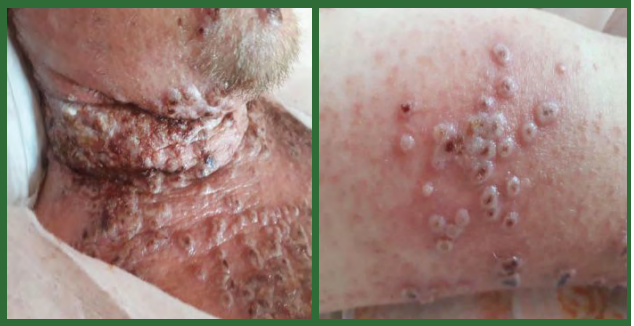
FORUM MŁODYCH PTD POLSKIEGO TOWARZYSTWA DERMATOLOGICZNEGO

FORUM DERMATOLOGICUM

Journal of Youth Forum of the Polish Dermatological Society

Vol. 10, Number 3, 2024

ISSN 2451–1501
e-ISSN 2451–151X



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Journal of Youth Forum of the Polish Dermatological Society

Editorial policies and author guidelines are published on journal website:
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FORUM DERMATOLOGICUM is published by
VM Media Group sp. z o.o.
Świętokrzyska 73, 80–180 Gdańsk, Poland
phone: +48 58 320 94 94, fax: +48 58 320 94 60
www.viamedica.pl

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Polish Ministry of Science and Higher Education — 40 points
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23-0678.003.001

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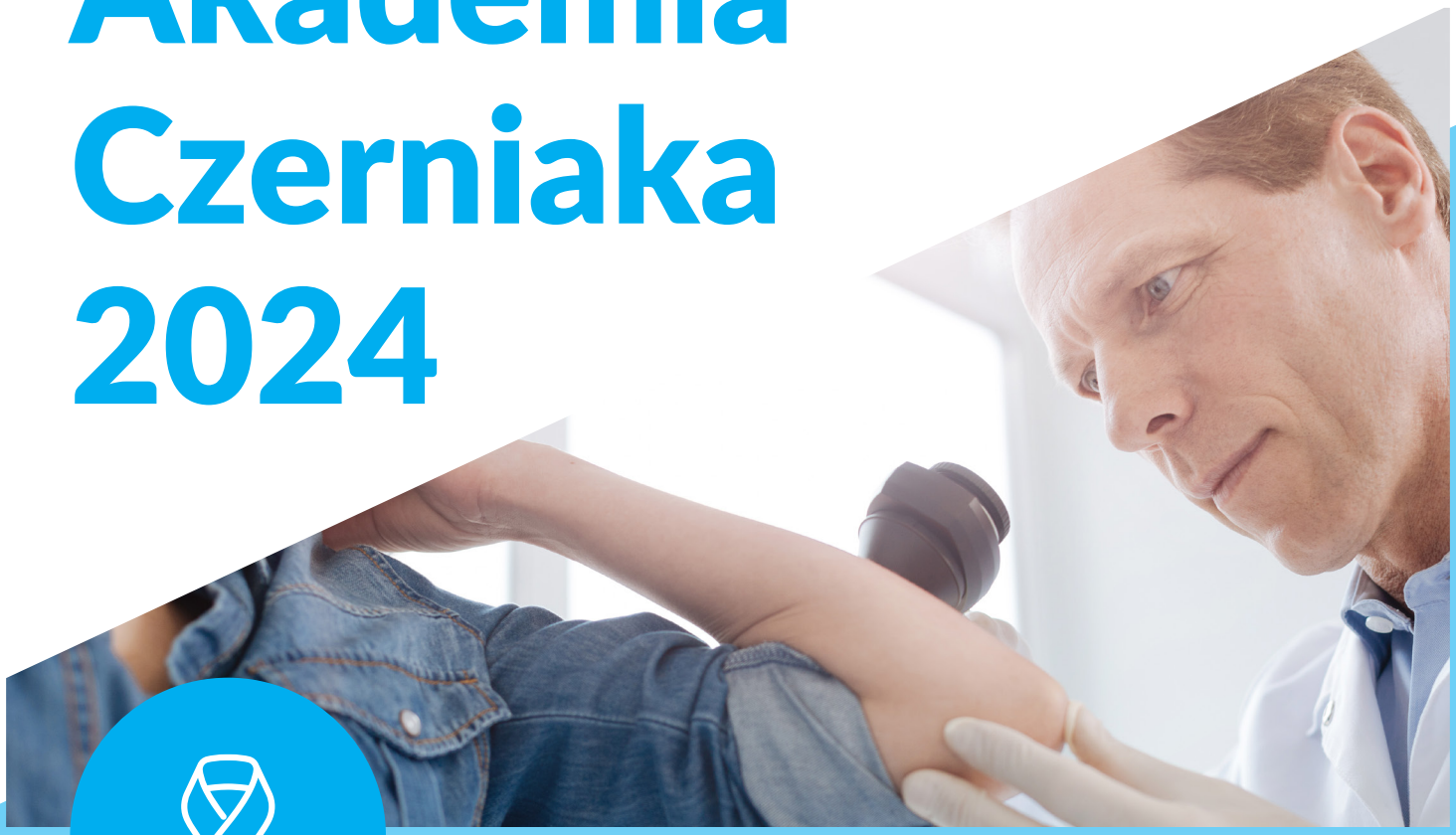

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REVIEW ARTICLE

Forum Dermatologicum
2024, Vol. 10, No. 3, 61–70
DOI: 10.5603/fd.100842

ISSN 2451–1501, e-ISSN 2451–151X

Complications associated with needle-based medical aesthetic procedures: clinical and medico-legal aspects from the Polish perspective

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ABSTRACT

Aesthetic medicine is a rapidly developing branch of modern medicine. Its main procedures include needle-based procedures such as mesotherapy, botulinum toxin injections and filler injections. Each of them may result in unwanted complications. In the case of mesotherapy, the complications are usually local, while in the case of the usage of botulinum toxin, there have been reports of deaths, whereas filler injections have been reported to cause stroke and loss of vision. It is of the highest importance for the professional to properly prepare for the procedure. In Poland, there is no such thing as a specialization in aesthetic medicine. The lack of precise regulations contributes to an increased number of complications caused by people without appropriate qualifications and offences defined in law as damage to health. It is especially important in cases when the procedure is carried out by people, who are underqualified and do not have appropriate permissions.

Forum Derm. 2024; 10, 3: 61–70

Keywords: needle-based procedures, aesthetic medicine, botulinum toxin, hyaluronic acid, complications

INTRODUCTION

Aesthetic medicine is a relatively young, yet dynamically developing field that was initiated in Paris, in 1973. This is when the first aesthetic medicine association was established. Since then, it has spread all over the world. Its main goal is to improve patient's appearance and their general well-being by reducing the visible effects of ageing and perfecting their bodies [1]. Nowadays, more and more different treatments are performed in aesthetic medicine. This is due to the emergence of newer, more sophisticated products and devices on the market. In 2023, the global aesthetic medicine market grew to 62.8 billion USD compared to 56.93 billion USD in 2022 at a compound annual growth rate (CAGR) of 10.3% [2]. Aesthetic medicine procedures are minimally invasive, performed on an ambulatory basis and usually do not require any anaesthesia or only local anaesthesia, which distinguishes aesthetic medicine from plastic surgery [3]. These include needle-based procedures such as mesotherapy, botulinum toxin and fillers. The patients of aesthetic medicine doctors are healthy adults. The goal of aesthetic medicine is not to treat patients but to improve their appearance. Among the main reasons with which patients come forward are the desire to reduce wrinkles, improve the quality of their skin, reduce stretch marks or improve hair growth [2, 4, 5]. In aesthetic medicine, it is of great importance for the doctor to be adequately prepared for the procedure since each procedure is associated with possible complications. In Poland, aesthetic medicine does not exist as a separate medical specialization, and its procedures can be performed by any doctor or dentist. Due to the lack of strict legal regulations, some treatments are also performed by beauticians and representatives of other professions bordering on medicine [5]. In order to properly prepare before the procedure, a thorough interview should be conducted with the patient, paying particular attention to diseases including allergies. The plan of the treatment should be developed based on the patient's expectations [6]. It is important that all products used during aesthetic medicine procedures come from known sources, and are properly tested and approved for use in humans [7]. Appropriate preparation by both the doctor and the patient reduces the risk of complications and unwanted side

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Received: 23.05.2024 Accepted: 27.06.2024 Early publication date: 22.07.2024

effects. The study aims to present complications related to needle-based aesthetic medicine procedures and to discuss their effects in the context of forensic medical opinions.

EPIDEMIOLOGY

In 2022, non-surgical procedures such as soft tissue fillers and botulinum toxin injections dominated over invasive plastic surgery procedures with a 54.6% market share [8]. Botulinum toxin (BoNT) injections have become one of the most popular treatments in aesthetic medicine. In North America, between 2000 and 2018, the number of BoNT injections performed increased by as much as 845% [8]. Approximately, 3 million injections are made annually around the world [9]. The American Society for Dermatologic Surgery found a 50% increase in the use of botulinum toxin in patients 30 years of age and younger from 2012 to 2016. The society predicts that by 2025, young adults will be the largest users of preparations containing botulinum toxin [10]. In turn, according to the report of the American Society for Aesthetic Plastic Surgery, in 2015, over 2 million procedures were performed using soft tissue fillers [11]. According to a report published by the British College of Aesthetic Medicine (BCAM) in 2023, the highest risk of complications occurred during treatments using fillers and botulinum toxin. It was also shown that as many as 69% of these complications were caused by people without appropriate qualifications, such as beauticians, representatives of various medical-related professions and people without the required training [12].

MESOTHERAPY

Mesotherapy is an intradermal drug delivery technique that uses needles to stimulate the production of collagen and elastin by fibroblasts in the field of aesthetic medicine [13, 14]. The low cost and minimal qualification requirements of mesotherapy have contributed to its rise in popularity in recent years [14]. Indications for this type of treatment in aesthetic medicine include skin bio revitalization, baldness treatment, cellulite and fat reduction. The substances administered by the mesotherapy technique include a variety of meso-cocktails, plasma, fibrin or stimulators [13, 15]. In this case, the aim is to focus on complications after meso-cocktail administration. The substances most commonly used in the creation of them include, among others, hyaluronic acid, dimethylaminoethanol (DMAE), vitamin C, phosphatidylcholine and caffeine [16]. The choice of the appropriate meso-cocktail depends on the patient's indications and expectations. Mesotherapy is believed to be a safe treatment. There are a few complications it can result in, most of which can be prevented [17]. After mesotherapy procedures, most patients experience pain, swelling, bleeding and redness associated with disruption of the skin. Allergic reactions to the ingredients of the mixtures or infections at the injection sites may also occur [18]. Several moderate and severe complications following needle-based mesotherapy procedures have been described in the literature.

Phosphatidylcholine is a glycerophospholipid that participates in the metabolism of many different lipid compounds. It is an ingredient of cocktails administered using mesotherapy in a cellulite reduction procedure [16]. The most frequently described complication following the administration of phosphatidylcholine is the formation of granulomas at the injection sites and inflammation of the subcutaneous tissue. It may also turn into fat tissue necrosis [14, 19]. Another substance used in lipolysis cocktails is deoxycholate. Following a mesotherapy with its use, the observed complication was non-infectious inflammation of adipose tissue [19, 20]. Acetyl-L-carnitine (ALC) is also utilized for lipolysis. Additionally, it has a modulating effect on the human immune system. Hence, a complication was observed after its use during mesotherapy, which was the induction of a severe form of lupus in the patient's abdominal area [21]. Triiodothyroacetic acid is a derivative of thyroid hormone used in mesotherapy to reduce cellulite. In this case, the literature reports iatrogenic thyrotoxicosis as a complication after mesotherapy of the patient's buttocks and thighs. This example shows how incredibly important it is to collect an appropriate interview with the patient before the procedure, with an emphasis on autoimmune diseases [22]. Dutasteride is a substance used for scalp mesotherapy. Its usage was reported to cause painful changes related to hair loss, bald spots on the head and facial swelling were observed [23]. Another ingredient used in scalp mesotherapy cocktails is mesoglycan, which is a heparinoid derivative. A case has been described, in which a few days after a procedure with its use to rebuild hair, the formation of bald spots on the scalp could be observed [24, 25]. Table 1 presents a comparison of the number of complications resulting from the treatment itself versus those caused by the active substances administered [14, 18, 19, 21–25].

Table 1. Comparison of the number of complications caused by the treatment itself and those caused by the active substances administered

Mesotherapy with meso-cocktail complications	
Procedure-related	**Substance-related**
Pain	Allergic reactions
Swelling	Granulomas
Bleeding	Hair loss
Redness	Inflammation of the subcutaneous tissue
Infections	Tissue necrosis
	Severe and rare complications (*e.g.* induction of lupus, thyrotoxicosis)

BOTULINUM TOXIN INJECTIONS

Botulinum toxin is an exotoxin produced by the anaerobic bacteria *Clostridium botulinum* [26]. In aesthetic medicine, it is used mainly to correct wrinkles. It is currently the most popular cosmetic procedure performed on adults worldwide. It works by blocking the release of acetylcholine from the presynaptic terminals of the neuromuscular junction, causing flaccid paralysis of the muscle. Botulinum toxin is administered through an intramuscular injection [27]. Intradermal administration of botulinum toxin is used to treat hyperhidrosis [28]. The original motor function of the muscle, from before the procedure, returns within 3 to 6 months [29]. The most commonly used type of botulinum toxin is the type A. It is given in units, its amount depends on the area and the muscles involved [30]. Three types of botulinum toxin are approved: onabotulinumtoxin (ONA), abobotulinumtoxin (ABO) and incobotulinumtoxin (INCO). They differ primarily in molecular weight and additives. Depending on the type of botulinum toxin, attention should be paid to its dosage. In aesthetic medicine, ONA and INCO doses are used in a 1:1 ratio. The ABO dose relative to ONA in aesthetic indications is taken as 2.5:1 [31]. Depending on the medical preparations, botulinum toxin is registered for administration in different areas. Before administering a substance as part of an aesthetic medicine procedure, registration information and product characteristics should be known. The comparison of botulinum toxin doses in registered indications in the face according to the types of preparations is presented in Table 2 [32–34].

Most side effects associated with botulinum toxin are temporary and mild [35, 36]. Most often, after botulinum toxin injection; pain, swelling, bleeding or bruising might occur at the injection site, even despite the correct technique [37]. In order to avoid bruising and similar side effects, patients are advised not to take medications that inhibit clotting, such as aspirin or non-steroidal anti-inflammatory drugs, for up to 2 weeks before the procedure, unless there are significant medical indications for taking such medications [38, 39]. More serious complications are usually related to poor toxin injection technique and arise from the diffusion of botulinum toxin into adjacent muscles, also causing their paralysis [35].

Correction of wrinkles in the upper part of the face is the most common use of botulinum toxin in aesthetic medicine [27]. One of the complications of the procedure in this area is the dropping of eyebrows. It is a common complication. It occurs during treatments in the area of the frontalis muscle. The causes are too high a dose and incorrect injection site. Ptosis may appear up to 7–10 days after the procedure and last even longer than 4 weeks. The complication can be prevented by administering the toxin approximately 2–3 cm above the supraorbital rim [27].

Another complication is the development of a "spock" eyebrow or the so-called Mephisto sign, *i.e.* lifting the lateral part of the eyebrow upwards caused by relaxation of the central part of the frontalis muscle while maintaining the activity of the lateral part of this muscle. To correct the complication, the lateral part of the muscle should also be relaxed [27, 40]. Iatrogenic asymmetry occurs when doses of botulinum toxin are unevenly injected, anatomical differences between muscle fibres or when the toxin diffuses improperly. In order to mitigate the undesirable effect, an additional dose should be administered in the right place [27].

Complications in the mid-face area occur mainly when correcting crow-feet wrinkles [26]. One of the complications is drooping of the upper eyelid as a result of paralysis of the levator palpebrae superioris muscle. It may appear for up to 14 days of the procedure and lasts approximately 6 weeks [35]. It is caused by injecting too much botulinum toxin or administering it too close to the superior rim of the orbit, which promotes diffusion [41]. Apraclonidine 0.5% eye drops can be used to alleviate eyelid ptosis, which cause contraction of the superior papilledema muscle, which is also responsible to a lesser extent for lifting the upper eyelid. A possible complication is also the development of iatrogenic strabismus. It is caused by administering too much botulinum toxin or injecting it too close to the edge of the eye socket. The inferior oblique muscle of the eye becomes paralyzed most often. This is a relatively rare complication [27, 41, 42]. This may result in the patient developing

Table 2. Comparison of botulinum toxin doses in registered indications in the face according to the types of preparations

Types of botulinum toxin and units			
Indication	**ONA**	**ABO**	**INCO**
Glabellar lines	20 units	50 Speywood	20 units
Lateral canthal lines	12 units per side	30 Speywood per side	12 per side
Forehead lines	20 units	No registration	20 units
Hyperhidrosis of the axillae	50 units per axillae (Botox®)	No registration	No registration

ABO — abobotulinumtoxin; INCO — incobotulinumtoxin; ONA — onabotulinumtoxin

diplopia, or double vision. It is also a rare complication caused by the administration of botulinum toxin beyond the safe margin of the bony orbit, which is an incorrect injection technique [26]. The lateral rectus muscle of the eye and other extraocular muscles then become paralyzed [27].

The lower part of the face is much more complex anatomically than the upper part, therefore the administration of botulinum toxin in this area requires far greater precision from the doctor [43]. Lip asymmetry occurs either when botulinum toxin enters the levator muscle of the upper lip or the muscle of the levator of the upper lip and wing of the nose. If too large doses of botulinum toxin are directly administered to the upper lip, it may lead to articulation disorders and the inability to close the mouth. This side effect may last up to a month [27]. Also, when correcting the droopy corner of the mouth and injecting the depressor angularis oris muscle, there is a risk of botulinum toxin diffusing towards the orbicularis oris muscle, causing an asymmetric smile [26]. What is more, if chin wrinkles are treated with too high doses, the lower lip may droop and the mouth cannot be closed [27]. Injecting too much botulinum toxin into the masseter muscles causes expression disorders of the lower part of the face, such as a change in facial appearance, an unnatural smile or sunken cheeks. Most often there is a blockage of the musculus risorius. These complications disappear approximately 1–2 months after the procedure. To prevent this, injections should be made at least 1 cm from the anterior edge of the masseter muscle [27]. Additionally, in the area of the face, a swelling might occur. Treatments using botulinum toxin are also performed in the neck area to reduce wrinkles. The most common complications after injection in the area of the broad neck muscle are dysphagia and weakness of neck flexion [26, 44]. These side effects are more common in older patients because they require higher doses of botulinum toxin and because there is less fatty tissue in this area, the toxin penetrates more quickly into the deeper layers of the neck [27]. Botulinum toxin injections are also used to treat hyperhidrosis. In case of the hand treatment, after the procedure, weakness is often felt in the hand area, which may last a few months [26]. Common side effects of BoNT injections include headaches and dizziness, chronic fatigue and inflammation in the injection area (*e.g.* sinusitis or nasopharyngitis) accompanied by fever [45–47]. Importantly, adverse effects may also appear only during subsequent treatments, despite their absence in the prior ones [48]. Cases of systemic complications related to botulinum toxin injections in aesthetic medicine treatments have also been described, such as prolonged general fatigue and fever, allergic reaction or a set of symptoms resembling botulism [39, 49–52]. In addition, deaths have also been reported following BoNT injection procedures, even for cosmetic purposes [47, 53]. It is suggested that deaths may occur due to anaphylactic shock [53, 54]. Moreover, during botulinum toxin poisoning, no specific symptoms may occur during autopsy diagnosis, therefore additional tests, including toxicological and histopathological ones, will play a key role [53, 55]. It is also suggested that the severity of side effects depends on the dose [46]. When performing botulinum toxin treatments, one should keep in mind its registered indications, also depending on the preparation, as well as those off-label, and always inform the patient. A comparison of registered and off-label procedures using botulinum toxin is presented in Table 3 [56].

Table 3. Comparison of registered and off-label procedures using botulinum toxin

Botulinum toxin procedures	
Registered	**Off-label**
• Glabellar lines • Forehead lines • Lateral canthal lines • Axillary hyperhidrosis	• Eyebrow lift • Midface (*e.g.* bunny lines, lowered nasal tip) • Lower face (*e.g.*, gummy smile, platysmal bands) • Scar minimization • Rosacea • Face contouring • Oily skin • Hyperhidrosis (apart from axilla)

SOFT TISSUE FILLERS

Fillers are used in aesthetic medicine to rejuvenate the face and correction of abnormalities. They can be divided into temporary, semi-permanent or permanent, taking into account the period for which they remain in the tissues. The most commonly used fillers include cross-linked hyaluronic acid and calcium hydroxyapatite [57]. Autologous fillers are also used, including autologous fat [58]. The most frequently used one is hyaluronic acid due to its quick effect and the ability to reverse side effects by using hyaluronidase [41, 59]. It is very important to select the appropriate filler and its quantity for the patient. The doctor injecting fillers should possess detailed knowledge of the facial anatomy, with emphasis on its vascularization. A way to check whether the needle is in a blood vessel or not is aspiration before injecting [60]. Most fillers are injected into the dermis or subcutaneous tissue. Complications that appear immediately after the procedure include swelling, redness and bruising. Too shallow injection of the filler may result in the appearance of palpable and visible lumps [57]. Too superficial administration of hyaluronic acid can also cause the Tyndall effect. A blue shadow is then visible on the skin. Most often arises in areas where the skin is thin, such as under

the eye. A firm massage immediately after treatment can be an effective treatment. However, the primary treatment is the administration of hyaluronidase. Before using hyaluronidase, an allergy test should be performed to ensure that the patient is not allergic to it [61]. A very serious complication of filler treatments is central retinal artery occlusion and blindness [41, 62]. This is caused by incorrect administration of the filler into the vessel, most often around the area of the forehead, nose and temples [63]. It is the most common in procedures that use hyaluronic acid or autologous fat [64]. This leads to a decrease in visual acuity, which turns into blindness. Additional symptoms reported by patients include eye pain, headache, nausea and vomiting. Up to 1,500 units of hyaluronidase should administered to the ischaemic area while waiting for an ambulance. Treatment should be started immediately and should additionally include the administration of 600 mg of aspirin, to prevent clot formation, topical timolol and warm compresses. The longer the obstruction lasts, the worse the prognosis for vision recovery. Ophthalmologists with relevant experience can try administering hyaluronidase retrobulbar [65–67]. Improper administration of fillers also causes ophthalmoplegia. It is believed to occur as a result of ischaemia of the extraocular muscles and cranial nerves [66, 68]. Injecting fillers may also result in an ischaemic stroke [69]. Cases of death due to cerebral infarction as a result of hyaluronic acid entering the cerebral circulation have been reported [70]. Through the ophthalmic artery and internal carotid artery, the filler may enter the middle cerebral artery retrogradely, causing its occlusion. Particular care is advisable when treating the glabella, eye and nasolabial folds [66, 71]. As a result of venous filler administration, reticular cyanosis may appear on the face, which should be differentiated from bruises. Treatment in this case is warm compresses, aspirin and, in the case the filler used was hyaluronic acid, hyaluronidase (400 IU) [72]. Due to the vascularity of the nose in this area, complications may often occur [66]. The most common one, by a good margin, is pain [63]. If filler is injected into the lateral nasal artery and the dorsal nasal artery, necrosis may occur. The ala and tip of the nose are particularly sensitive to ischaemia [66]. The place, where infections occur most often after filler treatments are the cheeks. Scarring has also been reported during procedures with calcium hydroxyapatite [63]. The glabella is most predisposed to ischaemia due to vascular occlusion. It is supplied with blood by the supratrochlear artery, which is unable to generate sufficient collateral circulation in the event of occlusion [73], therefore too deep administration of complement may prevent blood supply and cause necrosis of the glabella [74, 75]. Following the administration of fillers, lumps may appear in the area of the nasolabial folds [75]. Providing the vessels are occluded by the filler, necrosis may also occur in this area [76]. A common problem is the administration of an excess amount of the filler, which disturbs the aesthetic effect of the treatment [77]. In addition, after the filler is injected, a biofilm, a cluster of bacteria, such as *Staphylococcus epidermidis* or *Staphylococcus aureus*, can form on the surface of the filler, embedded in the matrix that they produce. This can trigger a chronic immune response leading to infection. Treatment includes oral broad-spectrum antibiotic therapy and hyaluronidase (150–200 IU), which helps remove the filler if hyaluronic acid is used. If the inflammation is still severe, oral steroids are used, followed by intravenous steroids [78]. A milder complication is the formation of granulomas in response to a foreign body. They form up to several months after surgery. Treatment includes triamcinolone and 5-fluorouracil. Fillers applied to the lip may migrate to its inner surface, creating visible unevenness [77]. When administering filler, it can also be inadvertently administered into the superior or inferior labial artery, causing necrosis. To avoid this, the needle should be inserted no deeper than 3 mm [66]. There are also various types of illegal fillers available around the world, not approved by the competent authorities responsible for pharmaceutical control. However, they are significantly cheaper. The most popular illegal fillers include biopolymer, which is a type of silicone. It is often unsterile and mixed with other non-sterile substances. Such fillers are also able to migrate easily due to their low viscosity. Nodules then form in places distant from the injection sites. They cause facial deformation and are extremely difficult to remove. Some complications appear within 72 hours of the procedure, while others may appear up to several years after. Patients after procedures with illegal fillers may experience cellulitis, ulcerations or non-healing wounds that may lead to sepsis and even death [77]. Deaths resulting from the use of fillers have also been reported as a result of pulmonary embolism, moreover, infections also play an important role [70, 79–81].

GENERAL FACTORS AND CIRCUMSTANCES

Correct performance of the procedure plays an important role in preventing complications after needle-based medical aesthetic procedures. Appropriate medical training is required in this matter. Thorough knowledge of anatomy is necessary, with particular emphasis on the areas where the substances are injected [48]. If the substance is administered to the wrong area, the risk of complications during the procedure is greater. In addition, knowledge of pharmacology is also necessary to properly prepare the substance for administration and select the appropriate dose. Performing procedures by untrained people is associated with a higher risk of complications, also due to the lack of the ability to perform the procedure correctly. It is also necessary to conduct an appropriate interview with the patient in order to

qualify for treatments and to exclude potential interactions between the substance administered for cosmetic purposes and the patient's current condition or medications they use [39]. There have already been reports of deaths related to inappropriate medical procedures performed by people who were not trained to perform them [82]. What is more, the appropriate selection and preparation of substances used for treatments is also important. Only substances approved for human use should be used [48, 83, 84]. However, there are known cases of complications related to the administration of unlicensed products, despite the correct performance of the procedure. Moreover, products of unknown origin may contain excipients or impurities that contribute to the development of complications. In such cases, it becomes crucial to secure product packaging for further analysis [83]. In Poland, in accordance with the Pharmaceutical Law, all medicines must be registered by the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products and are subject to production and quality control by the Chief Pharmaceutical Inspectorate. The main principles of intended use are described in the Summary of Product Characteristics. Moreover, some of them (*e.g.* injection preparations containing botulinum toxin) require a prescription issued by a certified doctor with an active license to practice the profession.

The trade-in of medicines in Poland is strictly regulated by law. Placing a medicinal product on the market without marketing authorization and trading in medicinal products without authorization are considered prohibited. Moreover, medicinal products with a category of availability requiring a prescription issued by an authorized entity (*e.g.* a doctor) may be distributed retail only by establishments specified in the Pharmaceutical Law, such as, for example, pharmacies or pharmacy points. Each time such a medicine is issued, a prescription issued by an authorized body must be presented. Therefore, the possession, distribution and utilization in a beauty salon of a drug that has a prescription category (Rp.) in order to use it during a cosmetic treatment performed by a person who is not authorized to perform these activities should be considered unauthorized [85]. Importantly, each medicinal product has a Summary of Product Characteristics specifying the dosage and rules of use. If the patient obtains a prescription for a given drug from a doctor and purchases the drug himself in a pharmacy, its administration, with the consent of the client, as part of an aesthetic medicine treatment by a non-medical practitioner remains legally unresolved. In this respect, the content of the Supreme Court's judgment in case I KK 23/21 is particularly important, which indicates that the use of preparations in the form of injections, other than natural body orifices, thus interrupting the continuity of tissues, is a condition for qualifying an activity as a health service under the law in force in Poland [86, 87].

In the case of medical devices, which include *e.g.* hyaluronic acid, they are also supervised by the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. Another important issue is the uncontrolled and unregulated sale, mainly via the Internet, of unregistered preparations containing active substances and products pretending to be medicines (*e.g.* "botox-like" products), very often imported from abroad. In such cases, there is no control over the actual composition of the substance. Moreover, the black market is also an important phenomenon, where similar substances may be sold as chemical reagents or come from illegal sources of production. In the case of autologous preparations and their use, the legal situation is complex. Under the Pharmaceutical Law, they constitute medicinal products, but their use does not require registration with the relevant office. The very act of collecting blood for the purpose of preparing it is a medical procedure, which requires representatives of medical professions to have appropriate qualifications determined by legal provisions with a distinction between purposes, which are not granted to persons who do not practice medical professions [88]. The above regulations also apply to mesotherapy, depending on the products used to perform it. In addition, places where needle-based medical aesthetic procedures are performed must be properly arranged. Preparations used for procedures must often be stored in appropriate special conditions. Appropriate preparation also includes tools for carrying out treatments. They must be properly prepared and sterile to avoid infections that may result in serious consequences, *e.g.* necrosis [89].

MEDICO-LEGAL ASSESSMENT FROM POLISH PERSPECTIVE

In Poland, similar aesthetic medicine treatments are performed mainly in private offices and clinics after obtaining informed consent from the patient. For this reason, there is little data on the scale of complications after needle-based medical aesthetic procedures. Due to the classification of aesthetic medicine treatments in Poland as health services, they should be performed by doctors with appropriate education and technical training. However, there is no separate specialization covering this field of medicine, so the doctor performing the procedure is only required to have a full license to practice the profession, which is regulated by the medical self-government; a medical specialization, however, is not required [3]. Nevertheless, in practice, such treatments are often performed by representatives of other medical professions or even people not related to medicine, such as beauticians. Moreover, the lack of appropriate education and

qualifications translates into the frequency of the occurrence of complications and criminal liability for an incorrectly performed procedure, as professional liability cannot take place in cases, where such procedures are performed by people who do not have a medical profession. In Polish law, health damage and bodily injury are classified into three stages. It includes light, moderate and serious damage, corresponding to the provisions of the Penal Code: Article 157 § 2, Article 157 § 1, and Article 156 § 1 [90, 91]. A minor injury is the impairment of organ function or health disturbance for a period not longer than 7 days, and in the case of a complication after a cosmetic procedure, it may concern, for example, prolonged swelling limiting the interpalpebral fissure, but disappearing without leaving a trace in a time shorter than that specified in the regulation. When the duration of damage to health exceeds 7 days, it is then classified as moderate, and in the case of needle-based aesthetic medical procedures, an example of it may be a temporary paralysis of the branches of the facial nerve that disappears without permanent damage over time. Serious damage to health occurs when, for example, a person is deprived of sight or hearing, or other serious disability is caused [90]. One example of a serious health condition may be loss of vision due to iatrogenic occlusion of the central retinal artery. This provision also covers permanent significant disfigurement or deformation of the body, which becomes crucial in cases of procedures to improve a patient's image. However, the legal-criminal assessment of such an effect falls within the competence of the authority handling the case, while medical opinions should be limited to precisely documenting the changes of disfigurement and deformation of the body. Moderate and severe health damage are considered crimes prosecuted *ex officio*. Moreover, the legislator in Art. 160 of the Penal Code defined the crime of exposing a person to direct danger of loss of life or serious damage to health. Performing a procedure by an unauthorized person, using preparations not approved for human use, or performing procedures using inappropriate or incorrectly prepared tools may be classified as a crime under Art. 160 of the Penal Code. This kind of offence is prosecuted ex officio [91, 92].

Issues related to the performance of aesthetic medicine treatments are also addressed in documents issued by the Supreme Medical Chamber (*Naczelna Izba Lekarska*). The position of the Supreme Medical Council (*Naczelna Rada Lekarska*) defines aesthetic medicine as health services involving interference in tissues aimed at restoring or improving the patient's physical and mental well-being and social functioning. It emphasizes that these procedures should be performed by doctors or dentists, pointing out the key role of having the appropriate knowledge, skills and experience necessary to perform them [93]. Its framework is based on globally accepted definitions [94]. The Supreme Medical Council also clearly indicates in its position the need to legally regulate aspects related to the provision of aesthetic medicine services in the context of the provision of health services and the people and professions performing them [95, 96]. A resolution was also adopted modifying the definition of health care services, taking into account the aspect derived from aesthetic medicine treatments [97]. Issues related to the legal status of products and substances used in aesthetic medicine are also discussed [88]. Moreover, the resolution of the Supreme Medical Council prohibits doctors and dentists from participating as lecturers in practical training on providing health services if the event participants are people who are not authorized to provide medical services [98]. This is motivated, among other things, by causing an unfavourable effect in the form of legitimizing potential unauthorized medical activities [98].

CONCLUSIONS

Needle-based medical aesthetic procedures, such as mesotherapy, injections of botulinum toxin or the use of tissue fillers, despite the low invasiveness of the procedure, may be associated with serious consequences. Therefore, each procedure should be performed by a person with appropriate medical background. Performing the procedure in a technically incorrect manner may result in complications that, in extreme cases, may be life-threatening. The type and quality of products used during procedures also play an important role. In light of the rapidly growing number of aesthetic medicine treatments over recent years, the effects of their performance will become an increasingly important issue from the judicial and medical point of view, both in the case of criminal and civil cases, including for the purpose of obtaining compensation. Further research is necessary on the scale of complications, their types and causes. In addition, it is necessary to clarify and specify the legal issues related to the qualifications of medical professionals who may perform similar aesthetic medicine treatments.

Article information and declarations

Acknowledgements

None.

Author contributions

KB — 40%; SzRz — 30%; BB — 10%; JL — 10%; BB — 5%; PŚ — 5%.

Conflict of interest

The authors declare no conflict of interest.

Funding

This research received no external funding.

Supplementary material

None.

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VIA MEDICA

REVIEW ARTICLE

Forum Dermatologicum
2024, Vol. 10, No. 3, 71–78
DOI: 10.5603/fd.101208

ISSN 2451–1501, e-ISSN 2451–151X

Topical solutions for androgenetic alopecia: evaluating efficacy and safety

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ABSTRACT

Androgenetic alopecia (AGA) presents a significant challenge in clinical practice due to its prevalence and impact on patients' quality of life. With a diverse array of available treatment options, selecting the most appropriate therapy demands careful consideration of factors such as efficacy, safety, practicality, and cost. This review aims to evaluate the efficacy and safety profiles of various topical treatments for AGA, investigating their potential advantages in limiting systemic side effects compared to oral medications. This article explores the pharmacology, mechanisms of action, clinical efficacy, and adverse events associated with topical medications like minoxidil, finasteride, ketoconazole shampoo, clascoterone, latanoprost, spironolactone, flutamide, cetirizine, pyrilutamide, and GT20029.

Forum Derm. 2024; 10, 3: 71–78

Keywords: androgenetic alopecia, topical, treatment, minoxidil, finasteride, clascoterone

INTRODUCTION

Androgenetic alopecia (AGA) is a common dermatologic condition that, while not life-threatening, often leads to considerable distress and negatively impacts patients' quality of life (QOL). It is thought to be caused by androgens in genetically predisposed men and women [1, 2]. As individuals age, the prevalence of AGA increases and affects approximately 50% of older men and 15% of postmenopausal women [3]. It poses a formidable challenge for clinicians in treatment selection. Factors such as efficacy, side effect profiles, practicality, and cost demand meticulous consideration, further complicated by the absence of standardized grading techniques and the diverse array of available treatment options. In men, AGA typically manifests as frontal recession and vertex thinning, while female-pattern hair loss (FPHL) is characterized by reduced hair density over the crown without frontal hairline involvement [4, 5]. Hair follicles are affected mainly through the local transformation of testosterone into more potent dihydrotestosterone (DHT) by type II 5α-reductase in androgen-sensitive dermal papilla cells [6]. Finasteride, a 5α-reductase inhibitor that blocks the conversion of testosterone into DHT, is a Food and Drug Administration (FDA)-approved treatment for AGA. While its effectiveness is well-established, some research reports an array of adverse side effects, often referred to as "post-finasteride syndrome", that can develop in some patients treated with oral finasteride and sometimes persist even after discontinuing the medication [7, 8]. Hence the topical application of finasteride has been investigated in hopes of providing a similar reduction in scalp DHT levels while having less of a systemic effect. Similarly, an oral version of FDA-approved medication minoxidil seems to be as effective as the topical application [9], however, reported side-effects such as electrocardiogram (ECG) changes (tachycardia, t-wave changes, preventricular contractions), postural hypotension, dizziness, pericardial effusion, lower limb oedema, and hypertrichosis seem to make oral administration of minoxidil less desirable [10]. It appears that topical treatments for AGA might be a sensible route of treatment, provided they may offer similar effectiveness while presenting with fewer side effects. This paper aims to assess the efficacy and safety profiles of topical medications

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Received: 17.06.2024 Accepted: 12.07.2024 Early publication date: 25.07.2024

in the management of AGA, with a specific emphasis on their potential to limit systemic side effects. This analysis seeks to provide clinicians and researchers with valuable insights into the emerging therapeutic landscape of AGA, highlighting possible new treatment options and facilitating informed decision-making and optimizing patient care.

MINOXIDIL

Topical minoxidil is an FDA-approved treatment for AGA and has been widely prescribed for this condition for several decades. It has also been used off-label for other hair disorders such as scarring alopecia, alopecia areata (AA), chemotherapy-induced alopecia and others, as well as a beard and eyebrow enhancement. Minoxidil was first developed for the treatment of hypertension and the commonly observed side-effect of hypertrichosis led to its topical form use in hair growth stimulation. It is available on the market in different forms, such as foam, shampoo and solutions.

The main active metabolite is minoxidil sulfate, conversion to which is higher in hair follicles than the surrounding skin. It is thought to bind to adenosine triphosphate (ATP) sensitive potassium channels causing smooth muscle relaxation, which is generally proposed to contribute to its hypotensive effect. Relaxation of blood vessels results in increased blood flow and a greater supply of oxygen and nutrients to the hair follicle. Production of vascular endothelial growth factor (VEGF), a potent vasodilator, stimulator of angiogenesis and a multifunctional growth factor is also increased [11]. Minoxidil is also hypothesized to cause an anti-inflammatory effect, reducing perifollicular microinflammation [12–14]. Topical application of 3% minoxidil solution resulted in increased anagen hair count and decreased the count of hair in the telogen phase in AGA patients [15].

Multiple studies have demonstrated minoxidil's effectiveness in promoting hair growth. In a 12-month observational study on 904 male patients with AGA treated with 5% minoxidil solution applied twice daily, the affected region has been reported to significantly decrease in 62% of eligible patients and has become larger in only 2.9% of subjects. 84.3% of patients reported hair regrowth of various degrees [16]. In a 48-week randomized controlled trial (RCT) on 352 males with AGA, 5% minoxidil solution produced 45% more hair regrowth than the 2% solution at the end of the study. An earlier response to treatment was also noted, with a non-vellus hair count at 8 weeks equivalent to that of a 16-week treatment with 2% minoxidil. Both concentrations were well tolerated with no evidence of systemic effects [17]. Side effects with topical minoxidil use include irritant and allergic contact dermatitis, scalp irritation, pruritus and facial hypertrichosis, which present more often with higher per cent formulations [18].

TOPICAL FINASTERIDE

5α-reductase is an enzyme responsible for converting testosterone into the more potent DHT. Hair follicles are primarily impacted by the local conversion of testosterone to DHT through the action of type II 5α-reductase in androgen-sensitive dermal papilla cells. Finasteride, a type II 5α-reductase inhibitor, blocks the conversion to DHT and minimizes androgen-mediated follicle miniaturization. Oral finasteride has been approved by the FDA for male-pattern hair loss since 1997. Although it remains a topic of debate, a growing body of research recognizes a consistent range of side effects linked to finasteride use, commonly referred to as "post-finasteride syndrome" [19]. This syndrome includes sexual dysfunction, decreased libido, and gynecomastia [8, 20, 21]. While these symptoms typically resolve after discontinuing the medication, they can sometimes persist for three months or longer and may even lead to depression and suicidal thoughts [7]. This issue has sparked interest in topical finasteride application in hopes of reducing its adverse systemic effects while providing a local therapeutic effect in AGA patients.

Topical finasteride is usually applied as 1% topical finasteride gel or 0.25% finasteride spray, applied twice daily to the scalp. Its effects on hair regrowth and reduction of balding were first reported by Mazzarella et al. [22] in 1997 in a 16-month placebo-controlled trial of 52 patients. In a phase III randomized, controlled clinical trial of 458 patients hair count in a targeted area was significantly improved compared to placebo, and the improvement was similar to that of oral finasteride. At the same time, the reduction in mean serum DHT concentrations was lower with topical *vs.* oral finasteride (34.5% *vs.* 55.6%), indicating a lesser chance of sexual side effects related to a decrease in systemic DHT. There were no serious side effects related to the treatment [23]. Another study on 40 male patients treated with a topical solution of 0.25% finasteride mixed with 3% minoxidil versus 3% minoxidil solution alone, reported superior effects on hair diameter and density compared to 3% minoxidil. No systemic adverse events or sexual dysfunction were reported [24]. A randomized controlled trial on 45 male patients, found no significant difference in therapeutic effect between 1% finasteride gel and 1 mg finasteride tablets and a significant difference in hair count and terminal hair count in both groups. Potential side effects of topical finasteride include contact dermatitis, skin erythema, increased liver enzymes, nocturnal enuresis, testicular pain, headaches, presyncope, and oropharyngeal pain [25].

KETOCONAZOLE SHAMPOO

Ketoconazole is an imidazole derivative with antifungal and anti-inflammatory properties, used in the treatment of seborrheic dermatitis. In addition, ketoconazole has

antiandrogenic properties, inhibiting testosterone synthesis and consequently diminishing DHT levels. This multifaceted pharmacological profile supports its theoretical viability in the treatment of AGA. A systematic review of ketoconazole for AGA treatment which included 5 human studies supports the potential efficacy of ketoconazole shampoo in AGA treatment [26]. Three of those studies evaluated the impact of ketoconazole on hair shaft diameter, a critical parameter in AGA characterized by hair follicle miniaturization [27]. An increase in hair shaft diameter [28, 29] and the pilary index (a measure combining per cent anagen phase and diameter) [29] was reported. Clinical improvements in AGA, as evidenced by photographic evaluation, were also noted [30]. Additionally, two studies investigated the effect of ketoconazole shampoo on hair density, yielding conflicting results. One study reported an increase in hair density, [29] while the other found no significant change [28]. While most studies utilized a 2% formulation, one human study employed 1% ketoconazole shampoo [28]. The frequency of treatment varied from twice weekly to daily use, with positive outcomes even with the least frequent application of 2–3 times per week [30]. Notably, topical ketoconazole demonstrated a favourable safety profile since there were no significant side effects associated with treatment. Considering this, ketoconazole might be an alternative or adjuvant therapy in the treatment of AGA. Further large-scale prospective trials are warranted to establish its definitive role in AGA management and to better understand its mechanism of action.

CLASCOTERONE

Clascoterone is a novel androgen antagonist and the first topical antiandrogen approved by the FDA for the treatment of acne vulgaris. Clascoterone seems to effectively inhibit androgen receptor (AR) regulated transcription, comparable to the performance of the 5α-reductase inhibitor, finasteride. Furthermore, clascoterone demonstrates superior efficacy over enzalutamide, a direct AR-antagonist, in inhibiting interleukin-6 (IL-6) synthesis in DHT-stimulated cells [31]. By blocking DHT-induced signalling pathways and cytokine production, clascoterone may mitigate hair follicle miniaturization. Its unique mechanism of action involves competitively binding with AR, antagonizing DHT, and reducing dermal inflammation. This profile distinguishes clascoterone from existing therapies for AGA. In the Phase II exploratory study involving 70 adult male subjects with AGA, clascoterone demonstrated superior efficacy compared to cyproterone acetate or 17α-estradiol across various measures, including scalp sebometric measurement, hair shaft diameter, hair follicle density, and pull test/wash test. In a Phase II proof-of-concept (POC) study on 73 patients, clascoterone exhibited superior (39%) improvements in target area hair count (TAHC) changes compared to the vehicle group (16%). Its efficacy was similar to that of minoxidil (36%) [32]. In a phase II dose-ranging clinical trial involving 344 male subjects, patients applied various concentrations of Clascoterone solution or vehicle twice daily for 12 months. Significant improvements in hair count were seen across all Clascoterone groups compared to the vehicle, with the highest improvement in the Clascoterone 7.5% solution group. More patients in the Clascoterone groups experienced increased hair growth compared to the vehicle [33]. Phase II trials conducted in acne patients did not reveal indications of systemic effects [34]. However, further research, including large-scale clinical trials, is warranted to validate its efficacy and safety profile in AGA management.

LATANOPROST

Latanoprost, a prostaglandin F2α analogue initially employed for glaucoma treatment, garnered attention for its potential in addressing alopecia following observations of eyebrow and eyelash growth in glaucoma patients [35]. Latanoprost was reported to extend the anagen phase of the hair cycle, which indicated it might be a viable option for mitigating hair loss [36]. In a double-blinded, placebo-controlled clinical trial involving 16 male patients with mild AGA, latanoprost 0.1% and placebo were applied daily for 24 weeks on separate scalp areas. Results showed a significant increase in hair density on the Latanoprost-treated site compared to the baseline and the placebo-treated site at the end of the study [37]. These findings suggest the effectiveness of Latanoprost in increasing hair density. However, further trials are necessary to evaluate its efficacy and safety profile.

TOPICAL SPIRONOLACTONE

Spironolactone, a potassium-sparing diuretic, also exhibits antiandrogenic effects. It blocks the AR in target tissues, which is often used by dermatologists to diminish the effects of testosterone on skin and hair such as FPHL, acne, and hirsutism, especially in female patients [38]. Recent trials have explored the efficacy of topical spironolactone for the treatment of AGA, yielding promising results. One RCT on 60 patients (39 male, 21 female) found that 1% spironolactone gel led to clinical improvement in 80% of patients after 12 months. When used alone, spironolactone gel showed significant improvement, with even better results seen when combined with 5% minoxidil [39]. Another non-randomized comparative study involving 40 patients applying a solution containing 5% spironolactone and 5% minoxidil reported a decrease in vellus hair and an increase in upright regrowing hair compared to 5% minoxidil solution alone, over a 12-week period [40]. These findings indicate that topical spironolactone may effectively treat AGA, either alone or in combination with minoxidil. Although some adverse effects

like contact dermatitis and dizziness were reported in a few patients, overall, those using only topical spironolactone gel experienced minimal and tolerable side effects, with no impact on libido or sexual performance. Further trials are warranted to validate the efficacy and safety of topical spironolactone, particularly in larger and more diverse patient populations.

TOPICAL FLUTAMIDE

An emerging possibility for promoting hair growth is topical flutamide, a nonsteroidal anti-androgen. Unlike its systemic administration, which can lead to adverse systemic effects such as decreased libido, topical application seems to offer a safer route, especially in the treatment of skin disorders. In an experimental model of human scalp skin graft transplanted onto severe combined immune deficient (SCID) mice, comparing topical formulations of flutamide and finasteride for AGA, flutamide demonstrated superior efficacy in enlarging hair follicles. Topical flutamide gel significantly increased hair length, diameter, and the number of hairs per graft, surpassing the effects of the vehicle alone. Histological examination supported these findings, showing more hairs in the growth phase with flutamide treatment, indicating its ability to reverse alopecia. Plasma monitoring revealed no systemic effects of flutamide, suggesting its localized action [41]. In a randomized, double-blinded clinical trial involving 40 patients with AGA, combination therapy with 2% topical flutamide and 5% minoxidil was compared to 5% minoxidil alone. The results showed that topical flutamide combined with a minoxidil solution was significantly more effective in increasing hair density, hair thickness, and patient satisfaction compared to the minoxidil-only group [42]. These findings suggest that topical flutamide has potential as a treatment for AGA. However, further research, including prolonged studies with a larger cohort and exploration of different vehicles, is needed to better evaluate the efficacy and safety profile of topical flutamide.

TOPICAL CETIRIZINE

Topical cetirizine, an antihistamine medication, has shown encouraging potential for treating hair loss, particularly AGA in both male and female patients. A 24-week RCT including 66 female patients with AGA compared topical cetirizine and minoxidil *vs.* minoxidil and placebo. The study reported a significant increase from baseline in frontal and vertex terminal and vellus hair density with a significant improvement in vertex hair shaft thickness and average number of hairs per follicular unit. Furthermore, patient self-assessment scores favoured the cetirizine group, indicating a higher satisfaction level. Notably, the study reported no significant difference in side effects between the cetirizine and minoxidil groups, suggesting a favourable safety profile for cetirizine [43]. Another study on 40 male patients, compared 1% topical cetirizine *vs.* 5% minoxidil, revealing a notable increase in total and vellus hair density after 16 weeks of treatment. An increase in the percentage of hair in the anagen phase in both groups was also reported. Although minoxidil demonstrated superior results, cetirizine exhibited effectiveness without adverse reactions, making it a promising alternative for male AGA treatment [44]. In a 6-month study involving 60 female patients, while minoxidil showed greater efficacy in terms of hair density, cetirizine still provided favourable therapeutic effects, particularly for patients who cannot tolerate minoxidil [45]. These findings underscore the potential of topical cetirizine as a safe and effective alternative for hair loss treatment.

TOPICAL PYRILUTAMIDE

KX-826, previously known as pyrilutamide, is a topical drug that blocks the signalling pathway of AR when applied locally to peripheral skin tissue. By reducing the sensitivity of AR to androgens in the pilosebaceous gland, it aims to limit systemic side effects. It is being developed in tincture and gel forms as a potential first-in-class treatment for AGA and acne vulgaris. Phase II trials for male and female AGA in China have shown promising results, with significant improvements in non-vellus TAHC observed after 24 weeks of treatment with KX-826. The safety profile was favourable, with no serious adverse events reported [46]. The ongoing clinical trials are focused on evaluating its efficacy and safety for treating AGA in male adults in China. Notably, a 1.0% tincture formulation is being tested, which has shown increased retention and concentration on scalp cells compared to the 0.5% tincture used in prior studies, suggesting a potential for enhanced clinical efficacy [47]. KX-826 has undergone multiple successful clinical trials in both China and the US, demonstrating a promising safety profile and effectiveness for both male and female AGA patients. The recently concluded Phase II trial in the US indicated significant improvements in hair growth with a dose-response relationship observed, particularly with the 0.5% twice daily dosage [48]. Following these encouraging results, Kintor Pharma is preparing for a Phase III trial in the US. Concurrently, a long-term safety trial is underway in China to further assess the prolonged use of KX-826, involving 270 participants over a 52-week period [49]. These trials aim to solidify the drug's safety and efficacy profile, ultimately supporting its use as a long-term treatment for AGA.

GT20029

GT20029, developed using Kintor Pharma's proprietary Proteolysis Targeting Chimera (PROTAC) platform, works by targeting AR proteins for degradation, acting locally to

avoid systemic exposure and reduce androgen sensitivity in hair follicles and sebaceous glands. Studies in DHT-induced mouse models demonstrated significant hair growth promotion, while trials on testosterone propionate-induced skin hamster flank organ acne models showed inhibition of flank organ enlargement. Phase I clinical trials in China and the US showed good safety, tolerability, and pharmacokinetics [50]. Recently, the China phase II clinical trial for treating male AGA reached its primary endpoint, demonstrating statistically significant and clinically meaningful results with good safety and tolerability. This multi-centre, randomized, double-blind, placebo-controlled study involved 180 male AGA patients and evaluated the efficacy and safety of GT20029 in 0.5% and 1% dosages administered once daily (QD) or twice weekly (BIW). The trial results indicated a significant increase in non-vellus TAHC compared to placebo, with the 0.5% QD group showing an increase of 16.80 hairs/cm^2 from baseline and the 1% BIW group showing an increase of 11.94 hairs/cm^2. No adverse sexual effects were observed, and the incidence of other adverse events was comparable to the placebo [51]. Based on these results, the company plans to initiate a phase III clinical trial in China and a phase II clinical trial in the U.S. Additionally, a phase II trial for acne treatment is also in preparation.

DISCUSSION

Currently, there are numerous treatments for AGA available, including oral and topical medications, hormonal therapies, laser therapy, mesotherapy, microneedling, platelet-rich plasma (PRP), and surgical procedures of hair transplantation. Nonetheless, treating AGA remains particularly challenging due to the variability in patient response to conventional therapies as well as the incomplete understanding of the condition's pathogenesis. Topical minoxidil, oral finasteride, and low-level laser therapy (LLLT) are the only treatments for AGA approved by the FDA, all of which may be effective in treating patients. However, patients must adhere to lifelong therapy as AGA continues to progress if treatment is discontinued, highlighting the importance of side effect profile consideration.

This review aimed to evaluate the efficacy and safety profiles of various topical treatments for AGA, emphasizing their potential to limit systemic side effects compared to oral counterparts. The findings indicate that topical treatments offer a promising alternative to oral medications, combining effective management of AGA with a reduced risk of systemic adverse effects (Tab. 1). By delivering medication directly to the affected area, these treatments can limit systemic absorption and reduce the risk of systemic side effects. For instance, topical minoxidil has been shown to effectively promote hair growth with localized side effects such as irritant and allergic contact dermatitis, pruritus, and facial hypertrichosis. Similarly, topical finasteride is gaining traction as a viable alternative to its oral counterpart. By applying finasteride directly to the scalp, patients can mitigate the risk of systemic absorption and associated side effects, such as sexual dysfunction, which are more commonly reported with oral administration. Studies indicate that topical finasteride maintains comparable efficacy to oral forms in reducing hair loss and promoting regrowth while offering a better safety profile.

Ketoconazole, primarily an antifungal agent, also reduces scalp inflammation and inhibits DHT production, benefiting hair density and thickness in AGA patients. Clascoterone, a newer topical anti-androgen, prevents DHT from binding to hair follicle receptors, showing promising results in improving hair count and density. Emerging treatments like topical spironolactone, flutamide, cetirizine, pyrilutamide and GT20029 have shown varying degrees of efficacy in clinical trials. These treatments may offer additional options for patients, particularly those who may not tolerate minoxidil or finasteride. Topical spironolactone, for instance, has demonstrated significant improvements in hair density and thickness with a minimal side effect profile, making it a valuable alternative for patients with AGA.

Although the results with topical treatments are encouraging, current research is limited by sample size, study design, and measurement techniques. Future research should focus on larger, long-term studies with standardized metrics and comprehensive safety monitoring to better evaluate the efficacy and safety of these treatments. Further exploration should provide more insight into the effectiveness of different treatments across diverse patient populations and varying degrees of AGA, potentially offering a safer and more tolerable approach for patients. The diversity of topical agents available also allows for personalized treatment plans, addressing individual patient needs and preferences.

CONCLUSIONS

The evaluation of various topical treatments for AGA highlights their potential as effective and safer alternatives to oral medications. Topical minoxidil and finasteride have robust evidence supporting their efficacy and favourable safety profiles, making them mainstays in AGA management. Emerging treatments such as clascoterone, spironolactone, and other topical agents show promise and warrant further investigation.

Topical treatments offer several advantages, including localized action (Fig. 1), reduced systemic absorption, and fewer systemic side effects. These benefits are particularly important given the chronic nature of AGA and the need for

Table 1. Efficacy, safety and mechanism of action of various topical treatment options in AGA

Treatment	Mechanism of action	Formulation	Main findings	Adverse events
Minoxidil	Increases blood flow, increases VEGF, anti-inflammatory	Foam, shampoo, solution (2%, 5%)	Significant hair regrowth, higher efficacy with 5% solution	Contact dermatitis, scalp irritation, pruritus, facial hypertrichosis
Topical finasteride	Inhibits type II 5α-reductase, reduces DHT levels	Gel (1%), spray (0.25%)	Efficacy comparable to oral finasteride, lower systemic DHT reduction	Contact dermatitis, skin erythema, increased liver enzymes, nocturnal enuresis, testicular pain, headaches, presyncope, oropharyngeal pain
Ketoconazole	Anti-inflammatory, reduces androgen synthesis	Shampoo (1%, 2%)	Increase in hair shaft diameter, potential improvement in hair density	Oiliness/dryness of the hair and scalp; discolouration, irritation of the scalp
Clascoterone	AR inhibition, anti-inflammatory	Cream (1%), solution (up to 7.5%)	Superior efficacy in hair count improvement, comparable to minoxidil	Erythema, pruritus, dryness, telangiectasia
Latanoprost	PGF2α analogue prolongs the anagen phase of the hair cycle	Solution (0.1%)	Increase in hair density	Further trials are needed for the safety profile
Topical spironolactone	AR inhibition	Gel (1%), solution (5%)	Significant improvement in hair growth, decrease in vellus hair and increase in upright regrowing hair, especially when combined with minoxidil	Contact dermatitis, dizziness
Topical flutamide	AR inhibition	Gel (2%)	Increased hair density and thickness, more effective in combination with minoxidil	No systemic effects reported
Topical cetirizine	Antihistamine, anti-inflammatory	Solution (1%)	Increased hair density, effective for both male and female AGA	No significant side effects reported
Topical pyrilutamide (KX-826)	AR inhibition	Tincture (0.5%, 1%), gel	Significant improvement in hair count, favourable safety profile	Itching, dryness, redness, contact dermatitis
GT20029	AR degradation	Tincture (0.5%, 1%)	Significant hair count improvement, good safety and tolerability	Itching, dryness, redness

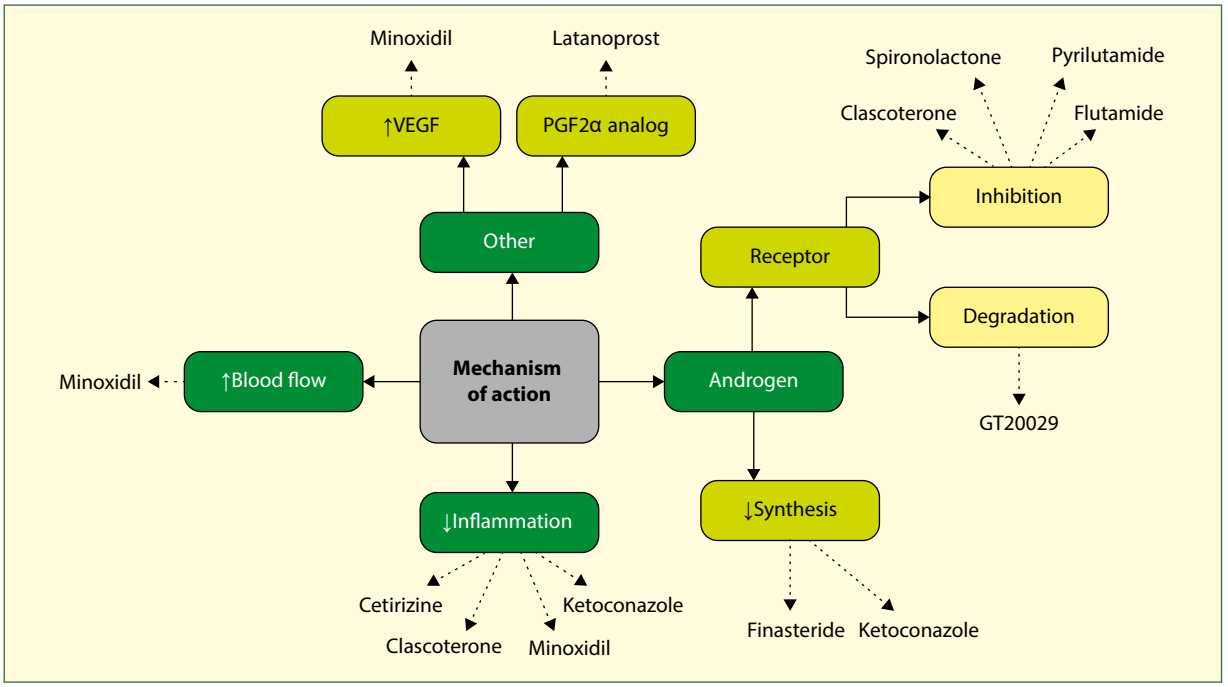

Figure 1. Mechanism of action of various topical hair loss medications

long-term treatment adherence. Clinicians should consider these factors when selecting appropriate therapies for their patients, balancing efficacy with safety to optimize outcomes.

Future research should focus on large-scale, long-term clinical trials to further validate the efficacy and safety of emerging topical treatments. Additionally, exploring combination therapies and understanding the mechanisms of action will enhance the therapeutic landscape of AGA, providing more comprehensive and individualized patient care.

Article information and declarations

Acknowledgements

None.

Author contributions

Conceptualization, investigation, visualization, writing: original draft — MK; conceptualization, writing: review and editing — OS.

Conflict of interest

The authors declare no conflict of interest.

Funding

None.

Supplementary material

None.

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VIA MEDICA

REVIEW ARTICLE

Forum Dermatologicum
2024, Vol. 10, No. 3, 79–88
DOI: 10.5603/fd.101083

ISSN 2451–1501, e-ISSN 2451–151X

Assessment of the efficacy of biological treatment in acne inversa

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ABSTRACT

Acne inversa is a chronic, progressive inflammatory skin disease. It is characterized by the occurrence of relapsing, painful, deep-seated nodules, abscesses, fistulae, sinus tracts, and scars in the axilla, inguinal area, submammary folds, and perianal area. The disease significantly affects patients' quality of life and is often associated with severe, debilitating pain and depression. Pro-inflammatory cytokines such as TNF-α, interleukin 17 (IL-17), IL-23, IL-12, IL-1α, and IL-1β play a significant role in the pathogenesis of hidradenitis suppurativa. Treatment is difficult and often ineffective, based on both surgical and pharmacological methods. Biologic drugs in hidradenitis suppurativa are the subject of many clinical trials and may be effective in patients for whom other therapies have failed. The first biological drug approved by the Food and Drug Administration for the treatment of hidradenitis suppurativa was the TNF-α inhibitor — adalimumab. The advancement of knowledge of immune mechanisms in the pathogenesis of hidradenitis suppurativa has allowed the development of clinical trials of new therapeutic targets. In 2023, the Food and Drug Administration (FDA) approved the IL-17 inhibitor — secukinumab as the second biological drug in hidradenitis suppurativa. The aim of this review is an update of the biological treatment and its effectiveness in hidradenitis suppurativa.

Forum Derm. 2024; 10, 3: 79–88

Keywords: hidradenitis suppurativa, biological treatment, TNF-α inhibitors, IL-17 inhibitors, IL-23 inhibitors, IL-1 inhibitors

INTRODUCTION

Hidradenitis suppurativa (HS) also known as acne inversa is a chronic inflammatory skin disease. This disease is characterized by chronic deep-seated nodules, abscesses, fistulae, sinus tracts, and scars in the axilla, inguinal area, submammary folds, and perianal area [1]. It significantly impacts patients' quality of life and is accompanied by pain and depression. Mostly it affects adults, but paediatric cases are also known [2]. Prevalence of HS is unknown, but estimates range from 0.00033–4.10%. HS is more than twice as common in women compared to men and is more common in African, Americans and biracial individuals than Caucasians [1]. HS is diagnosed clinically. There are several HS classification systems. The Hurley staging system classifies HS into 3 stages and it was originally developed in choosing treatment for specific areas of the body. The Sartorius system includes 1 — the area of the body, 2 — the number and types of lesions, 3 — the longest distance between two lesions, and 4 — whether all lesions are clearly separated by normal, intact skin. Hidradenitis Suppurativa Clinical Response (HiSCR) is designed to assess treatment response. The International Hidradenitis Suppurativa Severity Score System (IHS4) is the most widely used by physicians. The IHS4 is a validated instrument that scores lesions into three categories: inflammatory nodules, abscesses and draining tunnels. The IHS4 score is qualitatively interpreted as "mild", "moderate" or "severe" [3]. The Hidradenitis Suppurativa Severity Score Index (HSSI) scores disease activity and severity. The Physician's Global Assessment has been adapted into an HS-specific version (HS-PGA). Treatment for HS is multi-directional, including patient education, pharmacology treatment (antibiotics, retinoids, immunosuppressants and anti-inflammatory drugs) and surgical therapy [4].

TNF-α INHIBITORS

Tumour necrosis factor (TNF-α) is a cytokine secreted by macrophages, T lymphocytes and NK cells. There are two forms of TNF-α: soluble (sTNF-α) and transmembrane

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Received: 9.06.2024 Accepted: 17.07.2024 Early publication date: 26.07.2024

(tmTNF-α) [5]. Higher levels of TNF-α have been shown in the skin lesions and blood serum of HS patients compared to the healthy population [6]. TNF-α plays a significant role in the pathogenesis of acne inversa. It promotes polarization of Th17 lymphocytes leading to increased production of pro-inflammatory cytokines. In addition, it inhibits the secretion of adiponectin, which has anti-inflammatory effects and regulates blood glucose levels [7]. Biological drugs that inhibit TNF-α are used in the treatment of HS.

Adalimumab

Adalimumab (ADA) is a human recombinant IgG1 monoclonal antibody directed against both soluble and trans-membrane TNF-α [6]. Until October 2023, it was the only biologic drug approved for the treatment of HS by the FDA [8]. By binding to TNF-α, it regulates levels of pro-inflammatory cytokines [including interleukin 6 (Il-6), Il-8, Il-1β and soluble tumour necrosis factor receptor (sTNF-R)] and reduces levels of inflammatory white blood cells [9]. ADA is registered for the treatment of moderate to severe acne inversa [10]. ADA is administered subcutaneously, dosing includes a saturating dose of 160 mg, 80 mg in the second week of treatment, and a maintenance dose of 40 mg weekly [11]. Two randomized phase III trials (PIONEER I and II) evaluated the efficacy and safety of ADA in the treatment of HS. The trials included 307 and 326 patients with moderate to severe acne inversa. Treatment efficacy was evaluated by the HiSCR score, described as a reduction of at least 50% in the number of abscesses and inflammatory nodules, with no increase in the number of abscesses or fistulas compared to baseline. Patients treated with ADA and placebo were compared after 12 weeks. Both studies showed that a significantly higher percentage of patients treated with ADA achieved HiSCR compared to placebo (PIONEER I 41.8% *vs.* 26.0%, PIONEER II 58.9% *vs.* 27.6%). In addition, a higher percentage of patients receiving ADA achieved more than 30% pain reduction in the Patient's Global Assessment of Skin Pain (PGA-SP) score [11, 12]. Zouboulis et al. [13] in a study assessing the long-term efficacy of ADA showed a significant improvement in the Dermatology Life Quality Index (DLQI) at week 72 of treatment. Among patients who continued ADA treatment, the HiSCR rate at week 168 was 52.3% [11, 13]. The most commonly reported adverse effects of ADA therapy include injection site reactions, upper respiratory tract infections, headache, rash, and sinusitis [14].

Infliximab

Infliximab is a chimeric human-mouse monoclonal antibody directed against TNF-α. It binds the soluble and transmembrane form of TNF-α [7]. Infliximab has not been approved by the FDA for the treatment of acne inversa; however, its efficacy in this disease is being studied [15]. Shih et al. [16] in a meta-analysis based on 19 clinical trials showed that the overall response rate to infliximab treatment in HS was 83%. In the vast majority of studies, patients received 5–10 mg/kg of infliximab every 4–8 weeks. Adverse effects of therapy mainly include skin reactions at the injection site, pruritus, headache, and nausea [17]. In addition, flu-like symptoms, abscesses, and superinfection of skin lesions have also been described. Very rarely, anaphylactic shock, sepsis, tuberculosis and the development of malignancy have been reported [16].

Certolizumab

Certolizumab is a recombinant humanized Fab fragment of an antibody directed against TNF-α. By binding both the soluble and trans-membrane forms of TNF-α, it reduces the activity of cellular adhesion molecules, chemokines and pro-inflammatory mediators. Because it does not pass through the placenta, it can be used during pregnancy [18]. Shadid et al. [19] summarized 6 case reports in which 7 patients with HS were treated with certolizumab. All of the patients described had previously undergone biological treatment or antibiotic therapy without significant improvement or with only minimal improvement. The dosage of certolizumab varied from case to case, but in general, was based on 200 mg every two weeks or 400 mg every two weeks. In all cases, clinical improvement was reported after the initiation of certolizumab, and no serious side effects were registered. Certolizumab may provide an alternative treatment for pregnant patients with HS. Despite the promising results, further larger studies on the administration of certolizumab in HS are needed [7].

Golimumab

Golimumab is a human IgG1 monoclonal antibody that binds with high affinity to both the soluble and transmembrane forms of TNF-α [5, 6]. In a 2013 case report, a patient with HS was treated with golimumab 50 mg *subcutaneous* (*s.c.*) once a month, and treatment was continued for 8 months. This therapy did not result in clinical improvement [5, 20]. Tursi [21] described a case of a patient suffering from acne inversa stage II according to Hurley. In addition, the patient also suffered from ulcerative colitis (*colitis ulcerosa*) and *pyostomatitis vegetans*. Treatment with golimumab was initiated at an initial dose of 200 mg subcutaneously, followed by 100 mg *s.c.* every 4 weeks. The patient was also receiving amoxicillin with clavulanic acid at a dose of 2 g per day for 2 weeks. After 2 months of treatment, remission of both acne inversa as well as pyostomatitis vegetans and *colitis ulcerosa* was achieved [7, 15]. Ramos et al. [22] presented

a case report of two patients suffering from acne inversa and arthritis in whom golimumab was included after treatment with ADA was not successful. Clinical improvement was achieved in both cases [6, 22]. In a retrospective cohort study by Melendez-Gonzalez et al. [23] in a group of 13 patients with acne inversa and non-response to ADA or infliximab, golimumab was included. In 9 patients, the collected data allowed the evaluation of HiSCR; in this group, 6 patients achieved HiSCR. In addition, the IHS4 score decreased significantly in the described cohort [23]. Golimumab may be an alternative treatment method for HS, especially after the unsuccessful treatment with ADA. However, further studies on the use of this drug in HS are necessary [6].

Etanercept

Etanercept is a recombinant protein that is a combination of two soluble TNF receptor subunits (p75) with the Fc domain of human IgG1 [7]. It binds to TNF-α and inhibits its activity [15]. The use of etanercept in the treatment of HS was evaluated in a randomized, double-blind, placebo-controlled clinical trial. The study included 20 patients with moderate to severe HS. Etanercept was administered 50 mg in a twice-weekly dose. There was no significant difference in Physician Global Assessment PGA (PGA) and DLQI between the etanercept and placebo groups [6, 24].

IL-17 INHIBITORS

Over the past few years, IL-17 has emerged as a key player in many inflammatory diseases [25]. It stimulates neutrophils, monocytes, and Th17 lymphocytes and triggers the expression of other pro-inflammatory factors, further increasing IL-17 production and immune cell infiltration in HS lesions in a feed-forward inflammatory loop [26]. In the lesional dermis of patients suffering from HS, IL-17 is elevated compared to control skin [27]. IL-17 levels are also higher in serum and correlate with disease severity [28]. These findings likely underlie the observed therapeutic effect of IL-17 inhibitors in this disease.

Secukinumab

Secukinumab is a human monoclonal antibody that selectively binds to and inhibits IL-17A. It is approved for the treatment of moderate to severe plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and active non-radiographic axial spondyloarthritis [29]. In October 2023, the FDA approved the drug for the treatment of moderate to severe forms of acne inversa, and it has also been approved by the European Commission [8]. The presence of a second approved biologic therapy alongside ADA offers hope to patients for whom conventional treatment has been ineffective or impossible due to contraindications to previously known drugs. The efficacy of secukinumab has been widely discussed in the literature giving Prussick et al. [30] found that 55.5% (5/9) of patients achieved HiSCR at week 16 and 67% (6/9) at week 24. Casseres et al. [31] reported that 65% (13/20) of patients achieved HiSCR at week 12. Reguiaï et al. [32] showed that 75% of patients (15/20) achieved HiSCR at week 16. Ribero et al. [33] concluded that 26% (8/24) of patients achieved HiSCR at week 16 and 41% (7/17) at week 28. Melgosa et al. [34] recruited 23 patients and 73.9% (17/23) achieved HiSCR at week 16, 71.4% (15/21) at week 24, 71.4% (10/14) at week 36 and 83.3% (10/12) at week 52. Fernandez-Crehuet et al. [35] described patients mainly with stage III Hurley HS, 48.9% (23/47) of whom achieved HiSCR at week 16. In addition, the possible influence of female gender, lower body mass index (BMI) and lower treatment burden on a positive treatment outcome was noted. Promising results were confirmed by two phase III randomised, placebo-controlled, double-blind clinical trials, SUNSHINE and SUNRISE, which compared the efficacy of secukinumab at every 2 weeks and every 4 weeks versus control. In the 541-patient SUNSHINE study, 45% of patients receiving every 2-week dose achieved HiSCR at week 16, which was significant compared to placebo — 34%. In patients receiving the drug every 4 weeks, 42% achieved HiSCR, but this was not significant compared to placebo. The 543-patient SUNRISE study showed HiSCR in 42% of patients receiving the drug every 2 weeks and in 46% of patients receiving the drug every 4 weeks, observed after 16 weeks of treatment and in both cases significantly better than placebo (31%). When reassessed after 52 weeks of treatment in both clinical trials, 76% (SUNSHINE) and 84% (SUNRISE) of patients receiving the drug every 2 weeks and 81% (SUNSHINE) and 77% (SUNRISE) of patients receiving the drug every 4 weeks maintained the therapeutic effect. Side effects can include headache, nasopharyngitis, fungal infections, inflammatory bowel disease and worsening of acne inversa [36]. A multi-centre extension study, continuing both the SUNRISE and SUNSHINE trials, is designed to evaluate the maintenance of HiSCR responses at week 104 with two dose regimens and to assess long-term safety and tolerability as measured by adverse events [37]. However, the results of this large study are still awaited. Martora et al. [8] recently designed a prospective real-life study that confirmed the efficacy and safety of treatment with secukinumab. The trial included 21 patients with severe HS, 17/21 of whom had failed ADA. Results showed that 57.1% of patients achieved HiSCR at week 16, and this increased to 71.4% at week 52. However, real-life studies with large numbers of samples are still limited and a comprehensive study of different clinical outcomes is needed.

Bimekizumab

Bimekizumab is a monoclonal antibody that selectively blocks IL-17A, but also IL-17F, which may result in a broader and therefore more effective therapeutic profile of this drug [38]. Glatt et al. [39] assigned 90 patients with mild to severe HS to bimekizumab, placebo or ADA in a 2:1:1 ratio in a randomised phase II trial. To demonstrate efficacy, they assessed both HiSCR, HiSCR75 and HiSCR90 (≥ 75% or ≥ 90% reduction in total abscess and inflammatory nodule counts from baseline), as well as the PGA-SP and the DLQI. HiSCR was achieved by 57.3% of patients on bimekizumab compared to 26.1% on placebo. HiSCR75 was achieved by 46% and HiSCR90 by 32% compared to 10% and 0% in the placebo group and 35% and 15% in the ADA group. All treatment groups had a similar number of adverse events, most of which were mild or moderate. In the current randomised, placebo-controlled, phase III BE HEARD I and BE HARD II studies, which included 505 and 509 patients respectively, 48% and 52% of patients achieved a significant clinical improvement (HiSCR50) compared to placebo, with an enhancement in quality of life at week 16 that remained high through the 48-week assessment. In both studies, more than 55% of patients who remained on the drug achieved a higher reference level (HiSCR75) at week 48. The most common adverse events were worsening of HS, headache, oral candidiasis and diarrhoea, and the overall safety profile was consistent with previously reported data [40]. A comprehensive meta-analysis by Tsai et al. [41] confirms the efficacy of bimekizumab, placing it in second place behind ADA when HiSCR values achieved by both drugs are considered, and in first place when DLQI scores at weeks 12–16 are considered.

Brodalumab

Brodalumab is a human IgG2 monoclonal antibody that interacts with the A subunit of the IL-17 receptor (IL-17RA), thereby stopping signalling by multiple IL-17 isoforms (IL--17A, IL-17F, IL-17C and IL-17 A/F) [42]. It is currently approved for the treatment of moderate-to-severe plaque psoriasis. Frew et al. [43] in 2020 treated 10 patients with moderate to severe HS and 100% of them achieved HiSCR at weeks 12 and 24. No adverse effects were reported, but 2/10 patients experienced relapse after the saturating dose period. In 2021, the same investigators evaluated the effect of brodalumab in a group of 10 patients with moderate to severe HS, including 7 from a previous report. HiSCR was achieved at week 4 in the entire cohort and no relapses or adverse events were documented during the 24 weeks of treatment [44]. Yoshida et al. [45] described the results of a patient with long-term refractory HS and psoriasis, in whom brodalumab therapy proved effective against both diseases. Arenbergerova et al. [46] described a case of severe extensive gluteal HS after failed anti-TNF-alpha therapy, in which brodalumab was followed by marked clinical improvement, reduction of inflammatory lesions, decrease in IHS4 scores from 62 to 18, DLQI from 17 to 5, and a decrease in exponents indicating systemic inflammation [46]. Kearney et al. [47] described the cases of 8 patients previously treated with biologics without success. They were treated with brodalumab every other week, 7/10 reported a decrease in DLQI from 20.6 to 16.8 at week 16, 1/10 did not respond to the drug, 3/10 experienced secondary treatment failure, and their treatment was changed to guselkumab. Vagnozzi et al. [48] described the case of a patient suffering from HS (Hurley grade III, IHS 56, DLQI 28, VAS 10) and pustular psoriasis of the palms and soles, previously treated unsuccessfully with ADA, infliximab and etanercept. Due to the failure of multiple therapies and the coexistence of two diseases, treatment with brodalumab with acitretin was included. The acitretin was discontinued after 24 weeks due to the rapid resolution of the psoriasis lesions. HiSCR was achieved as early as week 12, and IHS4 was 20. At reassessment at week 48, IHS4 was 10, and improvements in pain (VAS 3/10) and quality of life (DLQI 8) were also achieved. At week 136, complete remission of active HS symptoms in the axillary area and low disease activity in the groin and perineal area was observed, achieving an IHS4 of 5, a VAS of 1, and a DLQI of 4. The study additionally included an MRI evaluation of the lower abdomen and pelvis, which confirmed improvement in acne lesions not seen on clinical examination [48]. Osorio-Gómez et al. [49] recently published a study involving 16 patients with moderate to severe HS. At week 16 of brodalumab treatment, HiSCR was achieved by 50% of them, and IHS4 dropped from 24.13 to 16.81 on average. There were also no serious side effects reported [49]. Brodalumab appears to be effective and safe in patients with moderate to severe HS, even in those who have not responded to previous biologic treatment and therefore represents a promising treatment option for HS.

CJM112

CJM112 is a human IgG1/κ monoclonal antibody with the ability to bind to IL-17A and IL-17AF with similar affinity. The 16-week, double-blind, placebo-controlled Phase II study involved 66 participants with moderate to severe HS. At week 16, 32.3% of the CJM112 group had a reduced HS-PGA score compared to 12.5% of the placebo group. However, a further 16 weeks of follow-up showed a greater-than-expected placebo effect. Finally, there were no significant differences in HS-PGA scores between the groups studied. CJM112 was generally well tolerated, and its safety profile was similar to placebo. The most common adverse events were nasopharyngitis, nausea, diarrhoea and

Table 1. Summary of biologic drugs used in the treatment of hidradenitis suppurativa

Target	Drug	Approved by FDA in HS	Other diseases	Dosage	Pregnancy	References
TNF-α	Adalimumab	+	• Rheumatoid arthritis • Juvenile idiopathic arthritis psoriatic arthritis • Ankylosing spondylitis • Crohn's disease • Plaque psoriasis • Ulcerative colitis • Hidradenitis suppurativa (HS) • Uveitis	160 mg *s.c.* at week 0, 80 mg *s.c.* at week 2, 40 mg *s.c.* at week 4 and 40 mg *s.c.* every week or 2 weeks	–	[10]
TNF-α	Infliximab	–	• Inflammatory bowel disease (IBD) • Rheumatoid arthritis • Ankylosing spondylitis • Psoriatic arthritis • Plaque psoriasis	5–10 mg *i.v.* every 4 or 8 weeks	–	[7]
TNF-α	Certolizumab	–	• Crohn's disease • Rheumatoid arthritis • Psoriatic arthritis • Ankylosing spondylitis • Plaque psoriasis	200–400 mg *s.c.* every 2 weeks	+	[7, 19]
TNF-α	Golimumab	–	• Rheumatoid arthritis • Psoriatic arthritis • Ankylosing spondylitis • Ulcerative colitis	200 mg *s.c.* at week 0, 100 mg *s.c.* every 4 weeks or 200 mg at week 0, 2 and every 4 weeks	–	[7, 23]
TNF-α	Etanercept	–	• Rheumatoid arthritis • Plaque psoriasis • Psoriatic arthritis • Juvenile idiopathic arthritis • Ankylosing spondylitis	50 mg *s.c.* every 2 weeks	–	[9]
IL-17	Secukinumab	+	• Hidradenitis suppurativa • Plaque psoriasis • Psoriatic arthritis • Ankylosing spondylitis • Axial spondyloarthritis • Juvenile idiopathic arthritis	300 mg *s.c.* every 2 or 4 weeks	–	[7, 36]
IL-17	Bimekizumab	–	• Plaque psoriasis • Psoriatic arthritis • Axial spondyloarthritis	320 mg *s.c.* every 2 or 4 weeks	–	[40, 50]
IL-17	Brodalumab	–	Plaque psoriasis	210 mg *s.c.* every week	–	[7, 44]
IL-17	CJM112	–	–	300 mg *s.c.* for the first 5 weeks and then every 2 weeks	–	[50]
IL-17	Isokibep	–	–	160 mg *s.c.* every week	–	[50]
IL-17	Sonelokimab	–	–	120 mg and 240 mg *s.c.*	–	[50]
IL-23	Guselkumab	–	Plaque psoriasis	100 mg *s.c.* at week 0 and 4 and every 8 weeks	–	[7, 54]
IL-23	Tildrakizumab	–	Plaque psoriasis	100 mg *s.c.* at week 0 and 4 and then 200 mg every 4 weeks	–	[57]
IL-23	Risankizumab	–	• Psoriatic arthritis • Psoriasis	150 mg *s.c.* at week 0 and 4 and every 12 weeks	–	[7]
IL-23/ /IL-12	Ustekinumab	–	• Psoriatic arthritis • Plaque psoriasis • Crohn's disease	45 mg *s.c.* or 90 mg *s.c.* if weight > 100 kg at week 0, 4, 16, 28	–	[10]
IL-1	Anakinra	–	• Rheumatoid arthritis • Cryopyrin-associated periodic syndromes • Interleukin-1 receptor antagonist deficiency	100 mg s.c. or 200 mg daily	–	[9, 10, 69]
IL-1	Canakinumab	–	Periodic fever syndromes, active Still's disease, gout flares	Every week/4 weeks/8 weeks — 150 mg *s.c.*	–	[7,74,75]
IL-1	Bermekimab	–	–	7.5 mg/kg every 14 days up to 7 infusions	–	[7,10]

IL — Interleukin; HS — hidradenitis suppurativa; IBD — inflammatory bowel disease; *s.c.* — subcutaneous

headache. The incidence of nasopharyngitis and nausea was higher in the CJM112 group compared to the placebo group [50].

Isokibep

Isokibep is a selective, potent IL-17A inhibitor developed using affibody molecules containing small triple-helical protein domains. It is a novel subcutaneous drug with a small molecular size that greatly enhances biodistribution to inflamed tissue. Isokibep was used in a randomised, double-blind phase IIb study in patients with moderate to severe HS. HiSCR were assessed in 180 patients at weeks 12 and 16, and initial observations at week 12 showed that HiSCR50 was achieved by 71% of participants, HiSCR75 — 57%, HiSCR90 — 38% and HiSCR100 — 33%. Side effects were mainly injection site reactions and one patient was reported to have developed inflammatory bowel disease. Recruitment is ongoing in a double-blind, placebo-controlled Phase III study to assess the proportion of patients with HiSCR75 at week 16 [50].

Sonelokimab

Sonelokimab is a novel trivalent nanobody (a new class of proteins based on single-domain antibodies) that is specific for IL-17A, IL-17F and human serum albumin. Due to the presence of serum albumin, drug concentrations at sites of inflammatory swelling can be increased. A phase II study of 234 participants with severe HS evaluated the efficacy and safety of sonelokimab in two dosing regimens (120 mg and 240 mg) compared to placebo and ADA. The results of the study showed that a higher proportion of patients treated with sonelokimab reached HiSCR75 at week 12 of the study. Additional secondary endpoints, such as HiSCR90 and IHS4, also showed statistically significant results remaining favourable safety profile [50].

IL-23 INHIBITORS

IL-23 is a pro-inflammatory cytokine essential for the differentiation of Th17 lymphocytes [51]. The IL-23/Th17 axis is implicated in the pathogenesis of acne inversa, which contributes to chronic inflammation. Schlapbach et al. [27] showed that skin lesions occurring in acne inversa are characterised by overexpression of IL-23 and IL-12 in macrophages infiltrating the papillary and reticular layers of the skin. Due to the significant role of the IL-23/Th17 signalling axis in acne inversa, anti-IL-23 antibodies may be an effective therapy [52].

Guselkumab

Guselkumab is an IgG1 lambda monoclonal antibody against IL-23, approved for the treatment of psoriatic arthritis and plaque psoriasis, but several studies are showing its efficacy in the treatment of acne inversa [53]. A pilot study by Repetto et al. [54] evaluated the efficacy of HS treatment with antibodies against IL-17 (secukinumab) and IL-23 (guselkumab, risankizumab) after ADA failure or side effects preventing its use. The study included 26 adult patients (16 treated with anti-IL-17 and 10 with anti-IL-23) with Hurley grade ≥ 2 disease severity. The drugs were administered at the dosage approved for the treatment of psoriasis (300 mg at weeks 0–4 and then every 4 weeks for secukinumab, 150 mg at week 0.4 and every 12 weeks for risankizumab, 100 mg at week 0.4 and every 8 weeks for guselkumab). Eight patients taking anti-IL-17 and 1 patient taking anti-IL-23 discontinued therapy due to inefficacy. DLQI, HiSCR and IHS4 were assessed. In the case of anti-IL-23 antibodies, a significant improvement in IHS4 was observed after 12 months. In turn, there was an improvement in DLQI in both groups and no severe side effects were reported. At 6 months of treatment, patients taking anti-IL-23 presented a better response compared to anti-IL-17 (HiSCR for anti-IL-23 was achieved by 90% of patients) [54]. A retrospective study regarding the effectiveness of guselkumab in the treatment of HS was conducted in Spain between 2020 and 2022. It included mostly patients with Hurley III. HiSCR was achieved in more than half of the patients [55]. The literature also presents numerous case reports of HS treatment with guselkumab. One of these is the case of a 17-year-old male suffering from Hurley stage II HS, who received guselkumab at the therapeutic dosage approved for psoriasis (100 mg at week 0 and 4 and every 8 weeks thereafter). The patient achieved HiSCR at week 16 of treatment and clinical response was maintained at follow-up after 52 weeks. No adverse effects associated with guselkumab therapy were observed [53]. In the phase II study by Kimball et al. [55], despite an improvement in HiSCR in patients treated with guselkumab, no statistical significance level was reached.

Tildrakizumab

Tildrakizumab is a humanised monoclonal antibody targeting the p19 subunit of IL-23. Clinical cases are confirming the efficacy of tildrakizumab in the treatment of HS. One of them is the case of a 38-year-old man with HS and plaque psoriasis, who showed a clinical response after treatment with tildrakizumab in a dose of 200 mg [56]. Kok et al. [57] described a case series of 5 patients treated with tildrakizumab 100 mg at weeks 0 and 4 and then 200 mg every 4 weeks. DLQI and number of skin lesions were assessed at week 8 and 20. Quality of life improved in all cases, but further studies including a larger group of patients and parameters such as IHS4 and HiSCR are needed to assess the efficacy of HS therapy with tildrakizumab.

Risankizumab

Risankizumab is also an anti-IL-23 antibody approved by the FDA for the treatment of plaque psoriasis, psoriatic arthritis and Crohn's disease. Studies of its efficacy in the treatment of HS are currently underway. The phase II study by Kimball et al. [58] involved 243 moderate to severe patients. Patients received risankizumab at a dose of 180 mg or 360 mg. After 16 weeks, the efficacy of the treatment was assessed. The percentage of patients taking risankizumab who achieved HiSCR did not differ from patients taking a placebo, which led to the earlier termination of the study [58]. Repetto et al. [59] described a case series of 6 patients treated with risankizumab at the therapeutic dose for psoriasis. The study included 4 patients in Hurley III and 2 patients in Hurley II. All patients achieved clinical improvement and a reduction in IHS4. 3 patients achieved HiSCR after 3 months of treatment and 3 after 6 months. None of the patients reported adverse symptoms. Despite the proven efficacy of risankizumab in the treatment of HS in many case reports, the phase II study does not confirm its effectiveness [58, 59].

IL-12/23 INHIBITOR

Ustekinumab

Ustekinumab is an IgG1κ monoclonal antibody directed against the p40 subunit common to IL-23 and IL-12 preventing their interaction with the β1 subunit of the IL-12 receptor [60]. The interaction of IL-12 and IL-23 with the receptor protein activates the JAK/STAT pathway, which consequently leads to increased inflammation of the skin lesions [61]. It has been shown that certain variants of the IL-12RB1 gene are associated with a more severe form of HS [62]. Montero Vichez et al. assessed the efficacy of treatment of acne inversa with ustekinumab in patients with Hurley II–III. Patients received a dosage of ustekinumab approved for the treatment of psoriasis. Disease severity was assessed with the HS-PGA and pain severity with the Numerical Rating Scale (NRS) before therapy and every four weeks thereafter. The primary endpoint was a > -1 point reduction in HS-PGA and the secondary endpoint was a $> -20\%$ reduction in NRS. Seventy per cent of patients had an improvement in HS-PGA and 80 per cent had an improvement in NRS. Patients did not report any serious adverse effects. The obtained results may prove the efficacy of ustekinumab therapy in patients after unsuccessful first-line treatment [63]. Blok et al. [64] carried out a prospective study including 17 patients who received ustekinumab at a dosage of 45 mg or 90 mg for patients weighing over 100 kg. Ustekinumab was administered at weeks 0, 4, 16, and 28 with follow-up at week 40. The most common adverse effects were headache, fatigue and upper respiratory tract infections. At follow-up after 40 weeks, 82% of patients achieved improvement in modified Sartorius Score (mSS) and 47% of patients achieved HiSCR [64].

IL-1 INHIBITORS

IL-1 receptor antagonists block the inflammatory response of the proinflammatory cytokine IL-1 [17]. IL-1, similarly to TNF-α, is one of the major mediators of the inflammatory response that is also involved in the pathogenesis of HS [65]. This group of drugs includes anakinra, bermekimab and canakinumab.

Anakinra

Anakinra is a recombinant IL-1 receptor antagonist. It blocks the biological activity of naturally occurring IL-1 by competitively inhibiting the binding of both IL-1α and IL-1β to the IL-1 type 1 receptor [66]. So far, this drug has been approved by the FDA for the treatment of rheumatoid arthritis, cryopyrin-associated periodic syndromes and interleukin-1 receptor antagonist deficiency. Although the FDA has not approved Anakinra for the treatment of acne inversa, there are studies reporting its effectiveness [67, 68]. In double-blind, randomized, placebo-controlled prospective clinical trial in a group of 20 patients with Hurley stage II/III HS showed 78% efficacy of the drug compared to a placebo group of 30%, and no serious side effects were observed [9, 69]. Failures in the treatment of HS with anakinra have also been described [70–72], so further research is needed on the efficacy of this drug in the treatment of HS. In addition, Anakinra is administered by daily subcutaneous injections, which may reduce patients' willingness to use it.

Canakinumab

Canakinumab is a human IL-1 beta antibody. To date, several case reports have been described in which it has been used to treat HS. The results of these cases are divergent [73]. In several cases, significant improvement and regression of HS lesions are described [74–76]. In contrast, another case report describes that the drug did not show efficacy [77], and another even observed a worsening of the lesions [78]. Due to conflicting observations and a small amount of data, longer (long-term) studies are needed to assess its efficacy.

Bermekimab

Bermekimab also known as MABp1 is a human IL-1α monoclonal antibody. It is currently in phase 2 clinical trials for the treatment of rheumatoid arthritis and colorectal cancer [79]. In one phase II, multicentre, open-leben study of two dose cohorts of bermekimab in patients with moderate-to-severe HS who are naïve to or have failed prior anti-TNF therapy the results bermekimab was effective despite treatment history, with 61% and 63% of patients naïve to and having failed anti-TNF therapy, respectively, achieving HS clinical response after 12 weeks of treatment [80].

In another double-blind study in patients who had failed ADA treatment, the efficacy of bermekimab was 60%, compared to 10% in the placebo group. Ultrasonographically, the drug resulted in a reduction in neovascularization and the depth of skin lesions. No serious side effects were observed [81].

CONCLUSIONS

Biological agents are increasingly used in the treatment of many diseases. They are used to treat acne inversa when other treatments are ineffective. FDA-approved biologic drugs for the treatment of HS are ADA and secukinumab. Numerous clinical trials and case series reports indicate the efficacy of biologic therapy in HS, but further studies involving a larger group of patients are needed. In addition, many agents are in clinical trials. Biologic drugs are mostly well tolerated by patients, and side effects are mostly mild, with isolated cases of severe side effects reported.

Article information and declarations

Acknowledgements

None.

Author contributions

The contribution of each author in the creation of the review article was equal, accounting for 20% per author.

Conflict of interest

The authors declare no conflict of interest.

Funding

There was no funding.

Supplementary material

None.

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VIA MEDICA

CASE REPORT

Forum Dermatologicum
2024, Vol. 10, No. 3, 89–92
DOI: 10.5603/fd.101564

ISSN 2451–1501, e-ISSN 2451–151X

Pemphigus foliaceous following vaccinations

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ABSTRACT

Pemphigus is a rare autoimmune bullous disease, with pemphigus vulgaris (PV) and pemphigus foliaceous (PF) being its most common forms. This report presents a case of PF triggered by vaccinations. A previously healthy 38-year-old Caucasian man developed skin lesions six months after receiving vaccinations for hepatitis A, rabies, cholera, typhoid fever, and yellow fever before travelling to Sudan. Examination revealed pruritic erosions, crusts, and flaccid blisters primarily on the trunk and limbs. Histopathology was nonspecific, but direct immunofluorescence showed intercellular IgG, C3c, and C1q deposits. Elevated autoantibodies against desmoglein 1 (DSG1) confirmed the PF diagnosis. The patient responded well to oral prednisone and topical treatments, with complete resolution of symptoms within six months. The aetiology of pemphigus remains unclear, but vaccines can nonspecifically activate the immune system, potentially triggering pemphigus in predisposed individuals. This case highlights the need to consider pemphigus as a potential adverse effect of vaccination.

Forum Derm. 2024; 10, 3: 89–92

Keywords: pemphigus foliaceous, vaccinations

INTRODUCTION

Pemphigus is known as a rare autoimmune bullous disease that can be fatal if left untreated. Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are the most common forms of pemphigus. In contrast to PF, almost all patients with PV will develop oral lesions at some stage of the disease. This research presents the case of a patient who developed PF after a series of vaccinations. There were just a few reports of patients who developed pemphigus following vaccinations (Tab. 1) [1–9] and several cases of pemphigus exacerbation after vaccinations described in the literature [10, 11], before the coronavirus disease 2019 (COVID-19) pandemic. Most new scientific papers on the development of PV or PF after vaccination, describe the occurrence of these dermatoses after immunization against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Tab. 1) [12–37]. This global pandemic and the mass vaccinations against COVID-19 that have taken place in recent years, have increased the demand for research on the relationship between autoimmune bullous diseases and specific immunization.

CASE REPORT

A previously healthy 38-year-old Caucasian man was admitted to the department with skin lesions lasting half a year. About one month before the first symptoms had occurred, the patient had taken a series of vaccinations before his journey to Sudan [against hepatitis A, rabies (3 doses), cholera (2 doses), typhoid fever, and yellow fever].

The physical examination revealed numerous itching erosions, crusts, hyper- and hypopigmentation mainly on the trunk and limbs, and single thin-walled flaccid blisters filled with clear fluid that easily ruptured (Fig. 1). The hair, nails and mucous membranes were not affected.

The histopathological examination of the skin biopsy showed that the surrounding epidermis exhibited a slightly loosened structure in the deeper layers without evident acantholysis. The stroma showed a fairly intense perivascular lymphocytic infiltrate with occasional eosinophils. Direct immunofluorescence (DIF) of a perilesional skin biopsy revealed intercellular space deposition of IgG, C3c, and a granular pattern of C1q in the walls of superficial vessels. Enzyme-linked

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Received: 13.07.2024 Accepted: 18.07.2024 Early publication date: 13.08.2024

Table 1. Pemphigus following vaccinations — literature review

References	Patient age/sex	Vaccine against (type)	Diagnosed
Bellaney et al. 1996 [1]	46 y/female	Typhoid (Typhim Vi)	Pemphigus vulgaris
Mignogna et al. 2000 [2]	Not know	Influenza (n/a)	Pemphigus vulgaris
Cozzani et al. 2002 [3]	11 y/female	Tetanus, diphtheria	Pemphigus
Muellenhoff et al. 2004 [4]	41 y/male	Anthrax (Anthrax vaccine adsorbed)	Pemphigus vulgaris
Berkun et al. 2005 [5]	43 y/male	Hepatitis B (Engerix B)	Pemphigus vulgaris
Yalçin et al. 2007 [6]	43 y/female	Rabies	Pemphigus vulgaris
Albavera et al. 2012 [7]	54 y/female	Influenza	Pemphigus vulgaris
Hviid et al. 2017 [8]	Not know/female	Human papilloma virus	Pemphigus vulgaris
Sharma et al. 2020 [9]	5 y/female	Diphtheria	Pemphigus vulgaris
Solimani et al. 2021 [12]	40 y/female	SARS-CoV-2 (Comirnaty)	Pemphigus vulgaris
Thongprasom et al. 2021 [13]	38 y/female	SARS-CoV-2 (AstraZeneca)	Pemphigus vulgaris
Lua et al. 2021 [14]	83 y/male	SARS-CoV-2 (Comirnaty)	Pemphigus foliaceus
Hatami et al. 2021 [15]	34 y/male	SARS-CoV-2 (AstraZeneca)	Pemphigus vulgaris
Knechtl et al. 2021 [16]	89 y/male	SARS-CoV-2 (Comirnaty)	Pemphigus vulgaris
Koutlas et al. 2021 [17]	60 y/male	SARS-CoV-2 (Moderna)	Pemphigus vulgaris
Akoglu 2022 [18]	69 y/female	SARS-CoV-2 (CoronaVac)	Pemphigus vulgaris
Calabria et al. 2022 [19]	60 y/female	SARS-CoV-2 (Comirnaty)	Pemphigus vulgaris
Saffarian et al. 2022 [20]	76 y/female	SARS-CoV-2 (Sinopharm/BBIBP-CorV)	Pemphigus vulgaris
Yıldırıcı et al. 2022 [21]	65 y/male	SARS-CoV-2 (Comirnaty)	Pemphigus foliaceus
Falcinelli et al. 2022 [22]	63 y/female	SARS-CoV-2 (Comirnaty)	Pemphigus foliaceus
Gui et al. 2022 [23]	25 y/male	SARS-CoV-2 (Comirnaty)	Pemphigus vulgaris
	67 y/female	SARS-CoV-2 (Moderna)	Pemphigus foliaceus
Hali et al. [24]	50 y/female	SARS-CoV-2 (Comirnaty)	Pemphigus foliaceus
	58 y/female	SARS-CoV-2 (Comirnaty)	Pemphigus vulgaris
Corrá et al. 2022 [25]	61 y/female	SARS-CoV-2 (Comirnaty)	Pemphigus vulgaris
	80 y/male	SARS-CoV-2 (Comirnaty)	Pemphigus foliaceus
	66 y/female	SARS-CoV-2 (Comirnaty)	Pemphigus foliaceus
	73 y/female	SARS-CoV-2 (Comirnaty)	Pemphigus vulgaris
	63 y/female	SARS-CoV-2 (AstraZeneca)	Pemphigus vulgaris
Aryanian et al. 2022 [26]	43 y/male	SARS-CoV-2 (AstraZeneca)	Pemphigus vulgaris
Singh et al. 2022 [27]	44 y/male	SARS-CoV-2 (AstraZeneca)	Pemphigus vulgaris
Pourani et al. 202 [28]	75 y/male	SARS-CoV-2 (Sinopharm/BBIBP-CorV)	Pemphigus foliaceus
Reis et al. 2022 [29]	35 y/female	SARS-CoV-2 (Comirnaty)	Pemphigus foliaceus
Rouatbi et al. 2022 [30]	70 y/male	SARS-CoV-2 (Comirnaty)	Pemphigus foliaceus
	48 y/male	SARS-CoV-2 (AstraZeneca)	Pemphigus foliaceus
Agharbi et al. 2022 [31]	72 y/male	SARS-CoV-2 (Comirnaty)	Pemphigus vulgaris
Shakoei et al. 2022 [32]	28 y/female	SARS-CoV-2 (Sinopharm/BBIBP-CorV)	Pemphigus vulgaris
	30 y/female	SARS-CoV-2 (Sinopharm/BBIBP-CorV)	Pemphigus vulgaris
Alami et al. 2022 [33]	44 y/male	SARS-CoV-2 (Sinopharm/BBIBP-CorV)	Pemphigus foliaceus
Norimatsu et al. 2023 [34]	86 y/male	SARS-CoV-2 (Comirnaty)	Pemphigus vulgaris
Almasi-Nasrabadi et al. 2023 [35]	62 y/female	SARS-CoV-2 (AstraZeneca)	Pemphigus foliaceus
Nguyen Nhat Pham et al. 2023 [36]	53 y/female	SARS-CoV-2 (AstraZeneca)	Pemphigus foliaceus
	30 y/female	SARS-CoV-2 (Moderna)	Pemphigus foliaceus
Kadylak et al. 2024 (present article)	38 y/male	Hepatitis A (Avaxim 160U), rabies (Verorab), cholera (Dukoral), typhoid fever (Typhim Vi), yellow fever (Stamaril)	Pemphigus foliaceus

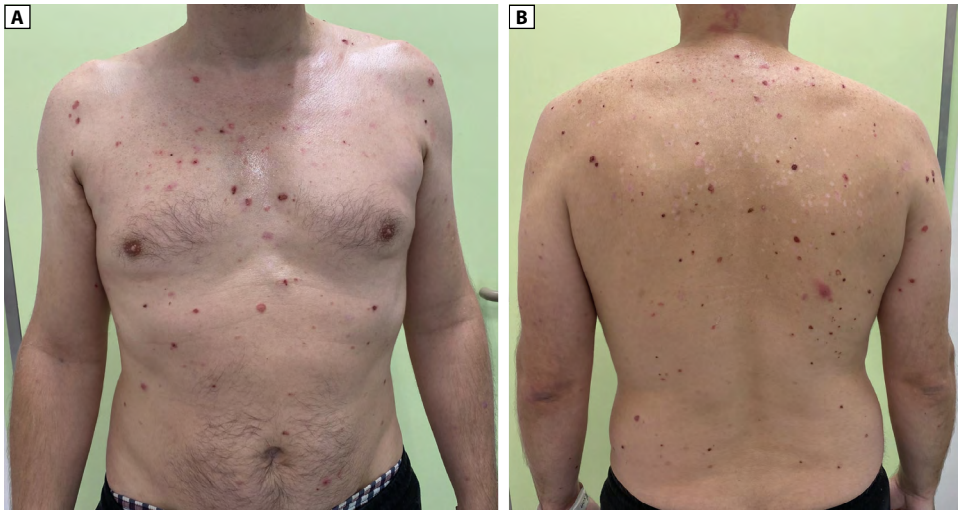

Figure 1A, B. Flaccid blistering, scabbing erosions, hyper- and hypopigmentation on the patient's trunk

immunosorbent assay detected circulating pemphigus autoantibodies against desmoglein 1 (DSG 1). PF was diagnosed based on clinical presentation, DIF and serological findings. Oral prednisone at 0.5 mg/kg/day and topical supportive treatment (clobetasol propionate, emollients) were introduced with good clinical response. Six months after onset skin was completely clear and asymptomatic.

DISCUSSION

The exact aetiology and pathogenesis of pemphigus are still unknown. Several exogenous factors may trigger pemphigus initiation in susceptible individuals or be exacerbated in affected patients (*e.g.* cancer, infection and drugs) [10]. Vaccines as well as drugs, can cause a non-specific activation of the immune system and *de novo* induce or trigger an already existing but latent pemphigus in a predisposed population [5, 37]. An induced pemphigus may resolve after drug withdrawal [38]. Three groups of chemical structures in vaccines/drugs can trigger, exacerbate or induce pemphigus flare-ups: 1) thiol group (*e.g.* captopril, penicillamine); 2) phenol drugs (*e.g.* aspirin, levodopa, heroin); 3) non-thiol, nonphenol drugs (*e.g.* nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, calcium channel blockers) [39]. In the presented case the composition of all vaccines was checked and none of them contained thiol and phenol groups.

There are several possible hypotheses explaining blistering after vaccination: 1) genetically predisposed individuals may develop a hyperimmune reaction, which may result in the development of autoantibodies to DSG antigen [4]; 2) vaccines can directly affect DSG 1 and/or 3, adhesion molecules on keratinocytes or modify their structure [6]; 3) vaccination causes an increase of concentration of pro-inflammatory cytokines and proteolytic enzymes, which may affect the skin and mucous membranes [9]. There have also been reports of PV following the use of exogenous interferon and interleukin therapy [4]; 4) nonspecific activation of the innate immune system can also trigger autoimmunity by promoting the activation or expansion of autoreactive T cells [6]; 5) the immunization components may themselves act as foreign antigens, leading to cross-reactivity of antibodies directed against both the foreign antigen and the DSG [1]; 6) multiple antigenic stimulations activate the IgG4 synthesis pathway, which could be trigger factor of pemphigus [37].

CONCLUSIONS

In conclusion, the authors believe that vaccinations were associated with PF in the described case. Unfortunately, it is not possible to determine exactly which one could have caused the disease. Although the occurrence is exceedingly uncommon, pemphigus can result from vaccination. It remains an undesirable consequence that clinicians should consider, particularly in predisposed individuals.

Article information and declarations

Acknowledgements

None.

Author contributions

Conceptualization — DK; methodology — DK; formal analysis — DK; investigation — DK; resources — DK; data curation — DK; writing: original draft preparation — DK, JS; writing: review and editing — DK, JS, WB-R, RJN and MS-W; visualization — DK; supervision — WB-R, RJN. and MS-W; project administration — DK. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

Ethics statement

Case report, consent of the bioethics committee is not required.

Funding

There was no funding.

Supplementary material

None.

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VIA MEDICA

CASE REPORT

Forum Dermatologicum
2024, Vol. 10, No. 3, 93–96
DOI: 10.5603/fd.101656

ISSN 2451–1501, e-ISSN 2451–151X

Undiagnosed Darier's disease comorbid with ambiguous viral infection

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ABSTRACT

Introduction: Darier's disease (DD) is a rare autosomal dominant genodermatosis characterized by hyperkeratotic papules, primarily located on seborrheic areas as well as with palmoplantar, nail or oral mucosa involvement. The course of the disease is chronic with the possible occurrence of coinfection, most commonly with the herpes simplex virus. Each new infection can significantly intensify the symptoms.

Case description: A 42-year-old patient presented with a prolonged history of undiagnosed brownish-grey papules on the limbs and trunk, worsening in the summer was admitted to the dermatology department, to diagnose and treat the one-week history of skin lesions on his arms, chest, and neck, and partially face. Lesions were more intensified on the left side, initially displaying as intense erythema, then covered with multiple papules and grouped vesicles, accompanied by a burning sensation and fever. Laboratory tests showed elevated inflammatory markers. Ultrasonography revealed oedema of the subcutaneous tissue and enlarged cervical lymph nodes on the left side. In the blood culture methicillin-resistant *Staphylococcus Aureus* (MRSA) was detected. Systemic intravenous treatment with antibiotics and acyclovir resulted in slow clinical improvement with normalization in laboratory tests. Histopathological examination in correlation with the clinical data suggested a *Poxviridae* infection along with a typical Darier's disease picture.

Conclusions: Darier's disease, particularly when complicated by cutaneous viral infections, may be misleading, as seen in this case. Eczema herpeticum, eczema vaccinatum, or other pox-zoonoses may explain the severe course observed. The histopathological examination is crucial for accurate diagnosis.

Forum Derm. 2024; 10, 3: 93–96

Keywords: Darier's disease, genodermatosis, viral infection, coinfection, hyperkeratotic papules

CASE DESCRIPTION

The 42-year-old patient with a longstanding history of previously undiagnosed brownish-grey papules and plaques on the limbs and torso, with flares during the summer, presented to the dermatology department due to the exacerbated skin lesions on the arms, chest, neck, and partially on the face, mainly on the left side of the body, persisting for a week. The skin lesions were intense in places particularly exposed to sunlight (Fig. 1). Initially, they appeared as intense erythema, then progressed into numerous vesicles and papules, partially grouped and confluent (Fig. 2), accompanied by a burning sensation and fever. Laboratory test results revealed elevated markers of inflammation: C-reactive protein (CRP) was 67.06 mg/L (norm < 5 mg/L); red blood cells (RBC) was 4.4 × 10^6/µL (norm 4.2–5.4 10^6/µL); white blood cells (WBC) 11.92 × 10^3/µL (norm 4–10 × 10^3/µL); neutrophils (NEU) was 9.13 × 10^3/µL (norm 1.6–7.2 × 10^3/µL). Ultrasonographic examination of the left cheek and neck unveiled subcutaneous tissue swelling without abscess, along with numerous enlarged neck lymph nodes. Blood analysis indicated the presence of methicillin-resistant *Staphylococcus Aureus* (MRSA). The culture from the skin lesion revealed the presence of MRSA and *Pseudomonas putida*. Stool examination did not detect any parasitic presence. Antibodies against HSV-2 were negative, and IgG antibodies against HSV-1 were positive. Histopathological examination of the skin lesion revealed focal necrosis of keratinocytes with abundant, partially purulent inflammatory infiltrate, eosinophil admixture, signs of vascular damage, and erythrocyte extravasation. Within the infiltrate, isolated cells with eosinophilic inclusion bodies in the cytoplasm were present. Focal parakeratosis, dyskeratosis with the presence of occasional round bodies, and mild acantholysis above the basal layer were observed in

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Received: 19.07.2024 Accepted: 25.07.2024 Early publication date: 14.08.2024

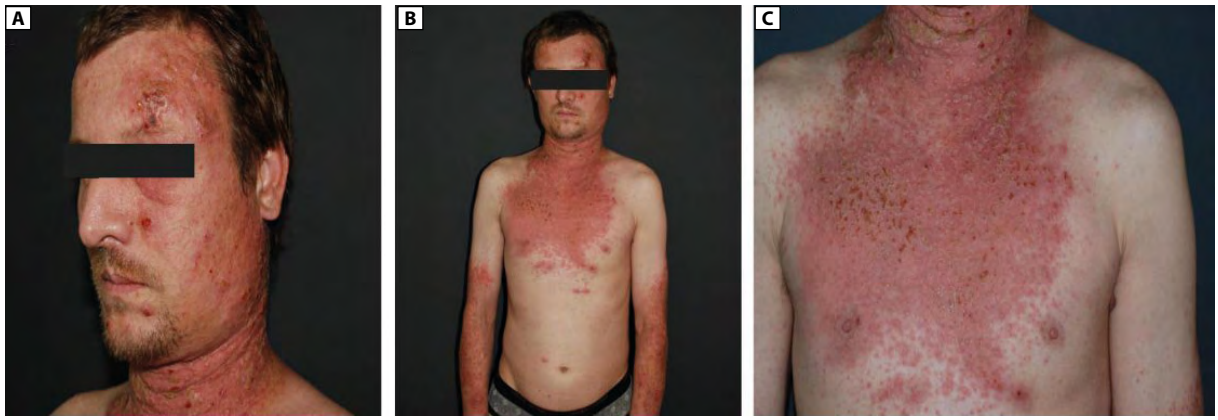

Figure 1A–C. The skin lesions on the day of admission

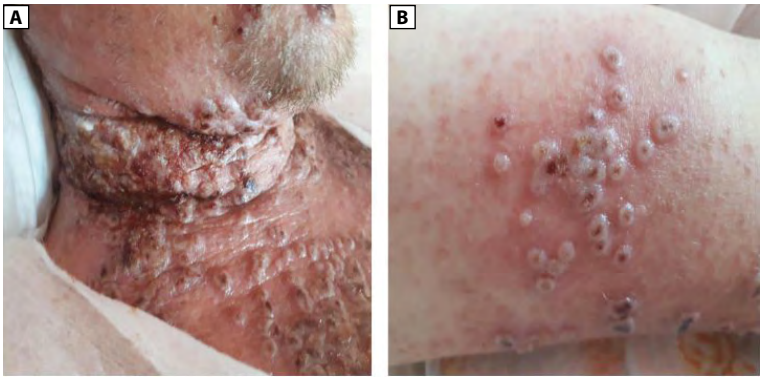

Figure 2A, B. Three days after the admission

the preserved epidermis. This pattern, in correlation with clinical symptoms, suggested Darier's disease with overlapping infection, most likely with a virus from the *Poxviridae* family. Intravenous antibiotic therapy with ceftriaxone (1 g), ciprofloxacin (400 mg twice daily), imipenem with cilastatin (1 g + 1 g three times daily), vancomycin, and intravenous acyclovir treatment (3 times 500 mg) resulted in normalization of laboratory test results and gradual clinical improvement (Fig. 3, 4).

DISCUSSION

Darier's disease, also known as Darier–White disease, follicular keratosis, or follicular dyskeratosis, is a rare genodermatosis inherited in an autosomal dominant manner. It is associated with a mutation in the *ATP2A2* gene, leading to impaired function of the sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2) calcium pump in the sarcoplasmic reticulum. This ultimately results in desmosome breakdown and the process of acantholysis. The prevalence in the population ranges from 1:30,000 to 1:100,000, with no gender difference, however, sporadic cases are in 40–50% of cases have been reported [1, 2]. Characteristic is the presence of numerous hyperkeratotic papules, mainly located in seborrheic areas: the head, neck, trunk, and mucous membranes [3]. The skin lesions can range in colour from skin tone to dark brown and typically coalesce to form a confluent larger surface area. They may cause itching and an unpleasant odour associated with the accumulation of dead epidermis. DD is typical during adolescence and tends to be chronic. Symptoms worsen during the summer due to increased exposure to sunlight and heat. Other exacerbating factors may include stress, infections, and friction, thus patients are advised to wear loose, cotton clothing and maintain weight loss [4]. Diagnosis relies primarily on histopathological examination results, where dyskeratosis, premature keratinocyte cornification, and acantholysis can be observed. Changes such as subbasal clefts with dyskeratotic acanthotic cells, grains, and corps may occur in the cornified, granular, and spinous layers and are visualized with haematoxylin and eosin staining [3]. In 2023, an interesting study revealing an alternative to histopathological examination was published. Following the guidelines of the International Dermoscopy Society (IDS), observations were conducted on a patient group, with

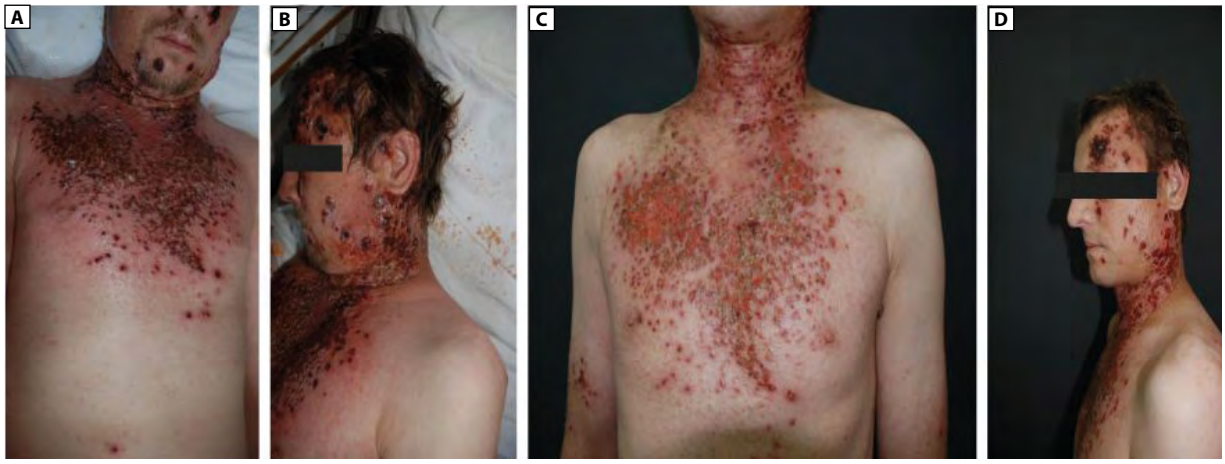

Figure 3A–D. Continuous clinical improvement achieved within the treatment

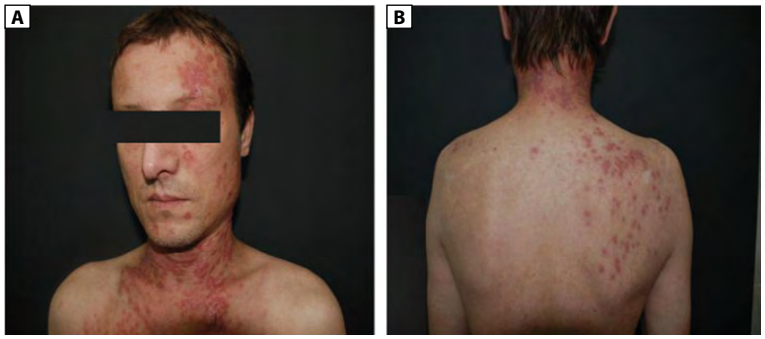

Figure 4A, B. Clinical improvement after 3 weeks, before the discharge

5 individuals with Darier's disease. Dermoscopic examination revealed characteristic features, such as star-shaped or oval yellow areas surrounded by a whitish halo and a pink, homogeneous, structureless background. This resulted in 100% effectiveness in diagnosing DD using dermoscopy, providing hope for future non-invasive diagnostics [5].

Frequently mentioned in the literature as a triggering factor for DD is superinfection with herpes simplex virus (HSV), which induces an increase in interleukin 6 (IL-6) levels in the serum, impacting the exacerbation of DD symptoms by down-regulating the expression of responsible genes [6, 7]. Recently, there has been an increase in reports describing exacerbation of DD during COVID-19. This is due to a cytokine storm characterized by elevated levels of IL-6 and tumor necrosis factor alpha (TNF-α). As a result, besides reducing *ATP2A2* mRNA levels, and decreasing the efficiency of the SERCA2b calcium pump, there is an intensified necroptosis of epidermal keratinocytes, thereby enhancing the processes of acantholysis and apoptosis in the epidermis [6, 7]. To date, two cases of *Poxviridae* infection, specifically *Orthopoxvirus*, during the course of DD have been described [8, 9]. In both cases, it was the cowpox virus transmitted by animals, most commonly by wild cats whose reservoirs are wild rodents [10]. Such superinfections are particularly dangerous for individuals with weakened immunity and patients with extensive skin diseases such as Darier's disease, erythroderma, or atopic dermatitis [8].

In the treatment of DD, retinoids, especially acitretin, have the broadest evidence base. The recommended initial dose is 0.2–0.3 mg/kg body weight (BW), gradually increasing until achieving a therapeutic effect [4]. Publications also suggest the effectiveness of isotretinoin at an initial dose of 0.5 mg/kg BW, prednisolone at the same initial dose, or cyclosporine (3 mg/kg BW per day) [11]. Studies have reported the successful use of 3% sodium diclofenac. It inhibits cyclooxygenase-2, leading to suppression of prostaglandin E2 activity, lowering *ATP2A2* gene levels, and normalizing SERCA2 levels in keratinocytes. Additionally, it is combined with 2.5% hyaluronic acid, improving skin retention and local action [12, 13]. Recent studies report the effectiveness of oral doses of vitamin A and the positive effects of bexarotene [14, 15].

Due to the frequent occurrence of superinfections in the location of DD lesions, accurate diagnosis can be challenging or misleading. Therefore, histopathological examination remains crucial in diagnosis, especially considering that viral infections may contribute to the morbidity and mortality of this condition. To avert disease exacerbation, it is also essential to emphasize preventive measures, including photoprotection. It is important to recognize this manifestation, especially in patients without classic clinical presentation, to implement earlier diagnosis, management, and appropriate counselling to patients and their family members with this genodermatosis.

Article information and declarations

Acknowledgements

None.

Author contributions

Writing: original draft preparation — MD, KB; conceptualization, patient's attending physician — PL; writing: review and editing, supervision — AB; supervision — IF.

Conflict of interest

The authors declare no conflict of interest.

Ethics statement

No ethical issues.

Funding

None.

Supplementary material

None.

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VIA MEDICA

CASE REPORT

Forum Dermatologicum
2024, Vol. 10, No. 3, 97–100
DOI: 10.5603/fd.100812

ISSN 2451–1501, e-ISSN 2451–151X

A benign form of epidermolysis bullosa pruriginosa with a novel mutation in *COL7A1* gene in a Polish family: a case series and literature review

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ABSTRACT

Epidermolysis bullosa pruriginosa is an extremely rare form of dystrophic epidermolysis bullosa. Its cause is the underlying mutation, most often in the *COL7A1* gene. Based upon a specific type of mutation in a patient (missense, non-sense, frameshift, splice-site mutations), a distinct, specific phenotype can be observed. This study presents a case series of three family members from the Pomerania region in Poland, with a novel missense mutation of p.Val2402Gly/-c.7205T>G in exon 94 of the *COL7A1* gene.

Forum Derm. 2024; 10, 3: 97–100

Keywords: epidermolysis bullosa pruriginosa, dystrophic epidermolysis bullosa, genodermatoses

CASE REPORT

A 34-year-old female patient (Fig. 1), her 12-year-old daughter and her 66-year-old father (Fig. 2) presented to the Dermatological Outpatient Clinic because of chronic, relapsing skin eruptions of non-specific character. Clinical examination revealed in the 34-year-old woman and her father multiple, diffuse firm papules, plaques and nodules located on the back and extensor surfaces of the extremities. The lesions were very pruritic, and numerous excoriations and scattered scars were observed. The clinical manifestation was consistent with prurigo nodularis. The following conditions were included in differential diagnosis: pemphigoid nodularis, lichen simplex, lichen planus, nodular scabies, dermatillomania, Münchhausen syndrome by proxy, as well as epidermolysis bullosa pruriginosa (EBP). Laboratory tests did not reveal any abnormalities. Evaluation of severe pruritus causes were performed: complete blood cell count, metabolic panel, thyroid studies [free T4 (fT4) and thyroid stimulating hormone (TSH)], urinalysis, stool exam, HIV antibodies, serum IgE and chest X-ray. Laboratory tests did not reveal any abnormalities. The histopathological assessment demonstrated thickening of the epidermis, ortho-hyperkeratosis, irregular epidermal hyperplasia, and pseudoepitheliomatous hyperplasia. Moreover, focal parakeratosis with irregular acanthosis, diminished nerve fibre density and a nonspecific dermal infiltrate containing lymphocytes, macrophages, eosinophils, and neutrophils were observed (Fig. 3). Direct immunofluorescence test was negative. No circulating antibodies indicative of bullous diseases were detected.

Molecular genetic tests were performed — firstly by new generation sequencing (NGS) study that covered 33 mutations related to EB (this included: CAST, CD151, CDSN, COL17A1, COL7A1, CSTA, DSG1, DSP, DST, EXPH5, FERMT1, ITGA3, ITGA6, ITGB4, JUP, KLHL24, KRT1, KRT2, KRT5, KRT10, KRT14, KRT16, KRT17, LAMA3, LAMB3, LAMC2, PKP1, PLEC, PLOD3, SERPINB8, SPINK5, TGM5, VPS33B). A novel missense mutation of p.Val2402Gly/- c.7205T>G in exon 94 of the *COL7A1* gene was found in the patient, her daughter and her father (Tab. 1). As of the 2nd of August 2023, this mutation is not yet present in Mondo Global Medical Database (MGMD) and Clinical Variant Database (ClinVar). Based on the Genome Aggregation Database (GnomAD), the incidence of this mutation in the general population is very low — that is 0,00089%. NGS study was later confirmed with Sanger

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Received: 23.05.2024 Accepted: 1.08.2024 Early publication date: 21.08.2024

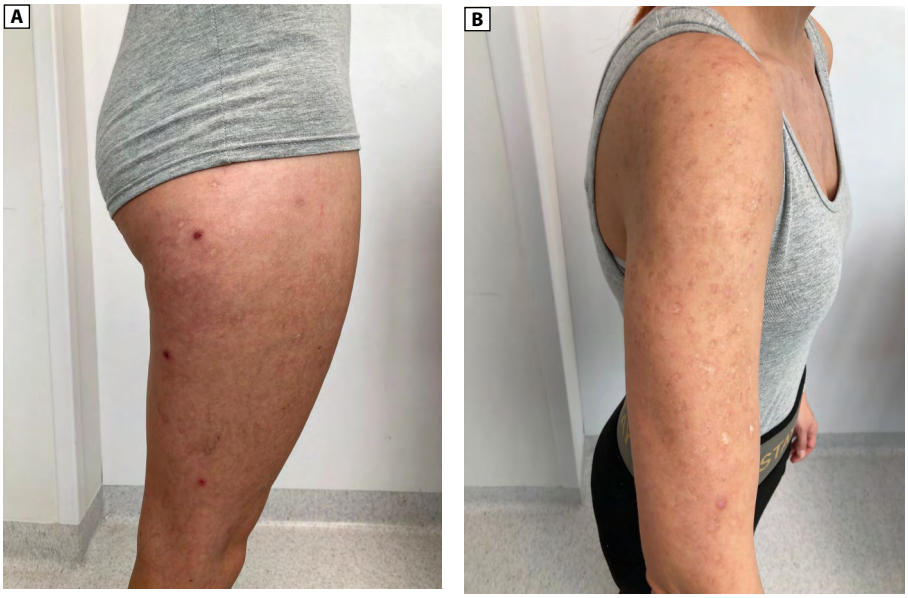

Figure 1A, B. Numerous scars and post-inflammatory hyperpigmented macules on the patient's upper extremities (a 34-year-old female) with erosions and prurigo-nodularis-like nodules on lower extremities

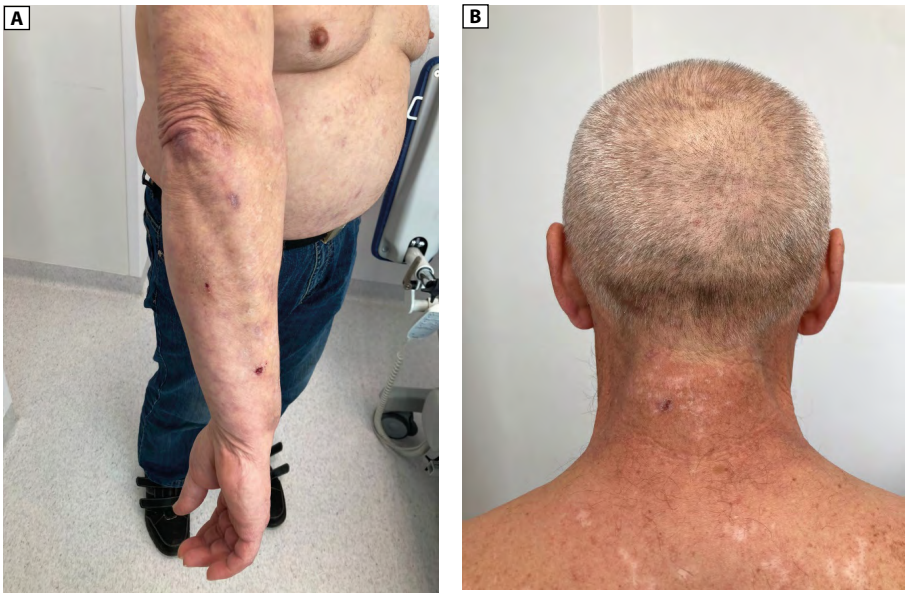

Figure 2A, B. Numerous scars, singular erosion on the patient's father (a 66-year-old male)

sequencing. Finally, the diagnosis of EBP was made based on the family history, symptoms and results of molecular genetic tests. The patient's asymptomatic 6-year-old son was also included in the study, but the result of the genetic tests was negative. Treatment was implemented: topical emollients and potent topical steroid creams that resulted in improvement in the patient's daughter and father. Due to the lack of substantial clinical benefits, the patient was given local corticosteroid injections (triamcinolone acetonide 40 mg/mL), oral antihistamines and phototherapy with ultraviolet B (UVB) 311 nm. After a 3-month treatment period, complete skin lesions and reduction of itch were achieved. The patient and their family remain in constant care and observation.

DISCUSSION

Epidermolysis bullosa pruriginosa (EBP) is an extremely rare form of dystrophic epidermolysis bullosa (DEP). Its cause is the underlying mutation, most often in the *COL7A1* gene. Based upon a specific type of mutation in a patient (missense,

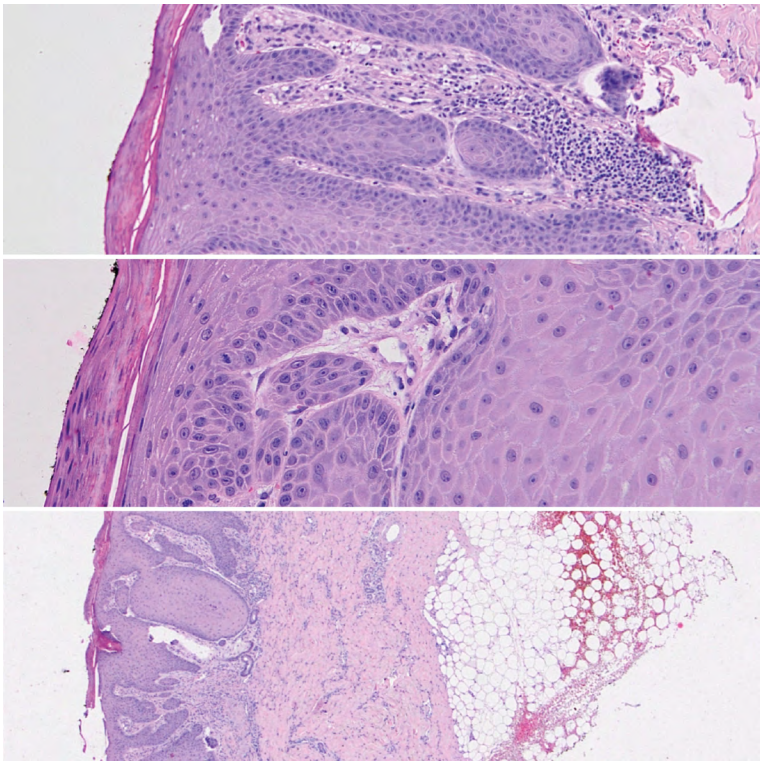

Figure 3. The result of the histological picture of the 34-year-old female patient

Table 1. The result of DNA analysis

Patient	1	2	3
Age	34	12	66
Sex	Female	Female	Male
Indication	Prurigo-like skin lesions	Prurigo-like skin lesions positive result of NGS — Col7A1 in patient 1	Prurigo-like skin lesions positive result of NGS — Col7A1 in patient
Material for laboratory testing	**DNA**	**DNA**	**DNA**
Medical procedure	Analysis of any mutation without DNA isolation (GEN23A)	Analysis of any mutation without DNA isolation (GEN23A)	Analysis of any mutation without DNA isolation (GEN23A)
Result	Col7A1:Val2402Gly/-VUS	Col7A1:Val2402Gly/-VUS	Col7A1:Val2402Gly/-VUS

NGS — next-generation sequencing; DNA — deoxyribonucleic acid; VUS — variant of uncertain significance

non-sense, frameshift, splice-site mutations), a distinct, specific phenotype can be observed [1–3]. Clinically, the mean time of symptoms onset is the age of 14. Constant, intense pruritus is present in nearly all patients. The main skin lesions found in EBP are hypertrophic prurigo-like papules and plaques nodules, and violaceous papules, often in a linear or circular configuration, often with secondary lichenification, nodule, plaque and scar tissue formation. Other skin findings are millia, nail dystrophy, albopapuloid lesions, and atrophic scars [4]. The phenotype-genotype correlation of EBP is substantially wide and is based on the mutation type. However, some family members with the same mutation can present significantly different manifestations of the condition. Thus, other environmental factors must be accounted for EBP's non-negligible heterogeneity, however, no specific factors were found in its pathogenesis. In 2015 Kim et al. [1] analysed this correlation and divided 74 patients into four mutation groups: glycine substitution (GS) — 52.7%, in-frame skipping (IFS) — 33.8%, non-glycine substitution (NGS) — 8.1%, and premature terminal codon (PTC) — 5.4%. Except for IFS carriers, EBP patients were predominantly female (66.2%). IFS patients were more prone to develop blisters and shared a more linear or circular configuration of the lesions, but had lower nail involvement, presence of milia, and atrophic scars and showed no albopapuloid lesions (which were mostly present in the PTC group). GS was also found to be a group with the most clinical features [1].

CONCLUSIONS

Epidermolysis bullosa pruriginosa is usually inherited in an autosomal dominant manner, but an autosomal recessive pattern is also present in the literature [1]. Another study points to a possible skewed T-helper type 2 (Th2)-related immunity in patients with EBP [4].

Treatment in EBP is purely symptomatic and revolves around reducing the itch. Traditionally, topical glucocorticosteroids and emollients are applied to the skin to reduce the itch. Some patients are treated with phototherapy, most commonly (narrowband ultraviolet B) NB-UVB with moderate success.

Recently, some cases of EBP treated with dupilumab were reported with positive clinical outcomes [5–8]. No causal treatment is currently available for EBP.

Article information and declarations

Acknowledgements

None.

Author contributions

Writing: original draft, data curation, conceptualization — KK; supervision — RN; writing-original draft, analysis and description of histopathological examination — EGD; data curation, table and figure preparation — AK; supervision — IB. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. All authors had full access to all of the data in this study and took complete responsibility for the integrity of the data and the accuracy of the data analysis. No medical writing or editorial assistance was received in the preparation of this manuscript.

Funding

The authors declare that no financial support was received for the research, authorship, and/or publication of this article.

Supplementary material

None.

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VIA MEDICA

LETTER TO THE EDITOR

Forum Dermatologicum
2024, Vol. 10, No. 3, 101–103
DOI: 10.5603/fd.100354

ISSN 2451–1501, e-ISSN 2451–151X

The use of botulinum toxin in the treatment of androgenetic alopecia

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Forum Derm. 2024; 10, 3: 101–103

Keywords: androgenetic alopecia, botulinum toxin, hair loss, alopecia, quality of life

DEAR EDITOR,

Androgenetic alopecia (AGA) is the most common type of hair loss worldwide [1, 2]. In men, the likelihood of developing AGA increases with age: nearly 50% will experience AGA by age 50, and up to 80% by age 70 [1, 3]. The underlying mechanism involves the miniaturisation of the hair follicle, transforming hair into vellus hair [1]. The process includes microinflammation of the hair follicle leading to gradual perifollicular fibrosis, pathological hair follicle hypersensitivity to circulating androgens, in particular dihydrotestosterone (DHT), produced from testosterone by 5α-reductase, and periapical muscle disorders [4, 5].

Treatment of AGA includes topical minoxidil and oral finasteride. New methods, like injecting botulinum toxin (BTX), are also being explored. BTX is already used in various dermatological and aesthetic treatments, such as hyperhidrosis, Raynaud's phenomenon, facial erythema, reducing facial and neck wrinkles, correcting a gummy smile or decreasing masseter muscles [6, 7]. There is limited research on BTX for AGA, highlighting the need for randomised clinical trials.

Analysed were articles from the PubMed database up to November 2022 using search terms "male pattern baldness", "androgenetic alopecia", or "hair loss", and "botulinum toxin" or "botox". Both authors independently selected relevant papers from the 227 articles, focusing on original studies investigating BTX in treating AGA and comparing it with other methods. Seven articles met the inclusion criteria.

A total of 265 patients aged 18–65 participated in these studies, including 49 women. Studies used the Hamilton–Norwood scale in five cases and the Ludwig scale in one. BTX doses ranged from 30 to 150 units. Four studies assessed BTX alone, one compared it with LC Cell Hair Solution, one with a combination of BTX and oral finasteride, and one compared oral finasteride and topical minoxidil with and without BTX. In six studies, BTX was injected across the entire scalp, covering frontal, temporal, auricular, and occipital areas; one study treated half the scalp.

All studies that measured hair count in a selected scalp area reported a statistically significant increase. Subjective assessments rated the therapy as at least satisfactory in those studies where patient feedback was included. No severe side effects were noted; minor side effects included skin irritation, mild headache, swelling, and itching. Detailed data from these seven papers are presented in Table 1 [8–14].

The mechanism by which BTX treats AGA remains unclear. Hair follicle involution in AGA involves DHT, formed from testosterone via 5α-reductase. The conversion of DHT to estradiol is oxygen-dependent [15]. In AGA-affected areas, they reduce blood flow and hypoxia, which result in higher DHT concentrations. By relaxing the scalp, BTX injections might enhance blood flow and oxygen delivery to hair follicles [8, 16]. Additionally, DHT-induced mediators such as DKK-1, interleukin-6, and TGF-1 contribute to AGA [17]. Research indicates that BTX can inhibit TGF-1 secretion in hair follicles, addressing the disease's underlying cause [11].

However, the reviewed studies have limitations, including small sample sizes and a lack of control groups, as noted in a 2022 review [18]. The long-term effects of BTX treatment beyond 60 weeks remain unknown. Future research should

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Received: 22.04.2024 Accepted: 9.07.2024 Early publication date: 23.07.2024

Table 1. The detailed description of research on treating androgenetic alopecia with botulinum toxin

Article	Study group	Methodology	Results	Comment
Freund et al. [8]	50 male patients aged 19–57 years	Two courses of injections with a 24-week interval with 150 units of botulinum toxin A in frontal, temporal, periauricular and occipital muscles (doses equally divided into 30 injection sites) Follow-up for 60 weeks — 12 weeks of run-in followed by two treatment cycles of 24 weeks The results were evaluated by measuring the number of hairs on a fixed area determined by the Canfield method	The trial was completed in 40 out of 50 men The response rate was 75% Mean hair counts showed a significant ($p < 0.0001$) increase of 18 per cent between baseline and week 48	The first study that evaluated treating AGA with BTX The protocol included more than one course of BTX injection Precise measurement method showing encouraging results Lack of control group No follow-up after the study
Singh et al. [9]	10 male patients aged 22–42 years	A single course on injections with 150 units of botulinum toxin A in frontal, occipital, temporal and periauricular muscles (doses equally divided into 30 injection sites) Efficacy was evaluated through photography, and patients performed self-assessment scoring Follow-up 24 weeks after the treatment	80% had good to excellent responses on the photographic assessment In self-assessment, 70% of the patients had good to excellent responses, 20% had a fair response and 10% showed poor responses	The study was based only on one course of BTX injection Small study group. Lack of control group The measurement method was not objective, however, the results seem to be promising
Zhang et al. [10]	25 male patients aged 30–45 years	A single course of injections with 50 units of botulinum toxin A in frontal, temporal, periauricular and occipital muscles (in a minimum of 30 injection sites) Efficacy was measured with Derma-Expert MC760 (grease content) and hair count at each visit Follow-up after 3 and 6 months	The trial was completed in 24 out of 25 patients At 3 months, 37.5% of patients showed obvious hair regrowth (> 10% increase from baseline) At 6 months, this percentage rose to 45.8% Additionally, almost 80% of the patients showed a significant decrease in grease secretion after 3 months, which restored to normal after 6 months	The study was based only on one course of BTX injection Small study group. Lack of control group No specific details about the hair count performed as an efficacy measurement
Shon et al. [11]	18 male patients; mean age of 49 +/– 6.5 years	Injections with 30 units of botulinum toxin A every 4 weeks for 24 weeks at 20 different sites on the balding scalp Efficacy was measured based on an unblinded phototrichogram image analysis Follow-up at 0, 12 and 24 weeks	The number of hairs significantly increased at week 24 ($p = 0.012$) but not at week 12 ($p = 0.803$) A comparison of the pre- and post-treatment photographs at week 24 showed significant improvement ($p = 0.031$)	Small study group. Lack of control group Precise measurement of the treatment efficacy showing promising results The protocol included 6 courses of injections with BTX No long-term follow-up
Zhou et al. [12]	63 male patients were divided into two randomised study groups — the first received BTX injections (30 patients) and the second received BTX injections and oral finasteride (FNS; 33 patients)	Both groups received 4 courses of injections with 100 units of BTX every 3 months for 12 months Injections were done in frontal, temporal, periauricular, and occipital muscles — 30 injection target sites, each 1.5–2 cm apart The second group received oral finasteride as well Follow-up was provided every 3 months, 4 times in total during and after completion of the treatment	Hair counts in both groups at all times were significantly higher compared with before treatment ($p < 0.05$) Hair counts in both groups increased gradually with the prolongation of the treatment time There was no significant difference in the efficacy of BTX and BTX + FNS groups	The results did not favour BTX, nor BTX + FNS treatment, nevertheless, in both groups, a significant increase in hair density was observed Precise measurement of hair count Small study, but randomised study groups No information about FNS dosage
Tian et al. [13]	37 male patients aged 20–51 years were treated with 5% minoxidil topically and 1 mg finasteride orally	One course of injection with 50 units of botulinum toxin A on one hemisphere of the head — contralaterally, injections with normal saline as a control Follow-up at 3 and 6 months after the treatment	The number of hair roots on the hemisphere injected with BTX was higher than on the control side 3 and 6 months after the treatment ($p < 0.05$) The effectiveness rate was assessed at 75.7% ($p > 0.05$)	The results show that BTX might improve the effects of standard treatment of AGA Small study group. Comparison of the treatment efficacy only on one hemisphere, instead of collecting a control group
Nassar et al. [14]	62 patients (13 males and 49 females) aged 18–65, were divided into two groups	In the first group, 50 units of BTX were injected into the frontal, temporal, periauricular, and occipital muscles The patients in the second group underwent a needle mesotherapy treatment with 1 mL of LC Cell Hair Solution in the frontal and lateral areas of the scalp once a week for eight consecutive weeks Follow-up for every 2 weeks for 6 months	There was a significant difference between baseline and 6 months in the Ludwig and Hamilton–Norwood scale in both groups with a highly significant difference in the LC group in both male and female patients	Comparison of injections BTX and LC Cell Hair Essence Randomised groups, but small study groups, especially females

AGA — androgenetic alopecia; BTX — botulinum toxin; FNS — finasteride

incorporate additional parameters such as hair follicle morphology for a more comprehensive assessment.

While initial findings are promising, definitive treatment recommendations cannot be made based on current data. Methodological disparities among studies underscore that controlled clinical trials must thoroughly evaluate BTX as an AGA treatment. Given the substantial impact of alopecia on the quality of life for both men and women, further research in this area is imperative.

Article information and declarations

Acknowledgements

None.

Conflict of interest

The authors declare no conflicts of interest.

Funding

None.

Supplementary material

None.

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