trunk and lower limbs, hands/wrists.
Lo Y. H.et al[25], 2010 Multicenter, open-label, non-comparative	56 (19 M, 37 F) Mean age 44.4 (11–72) Patients were at least 16 years old		Tacrolimus 0.1% ointment twice daily 3 months	15 adverse events : namely acne in one, pruritus in five, dysesthesia in six and stinging in three.	We noted that although 28.3% of the patients showed no response at week 4, all of them showed variable degrees of repigmentation at week 12.
Udompataikul M.et al.[23], 2011 Open-label prospective	38 (13 M, 25 F) Mean age 27.8 (22 adults and 20 children)	Head and neck=24 lesions Trunk and extremities= 22 lesions	Topical 0.1% tacrolimus twice daily 6 months	Adverse events were observed in 28.6% of adult patients and 15% of children. These included burning sensation and erythema.	The overall response rate, defined as at least some repigmentation, was 76.09%.
Ho N. et al.[27], 2011 Double-blind, randomized, placebo-controlled trial	33 (17 F, 16 M) Mean age 8.4 (range 2-16)	Face, the periorbital area was the most commonly affected area (25%) followed by the perioral area (13%), trunk (35%),upper extremity (31%), lower extremity (36%); seven patients had periungual, four perineal and one vulval, involvement.	Tacrolimus 0.1% ointment 6 months	Folliculitis	Successful response was defined as repigmentation of > 50%. Responded successfully: 58% facial 23% non-facial.

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Chart 1: Overview of clinical studies on vitiligo treatment with tacrolimus ointment monotherapy

CONTINUATION

Author(s), year Type of study	No. of patients, sex, Age(-years)	Localization	Treatment type Treatment time	Adverse effects	Outcome
Silverberg J.I.et al.[11], 2011 Retrospective cohort	90 (35 M, 55 F) Mean age 25.6 years	Sixty-six patients had vitiligo lesions on the body, 65 patients on the face	Topical 0.03% tacrolimus ointment for children aged 2-15 years 0.1% ointment for children aged 16 or more At least 3 months		Repigmentation was good in all patients. More than 75% repigmentation of body lesions was noted in 62.5% of subjects with Fizpatrick types 3-4, compared with only 33.3 percent of Fizpatrick 1-2 and 21.7% of Fitzpatrick 5-6.
Bhuvana K.et al.[35], 2011 Open uncontrolled trial	55(30F,25M) Mean age 30 (range 3-57)	Thirty-seven patients had 1% of body surface area involved, followed by 11 patients with 2% involvement. Also, 3 and 4% of body surface area was involved in four and three patients, respectively. In 32 patients, single region was affected; 20 patients had lesions on the face, especially the lips, eyelids, and ears.	Tacrolimus ointment 0.1% twice daily 3 months		Of the 55 patients, 36 showed response to treatment and 19 showed no response after 3 months.
Tamler C.et al.[22], 2011 Case series	10 (4 F, 6 M)	Face, neck and limbs	Tacrolimus 0,1% ointment 4 months	Mild burning (2 patients)	Extremities and chest >50% repigmentation in 27% of cases. Six patients with lesions on the cephalic region showed >75% of repigmentation.
Kathuria S.et al.[17], 2012 Randomized controlled trial	29 (13 F, 16 M) Mean age 14 (range 5-55)		0.1% tacrolimus ointment twice daily 6 months		Only 5.3% patients with tacrolimus had >50% repigmentation, showing the limitation of the drug.
Sahni K.et al.[12], 2014 Case report	1 (M) 23 years old	Scalp, periorbital regions, elbows, thighs, legs, and feet	Topical tacrolimus 0.03% once daily 2 months	Hyperpigmentation over the periorbital macules.	There was some perifollicular repigmentation in most of the other vitiligo lesions.
Hartmann A. et al.[16], 2014 Open-label comparative prospective	11 (8F,3M) Mean age 41	Depigmented lesions on the face, trunk, and extremities of the right side, on the shins	Tacrolimus 0.1% ointment twice daily with overnight hydrocolloid dressing	Initial mild prickling	After 9 months, 38% of lesions on the tacrolimus-treated side on the trunk showed repigmentation. Four patients showed moderate to excellent repigmentation.
Baldo A. et al[26], 2014 Comparative randomized study	48 (32F,12M) Mean age 27 years (range 6-67 years)	Face/neck Hands Trunk Arms/legs	Tacrolimus ointment 0.1% Twice a day 36 weeks (9 months)	Erythema and folliculitis-like manifestations (2 patients discontinued the therapy because of side effects).	Partial repigmentation 71% of patients. No repigmentation 14% of patients.

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safe and free of major local side effects. No serious adverse events occurred that required treatment to be stopped. In a single study, erythema and folliculitis-like manifestations on the treated area led 2 patients to discontinue therapy with tacrolimus ointment 0.1% twice a day. [26]

In the open, randomized trial conducted by Stinco et al.[15] (total of 12 patients, age range 30-61, treatment with tacrolimus 0.1% ointment twice daily), 9 patients described a heat sensation on the face during the first days of application. One female patient related the appearance of soreness; another female patient reported pruritus on the eyelids associated with formication of the lips, while one female patient presented erythema of the bulbar conjunctiva. Five patients described redflushing on their faces after consuming small amounts of alcohol (a glass of beer or wine). All local side effects resolved within 2-3 weeks after the topical treatment regimen was reduced from two daily applications to one daily application.

Tacrolimus 0.03% ointment has been reserved for children <16 years and associated with hyperpigmentation, as well as hypertricosis, in the target area.[12,10,31] In adult patients, treatment with tacrolimus 0.03% yielded similar results to tacrolimus ointment 0.1%.

Although tacrolimus monotherapy seems to have good efficacy and tolerability, only small trials and case series are available in the literature[32,33,34,35] The largest study ever published in terms of the number of patients enrolled, only included 90 patients. [11]

Hence, further, standardized investigations on a greater number of patients are needed.❑

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