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A systematic review of transforming growth factor beta inhibitor treatments on keloid scars

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Objectives: The primary objective of this study was to evaluate the most appropriate transforming growth factor beta (TGF-β) inhibitor drug on keloid scars.
Methods: Search strategy was done by using the PubMed, MEDLINE, and Wiley. The search terms were “keloids”, “treatment”, “transforming growth factor beta” and “scar”. Data was grouped and calculated proportionally, including 95% confidence interval by MEGASTAT.
Results: The TGF-β inhibitor drugs were found to be effective in treating keloids. There was consistency in the same direction of the improvement in keloid appearance. Complications and recurrent rate of each drug were investigated. Major complications of bleomycin and fluorouracil were hyperpigmentation that occurred after using drugs, which gradually subside after discontinuation or applying of bleaching agent. Botulinum toxin had less complication, but its use was limited to some sites for keloid formation. Side effects of imiquimod were local skin reaction and lymphadenopathy. Mitomycin C had some reports of infected wound. Low recurrent rate was seen in bleomycin, botulinum toxin, imiquimod (only earlobes), and mitomycin C.
Conclusion: TGF-β inhibitor drugs appeared to have less permanent side effects and lower recurrent rates in overall compared to the standard treatment; intralesional steroid. TGF-β inhibitor drugs were separated into the local infiltration group and the after surgery application group. For the local group, bleomycin and fluorouracil provided better results affecting keloids. Botulinum toxin injection was reported with a good result on keloids but its limitation on the injection site was still concerned. In the other group, mitomycin C was more effective than imiquimod. It could be applied on both earlobe and trunk with no systemic adverse effect. Therefore, TGF-β inhibitor drugs had proven to be a new effective option for keloids treatment.

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Introduction

Keloid scar is a benign fibrotic skin disease resulting from abnormal wound healing process, especially during the proliferative and remodeling phases. The characteristics of keloids are firm with well-defined border erythematous nodule or plaque. The boundary of scar is over the origin of wound that differs from hypertrophic scar. There are frequently symptomatic such as tender, itching, hyperesthesia or limited range of motion. The cosmetic concern may lead to a psychosocial trouble. Most common spots of keloids are chest, shoulder, upper arm, upper back, back of the neck, and earlobes. Ear piercing, vaccinations, surgical procedure and burn could be induced to become scars. Risks of having keloids increase with darker skin type approximately 15-20 folds. They occur in Black, Hispanic, Asian and white persons respectively. Patients with family history of keloids tend to have greater chance of keloids than people who have not.

Treatments of keloids are offered in different choices. Laser, intralesional drugs, topical drugs, and silicone gel sheeting are common to treat excessive scar. Intralesional steroid is the most popular treatment to help reduce symptoms and appearances of scar. Although it is cost-effective and easy to acquire, some side effects are not acceptable. The disadvantages are pain, skin atrophy, telangiectasia, skin discoloration, and the numbers of treatment sessions are required. At present, other treatments have been developed to replace steroid injection. Currently, it is believed that transforming growth factor beta (TGF-β) plays an important role in pathogenesis of keloids. The major function of TGF-β is to produce collagen by stimulating Smad pathway. Other function includes changing fibroblast into myofibroblast, inducing inflammatory phase by recruiting inflammatory cells, promoting angiogenesis, and inhibiting apoptotic mediation. Thus, the inhibition of transforming growth factor β may be necessary to treat keloid scar.[1]

Material and Methods

Searching of medical literatures was conducted by using the PubMed, MEDLINE, and Wiley databases. The search terms were “keloids”, “treatment”, “transforming growth factor beta” and “scar”. The lists of references of all included studies were also reviewed. Only patients with improvement, complications of drugs, and follow-up outcomes were considered. Exclusion criteria were patient satisfactory outcomes, undisclosed data, and small subjected groups that could not be evaluated. The improvement of the size of scars was carried out using MEGASTAT to calculate proportion

and 95% confidence interval by binomial distribution for statistic evaluation.

Results

The standard treatment used in this study was triamcinolone. bleomycin, fluorouracil (5-FU), botulinum toxin type A, imiquimod, and mitomycin C were used in this study to compare with the standard treatment. Route of administration of bleomycin, 5-FU, botulinum toxin type A, and triamcinolone were intralessional injection, dermojet, or tattooing. Mitomycin C and imiquimod were used after surgery procedure. By using MEGASTAT, results from the intralesional group were divided into two categories; Improvement >50% and improvement ≤ 50%. Complications and recurrence rates were evaluated in all drugs.

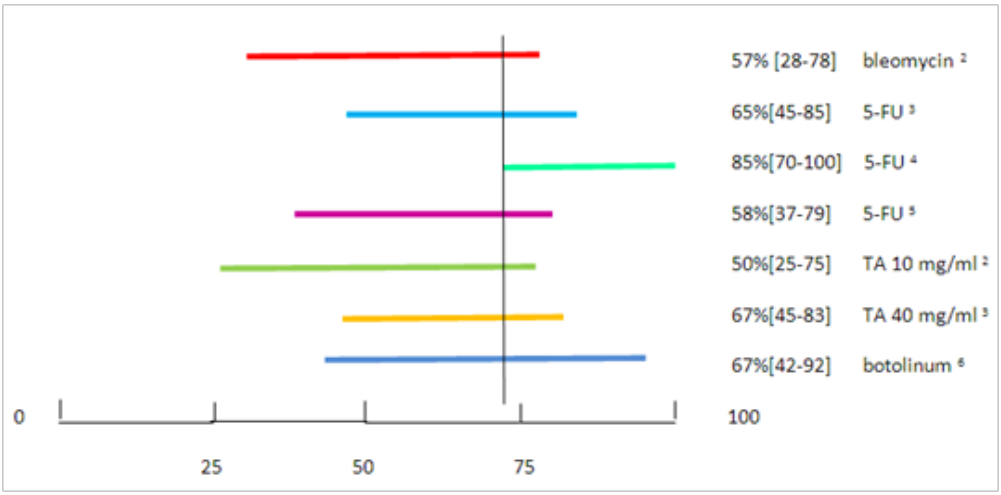

Figure 1. Graph shows proportion and 95% confident interval of size improvement in treated groups of bleomycin, fluorouracil, triamcinolone (concentration 10 mg/ml and 40 mg/ml), and botulinum toxin type A.

There was consistency in the same direction of the improvement in keloid appearance. However, there was no significant difference between groups.

Drug	Journal	Complication/adverse effect	Recurrent rate
Triamcinolone (10 mg/ml)	Bayo aloko olokun [7] N= 54	Hypopigmentation 46.29% Hyperpigmentation 14.81% Skin atrophy 14.81% Telangiectasia 14.81%	
	Kittisak payapripapong [8] N=12	Pruritus 33.3%, Pain 8.3%, Skin atrophy 8.3%	
	Eman Shaarawy [9] N=12	Skin atrophy and telangiectasia 25%	
Triamcinolone (40 mg/ml)	Anil K. saha [2] N=24	Hyperpigmentation 12.5%	6 mo 36.36%
	FX Margaret Shanthi [3] N=27	Hypo-hyperpigmentation 25%	
	Muhammad Uzair [10] N=40	Hypopigmentation 12.5% Irregular menstrual cycle 5%	3 mo no recurrence
Bleomycin	Farahnaz Fatemi Naeini [11] N=17	Hyperpigmentation 75%	3 mo no recurrence
	Agustin Espana [12] N=13	Slightly residual pigmentation 15.38%	5-36 mo 15.4%
	Kittisak payapripapong [8] N=14	Hyperpigmentation 71.4%, Pruritus 50% Pain 21.4%, Burning sensation 14.3% Vesicle formation 7.1%	
	Yasemin Saray [13] N=15	Hyperpigmentation 26.67% Dermal atrophy 20%	Average 19 mo no recurrence
5-FU	Somesh Gupta [3] N=24	Ulcer at site of injection 4.17% Mild to moderate hyperpigmentation 100%	3-6 mo no recurrence in 19 follow-up patients
	George Kontochristopoulos [4] N=20	Pain 100%, Hyperpigmentation 100% Superficial ulceration and easy to heal 30%	1 yr 47% (9 in 20 but 4 in 9 biopsy)
	Anil K. saha [2] N=20	Ulceration 65% , Hyperpigmentation 90% Pain at injection site 95%	6 mo 35.29%
	Ali Sadeghinia [14] N=20	No side effect detected	
Imiquimod	Fernanda marson cacao [15] N=9	Local skin reaction with complete treatment 88.89%	8 mo 100% (trunk)
	Mitchell E. Stashower [16] N=4	Tender at anterior cervical lymphadenopathy 25%	1 yr no recurrence (earlobe)
	Rafael F. Martin-Garcia [17] N=8	Local skin reaction and temporary discontinuation 37.5%	6 mo 25% (earlobe)
Botulinum toxin type A	Xiao Zhibo [6] N=12	No report side effect	1yr no recurrence
Mitomycin C	J.N.R. Bailey [18] N=10	Pain 80%, Infected wound 10%	18 mo 10%
	Charles E. Stewart IV [19] N=10	No any side effects	8 mo 10%

Table 2. Complications and recurrent rates of TGF-β drugs.

Discussion

Triamcinolone 10 mg/ml – 40 mg/ml is considered as the standard treatment for keloids. Although benefits of this drug are well-known, but side effects and recurrent rate are also concerned. Skin atrophy, telangiectasia, and pigment discoloration are the most common side effects found in this review.[7] Recurrence rate of keloids when using this drug is quite high, but is not different improvement than other drugs. Therefore, newer treatments have been searched as alternative to triamcinolone.

Bleomycin is a cytotoxic antibiotic that reduces collagen synthesis by inhibiting lysyl-oxidase and TGF-β1. Evidence shows that it induces apoptosis in mammalian cells.[2,11,13] In this review, results of the efficacy of bleomycin in all of the included studies have no statistically significant. However, only the study by Saray Y*et al*. that used difference modality; dermojet instead of intralesion or tattooing reported permanent side effects.[13] The chance of hyperpigmentation is also observed in Fitzpatrick skin type III and above. This drug is safe when applying as local application because the absorption level is very low.[2] Overall, recurrence rate and complications are lower than triamcinolone.

Fluorouracil (5-FU) is a pyrimidine analogue with antimetabolite activity. This drug inhibits fibroblast proliferation, myofibroblast differentiation, and TGF-β expression.[4,5,14] Efficacy of 5-FU in improving treatment of keloids is similar to bleomycin, only with higher rate of post-inflammatory hyperpigmentation, the presence of short-duration ulceration, and severe pain. Sadeghinia A *et al*. suggested that the ulceration and pain were caused by short interval weekly of drug administration and the injection technique. The study used tattooing method and prolonged interval with reports of no side effects.[14]Kontochristopoulos G *et al*. reported 47% of recurrences in a 1-year follow up.[4] Biopsies of almost half of renew lesions were done for histology evaluation. This means biopsy procedure causes new injury and it may be a cause of new keloid formation. The high percentage of recurrent rate is unbelievable in this study.

Botulinum toxin type A is one of the most interesting drugs. No side effects and no recurrence are reported. Disadvantages of using botox are limitation of injection site and dosage. Botulinum toxin decreases TGF-β1 expression and acethycholine.[8,20] Muscle relaxation is mostly concerned in all cases. ZhiboX.*et al*. selected only keloids on earlobe, chest, and shoulder. This explained no report in abnormal neuromuscular.[6] In addition, Wilson AD. suggested that botulinum toxin injection at cheek scar patient would occur asymmetry of facial expression.

Imiquimod and mitomycin C are applied after surgical excision. Imiquimod is a local production of immune stimulating cytokine such as interferon α, tumor necrosis factor, and interleukin 6. It can also cause antineoplastic activity and apoptotic effects. Interferon γ is also stimulated by imiquimod down regulation of TGF-β[16,17]. Side effects of local skin reaction such as erythema, crust, and erosion are most commonly seen. They can be healed with drug discontinuation. Lymphadenopathy may occur from robust immune response and appear after oral antibiotic administration.[16] Although imiquimod shows a positive result on earlobe keloids, it is worse results on the trunk area.

Mitomycin C is an antineoplastic agent that inhibits DNA synthesis.[18] From reviews, mitomycin C is better than imiquimod in no local skin reaction or any lymphadenopathy. It also works well on the trunk area. Side effects of mitomycin C include long-period of pain, infected wound, and hypopigmentation. Bailey *et al*. suggested that dividing treatment areas when using this drug could help decrease risk of effects.[18]

Conclusion

Transforming growth factor β plays a major role in keloids formation, especially TGF-β1 and TGF-β2. A new trend of keloid treatment includes applying drugs that can inhibit or decrease TGF-β. The TGF-β inhibitor drugs that were included in this study are consist of bleomycin, fluorouracil, botulinum toxin type A, imiquimod and mitomycin C. Results have no show of statistically different from standard triamcinolone injection. Although some drugs cause frequent side effects, but most of them only occur temporary. The local application is recommended in bleomycin and fluorouracil. They show no serious side effects and with acceptable recurrence rate. However, cautions in darker pigmented skin patients are necessary. The other modality, mitomycin C is more recommended than imiquimod because it can apply on any site of keloid with lower risk.

This study has several limitations. Firstly, many studies use a small group of participants with different criteria such as duration of keloids, site, and race. Secondly, if a follow-up period could be longer, the result would be more reliable. Lastly, there are few included studies because many studies are reported with patient satisfaction results.

In the future, comparing of the efficacy of TGF-β inhibitor drugs in the larger subjects group of subjects should be conducted. For clinical purposes, I suggest that the combination of TGF-β inhibitor treatment such as fluorouracil and botulinum toxin may be effective use because they help increase efficacy and reduces side effects when treating keloids.

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