Dermatology Practical & Conceptual

Clinical Efficacy and Safety of Intralesional Bevacizumab in Dermatology: Insights from a Systematic Review

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ABSTRACT

Introduction: Bevacizumab is a humanized monoclonal antibody specifically targeting the vascular endothelial growth factor (VEGF). In addition to cancer and ophthalmology, bevacizumab has other off-label uses. Among these, the treatment of hereditary hemorrhagic telangiectasia and hemangioma can be mentioned.

Objectives: Although there are reports of successful treatments by bevacizumab, there is no systematic review on the topical use of this medication in dermatology. Therefore, this study aimed to investigate this topic.

Methods: A systematic search on topical bevacizumab was done with MeSh-based keywords on online databases of PubMed, Scopus, and Web of Science in December 2022. The records were evaluated, and the eligible articles were selected.

Results: We reviewed related studies, and the disease name, treatment protocol (injection dosage and intervals), outcomes, and complications were summarized for conclusions.

Conclusions: In this study, we systematically reviewed related papers and summarized the use of bevacizumab in dermatology in four categories, including hereditary hemorrhagic telangiectasia, vascular malformation, vascular proliferation, and others (lichen planus, and basal cell carcinoma).

Introduction

Bevacizumab, an anti-VEGF-A medication, is a humanized monoclonal antibody specifically targeting the vascular endothelial growth factor (VEGF). Bevacizumab binds to VEGF-A and inhibits VEGF-A from connecting to its receptor. This process stops vascular endothelial growth, endothelial cell proliferation, and angiogenesis [1-3].

Neovascularization and angiogenesis are involved in the pathogenesis of several conditions, such as inflammatory and malignant processes. Theoretically, anti-VEGF medication can improve these conditions by inhibiting angiogenesis [4]. Bevacizumab prevents the growth of blood vessels that supply nutrients and oxygen to tumors, which results in slowing down their growth and spread [2,5].

In 2004, the US Food and Drug Administration (FDA) approved the use of bevacizumab (Avastin) for the treatment of metastatic colorectal cancer, and in 2009, for glioblastoma; since then, it has been authorized for use in many other types of cancer, including non-squamous cell lung carcinoma, prostate cancer, metastatic breast cancer, and metastatic renal cell carcinoma [2,6]. It is also one of the first choices for inhibiting angiogenesis approved by the FDA [2].

Avastin is widely used in ophthalmology to treat neovascular glaucoma, retinal vein occlusion, and diabetic retinopathy and as an intravitreal injection to treat macular edema [7-9]. It has also been increasingly used in the treatment of retinopathy of prematurity, alone or in combination with standard laser therapy [10,11].

In addition to the field of cancer and ophthalmology, bevacizumab has some off-label applications in the treatment of mucocutaneous conditions [12], including hereditary hemorrhagic telangiectasia (HHT) [13,14] and hemangioma [15].

Although there are several reports of successful treatments with bevacizumab in dermatological conditions, there is no systematic review about the use of this medication in dermatology.

Objectives

In this study, we systematically reviewed related papers and summarized the use of bevacizumab in dermatology in four categories, including HHT, vascular malformation, vascular proliferation, and others (lichen planus, and basal cell carcinoma).

Methods

In this study, online databases were searched systematically in December 2022. Keywords including "anti-vascular endothelial growth factor", "anti-VEGF", "bevacizumab", "Avastin", "derma*", "skin", "cutaneous", "intralesional", and "topical" were selected according to the MeSh terms.

All keywords were searched in PubMed, Scopus, and Web of Science with the following query: ((anti-vascular endothelial growth factor[Title/Abstract]) OR (anti-VEGF [Title/Abstract]) OR (bevacizumab[Title/Abstract]) OR (avastin[Title/Abstract])) AND ((derma*[Title/Abstract]) OR (skin[Title/Abstract]) OR (cutaneous[Title/Abstract]) OR (intralesional[Title/Abstract]) OR (topical[Title/Abstract])). All articles consisting of these keywords were included. Duplicated articles were removed by EndNote version 20 software.

First, titles of articles were screened, and any irrelevant record such as cancer or ophthalmological use was excluded. Also, reviews of any type were excluded. In the next step, the abstracts were screened, and reviews, experimental studies, and intravenous injections were omitted. In the final step, efforts aimed to screen the full texts of articles based on the same criteria.

Then the remaining full texts were evaluated, and the data were excluded. Finally, the disease name, treatment protocol (injection dosage and intervals), outcomes, and complications were summarized for conclusions.

Results

After conducting the systematic search, 3014 articles were found and inserted into EndNote software. By removing the duplicated records, 1229 articles remained, and 1199 articles were excluded due to their irrelevant title or abstract. The full text of 30 articles was screened and 14 of them were selected. An Explorer search was also conducted, and seven new article was added. Figure 1 shows the PRISMA flow diagram of the current review.

This study discusses the use of bevacizumab in dermatology in four categories: HHT, vascular malformation, vascular proliferation, and others (lichen planus (LP), and basal cell carcinoma (BCC)) (Table 1).

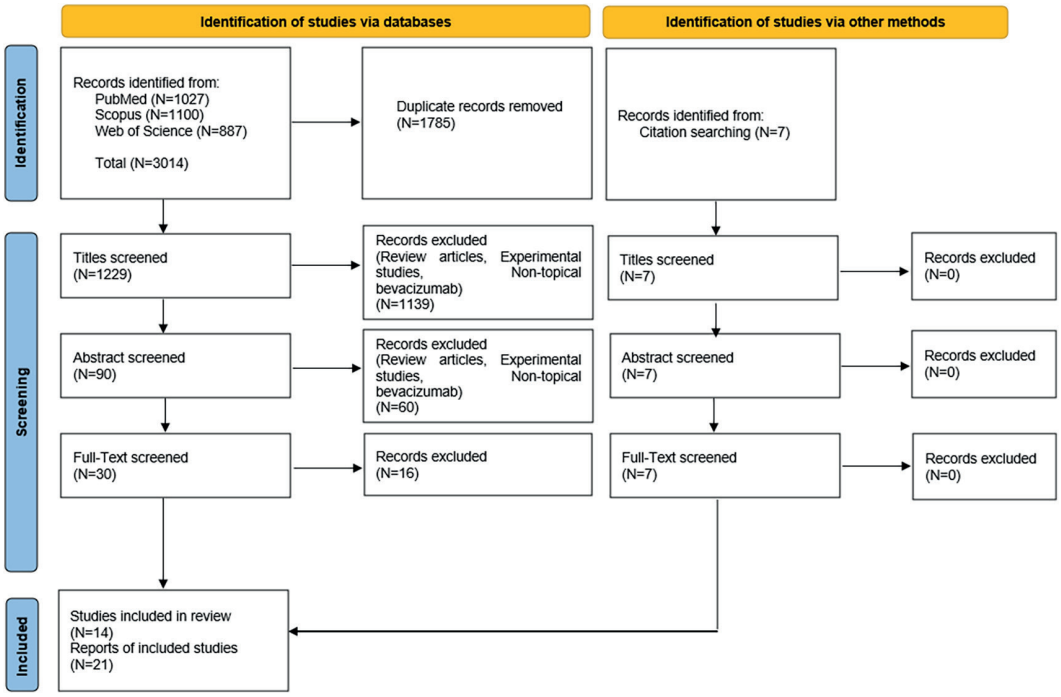

Figure 1. The PRISMA flow diagram of the study.

Hereditary Hemorrhagic Telangiectasia (HHT)

The use of bevacizumab for HHT, also known as Osler-Weber-Rendu syndrome, has been reported in 14 studies. Affected patients with HHT often develop arteriovenous malformations and mucocutaneous telangiectasias, including nasal mucosa with a susceptibility to bleeding [16]. Due to the elevated levels of serum and mucosal VEGF and transforming growth factor-β (TGF- β) in the affected patients, bevacizumab, as an anti-VEGF, inhibits angiogenesis and can help improve recurrent epistaxis [16]. Epistaxis severity is judged by epistaxis severity score (ESS), which was assessed pre- and post-treatment in most of the studies [17]. A proper evaluation of pre-treatment ESS is required to choose the best treatment protocol [18]. Intranasal spray, 50–100 mg, can treat mild symptoms, while a 100 mg submucosal injection is indicated for moderate-to-severe cases [16].

A randomized clinical trial (RCT) concluded that a single dose nasal spray had no clinical effect and that there should be repeated doses to reach sufficient epistaxis improvement [19]. Another RCT revealed that 4 mg topical bevacizumab per day for seven days had no clinical effect and concluded that the dosage may be inadequate [14]. This study aimed to compare the effect of bevacizumab, estriol, tranexamic acid, and placebo, and there was no difference between these groups [14]. A retrospective study was done on 32 patients with HHT receiving 25–100 mg bevacizumab, administered topically, submucosally, or both. Patients were interviewed about their post-treatment epistaxis severity and revealed a significant improvement [13]. Also, a prospective study was done on six patients receiving 10 treatment courses of 50 mg topical bevacizumab; an effective symptomatic treatment for patients with pre-treatment ESS<7 was found [14].

Bevacizumab can be injected intralesionally (IL) or intravenously (IV). In comparison to IV injection of bevacizumab, IL injection is a much better choice because of less systemic adverse effects; it is also more available and the more cost-effective. The intranasal submucosal injection is frequently administered to the lateral nasal wall, middle/inferior turbinate, nasal floor, and bony septum [16]. Nasal cartilaginous septum should not be injected with and without laser surgery due to the possibility of septal perforation [20,21]. A study introduced a 4-injection site technique as a new treatment option: the sphenopalatine area, the upper part of the bony septum, the upper part of the lateral nasal wall, and the anterior floor of the nose. These sites are near the entrance points of vessels, which may result in better control [22]. An RCT compared the effect of a 100 mg single-dose submucosal injection of bevacizumab with placebo in reducing HHT-related epistaxis. Reducing epistaxis was much greater in the bevacizumab group [23].

A 5-year-old female was reported with epistaxis since birth. Many treatment methods had been used, with no clinical improvement, including moisturizing therapy, aminocaproic acid, tranexamic acid, and cauterization. Finally, she was treated successfully with two injections of intranasal bevacizumab [24]. There are limited complications reported for intranasal therapy, including septal perforation [20,21], subfebrile body temperature [24], nasal symptoms, headache, abdominal pain [14], elevated blood pressure, body tingling [23], ageusia, and anosmia [18].

Table 1. Overview of Literature Included in this Systematic Review.

No.	First Author / Year	Study Design	Sample Size	Age	Disease	Bevacizumab Protocol	Outcome	Complications
1	Simonds et al. / 2009	Retrospective	10	58.3±8.2	HHT	100 mg submucosal injection	Effective	Septal perforation (N=4)
2	Davidson et al. / 2010	Case report	1	45	HHT	100 mg submucosal injection in addition to 2 courses of topical application	Effective	N/A
3	Chen et al. / 2011	Retrospective	58	54.99±11.8	HHT	50-100 mg topical (nasal spray) (N=18), 25-100 mg submucosal injection (N=26), Both (N=8)	Effective	Septal perforation (N=5)
4	Rohrmeier et al. / 2011	Retrospective	11	65 (46–77)	HHT	<7.5 mg submucosal injection	Effective	No complication
5	Karnezis et al. / 2011	Retrospective	32	53.8±13.2	HHT	50-100 mg topical (nasal spray) (N= 17), 100 mg submucosal injection (N=10), Both (N=5)	Effective	N/A
6	Karnezis et al. / 2012	Prospective	19	60 (40-80)	HHT	100 mg submucosal injection. In addition, 6 patients received 100 mg topical (nasal spray) for 8 times.	Effective	No complication
7	Steeples et al. / 2012	Case Letter	1	31	Hemangioma	2.5 mg/0.1 ml monthly intralesional injections, 4 times	Effective	No complication
8	Brinkerhoff et al. / 2012	Case report	1	55	HHT	100 mg topical (nasal spray), every 8-9 weeks	Effective	No complication
9	Dheyauldeen et al. / 2012	Prospective	8	56.5±12.7	HHT	100 mg submucosal injection	Effective	N/A
10	Guldmann et al. / 2012	Prospective	6	56.3	HHT	50 mg topical (nasal spray)	Effective	Headache, ageusia, and anosmia
11	Gaitanis et al. / 2013	Case series	7	70 (50-88)	BCC	25 mg intralesional injection, 1-3 times	Effective	Pain during injection (N=6), Flu-like symptoms (N=2), Reversible leukopenia (N=1)

No.	First Author / Year	Study Design	Sample Size	Age	Disease	Bevacizumab Protocol	Outcome	Complications
12	Kalinina et al. / 2014	Case report	1	5	HHT	10 mg/ml submucosal injection, 2 times every 3 weeks	Effective	Subfebrile body temperature up to 37.5°C
13	Riss et al. / 2014	RCT	9	59 (41-71)	HHT	100 mg submucosal injection	Effective	Elevated blood pressure (N=1), Rhinitis (N=1), Itching at the nose tip (N=1), Body tingling (N=1)
14	Dupuis-Girod / 2014	RCT	30	57 (39-75)	HHT	12.5, 25, 50, 75, or 100 mg topical (nasal spray), single episode	No clinical effect	No complication
15	Ablanedo-Terrazas et al. / 2015	RCT	7	35 (29–39)	Mucosal KS	0.2 mL (5 mg)/cm2 intralesional injection, 3 times every 2 weeks	No clinical effect	Mild pain and tenderness at the injection site (N=1), Fever (N=1)
16	Whitehead et al. / 2016	RCT	29	48 (42-53)	HHT	4 mg/day topical (nasal spray), for a week	No clinical effect	Nasal symptoms (N=11), Headache (N=10), Abdominal pain (N=5)
17	Mahmoud et al. / 2016	RCT	20	43±1.3	OLP	2.5 mg/0.5 ml intralesional injection	Effective	No complication
18	Hwang et al. / 2017	Case report	1	10	Lymphangioma	2.5-10 mg intralesional injection, 5 times monthly and then 4 times every 3 months	Effective	No complication
19	Kinzinger et al. / 2018	Case report	1	67	Sinonasal hemangioma	50 mg intralesional injection	Effective	N/A
20	Sabry et al. / 2019	RCT	15	3-9 months	Hemangioma	25 mg/ml (2mg/cm2) intralesional injection, 6 times monthly	Effective	No complication
21	Bowers et al. / 2020	Case report	1	61	HHT	100 mg Submucosal injection	Effective	No complication

Abbreviations: RCT: Randomized Controlled Trial, HHT: Hereditary Hemorrhagic Telangiectasia, BCC: Basal Cell Carcinoma, KS: Kaposi Sarcoma, OLP: Oral Lichen Planus, N/A: Not Available.

Persistent bleeding may occur even for a few weeks after submucosal injection because of the pre-existing telangiectasia. Therefore, combination therapies can help to improve these symptoms. Cauterization [16], potassium titanyl phosphate (KTP) laser [13,17,20,21], neodymium-doped yttrium aluminum garnet (Nd: YAG) laser [25], and topical bevacizumab [16,26] are used as adjuvant therapies accompanied by submucosal injection. Another case was a 55-year-old female dealing with HHT, breast cancer, and chemotherapy-induced anemia and increased epistaxis. Episodes of intravenous bevacizumab were initially used, then 100 mg topical therapy (nasal spray) every 8–9 weeks was used as an effective maintenance control for epistaxis and anemia [1].

In addition to nasal mucosa, HHT can present with other mucosal involvements, including the tongue. A study reported a case involving recurrent bleeding of tongue telangiectasia successfully treated with dual therapy of KTP laser and 100 mg submucosal bevacizumab injection, without any complication [13]. The patient had had two episodes of KTP laser previously but without any improvement.

Vascular Malformation

Lymphangioma

Lymphangioma is a benign tumor that can be treated by sclerotherapy or surgical intervention. Non-surgical treatments such as IL steroid or bleomycin may also be useful [25].

A 10-year-old female was reported with a hemorrhagic, swollen lesion on her tongue. She was initially treated with 40 mg/ml triamcinolone acetonide injection and 1 mg/ml bleomycin. The lesion shrank but did not disappear [25]. After adding 25 mg/ml IL bevacizumab to the previous medication, every three months for a year, the lesion completely regressed. No side effect or recurrence was observed after three years of follow-up. Therefore, bevacizumab can be used as a potential adjuvant treatment for extensive lymphangioma [27].

Vascular Proliferation

Recurrent Sinonasal Hemangioma

Sinonasal hemangioma usually originates from the nasal septum or lateral wall. It is a benign tumor that presents with epistaxis and nasal obstruction. Surgical intervention is the choice treatment [28]. These procedures may lead to aesthetic and functional complications such as excessive tearing, diminished sensation, scarring, deformities, and blockage of nasal passages [29].

A 67-year-old male with nasal hemangioma complained of recurrent epistaxis and nasal obstruction even after surgery. He was successfully treated with a single injection of 50 mg bevacizumab into the lesion and nasal septal mucosa. Ten months later, the lesion had improved, and at the 6-year follow-up, the patient was asymptomatic, with no recurrence or complication observed [28]. Therefore, IL bevacizumab may be an effective noninvasive option for treating sinonasal hemangioma.

Infantile Hemangioma

Infantile hemangioma (IH) is the most common vascular tumor in infants. VEGF overexpression may be responsible during the initial proliferative stage of IH [30]. An RCT was conducted on children aged 3–9 months with IH to compare the effectiveness of IL bevacizumab with triamcinolone acetonide. The children in each group were treated with 25 mg/mL of IL bevacizumab and 2 mg/2 cm^2 of triamcinolone acetonide monthly for six months. After three months, lesions were successfully healed, with no recurrence or side effect. This study concluded that IL bevacizumab and triamcinolone acetonide both could be safe and effective for infantile hemangioma. However, triamcinolone acetonide was more effective in this study [15].

Capillary Hemangioma in Pregnancy

Capillary hemangioma is a proliferative lesion with an overexpression of angiogenic growth factors such as VEGF. Pregnancy is associated with an increased risk of tumoral lesions, including vascular proliferative lesions. Hormonal factors may contribute to these complications [31]. In a case study, a female with hemangioma during her third trimester lasting until six months post-partum resisted invasive treatments. A 4 mg IL triamcinolone acetonide was administered, with no improvement. Finally, IL bevacizumab was initiated at a dose of 1.25 mg in 0.05 mL, leading to a significant improvement. Additional monthly injections with a dose of 2.5 mg in 0.1 mL were given four times, resulting in complete regression, without any complication or recurrence [31].

Kaposi Sarcoma

Therapeutic options for Kaposi sarcoma (KS) include chemotherapy and radiation therapy along with antiretroviral agents and immunomodulators [32]. An RCT was conducted on 14 human immunodeficiency virus (HIV)-infected individuals with mucosal KS. The disease involved the upper airway regions (oral cavity, pharyngeal, and laryngeal areas). The participants were divided into two groups: one received IL bevacizumab in addition to antiretroviral therapy (ART), while the control group received ART alone [32]. The intervention group received three injections every two weeks, each with a dose of 0.2 mL (5 mg/cm^2). IL bevacizumab resulted in side effects, including pain and tenderness at the injection site, which were relieved with a single dose of acetaminophen 1000 mg. In addition, one patient experienced a fever of 39° C three days after the injection,

leading to hospitalization [32]. In the end, the study revealed that the combination of IL bevacizumab and ART did not show any significant effect on mucosal KS involving the upper respiratory tract in HIV-infected patients [32].

Others

Lichen Planus

Oral lichen planus (OLP) is a chronic inflammatory disease affecting mucocutaneous regions. The standard approach suggests treatment with topical corticosteroids. However, due to the strong correlation between OLP and angiogenesis, anti-angiogenic drugs could emerge as an alternate option for patients who cannot use conventional therapy or who have shown inadequate response [33]. An RCT was conducted on 40 patients with atrophic/erosive lesions of OLP. Twenty patients were randomly selected to receive 2.5 mg IL bevacizumab, and other participants were instructed to use triamcinolone acetonide on the buccal mucosa. The patients underwent seven follow-up sessions, for a total duration of three months [33]. Tissue biopsy revealed that bevacizumab effectively reduced levels of IL-8 and stopped the activity of pro-inflammatory cells and cytokines, which inhibited VEGF and angiogenesis. A week after IL bevacizumab injection, the size of lesions and pain intensity improved, without complication. Therefore, IL bevacizumab may be an effective and a safe treatment for atrophic/erosive LP [33].

Basal Cell Carcinoma

The goal for the treatment of basal cell carcinoma (BCC) is to achieve complete tumor removal. This can be accomplished through conventional surgical excision, Mohs micrographic surgery, cryosurgery, electrodesiccation and curettage, topical application of imiquimod or fluorouracil, photodynamic therapy, or radiation therapy [34]. In a case series, seven patients with extensive local BCC were initially treated with immunocryosurgery alone, which was ineffective. IL bevacizumab was then used as an adjuvant treatment [35]. The treatment protocol was 12.5 mg of topical imiquimod 5% every night, 1 g of tazarotene 0.1% daily, and two cycles of cryosurgery every two weeks. As an adjuvant medication, three sessions of 25 mg IL bevacizumab were immediately used after cryosurgery [35]. The tumor shrank successfully after two bevacizumab injections. Pain during injection, flu-like symptoms, and reversible leukopenia were the only reported complications. Therefore, bevacizumab may be an effective and minimally invasive therapeutic option for BCC [35].

Conclusion

Intralesional bevacizumab has some off-label applications in dermatology beyond its previous advantages for the treatment of cancer and ophthalmological conditions. These dermatological applications can be summarized based on previous reports into four categories: hereditary hemorrhagic telangiectasia, vascular malformation, vascular proliferation, and others (lichen planus and basal cell carcinoma).

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